Industria y Comercio

SUPERINTENDENCIA

Delegatura de propiedad Industrial

División de Nuevas Creaciones

PCT

SOLICITUD

# PATENTE DE INVENCIÓN

(21) EXPEDIENTE No. 03-019100

(54) TÍTULO _____

_____

_____

_____

(51) CLASIFICACIÓN INTERNACIONAL A 61 K 31/5377

(71) SOLICITANTE _____

DOMICILIO _____

(74) APODERADO EMILIO FERRERO

(22) BOGOTÁ, D. C., _____

Industria y Comercio
SUPERINTENDENCIA

PETITORIO

03 019100 00

SUPERINDUSTRIA Y COMERCIO
Radicacion : 03019100 00000000 Folios: 735
Fecha (AAAA): 2003-03-06 13:08:44
Tramite : 011 PCT-PATENT 379 FASE NACI 411 PRESENTAC
Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

# FORMULARIO UNICO DE SOLICITUD DE PATENTE
## PCT
## ENTRADA EN FASE NACIONAL

**1 SOLICITUD DE:**

☒ Patente de Invención. ☐ Patente de Modelo de Utilidad.

☐ Capítulo I. ☒ Capítulo II.

**2 SOLICITANTE (71)**

Nombre: **BOEHRINGER INGELHEIM PHARMACEUTICALS, INC.** sociedad constituida y existente bajo las leyes del Estado de Delaware, Estados Unidos de América.

Dirección: 900 Ridgebury Road, Ridgefield, Connecticut 06877-0368 Estados Unidos de América.

Domicilio: Ridgefield, Connecticut, Estados Unidos de América.

**IDENTIFICACION**

C.C. ☐ NIT ☐

C.E. ☐ Otro ☐ Cual_____

Número: _____

**3 REPRESENTANTE APODERADO**

Nombre: EMILIO FERRERO

Dirección: Carrera 4ª. No. 72-35
Teléfono: 347 36 11
Fax:: 217 92 11
E-mail: clientes@camvp.com.
Domicilio: Bogotá, Colombia.

**IDENTIFICACION**

C.C. ☒ NIT ☐

C.E. ☐ Otro ☐ Cual_____

Número: 438.019 T.P. 31.929

**4 INVENTOR (ES) (72)**

1- **Younes BEKKALI**
60 Padanaram, Unit. #34,
Danbury, Connecticut 06811,
Estados Unidos de América.

2- **Eugene Richard HICKEY**
5 Woodbury Drive,
Danbury, Connecticut 06811,
Estados Unidos de América.

3- **Weimin LIU**
10 Russett Road,
Sandy Hoock, Connecticut 06482,
Estados Unidos de América.

4- **Usha, R. PATEL**
20 Dairy Farm Drive,
Brookfield, Connecticut 06804,
Estados Unidos de América.

5- **Denice Mary SPERO**
18 Limekiln Road,
West Redding, Connecticut 06896,
Estados Unidos de América.

6- **Sanxing SUN**
38-21 Padanaram Avenue,
Danbury, Connecticut 06811,
Estados Unidos de América.

7- **David S. THOMSON**
166 Minuteman Road,
Ridgefield, Connecticut 06877,
Estados Unidos de América.

8- **Yancey David WARD**
11 Narragansett Trail,
Sandy Hook, Connecticut 06482,
Estados Unidos de América.

9- **Erick Richard Roush YOUNG**
36 Faith Lane,
Danbury, Connecticut 06810,
Estados Unidos de América.

CAVELIER ABOGADOS- Colo 7612-841-001-6 JBP/MRM-ID-184

5 **PCT (86)**

Solicitud Internacional No. PCT/US01/08084 Fecha: 14 de marzo de 2001

Publicación Internacional No. WO 02/20485 A1 Fecha : 14 de marzo de 2002

6 **Título (54)** NITRILOS ESPIROHETEROCÍCLICOS, UTILES COMO INHIBIDORES REVERSIBLES DE CISTEÍNA-PROTEASAS

7 **Clasificación Internacional (51)** C07D 211/60 A61K 31/537

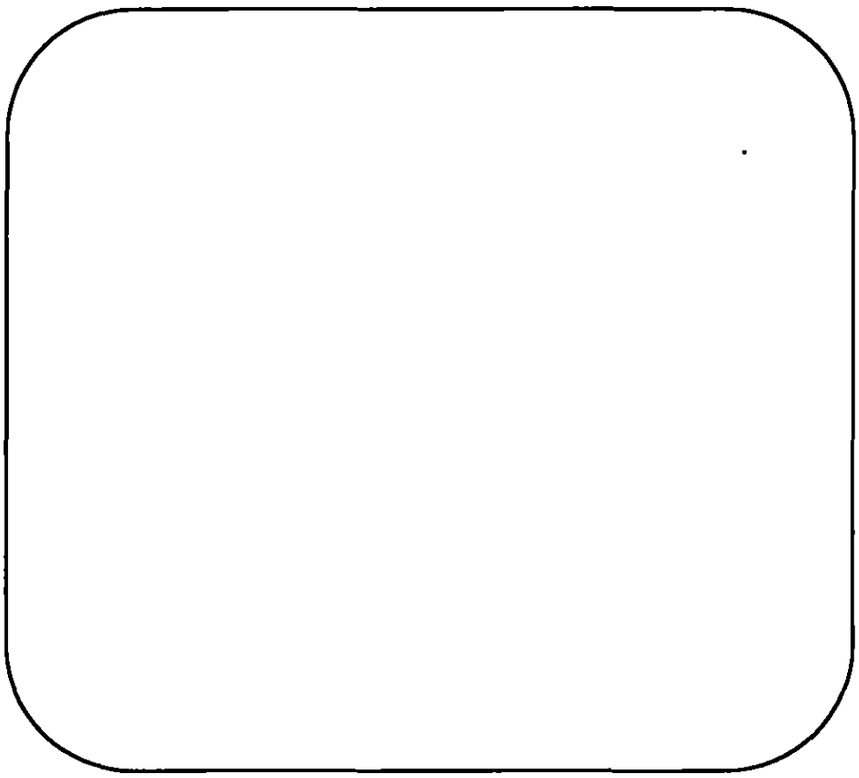
| 8 Prioridad | (33) País de Origen | (32) Fecha | (31) Número de Solicitud |
|---|---|---|---|
| SI ☒ NO ☐ | US. | 8 de sepbre. 2000 | 09/655.351 |

9 **Comprobante de pago No.:** 03 – 13.521 **Fecha:** 24 de febrero de 2003

10 **Anexos:**

- ☒ Comprobante de pago de la tasa de presentación de la solicitud por $ 400.000.oo.
- ☐ Comprobante de pago por reivindicación de prioridad.
- ☒ Documento que acredita la existencia y representación legal cuando el solicitante sea persona jurídica.
- ☒ Poderes, si fuere el caso.
- ☒ Documento de cesión del inventor al solicitante o a su causante.
- ☐ Declaraciones.
- ☒ Copia de la solicitud internacional. (Resumen, descripción, reivindicaciones, dibujos)
- ☒ Traducción de la solicitud internacional al castellano. (Resumen, descripción, reivindicaciones, dibujos)
- ☒ Copia del examen preliminar efectuado por la IPEA.
- ☐ Traducción del examen preliminar efectuado por la IPEA.
- ☐ De ser el caso, copia del contrato de acceso.
- ☐ De ser el caso, documento que acredite la licencia o autorización de uso de conocimientos tradicionales de las comunidades indígenas.
- ☐ De ser el caso, certificado de depósito del material biológico.
- ☐ Arte final 12x12
- ☐ De ser el caso, información sobre otras solicitudes de patente o títulos obtenidos en el extranjero por el mismo titular o su causante, relacionadas parcial o totalmente con la invención de esta solicitud.
- ☐ Otros

11 **FIGURA CARACTERISTICA:**



12 Solicito la concesión de la patente,

**NOMBRE:** EMILIO FERRERO

**FIRMA :**

C.C. 438.019 de Usaquén T.P. 31.929

**MRE/mrm-id-184**

CAVELIER
ABOGADOS
EDIFICIO SISKI
CARRERA 7ª Nº 72-35
BOGOTA, D. COLOMBIA

07612
0569

For patents, utility models, industrial designs, trademarks, commercial names, trade emblems, slogans.

Para patentes, modelos de utilidad, diseños industriales, marcas de fábrica, nombres comerciales enseñas, lemas comerciales.

# REPRESENTACION Y PODER

# REPRESENTATION AND POWER OF ATTORNEY

I (we) the undersigned/Yo (nosotros) abajo firmado (s)
BOEHRINGER INGELHEIM PHARMACEUTICALS INC

of/domiciliado (s) en 900 Ridgebury Road,
Ridgefield, Connecticut 06877, United
States of America,

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

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

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

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

Given and signed this/Dado y firmado hoy 29th day of August, 1996

In/en Ridgefield, Connecticut USA

JUAN MANUEL BOTE GALEANO
NOTARIO

Signature

Dr Robert P Raymond
Chief Patent Counsel
Boehringer Ingelheim Pharmaceuticals Inc

Firma

96912

ANA MARIA SALVATI
TRADUCTORA DE IDIOMA OFICIAL
INGLES ITALIANO ESPAÑOL
RES. No 158 M JUSTICIA

CAVELIER ABOGADOS
WI PODERE-3 (MINUTIAN 121126 USA)

9/087

## CERTIFICADO NOTARIAL (INDIVIDUO)

A los 29 días del mes de AGOSTO de 19 96

ante mí, Notario Publico de Connecticut, EE UU

compareció(eron) personalmente Dr Robert P Raymond

a quien(es) doy fe de conocer y me consta que es(son) la(s) persona(s) firmante(s) del documento que precede y quien(es) tiene(n) capacidad legal para otorgarlo.

MARY ELLEN M DEVLIN
NOTARY PUBLIC
MY COMMISSION EXPIRES OCT 31 2000

Notario Publico — Notary Public

## NOTARIAL CERTIFICATE (INDIVIDUAL)

On this 29 day of August 19 96

before me, a Notary Public of Connecticut, USA

personally appeared Dr Robert P Raymond

to me known and known to me to be the person(s) who executed that foregoing document, and who has(have) legal capacity to execute it

Mary-Ellen M Devlin
My Commission Expires 10/31/2000

## CERTIFICADO NOTARIAL (SOCIEDAD)

Hoy 29 de Agosto de 19 96

compareció(eron) ante mí

Dr Robert P Raymond

a quien(es) conozco personalmente y que firma(n) este documento en representación de la Sociedad/compañía

denominada BOEHRINGER INGELHEIM PHARMACEUTICALS INC

Certifico:

1 Que he visto los siguientes documentos

ESCRITURA DE LA SOCIEDAD ESTATUTOS Y VARIOS RESOLUCIONES DE LA JUNTA DIRECTIVA , BIL-071 de fecha 29 de noviembre de 1984

2 Que dichos documentos prueban lo siguiente

2.1 Que BOEHRINGER INGELHEIM PHARMACEUTICALS, INC.

es una Sociedad/Compañía legalmente constituída y existente

de acuerdo con las leyes de l Estado de Delaware, Estados Unidos de América

2.2. Que el domicilio de dicha Sociedad/Compañía es

900 Ridgebury Road, Ridgefield Connecticut 06877, Estados Unidos de América

2.3. Que el objeto u objeto para los cuales se otorga el presente poder están comprendidos dentro del objeto social de la mencionada Sociedad/Compañía

2.4. Que el(los) Sr (Sres.) DR ROBERT P RAYMOND

está(n) autorizado(s) para otorgar el presente Poder

Ciudad Ridgefield

Estado Connecticut EE UU

Hoy 29 Agosto de 19 96

Documentos deben identificarse con fecha y origen.

## NOTARIAL CERTIFICATE (CORPORATION)

On this 29 day of August 19 96

appeared before me

Dr. Robert P. Raymond

who(m) I know personally and who(m) signed this document as representative(s) of the Corporation/Company

named BOEHRINGER INGELHEIM PHARMACEUTICALS, INC

I Certify

1 That I have seen the following documents

Corporate Charter By-Laws and various board resolutions, BIL-071 dated November 29, 1984

2. That the above documents duly prove the following:

2.1 That BOEHRINGER INGELHEIM PHARMACEUTICALS, INC

is a Corporation/Company legally constituted and in existence

in accordance with the laws of the State of Delaware, United States of America

2.2. That the domicile of said Corporation/Company is

900 Ridgebury Road, Ridgefield, Connecticut 06877, United States of America

2.3. That the purpose of purposes for which the preset Power of Attorney is granted are comprised within the corporation purposes set forth in the charter of the mentioned Corporation/Company

2.4. That Mr (Messrs.) Dr. Robert P. Raymond

is(are) authorized to grant the present Power of Attorney

City Ridgefield

State Connecticut USA

This 29th day of August 19 96

MARY ELLEN M DEVLIN
NOTARY PUBLIC
MY COMMISSION EXPIRES OCT 31 2000

Notario Publico — Notary Public

Documents must be identified with date and origin.

5

STATE OF CONNECTICUT
COUNTY OF FAIRFIELD } ss. RIDGEFIELD

I, Barbara Serfilippi, Clerk of the Town of Ridgefield

in said County, do hereby certify that Mary Ellen M. Devlin
by and before whom the foregoing (or annexed) acknowledgment was taken, was at the time of taking the same a notary public (or other officer) residing (or authorized to act) in said County, and was authorized by the laws of said State to take and certify acknowledgments in said State, and, further, that I believe that the signature to the certificate of acknowledgment is genuine.

IN TESTIMONY WHEREOF, I have hereunto set my hand and affixed the seal of the State and Town this

29th day of August 19 96.

76912

ANA MARIA SALVETTI
TRADUCTORA E INTERPRETE OFICIAL
INGLES - ITALIANO - ESPAÑOL
RES. No. 158 MINJUSTICIA

Barbara Serfilippi
Town Clerk

ADKINS FORM 223

COMO NOTARIO SEXTO DEL CIRCULO DE BOGOTA, HAGO CONSTAR QUE LA FOTOCOPIA COINCIDE CON EL ORIGINAL QUE HE TENIDO A LA VISTA

04 MAR 2003

JUAN MANUEL GUTIERREZ MEDINA
NOTARIO

(0404/07/T/Rev 11-92)

6

**STATE OF CONNECTICUT**
**OFFICE OF THE SECRETARY OF THE STATE**

I **MILES S RAPOPORT** Secretary of the State of Connecticut and keeper of the seal thereof

**DO HEREBY CERTIFY** that BARBARA SERFILIPPI was duly elected or appointed to the office of TOWN CLERK for the town of RIDGEFIELD in the County of FAIRFIELD in said State for the term of JANUARY 1, 1996 to JANUARY 5, 1998

and that to his/her acts and attestations as such full faith and credit are and ought to be given in and out of Court

**In Testimony Whereof** I have hereunto set my hand and affixed the Great Seal of the State of Connecticut at Hartford on August 30, 1996

Miles S Rapoport

Secretary of the State

96912

ANA MARIA SALVETTI
TRADUCTORA E I TE BET CFICIAL
In L S ITALIANO ESPAÑOL
REG No 158 L USTI IA

COMO NOTARIO SEXTO DEL CIRCULO DE BOGOTA, HAGO CONST R QUE L FOTOCOPIA COINCIDE CON EL ORIGINAL QUE SE TUVO A V STA

04 MAR 2003

JUAN MANUEL GUTIERREZ CAICEDO
NOTARIO

7

# CONSULADO DE COLOMBIA

535 Boylston Street 11th Floor Boston, MA 02116 Tel (617)536-6222 Fax (617)536-9372

No 1156

El suscrito Consul de Colombia en Boston MA Estados Unidos vistos los documentos presentados

**CERTIFICA**

Que el señor(a) **MILES S RAPOPORT**, quien autenticó la firma de **BARBARA SERFILIPPI**, secretario de la ciudad de Ridgefield Connecticut, en el documento adjunto ejercia en la fecha alli indicada las funciones de **SECRETARIO DE ESTADO DEL ESTADO DE CONNECTICUT, USA** y su firma y sello son los que acostumbra a usar en sus actos oficiales Que la compañia **BOEHRINGER INGELHEIM FARMACEUTICALS INC**, con domicilio principal en la ciudad de **RIDGEFIELD, CONNECTICUT**, es sociedad constituida bajo las leyes del estado de **DELAWARE**, Estados Unidos y tienen y ejerce su objeto social conforme a las leyes de ese país Que el señor **ROBERT P RAYMOND** en su calidad de **CONSEJERO JEFE DE PATENTES** de dicha compania esta debidamente autorizado para otorgar este poder a nombre de estas companias y para los fines y propositos alli expresados.

La presente certificación se expide en cumplimiento del articulo 480 del Codigo de Comercio

El Consul no asume responsabilidad por el contenido del documento

Esta certificacion se expide en Boston a los 13 dias del mes de Septiembrede 1996

**Pagado Impuesto de Timbre US$56 oo**

CONSULADO DE COLOMBIA BOSTON

**LUIS FERNANDO LEMAITRE**
VICECONSUL

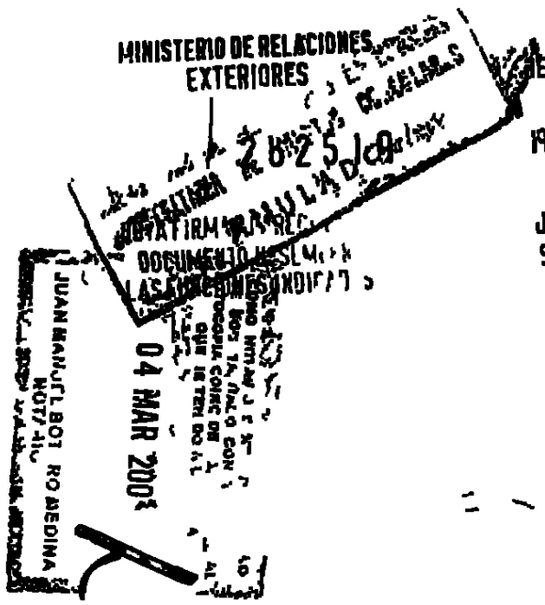
COMO NOTARIO SEXTO DEL CIRCULO DE BOGOTA D.C. CERTIFICO QUE LA FOTOCOPIA CORRESPONDE A LA QUE HE TENIDO A LA VISTA

04 MAR 2003

A 76912

ANA MARIA SAAVEDRA
TRADUCTORA E INTERPRETE OFICIAL
DEL INGLES AL ESPAÑOL
RES. No 1 8 5 3 JUSTICIA

JUAN MANUEL BUITRAGO SCHIA
NOTARIO


MINISTERIO DE RELACIONES EXTERIORES
NO SE ASUME RESPONSABILIDAD DEL TEXTO
1996 SET 25 A 11 45
JEFE DE LEGALIZACIONES
SANTAFE DE BOGOTA D C
04 MAR 2004

## CERTIFICACION NOTARIAL Y AUTENTICACION CONSULAR

1 Es necesaria la legalización con certificado notarial El Notario Publico debe certificar

1 1 Que la compañía está legalmente constituída y actualmente existente

1.2 Su domicilio

1 3 Que el propósito del poder está incluído en el objeto social de la compañía

1 4 Que el poderdante está autorizado para dar el poder en nombre de la compañía

2 Los documentos que hay que mostrarle al Notario Publico para probar los puntos anteriores deben estar expresados en el Certificado Notarial con fecha y origen

2 1 Respecto a los puntos 1 1 1.2 y 1 3 sugerimos referirse a los artículos de constitucion con fecha y lugar de otorgamiento y

2 2 Para el punto 1 4 sugerimos mencionar la resolución de la Junta Directiva o los estatutos segun los cuales la persona que otorga el poder está autorizada para ello

3 Enseguida el Señor Cónsul de Colombia debe autenticar la firma del Notario Público

## NOTARIAL CERTIFICATION AND CONSULAR AUTENTIFICATION

1 Notarial legalization is necessary The Notary Public must certify

1 1 That the company is legally constituted and presently existent

1.2 Its place of business

1 3 That the purpose of the Power-of-Attorney is included in the activities of the company

1 4 That the grantor is empowered to give the Power of Attorney in the name of the company he represents

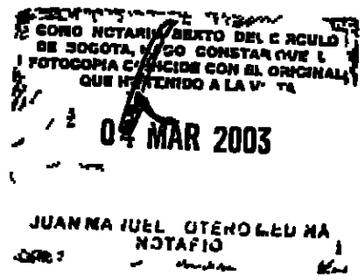
2 The documents which the Notary Public had before him to prove the above points must be listed by him in the Notarial Certificate with dated and origin

2 1 In connection with points 1 1 1.2 and 1 3 we suggest referring to the articles of incorporation with date and place of execution

2.2 For point 1 4 we suggest to mention the resolution of the Board of Directors and/or the by laws whereby the person who grants the Power of Attorney has been authorized to give it

3 Then the Colombian Consul must legalize the signature of the Notary Public

NOTA PARA EL SENOR CONSUL COLOMBIANO Segun el artículo 259 del C de P C el Senor Cónsul debe autenticar la ultima precedente autenticación



**TRADUCCION OFICIAL No 96912** de un documento escrito en ingles el cual para su identificacion se sella con el sello del Traductor al mismo tiempo que la presente Esta Traduccion ha sido preparada por Ana Maria Salvetti Traductora Oficial debidamente reconocida por el Ministerio de Relaciones Exteriores y aprobada por el Ministerio de Justicia colombiano mediante Resolución No 158 de 1991

---

(Se traducen sellos y legalizaciones que aparecen a continuacion de un poder escrito en ingles y español otorgado por la sociedad **BOEHRINGER INGELHEIM PHARMACEUTICALS INC** a favor de German CAVELIER Gonzalo PERDOMO Emilio FERRERO y Luz Clemencia de PAEZ )

Dado y firmado el 29 de agosto de 1996 en Ridgefield Connecticut EE UU (Firmado) ilegible Robert P Raymond Principal Asesor de Patentes Boehringer Ingelheim Pharmaceuticals Inc

(en ingles y español) CERTIFICACION NOTARIAL (INDIVIDUO) referente a la firma que antecede (Firmado) Marry-Ellen M Devlin Notario Publico Mi comision expira el 31 de octubre del 2000 Sello seco del Notario

CERTIFICACION NOTARIAL (SOCIEDAD) referente a la existencia y representacion de la sociedad mencionada (Firmado) Mary-Ellen M Devlin Notario Publico Mi comision expira el 31 de octubre del 2000 Sello seco del Notario

COMO NOTARIO SEXTO DEL CIRCULO
FOTOCOPIA COTEJADA CON EL ORIGINAL
QUE SE TUVO A LA VISTA
24 MAR 2003
NOTARIO

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ESTADO DE CONNECTICUT

CONDADO DE FAIRFIELD ss RIDGEFIELD

Yo Barbara Serfilippi Escribano de la Poblacion de

Ridgefield en dicho Condado por medio del presente certifico que Mary Ellen M Devlin por y ante quien el anterior reconocimiento (o adjunto) fue tomado era al momento de tomarlo un Notario Publico (u otro funcionario) domiciliado (o autorizado para actuar) en dicho Condado y que estaba autorizado por las leyes de dicho Estado para tomar y certificar reconocimientos en dicho Estado y ademas que creo que la firma que aparece en el certificado de reconocimiento es autentica

En Testimonio de lo Cual he firmado y estampado del sello del Esado y Poblacion hoy 29 de agosto de 1996 (Firmado) Barbara Serfilippi Escribano

---

(0404/07/T/Rev 11-92)

ESTADO DE CONNECTICUT

OFICINA DEL SECRETARIO DEL ESTADO

Yo Miles S Rapoport Secretario del Estado de Connecticut y guardian de su Sello POR MEDIO DEL PRESENTE CERTIFICO que BARBARA SERFILIPPI fue debidamente elegida o nombrada para el cargo de ESCRIBANO DEL CONDADO para la poblacion de RIDGEFIELD en el Condado de FAIRFIELD en dicho Estado para dicho periodo que va del 1o de enero de 1996 al 5 de enero de 1998 y que sus actos oficiales en calidad de tal merecen completa fe y credito dentro y fuera de la Corte En testimonio de lo cual he firmado y estampado el Gran Sello del Estado de Connecticut en Hartford el 30 de agosto de 1996 (Firma facsimilar) Miles S Rapoport Secretario del Estado Adherido se encuentra sello de oblea del Estado de Connecticut Sello seco del Consulado de Colombia en Boston

COMO NOTARIO SEXTO DE LO DE BOGO A HAGO CONS QUE HE TENIDO A LA

04 MAR 2005

JUAN MANUEL BOTERO MEDINA

EE.UU.

---

(en español): **Certificación No.1156** del 13 de septiembre de 1996, de la firma que antecede por el Consulado de Colombia en Boston. Pagados impuesto de timbre y derechos de fondo rotatorio. (Firmado), Luis Fernando Lemaitre, Cónsul. Sello consular en tinta. **Certificación No.213241** del 24 de septiembre de 1996 de la firma que antecede por el Ministerio de Relaciones Exteriores. (Firmado), Jefe Legalizaciones.

---

Es traducción fiel y completa de la cual se deja constancia en los archivos de esta oficina para su confrontación y a la cual me remito.

Santa fe de Bogotá, 30 de septiembre de 1996.

COLO-7612-801-005-5

ams/~~59~~-60

COMO NOTARIO SEXTO DEL CIRCULO DE BOGOTA, HAGO CONSTAR QUE LA FIRMA QUE APARECE EN EL DOCUMENTO QUE HE TENIDO A LA VISTA

04 MAR 2003

JUAN MANUEL BOTERO MEDINA
NOTARIO

ANA MARIA SALVETTI
TRADUCTORA E INTERPRETE LEGAL
INGLES - ITALIANO - ESPAÑOL
SEG. No. 158 MINJUSTICIA

MINISTERIO DE RELACIONES EXTERIORES
Ana María
26398

LA FIRMA APARECIDA EN EL DOCUMENTO DESEMPEÑA LAS FUNCIONES INDICADAS

COMO NOTARIO SEXTO ENCARGADO DE SANTAFE DE BOGOTA HAGO CONSTAR QUE LA FIRMA DE

C.C.

COINCIDE CON LA REGISTRADA POR EL (LA) EN ESTA NOTARIA.

30 SET. 1996

SANTAFE DE BOGOTA, D.C.

NOTARIA SEXTA
Juan C. Vélez
Notario Sexto Encargado

JEFE DE LEGALIZACIONES
SANTAFE DE BOGOTA D.C.

1996 SET 30 12:07

NO SE ASUME RESPONSABILIDAD DEL TEXTO

12

CAVELIER
ABOGADOS

TELEFAX: (57) (1) 2388880
CABLES CAVELEYES
TELEX: 45479

EDIFICIO SISKI
CARRERA 41, No. 72-35
BOGOTA 8, COLOMBIA

CORREO ELECTRONICO MUNDIAL: CAVE
TELEFONO: (57) (1) 2120100

Señor Jefe de la
DIVISION DE NUEVAS CREACIONES
Superintendencia de Industria y Comercio
E. S. D.

Poderdante: BOEHRINGER INGELHEIM PHARMACEUTICALS, INC.

Poder conferido el: 29-08-96

Yo, GERMAN CAVELIER, obrando en mi calidad de apoderado principal del poderdante arriba mencionado, atentamente manifiesto a Usted que sustituyo el poder que me ha sido conferido en la persona del doctor EMILIO FERRERO, Abogado con Tarjeta Profesional No. 31.929, con todas las facultades que me fueron conferidas.

Hago la anterior sustitución conforme al artículo 66 del Código de Procedimiento Civil ya que los otros sustitutos faltan en este momento.

Señor Jefe,

GERMAN CAVELIER
T.P.A. No. 832
C.C. No. 2.877.924 de Bogotá

Acepto:

EMILIO FERRERO
T.P.A. Nº 31.929
C.C. No. 438.019 de Usaquén

COMO NOTARIO SEXTO DEL CIRCULO DE BOGOTA, HAGO CONSTAR QUE LA FOTOCOPIA CONCUERDA CON EL ORIGINAL QUE HE TENIDO A LA VISTA
04 MAR 2003
JUAN MANUEL PUTRINO MEDINA
NOTARIO

2e-780-2

NOTARIA SEXTA DE BOGOTA

RECONOCIMIENTO Y PRESENTACION PERSONAL

Santafé de Bogotá D. C. 06 SET 1996

Ante Mi JUAN MANUEL BUITRAGO MEDINA

NOTARIO SEXTO DEL CIRCULO DE BOGOTA

Compareció(eron) personalmente el

[illegible]

quien(es) exhibió(eron) la(s) C.C. [illegible]

y la(s) Libreta(s) [illegible]

[illegible]

domiciliado(s) en [illegible] y reconoce(n) la(s) firma(s) que aparece(n) en el presente escrito como suya(s) y que el contenido es [illegible]

En constancia se firma la presente diligencia

04 MAR 2003

JUAN MANUEL BUITRAGO MEDINA

NOTARIO SEXTO DE BOGOTA

REPUBLICA DE COLOMBIA

Juan Manuel Buitrago Medina

NOTARIO

SANTAFE DE BOGOTA D.C.

94
13

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

## CESION

Yo, (nosotros), abajo firmado (s)
Younes BEKKALI

domiciliado (s) en Unit 34, 60 Padanaram Road
Danbury, CT 06811 / USA

declaro(amos) bajo juramento ser único(s) y verdadero(s) inventor(es) de la invención:
nitrilos espiro heterociclicos utiles como inhibidores reversibles de proteasas de cisteina

declaro(amos) así mismo que cedo(emos) y transfiero(erimos), sin limitación, a favor de la sociedad
BOEHRINGER INGELHEIM PHARMACEUTICALS, INC.

constituida y existente de conformidad con las leyes de
USA

domiciliada en 900 Ridgebury Road
Ridgefield, CT 06877, USA

todos los derechos inherentes a dicha invención y que la citada Compañía queda facultada para solicitar en su nombre la patente correspondiente en la República de Colombia.

## ASSIGNMENT

I (we), the undersigned
Younes BEKKALI

of Unit 34, 60 Padanaram Road
Danbury, CT 06811 / USA

state(s) under oath to be sole and true inventor(s) of the invention:

Spiroheterocyclic nitriles useful as reversible inhibitors of cysteine proteases

state as well, that assign, without reservations or limitations in favour of
BOEHRINGER INGELHEIM PHARMACEUTICALS, INC.

a corporation constituted and existing in conformity with the laws of
USA

domiciled in 900 Ridgebury Road,
Ridgefield, CT 06877, USA

all rights inherent to said invention and that the above mentioned company hereby is enabled to apply, in its name, for the corresponding patent in the Republic of Colombia.

Dado y firmado hoy/Given and signed this
01/24/03

en/in Ridgefield, Connecticut 06877 USA

Firma / Signature

© CAVELIER ABOGADOS
WPPODER6-343

14

**AUTENTICACION NOTARIAL (INDIVIDUO)**

A los ____ días del mes de _____ de 200____
ante mí, Notario Público de _____
compareció (eron) personalmente _____

_____

a quien(es) doy fe de conocer y me consta que es(son) la(s) persona(s) firmante(s) del documento que precede, y quien(es) tiene(n) capacidad legal para otorgarlo.

_____ Notario Público

**NOTARIAL AUTHENTIFICATION (INDIVIDUAL)**

On this 24th day of January 200 3
before me, a Notary Public of the State of Connecticut USA
personally appeared _____
Younes BEKKALI

to me known, and known to me to be the person(s) who executed that foregoing document, and who has (have) legal capacity to execute it.

Notary Public _____
Jeanne E. Rogers
Commission expires: 11/30/2006

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

1. Country: .....
   This public document
2. has been signed by .....
3. acting in the capacity of .....
4. bears the seal/stamp of .....

**Certified**

5. at ..... 6. the .....
7. by .....
8. No. .....
9. Seal/stamp 10. Signature

..... .....

# APOSTILLE

(Convention de La Haye du 5 octobre 1961)

1. Country: The United States of America

**THIS PUBLIC DOCUMENT**

2. has been signed by **JEANNE E. ROGERS**

3. acting in the capacity of **NOTARY PUBLIC**

4. in the State of Connecticut for the term of **November 26, 2001 to November 30, 2006**

## CERTIFIED

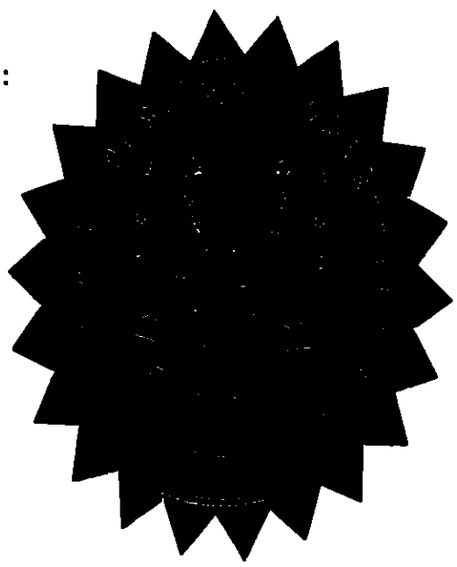
5. at Hartford, Connecticut

6. on **January 27, 2003**

7. by **SUSAN BYSIEWICZ,** Secretary of the State of Connecticut

8. Number : **2003-790**

9. Seal :



10. Signature

Susan Bysiewicz

Secretary of the State

TRADUCCIÓN OFICIAL No.2003/029de un documento escrito en inglés el cual para su identificación se sella con el sello del traductor al tiempo con la presente. Esta traducción ha sido preparada por Hilda Aguilera de Piedrahita, traductora e intérprete oficial debidamente reconocida por el Ministerio de Relaciones Exteriores y autorizada por el Ministerio de Justicia y del Derecho, por Resolución No. 323 de 1980, según consta en la escritura 5883 de 22 de septiembre de 1986, de la notaría sexta de Bogotá.

-.-.-.-.-

(Se traduce un documento de cesión de derechos de inventor a favor de BOEHRINGER INGELHEIM PHARMACEUTICALS, INC escrito en inglés y español, la Certificación notarial y la correspondiente Apostilla No. 2003-790, escritos en inglés).

---

**Cedente**: Younes BEKKALI el Objeto de la cesión es la invención Nitritos espiro heterocíclicos útiles como inhibidores de proteasas de cisteina. **Cesionario**: **Boehringer Ingelheim Pharmaceuticals, Inc.**, domiciliada en 900 Ridgebury Road, Ridgefield, CT 06877, EE.UU.

Dado y firmado en Ridgefield, Connecticut 06877 el día 24/01/03

(Firmado) Younes BEKKALI

CERTIFICADO NOTARIAL (Individuo)

Hoy día 24 de Enero, 2003, ante mi Notario Público del Estado de Connecticut, USA personalmente compareció Younes BEKKALI a quien conozco como la persona que firmó el anterior documento, y quien tiene capacidad legal para hacerlo.

17

(Firmado)Jeanne E. Rogers

Comisión Expira: 11/30/2006

**APOSTILLA**

(Convención de La Haya del 5 de Octubre, 1961)

1. País: Estados Unidos de América

ESTE DOCUMENTO PUBLICO

2. ha sido firmado por JEANNE E. ROGERS
3. obrando en calidad de NOTARIO PUBLICO
4. en el Estado de Connecticut desde Noviembre 26, 2001 hasta Noviembre 30, 2006

CERTIFICADA

5. en Hartford, Connecticut
6. el 27 de Enero, 2003
7. por SUSAN BYSIEWICZ, Secretario de Estado de Connecticut
8. Número: 2003-790
9. SELLO: GRAN SELLO DE OBLEA DEL ESTADO DE CONNECTICUT
10. Firma (Firmado) Susan Bysiewicz

Secretario del Estado

Es TRADUCCION FIEL Y COMPLETA de la cual se deja copia en los archivos de esta oficina para su confrontación y a la cual me remito habiendo visto el documento original hoy día 21 de Febrero, 2003.

[illegible] 2043/029

INTERPRETE OFICIAL

77

18

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

## CESION

Yo, (nosotros), abajo firmado (s)
Eugene R. HICKEY

domiciliado (s) en 5 Woodbury Drive,
Danbury, CT 06811 / USA

declaro(amos) bajo juramento ser único(s) y verdadero(s) inventor(es) de la invención:
nitrilos espiro heterocíclicos útiles como inhibidores reversibles de proteasas de cisteína

declaro(amos) así mismo que cedo(emos) y transfiero(erimos), sin limitación, a favor de la sociedad
BOEHRINGER INGELHEIM PHARMACEUTICALS, INC.

constituída y existente de conformidad con las leyes de
USA

domiciliada en 900 Ridgebury Road
Ridgefield, CT 06877, USA

todos los derechos inherentes a dicha invención y que la citada Compañía queda facultada para solicitar en su nombre la patente correspondiente en la República de Colombia.

## ASSIGNMENT

I (we), the undersigned
Eugene R. HICKEY

of 5 Woodbury Drive,
Danbury, CT 06811 / USA

state(s) under oath to be sole and true inventor(s) of the invention:
Spiroheterocyclic nitriles useful as reversible inhibitors of cysteine proteases

state as well, that assign, without reservations or limitations in favour of
BOEHRINGER INGELHEIM PHARMACEUTICALS, INC.

a corporation constituted and existing in conformity with the laws of
USA

domiciled in 900 Ridgebury Road,
Ridgefield, CT 06877, USA

all rights inherent to said invention and that the above mentioned company hereby is enabled to apply, in its name, for the corresponding patent in the Republic of Colombia.

Dado y firmado hoy/Given and signed this
01-24-03

en/in Ridgefield, Connecticut 06877 USA

Firma Eugene R Hickey Signature

© CAVELIER ABOGADOS
WPPODERE-343

**AUTENTICACION NOTARIAL (INDIVIDUO)**

A los ____ días del mes de _____ de 200____
ante mí, Notario Público de _____
compareció (ecun) personalmente _____

_____

a quien(es) doy fe de conocer y me consta que es(son) la(s) persona(s) firmante(s) del documento que precede, y quien(es) tiene(n) capacidad legal para otorgarlo.

_____ Notario Público

**NOTARIAL AUTHENTIFICATION (INDIVIDUAL)**

On this 21st day of January 2003
before me, a Notary Public of the State of Connecticut, USA
personally appeared _____
Eugene R. HICKEY

to me known, and known to me to be the person(s) who executed that foregoing document, and who has (have) legal capacity to execute it.

Notary Public _____
Jeanne E. Rogers
Commission expires: 11/30/2006

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

1. Country: .....
   This public document
2. has been signed by .....
3. acting in the capacity of .....
4. bears the seal/stamp of .....

**Certified**

5. at ..... 6. the .....
7. by .....
8. No. .....
9. Seal/stamp 10. Signature

..... .....

# APOSTILLE

(Convention de La Haye du 5 octobre 1961)

1. Country: The United States of America

**THIS PUBLIC DOCUMENT**

2. has been signed by **JEANNE E. ROGERS**

3. acting in the capacity of **NOTARY PUBLIC**

4. in the State of Connecticut for the term of **November 26, 2001 to November 30, 2006**

## CERTIFIED

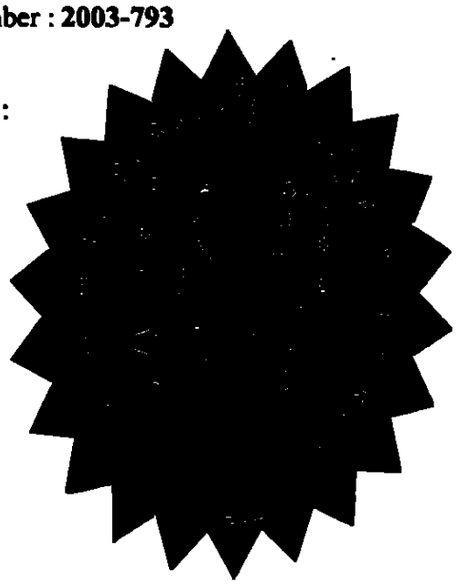
5. at Hartford, Connecticut

6. on **January 27, 2003**

7. by **SUSAN BYSIEWICZ,** Secretary of the State of Connecticut

8. Number : **2003-793**

9. Seal :



10. Signature

Susan Bysiewicz

Secretary of the State

TRADUCCIÓN OFICIAL No.2003/032de un documento escrito en inglés el cual para su identificación se sella con el sello del traductor al tiempo con la presente. Esta traducción ha sido preparada por Hilda Aguilera de Piedrahita, traductora e intérprete oficial debidamente reconocida por el Ministerio de Relaciones Exteriores y autorizada por el Ministerio de Justicia y del Derecho, por Resolución No. 323 de 1980, según consta en la escritura 5883 de 22 de septiembre de 1986, de la notaría sexta de Bogotá.

-.-.-.-.-

(Se traduce un documento de cesión de derechos de inventor a favor de BOEHRINGER INGELHEIM PHARMACEUTICALS, INC escrito en inglés y español, la Certificación notarial y la correspondiente Apostilla No. 2003-792, escritos en inglés).

---

**Cedente**: Eugene R. HICKEY el Objeto de la cesión es la invención Nitritos espiro heterocíclicos útiles como inhibidores de proteasas de cisteina. **Cesionario: Boehringer Ingelheim Pharmaceuticals, Inc.**, domiciliada en 900 Ridgebury Road, Ridgefield, CT 06877, EE.UU.

Dado y firmado en Ridgefield, Connecticut 06877 el día 24/01/03

(Firmado) Eugene R. HICKEY

CERTIFICADO NOTARIAL (Individuo)

Hoy día 24 de Enero, 2003, ante mi Notario Público del Estado de Connecticut, USA personalmente compareció Eugene R. HICKEY a quien conozco como la persona que firmó el anterior documento, y quien tiene capacidad legal para hacerlo.

(Firmado)Jeanne E. Rogers

Comisión Expira: 11/30/2006

**APOSTILLA**

(Convención de La Haya del 5 de Octubre, 1961)

1. País: Estados Unidos de América

ESTE DOCUMENTO PUBLICO

2. ha sido firmado por JEANNE E. ROGERS
3. obrando en calidad de NOTARIO PUBLICO
4. en el Estado de Connecticut desde Noviembre 26, 2001 hasta Noviembre 30, 2006

CERTIFICADA

5. en Hartford, Connecticut
6. el 27 de Enero, 2003
7. por SUSAN BYSIEWICZ, Secretario de Estado de Connecticut
8. Número: 2003-793
9. SELLO: GRAN SELLO DE OBLEA DEL ESTADO DE CONNECTICUT
10. Firma (Firmado) Susan Bysiewicz

Secretario del Estado

Es TRADUCCION FIEL Y COMPLETA de la cual se deja copia en los archivos de esta oficina para su confrontación y a la cual me remito habiendo visto el documento original hoy día 21 de Febrero, 2003.

TRADUCCION OFICIAL No. 2003 / 632
[illegible] AGUILERA DE FERNANDEZ
INTERPRETE OFICIAL
[illegible]

COMO NOTARIO SEXTO DEL CIRCULO DE SANTAFE DE BOGOTA, HAGO CONSTAR QUE LA(S) ANTERIOR(ES) FIRMA(S) PUESTA(S) POR

[illegible]

DEVUELTOS CON C C No (s)

ES(SON) AUTENTICA(S)

SANTAFE DE BOGOTA 25 FEB 2003

NOTARIA SEXTA
PABLO MENDEZ BARAJAS
Encargado

SE ASUME RESPONSABILIDAD DEL TEXTO
25 FEB 03 A 11 49
VALIDACIONES

MINISTERIO DE RELACIONES EXTERIORES
20080
CUYA FIRMA APARECE EN EL
ADJUNTO DESEMPEÑA
LAS FUNCIONES INDICADAS

✓ 91
Q3

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

## CESION

Yo, (nosotros), abajo firmado (s)
Weimin LIU

10 RUSSETT RD

domiciliado (s) en ~~56 Wakelee Avenue Ext., Unit 12, Shelton, CT 06484~~ / USA
SANDY HOOK 06482-1

declaro(amos) bajo juramento ser único(s) y verdadero(s) inventor(es) de la invención:
Aptiles cyano heterociclicos utiles como inhibidores reversibles de proteasas de cisteina

declaro(amos) así mismo que cedo(emos) y transfiero(erimos), sin limitación, a favor de la sociedad
BOEHRINGER INGELHEIM PHARMACEUTICALS, INC.

constituida y existente de conformidad con las leyes de
USA

domiciliada en 900R Ridgebury Road
Ridgefield, CT 06877, USA

todos los derechos inherentes a dicha invención y que la citada Compañía queda facultada para solicitar en su nombre la patente correspondiente en la República de Colombia.

## ASSIGNMENT

I (we), the undersigned
Weimin LIU

of 10 Russett Road
Sandy Hook, CT 06482 / USA

state(s) under oath to be sole and true inventor(s) of the invention:
Cyanoheterocyclic nitriles useful as reversible inhibitors of cysteine proteases

state as well, that assign, without reservations or limitations in favour of
BOEHRINGER INGELHEIM PHARMACEUTICALS, INC.

a corporation constituted and existing in conformity with the laws of
USA

domiciled in 900 Ridgebury Road,
Ridgefield, CT 06877, USA

all rights inherent to said invention and that the above mentioned company hereby is enabled to apply, in its name, for the corresponding patent in the Republic of Colombia.

Dado y firmado hoy/Given and signed this
1/24/03

en/in Ridgefield, Connecticut 06877 USA

Firma/Signature

© CAVELIER ABOGADOS
WPFODER5-343

# APOSTILLE

(Convention de La Haye du 5 octobre 1961)

1. Country: The United States of America

**THIS PUBLIC DOCUMENT**

2. has been signed by **JEANNE E. ROGERS**

3. acting in the capacity of **NOTARY PUBLIC**

4. in the State of Connecticut for the term of **November 26, 2001 to November 30, 2006**

## CERTIFIED

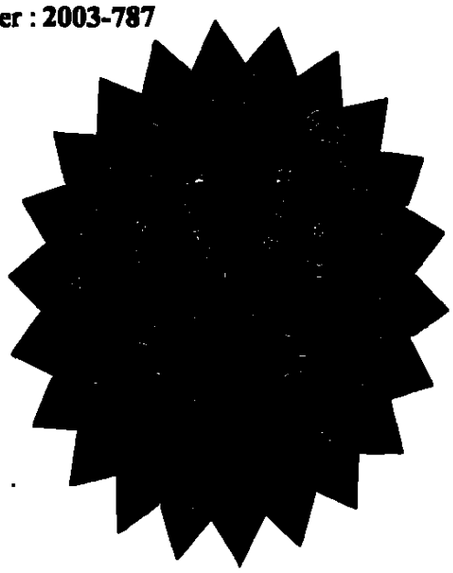
5. at Hartford, Connecticut

6. on **January 27, 2003**

7. by **SUSAN BYSIEWICZ,** Secretary of the State of Connecticut

8. Number : **2003-787**

9. Seal :



10. Signature

Susan Bysiewicz

Secretary of the State

**AUTENTICACION NOTARIAL (INDIVIDUO)**

A los ____ días del mes de _____ de 200____
ante mí, Notario Público de _____
compareció (eron) personalmente _____

_____

a quien(es) doy fe de conocer y me consta que es(son) la(s) persona(s) firmante(s) del documento que precede, y quien(es) tiene(n) capacidad legal para otorgarlo.

_____ Notario Público

**NOTARIAL AUTHENTIFICATION (INDIVIDUAL)**

On this 24th day of January 2003
before me, a Notary Public of the State of Connecticut, USA
personally appeared _____
Weimin LIU

to me known, and known to me to be the person(s) who executed that foregoing document, and who has (have) legal capacity to execute it.

Notary Public _____
Jeanne E. Rogers
Commission expires - 4/30/2006

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

1. Country: .....
   This public document
2. has been signed by .....
3. acting in the capacity of .....
4. bears the seal/stamp of .....

**Certified**

5. at ..... 6. the .....
7. by .....
8. No. .....
9. Seal/stamp 10. Signature

..... .....

TRADUCCIÓN OFICIAL No.2003/035 de un documento escrito en inglés el cual para su identificación se sella con el sello del traductor al tiempo con la presente. Esta traducción ha sido preparada por Hilda Aguilera de Piedrahita, traductora e intérprete oficial debidamente reconocida por el Ministerio de Relaciones Exteriores y autorizada por el Ministerio de Justicia y del Derecho, por Resolución No. 323 de 1980, según consta en la escritura 5883 de 22 de septiembre de 1986, de la notaría sexta de Bogotá.

-.-.-.-.-

(Se traduce un documento de cesión de derechos de inventor a favor de BOEHRINGER INGELHEIM PHARMACEUTICALS, INC escrito en inglés y español, la Certificación notarial y la correspondiente Apostilla No. 2003-792, escritos en inglés).

---

**Cedente:** Weimin LIU el Objeto de la cesión es la invención Nitritos espiro heterocíclicos útiles como inhibidores de proteasas de cisteina. **Cesionario: Boehringer Ingelheim Pharmaceuticals, Inc.**, domiciliada en 900 Ridgebury Road, Ridgefield, CT 06877, EE.UU.

Dado y firmado en Ridgefield, Connecticut 06877 el día 24/01/03

(Firmado) Weimin LIU

CERTIFICADO NOTARIAL (Individuo)

Hoy día 24 de Enero, 2003, ante mi Notario Público del Estado de Connecticut, USA personalmente compareció Weimin LIU a quien conozco como la persona que firmó el anterior documento, y quien tiene capacidad legal para hacerlo.

(Firmado) Jeanne E. Rogers

Comisión Expira: 11/30/2006

**APOSTILLA**

(Convención de La Haya del 5 de Octubre, 1961)

1. País: Estados Unidos de América

ESTE DOCUMENTO PUBLICO

2. ha sido firmado por JEANNE E. ROGERS
3. obrando en calidad de NOTARIO PUBLICO
4. en el Estado de Connecticut desde Noviembre 26, 2001 hasta Noviembre 30, 2006

CERTIFICADA

5. en Hartford, Connecticut
6. el 27 de Enero, 2003
7. por SUSAN BYSIEWICZ, Secretario de Estado de Connecticut
8. Número: 2003-787
9. SELLO: GRAN SELLO DE OBLEA DEL ESTADO DE CONNECTICUT
10. Firma (Firmado) Susan Bysiewicz

Secretario del Estado

Es TRADUCCION FIEL Y COMPLETA de la cual se deja copia en los archivos de esta oficina para su confrontación y a la cual me remito habiendo visto el documento original hoy día 21 de Febrero, 2003.

[illegible] 2003/035
[illegible]
INTERPRETE OFICIAL
[illegible]

COMO NOTARIO SEXTO DEL CIRCULO DE SANTAFE DE BOGOTA, HAGO CONSTAR QUE LA(S) ANTERIOR(ES) FIRMA(S) PUESTA(S) POR

IDENTIFICADOS CON C.C. No.(s)

ES(SON) AUTENTICA(S)

SANTAFE DE BOGOTA, 25 FEB 2003

NOTARIA SEXTA
PABLO MENDEZ BARAJAS

MINISTERIO DE RELACIONES EXTERIORES.
VALIDA SOLAMENTE LA FIRMA Y EL SELLO
DOCUMENTO DESEMPEÑA LAS FUNCIONES INDICADAS

HASE ASOME
RESPONSABILIDAD DEL TEXTO

FEB 25 A 11:50

226083 de 6

96
28

**CAVELIER**
**ABOGADOS**
EDIFICIO SISKI
CARRERA 4ª Nº 72-35
BOGOTA, 8 - COLOMBIA

## CESION

Yo, (nosotros), abajo firmado (s)
Usha R. PATEL

domiciliado (s) en 20 Dairy Farm Drive, Brookfield, CT 06804 / USA

declaro(amos) bajo juramento ser único(s) y verdadero(s) inventor(es) de la invención:
nitrilos espiro heterocíclicos útiles como inhibidores reversibles de proteasas de cisteína

declaro(amos) así mismo que cedo(emos) y transfiero(erimos), sin limitación, a favor de la sociedad
BOEHRINGER INGELHEIM PHARMACEUTICALS, INC.

constituída y existente de conformidad con las leyes de
USA

domiciliada en 900 Ridgebury Road Ridgefield, CT 06877, USA

todos los derechos inherentes a dicha invención y que la citada Compañía queda facultada para solicitar en su nombre la patente correspondiente en la República de Colombia.

## ASSIGNMENT

I (we), the undersigned
Usha R. PATEL

of 20 Dairy Farm Drive, Brookfield, CT 06804 / USA

state(s) under oath to be sole and true inventor(s) of the invention:
Spiroheterocyclic nitriles useful as reversible inhibitors of cysteine proteases

state as well, that assign, without reservations or limitations in favour of
BOEHRINGER INGELHEIM PHARMACEUTICALS, INC.

a corporation constituted and existing in conformity with the laws of
USA

domiciled in 900 Ridgebury Road, Ridgefield, CT 06877, USA

all rights inherent to said invention and that the above mentioned company hereby is enabled to apply, in its name, for the corresponding patent in the Republic of Colombia.

Dado y firmado hoy/Given and signed this
1/24/2003

en/in the State of Connecticut, USA

Usha R. Patel
Firma / Signature

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WPPODER5-343

**AUTENTICACION NOTARIAL (INDIVIDUO)**

A los ____ días del mes de _____ de 200____
ante mí, Notario Público de _____
compareció (eron) personalmente _____

_____

a quien(es) doy fe de conocer y me consta que es(son) la(s) persona(s) firmante(s) del documento que precede, y quien(es) tiene(n) capacidad legal para otorgarlo.

_____ Notario Público

**NOTARIAL AUTHENTIFICATION (INDIVIDUAL)**

On this 24th day of January 2003
before me, a Notary Public of the State of Connecticut, USA
personally appeared _____
Usha R. PATEL

to me known, and known to me to be the person(s) who executed that foregoing document, and who has (have) legal capacity to execute it.

Notary Public _____
Jeanne E. Rogers
Commission expires: 11/30/2006

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

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

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5. at ..... 6. the .....
7. by .....
8. No. .....
9. Seal/stamp 10. Signature

..... .....

# APOSTILLE

(Convention de La Haye du 5 octobre 1961)

1. Country: The United States of America

**THIS PUBLIC DOCUMENT**

2. has been signed by **JEANNE E. ROGERS**

3. acting in the capacity of **NOTARY PUBLIC**

4. in the State of Connecticut for the term of **November 26, 2001 to November 30, 2006**

## CERTIFIED

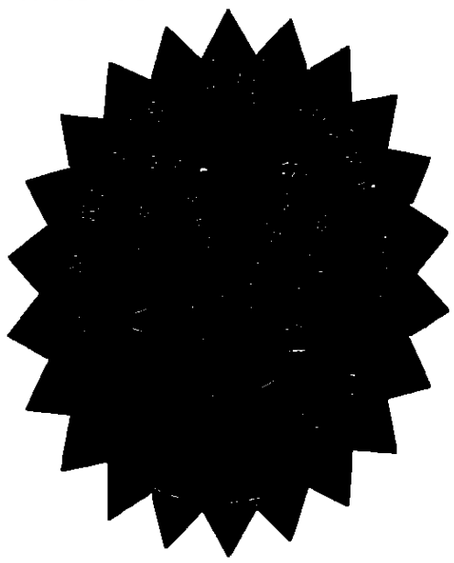
5. at Hartford, Connecticut

6. on **January 27, 2003**

7. by **SUSAN BYSIEWICZ,** Secretary of the State of Connecticut

8. Number : **2003-791**

9. Seal :



10. Signature

Susan Bysiewicz

Secretary of the State

TRADUCCIÓN OFICIAL No.2003/030de un documento escrito en inglés el cual para su identificación se sella con el sello del traductor al tiempo con la presente. Esta traducción ha sido preparada por Hilda Aguilera de Piedrahita, traductora e intérprete oficial debidamente reconocida por el Ministerio de Relaciones Exteriores y autorizada por el Ministerio de Justicia y del Derecho, por Resolución No. 323 de 1980, según consta en la escritura 5883 de 22 de septiembre de 1986, de la notaría sexta de Bogotá.

-.-.-.-.-

(Se traduce un documento de cesión de derechos de inventor a favor de BOEHRINGER INGELHEIM PHARMACEUTICALS, INC escrito en inglés y español, la Certificación notarial y la correspondiente Apostilla No. 2003-791, escritos en inglés).

---

**Cedente**: Usha R. PATEL el Objeto de la cesión es la invención Nitritos espiro heterocíclicos útiles como inhibidores de proteasas de cisteina. **Cesionario**: **Boehringer Ingelheim Pharmaceuticals, Inc.**, domiciliada en 900 Ridgebury Road, Ridgefield, CT 06877, EE.UU.

Dado y firmado en Ridgefield, Connecticut 06877 el día 24/01/03

(Firmado) Usha R. PATEL

CERTIFICADO NOTARIAL (Individuo)

Hoy día 24 de Enero, 2003, ante mi Notario Público del Estado de Connecticut, USA personalmente compareció Usha R. PATEL a quien conozco como la persona que firmó el anterior documento, y quien tiene capacidad legal para hacerlo.

(Firmado)Jeanne E. Rogers

Comisión Expira: 11/30/2006

**APOSTILLA**

(Convención de La Haya del 5 de Octubre, 1961)

1. País: Estados Unidos de América

ESTE DOCUMENTO PUBLICO

2. ha sido firmado por JEANNE E. ROGERS
3. obrando en calidad de NOTARIO PUBLICO
4. en el Estado de Connecticut desde Noviembre 26, 2001 hasta Noviembre 30, 2006

CERTIFICADA

5. en Hartford, Connecticut
6. el 27 de Enero, 2003
7. por SUSAN BYSIEWICZ, Secretario de Estado de Connecticut
8. Número: 2003-791
9. SELLO: GRAN SELLO DE OBLEA DEL ESTADO DE CONNECTICUT
10. Firma (Firmado) Susan Bysiewicz

Secretario del Estado

Es TRADUCCION FIEL Y COMPLETA de la cual se deja copia en los archivos de esta oficina para su confrontación y a la cual me remito habiendo visto el documento original hoy día 21 de Febrero, 2003.

TRADUCCION OFICIAL No. 2003230
HILDA AGUILERA DE PIEDRAHITA
INTERPRETE OFICIAL
CED No. 323 DEL COL. DE ABOGADO

COMO NOTARIO SEXTO DEL CIRCULO DE SANTAFE DE BOGOTA, HAGO CONSTAR QUE LA(S) ANTERIOR(ES) FIRMA(S) PUESTA(S) POR

IDENTIFICADOS CON C.C. No.(s)

ES(SON) AUTENTICA(S)

SANTAFE DE BOGOTA, 25 FEB. 2003

NOTARIA SEXTA
PABLO MENDEZ BARAJAS
Notario Sexto Encargado

NO SE ASUME RESPONSABILIDAD DEL TEXTO

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MINISTERIO DE RELACIONES EXTERIORES

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98
33

**CAVELIER**
**ABOGADOS**
EDIFICIO SISKI
CARRERA 4ª Nº 72-35
BOGOTA 8 - COLOMBIA

## CESION

Yo, (nosotros), abajo firmado (s)
Denice M. SPERO

domiciliado (s) en 18 Limekiln Road,
West Redding, CT 06896 /USA

declaro(amos) bajo juramento ser único(s) y verdadero(s) inventor(es) de la invención:
nuevas esferas heterocíclicas útiles como inhibidores reversibles de proteasas de cisteína

declaro(amos) así mismo que cedo(emos) y transfiero(erimos), sin limitación, a favor de la sociedad
BOEHRINGER INGELHEIM PHARMACEUTICALS, INC.

constituida y existente de conformidad con las leyes de
USA

domiciliada en 900 Ridgebury Road
Ridgefield, CT 06877, USA

todos los derechos inherentes a dicha invención y que la citada Compañía queda facultada para solicitar en su nombre la patente correspondiente en la República de Colombia.

## ASSIGNMENT

I (we), the undersigned
Denice M. SPERO

of 18 Limekiln Road,
West Redding, CT 06896 / USA

state(s) under oath to be sole and true inventor(s) of the invention:
Spiroheterocyclic nitriles useful as reversible inhibitors of cysteine proteases

state as well, that assign, without reservations or limitations in favour of
BOEHRINGER INGELHEIM PHARMACEUTICALS, INC.

a corporation constituted and existing in conformity with the laws of
USA

domiciled in 900 Ridgebury Road,
Ridgefield, CT 06877, USA

all rights inherent to said invention and that the above mentioned company hereby is enabled to apply, in its name, for the corresponding patent in the Republic of Colombia.

Dado y firmado hoy/Given and signed this
1/24/03

en/in Ridgefield, Connecticut 06877 USA

Denice M. Spero

Firma / Signature

© CAVELIER ABOGADOS
WPTODERE-343

**AUTENTICACION NOTARIAL (INDIVIDUO)**

A los ____ días del mes de _____ de 200____
ante mí, Notario Público de _____
compareció (eron) personalmente _____

a quien(es) doy fe de conocer y me consta que es(son) la(s) persona(s) firmante(s) del documento que precede, y quien(es) tiene(n) capacidad legal para otorgarlo.

_____ Notario Público

**NOTARIAL AUTHENTIFICATION (INDIVIDUAL)**

On this 24th day of January 2003
before me, a Notary Public of the State of Connecticut, USA
personally appeared _____
Denise M. SPERO

to me known, and known to me to be the person(s) who executed that foregoing document, and who has (have) legal capacity to execute it.

Notary Public _____
Jeanne E. Rogers
Commission Expires: 11/30/2006

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

1. Country: .....
   This public document
2. has been signed by .....
3. acting in the capacity of .....
4. bears the seal/stamp of .....

**Certified**

5. at ..... 6. the .....
7. by .....
8. No. .....
9. Seal/stamp 10. Signature

..... .....

3T

# APOSTILLE

(Convention de La Haye du 5 octobre 1961)

1. Country: The United States of America

**THIS PUBLIC DOCUMENT**

2. has been signed by **JEANNE E. ROGERS**

3. acting in the capacity of **NOTARY PUBLIC**

4. in the State of Connecticut for the term of **November 26, 2001 to November 30, 2006**

## CERTIFIED

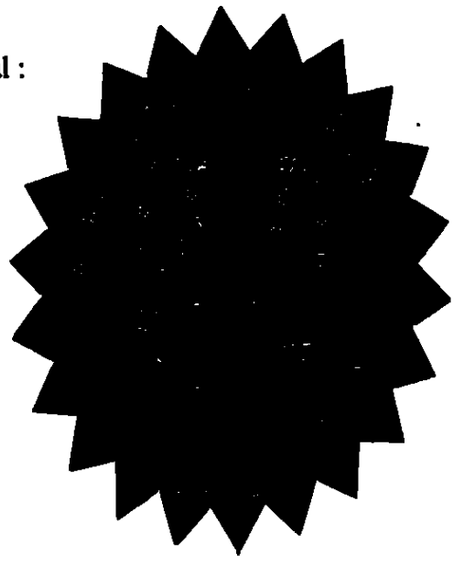
5. at Hartford, Connecticut

6. on **January 27, 2003**

7. by **SUSAN BYSIEWICZ,** Secretary of the State of Connecticut

8. Number : **2003-794**

9. Seal :



10. Signature

Susan Bysiewicz

Secretary of the State

TRADUCCIÓN OFICIAL No.2003/033de un documento escrito en inglés el cual para su identificación se sella con el sello del traductor al tiempo con la presente. Esta traducción ha sido preparada por Hilda Aguilera de Piedrahita, traductora e intérprete oficial debidamente reconocida por el Ministerio de Relaciones Exteriores y autorizada por el Ministerio de Justicia y del Derecho, por Resolución No. 323 de 1980, según consta en la escritura 5883 de 22 de septiembre de 1986, de la notaría sexta de Bogotá.

-.-.-.-.-

(Se traduce un documento de cesión de derechos de inventor a favor de BOEHRINGER INGELHEIM PHARMACEUTICALS, INC escrito en inglés y español, la Certificación notarial y la correspondiente Apostilla No. 2003-792, escritos en inglés).

---

**Cedente**: Denice M. SPERO el Objeto de la cesión es la invención Nitritos espiro heterocíclicos útiles como inhibidores de proteasas de cisteina. **Cesionario: Boehringer Ingelheim Pharmaceuticals, Inc.**, domiciliada en 900 Ridgebury Road, Ridgefield, CT 06877, EE.UU.

Dado y firmado en Ridgefield, Connecticut 06877 el día 24/01/03

(Firmado) Denice M. SPERO

CERTIFICADO NOTARIAL (Individuo)

Hoy día 24 de Enero, 2003, ante mi Notario Público del Estado de Connecticut, USA personalmente compareció Denice M. SPERO a quien conozco como la persona que firmó el anterior documento, y quien tiene capacidad legal para hacerlo.

(Firmado)Jeanne E. Rogers

Comisión Expira: 11/30/2006

**APOSTILLA**

(Convención de La Haya del 5 de Octubre, 1961)

1. País: Estados Unidos de América

ESTE DOCUMENTO PUBLICO

2. ha sido firmado por JEANNE E. ROGERS

3. obrando en calidad de NOTARIO PUBLICO

4. en el Estado de Connecticut desde Noviembre 26, 2001 hasta Noviembre 30, 2006

CERTIFICADA

5. en Hartford, Connecticut

6. el 27 de Enero, 2003

7. por SUSAN BYSIEWICZ, Secretario de Estado de Connecticut

8. Número: 2003-794

9. SELLO: GRAN SELLO DE OBLEA DEL ESTADO DE CONNECTICUT

10. Firma (Firmado) Susan Bysiewicz

Secretario del Estado

Es TRADUCCION FIEL Y COMPLETA de la cual se deja copia en los archivos de esta oficina para su confrontación y a la cual me remito habiendo visto el documento original hoy día 21 de Febrero, 2003.

TRADUCCION OFICIAL No. 2003033
OLGA AGUILERA DE FERNANDEZ
INTERPRETE OFICIAL

COMO NOTARIO SEXTO DEL CIRCULO DE SANTAFE DE BOGOTA, HAGO CONSTAR QUE LA(S) ANTERIOR(ES) FIRMA(S) PUESTA(S) POR

IDENTIFICADO CON C.C. No.(s)

ES(SON) AUTENTICA(S)

SANTAFE DE BOGOTA, 25 FEB. 2003

NOTARIA SEXTA
PABLO MENDEZ
BARAJAS

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

## CESION

Yo, (nosotros), abajo firmado (s)
Sanxing SUN

domiciliado (s) en 38 Padanaram Avenue, Danbury, CT 06811 / USA

declaro(amos) bajo juramento ser único(s) y verdadero(s) inventor(es) de la invención:
Nitrilos espiro heterocíclicos útiles como inhibidores reversibles de proteasas de cisteína.

declaro(amos) así mismo que cedo(emos) y transfiero(erimos), sin limitación, a favor de la sociedad
BOEHRINGER INGELHEIM PHARMACEUTICALS, INC.

constituída y existente de conformidad con las leyes de
USA

domiciliada en 900 Ridgebury Road Ridgefield, CT 06877, USA

todos los derechos inherentes a dicha invención y que la citada Compañía queda facultada para solicitar en su nombre la patente correspondiente en la República de Colombia.

## ASSIGNMENT

I (we), the undersigned
Sanxing SUN

of 38 Padanaram Avenue, Danbury, CT 06811 / USA

state(s) under oath to be sole and true inventor(s) of the invention:
Spiroheterocyclic nitriles useful as reversible inhibitors of cysteine proteases

state as well, that assign, without reservations or limitations in favour of
BOEHRINGER INGELHEIM PHARMACEUTICALS, INC.

a corporation constituted and existing in conformity with the laws of
USA

domiciled in 900 Ridgebury Road, Ridgefield, CT 06877, USA

all rights inherent to said invention and that the above mentioned company hereby is enabled to apply, in its name, for the corresponding patent in the Republic of Colombia.

Dado y firmado hoy/Given and signed this
1/24/03

en/in Ridgefield, Connecticut 06877 USA

Sanxing Sun

Firma / Signature

© CAVELIER ABOGADOS
WPPODERE-349

# APOSTILLE

(Convention de La Haye du 5 octobre 1961)

1. Country: The United States of America

**THIS PUBLIC DOCUMENT**

2. has been signed by **JEANNE E. ROGERS**

3. acting in the capacity of **NOTARY PUBLIC**

4. in the State of Connecticut for the term of **November 26, 2001 to November 30, 2006**

## CERTIFIED

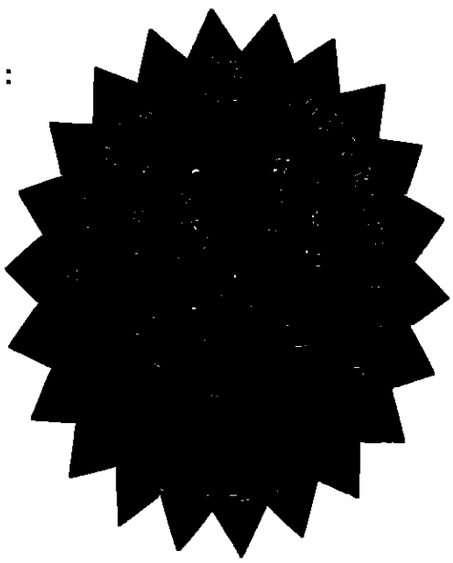
5. at Hartford, Connecticut

6. on **January 27, 2003**

7. by **SUSAN BYSIEWICZ,** Secretary of the State of Connecticut

8. Number : **2003-788**

9. Seal :



10. Signature

Susan Bysiewicz

Secretary of the State

**AUTENTICACION NOTARIAL (INDIVIDUO)**

A los ____ días del mes de _____ de 200____
ante mí, Notario Público de _____
compareció (eron) personalmente _____

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a quien(es) doy fe de conocer y me consta que es(son) la(s) persona(s) firmante(s) del documento que precede, y quien(es) tiene(n) capacidad legal para otorgarlo.

_____ Notario Público

**NOTARIAL AUTHENTIFICATION (INDIVIDUAL)**

On this 24th day of January 2003
before me, a Notary Public of the State of Connecticut, USA
personally appeared _____
Barsing SUN

to me known, and known to me to be the person(s) who executed that foregoing document, and who has (have) legal capacity to execute it.

Notary Public _____
Joanne E. Rogers
Commission Expires: 11/30/2006

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

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   This public document
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4. bears the seal/stamp of .....

**Certified**

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7. by .....
8. No. .....
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TRADUCCIÓN OFICIAL No.2003/027de un documento escrito en inglés el cual para su identificación se sella con el sello del traductor al tiempo con la presente. Esta traducción ha sido preparada por Hilda Aguilera de Piedrahita, traductora e intérprete oficial debidamente reconocida por el Ministerio de Relaciones Exteriores y autorizada por el Ministerio de Justicia y del Derecho, por Resolución No. 323 de 1980, según consta en la escritura 5883 de 22 de septiembre de 1986, de la notaría sexta de Bogotá.

-.-.-.-.-

(Se traduce un documento de cesión de derechos de inventor a favor de BOEHRINGER INGELHEIM PHARMACEUTICALS, INC escrito en inglés y español, la Certificación notarial y la correspondiente Apostilla No. 2003-788, escritos en inglés).

---

Cedente: Sanxing SUN el Objeto de la cesión es la invención Nitritos espiro heterocíclicos útiles como inhibidores de proteasas de cisteina. Cesionario: **Boehringer Ingelheim Pharmaceuticals, Inc.**, domiciliada en 900 Ridgebury Road, Ridgefield, CT 06877, EE.UU.

Dado y firmado en Ridgefield, Connecticut 06877 el día 24/01/03

(Firmado) Sanxing SUN

CERTIFICADO NOTARIAL (Individuo)

Hoy día 24 de Enero, 2003, ante mi Notario Público del Estado de Connecticut, USA personalmente compareció SANXING SUN a quien conozco como la persona que firmó el anterior documento, y quien tiene capacidad legal para hacerlo.

(Firmado)Jeanne E. Rogers

Comisión Expira: 11/30/2006

**APOSTILLA**

(Convención de La Haya del 5 de Octubre, 1961)

1. País: Estados Unidos de América

ESTE DOCUMENTO PUBLICO

2. ha sido firmado por JEANNE E. ROGERS

3. obrando en calidad de NOTARIO PUBLICO

4. en el Estado de Connecticut desde Noviembre 26, 2001 hasta Noviembre 30, 2006

CERTIFICADA

5. en Hartford, Connecticut

6. el 27 de Enero, 2003

7. por SUSAN BYSIEWICZ, Secretario de Estado de Connecticut

8. Número: 2003-788

9. SELLO: GRAN SELLO DE OBLEA DEL ESTADO DE CONNECTICUT

10. Firma (Firmado) Susan Bysiewicz

Secretario del Estado

Es TRADUCCION FIEL Y COMPLETA de la cual se deja copia en los archivos de esta oficina para su confrontación y a la cual me remito habiendo visto el documento original hoy día 21 de Febrero, 2003:

...CCION OFICIAL No. 2003027
...DA ACUERDA DE PITTSBURGH
INTERPRETE OFICIAL
...DEL RAMO DE JUSTICIA

COMO NOTARIO SEXTO DEL CIRCULO DE SANTAFE DE BOGOTA, HAGO CONSTAR QUE LA(S) ANTERIOR(ES) FIRMA(S) PUESTA(S) POR

IDENTIFICADOS CON C.C. No.(s)

ES(SON) AUTENTICA(S)

SANTAFE DE BOGOTA, 25 FEB. 2003

NOTARIA SEXTA
PABLO MENDEZ
BARAJAS

MINISTERIO DE
RELACIONES EXTERIORES

NO SE ASUME
RESPONSABILIDAD DEL TEXTO

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DOCUMENTO DESEMPEÑA
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95
42
43

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

## CESION

Yo, (nosotros), abajo firmado (s)
David S. THOMSON

domiciliado (s) en 166 Minuteman Road, Ridgefield, CT 06877 / USA

declaro(amos) bajo juramento ser único(s) y verdadero(s) inventor(es) de la invención:
nitrilos espiro heterocíclicos útiles como inhibidores reversibles de proteasas de cisteína

declaro(amos) así mismo que cedo(emos) y transfiero(erimos), sin limitación, a favor de la sociedad
BOEHRINGER INGELHEIM PHARMACEUTICALS, INC.

constituída y existente de conformidad con las leyes de
USA

domiciliada en 900 Ridgebury Road Ridgefield, CT 06877, USA

todos los derechos inherentes a dicha invención y que la citada Compañía queda facultada para solicitar en su nombre la patente correspondiente en la República de Colombia.

## ASSIGNMENT

I (we), the undersigned
David S. THOMSON

of 166 Minuteman Road, Ridgefield, CT 06877 / USA

state(s) under oath to be sole and true inventor(s) of the invention:
Spiroheterocyclic nitriles useful as reversible inhibitors of cysteine proteases

state as well, that assign, without reservations or limitations in favour of
BOEHRINGER INGELHEIM PHARMACEUTICALS, INC.

a corporation constituted and existing in conformity with the laws of
USA

domiciled in 900 Ridgebury Road, Ridgefield, CT 06877, USA

all rights inherent to said invention and that the above mentioned company hereby is enabled to apply, in its name, for the corresponding patent in the Republic of Colombia.

Dado y firmado hoy/Given and signed this
1/24/03

en/in Ridgefield, Connecticut 06877 USA

Firma / Signature

© CAVELIER ABOGADOS
WPPODERE-343

43

44

# APOSTILLE

(Convention de La Haye du 5 octobre 1961)

1. Country: The United States of America

**THIS PUBLIC DOCUMENT**

2. has been signed by **JEANNE E. ROGERS**

3. acting in the capacity of **NOTARY PUBLIC**

4. in the State of Connecticut for the term of **November 26, 2001 to November 30, 2006**

## CERTIFIED

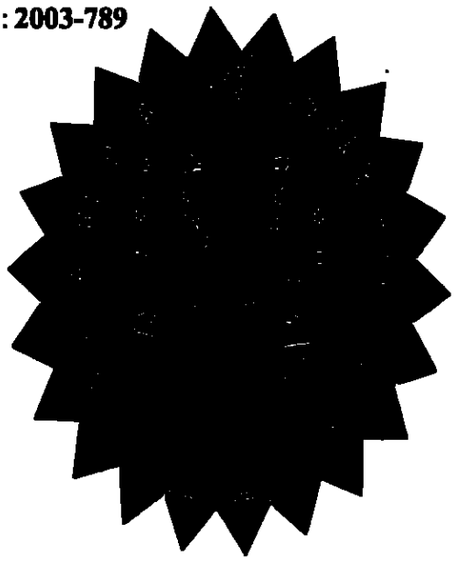
5. at Hartford, Connecticut

6. on **January 27, 2003**

7. by **SUSAN BYSIEWICZ,** Secretary of the State of Connecticut

8. Number : **2003-789**

9. Seal :



10. Signature

Susan Bysiewicz

Secretary of the State

44
45

**AUTENTICACION NOTARIAL (INDIVIDUO)**

A los ____ días del mes de _____ de 200____
ante mí, Notario Público de _____
compareció (eron) personalmente _____

_____

a quien(es) doy fe de conocer y me consta que es(son) la(s) persona(s) firmante(s) del documento que precede, y quien(es) tiene(n) capacidad legal para otorgarlo.

_____ Notario Público

**NOTARIAL AUTHENTIFICATION (INDIVIDUAL)**

On this 24th day of January 2003
before me, a Notary Public of the State of Connecticut, USA
personally appeared _____
David S. THOMSON
to me known, and known to me to be the person(s) who executed that foregoing document, and who has (have) legal capacity to execute it.

Notary Public _____
Jeanne E. Rogers
Commission Expires: 11/30/2006

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

1. Country: .....
   This public document
2. has been signed by .....
3. acting in the capacity of .....
4. bears the seal/stamp of .....

**Certified**

5. at ..... 6. the .....
7. by .....
8. No. .....
9. Seal/stamp 10. Signature

..... .....

TRADUCCIÓN OFICIAL No.2003/028de un documento escrito en inglés el cual para su identificación se sella con el sello del traductor al tiempo con la presente. Esta traducción ha sido preparada por Hilda Aguilera de Piedrahita, traductora e intérprete oficial debidamente reconocida por el Ministerio de Relaciones Exteriores y autorizada por el Ministerio de Justicia y del Derecho, por Resolución No. 323 de 1980, según consta en la escritura 5883 de 22 de septiembre de 1986, de la notaría sexta de Bogotá.

-.-.-.-.-

(Se traduce un documento de cesión de derechos de inventor a favor de BOEHRINGER INGELHEIM PHARMACEUTICALS, INC escrito en inglés y español, la Certificación notarial y la correspondiente Apostilla No. 2003-789, escritos en inglés).

---

**Cedente**: David S. THOMSON el Objeto de la cesión es la invención Nitritos espiro heterocíclicos útiles como inhibidores de proteasas de cisteina. **Cesionario: Boehringer Ingelheim Pharmaceuticals, Inc.**, domiciliada en 900 Ridgebury Road, Ridgefield, CT 06877, EE.UU.

Dado y firmado en Ridgefield, Connecticut 06877 el día 24/01/03

(Firmado) David S. THOMSON

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Hoy día 24 de Enero, 2003, ante mi Notario Público del Estado de Connecticut, USA personalmente compareció DAVID S.THOMSON a quien conozco como la persona que firmó el anterior documento, y quien tiene capacidad legal para hacerlo.

(Firmado)Jeanne E. Rogers

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5. en Hartford, Connecticut

6. el 27 de Enero, 2003

7. por SUSAN BYSIEWICZ, Secretario de Estado de Connecticut

8. Número: 2003-789

9. SELLO: GRAN SELLO DE OBLEA DEL ESTADO DE CONNECTICUT

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Alguien

IDENTIFICADO(S) CON C.C. No.(s)

ES(SON) AUTENTICA(S)

SANTAFE DE BOGOTA, 25 FEB. 2003

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PABLO MENDEZ BARAJAS
Notario Sexto Bogotá

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**CAVELIER**
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CARRERA 4ª Nº 72-35
BOGOTA, E - COLOMBIA

## CESION

Yo, (nosotros), abajo firmado (s)
Yancey D. WARD

domiciliado (s) en 11 Narragansett Trail,
Sandy Hook, CT 06482 / USA

declaro(amos) bajo juramento ser único(s) y verdadero(s) inventor(es) de la invención:
*Spiroheterocíclicos útiles como inhibidores reversibles de proteasas de Cisteina.*

declaro(amos) así mismo que cedo(emos) y transfiero(erimos), sin limitación, a favor de la sociedad
BOEHRINGER INGELHEIM PHARMACEUTICALS, INC.

constituida y existente de conformidad con las leyes de
USA

domiciliada en 900 Ridgebury Road
Ridgefield, CT 06877, USA

todos los derechos inherentes a dicha invención y que la citada Compañía queda facultada para solicitar en su nombre la patente correspondiente en la República de Colombia.

## ASSIGNMENT

I (we), the undersigned
Yancey D. WARD

of 11 Narragansett Trail,
Sandy Hook, CT 06482 / USA

state(s) under oath to be sole and true inventor(s) of the invention:
Spiroheterocyclic nitriles useful as reversible inhibitors of cysteine proteases

state as well, that assign, without reservations or limitations in favour of
BOEHRINGER INGELHEIM PHARMACEUTICALS, INC.

a corporation constituted and existing in conformity with the laws of
USA

domiciled in 900 Ridgebury Road,
Ridgefield, CT 06877, USA

all rights inherent to said invention and that the above mentioned company hereby is enabled to apply, in its name, for the corresponding patent in the Republic of Colombia.

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en/In Ridgefield, Connecticut 06877 USA

Firma / Signature

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On this 24th day of January 2003
before me, a Notary Public of the State of Connecticut USA
personally appeared _____
Yancey D. WARD

to me known, and known to me to be the person(s) who executed that foregoing document, and who has (have) legal capacity to execute it.

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Commission Expires: 11/30/2006

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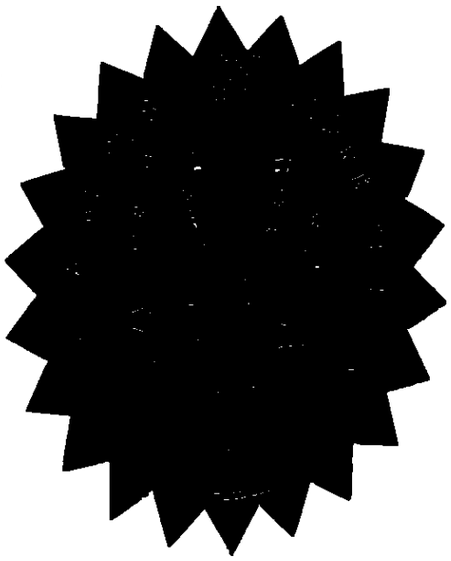
5. at Hartford, Connecticut

6. on **January 27, 2003**

7. by **SUSAN BYSIEWICZ,** Secretary of the State of Connecticut

8. Number : **2003-792**

9. Seal :



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Secretary of the State

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**Cedente**: Yancey D. WARD el Objeto de la cesión es la invención Nitritos espiro heterocíclicos útiles como inhibidores de proteasas de cisteina. **Cesionario**: **Boehringer Ingelheim Pharmaceuticals, Inc.**, domiciliada en 900 Ridgebury Road, Ridgefield, CT 06877, EE.UU.

Dado y firmado en Ridgefield, Connecticut 06877 el día 24/01/03

(Firmado) Yancey D. WARD

CERTIFICADO NOTARIAL (Individuo)

Hoy día 24 de Enero, 2003, ante mi Notario Público del Estado de Connecticut, USA personalmente compareció Yancey D. WARD a quien conozco como la persona que firmó el anterior documento, y quien tiene capacidad legal para hacerlo.

(Firmado)Jeanne E. Rogers

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6. el 27 de Enero, 2003

7. por SUSAN BYSIEWICZ, Secretario de Estado de Connecticut

8. Número: 2003-792

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|---|---|
| Yo, (nosotros), abajo firmado (s)<br>Erick R.R. YOUNG | I (we), the undersigned<br>Erick R.R. YOUNG |
| domiciliado (s) en ~~10292 Avalon Valley Drive,~~ 36 Faith Lane<br>Danbury, CT 06810 / USA | of 36 Faith Lane<br>Danbury, CT 06810 / USA |
| declaro(amos) bajo juramento ser único(s) y verdadero(s) inventor(es) de la invención:<br>nitrilos espiro heterocíclicos útiles como inhibidores reversibles de proteasas de cisteína | state(s) under oath to be sole and true inventor(s) of the invention:<br>Spiroheterocyclic nitriles useful as reversible inhibitors of cysteine proteases |
| declaro(amos) así mismo que cedo(emos) y transfiero(erimos), sin limitación, a favor de la sociedad<br>BOEHRINGER INGELHEIM PHARMACEUTICALS, INC. | state as well, that assign, without reservations or limitations in favour of<br>BOEHRINGER INGELHEIM PHARMACEUTICALS, INC. |
| constituída y existente de conformidad con las leyes de<br>USA | a corporation constituted and existing in conformity with the laws of<br>USA |
| domiciliada en 900 Ridgebury Road<br>Ridgefield, CT 06877, USA | domiciled in 900 Ridgebury Road,<br>Ridgefield, CT 06877, USA |
| todos los derechos inherentes a dicha invención y que la citada Compañía queda facultada para solicitar en su nombre la patente correspondiente en la República de Colombia. | all rights inherent to said invention and that the above mentioned company hereby is enabled to apply, in its name, for the corresponding patent in the Republic of Colombia. |

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en/in Ridgefield, Connecticut 06877 USA

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personally appeared _____
Erick R.R. YOUNG

to me known, and known to me to be the person(s) who executed that foregoing document, and who has (have) legal capacity to execute it.

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Jeanne E. Rogers
Commission expires: 11/30/2006

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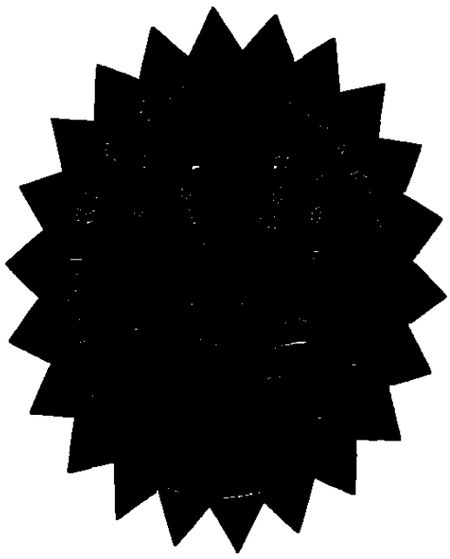
5. at Hartford, Connecticut

6. on **January 27, 2003**

7. by **SUSAN BYSIEWICZ,** Secretary of the State of Connecticut

8. Number : **2003-795**

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Susan Bysiewicz

Secretary of the State

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**Cedente:** Erick R.R. YOUNG el Objeto de la cesión es la invención Nitritos espiro heterocíclicos útiles como inhibidores de proteasas de cisteina. **Cesionario: Boehringer Ingelheim Pharmaceuticals, Inc.**, domiciliada en 900 Ridgebury Road, Ridgefield, CT 06877, EE.UU.

Dado y firmado en Ridgefield, Connecticut 06877 el día 24/01/03

(Firmado) Erick R.R.YOUNG

CERTIFICADO NOTARIAL (Individuo)

Hoy día 24 de Enero, 2003, ante mi Notario Público del Estado de Connecticut, USA personalmente compareció Erick R.R. YOUNG a quien conozco como la persona que firmó el anterior documento, y quien tiene capacidad legal para hacerlo.

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5. en Hartford, Connecticut
6. el 27 de Enero, 2003
7. por SUSAN BYSIEWICZ, Secretario de Estado de Connecticut
8. Número: 2003-795
9. SELLO: GRAN SELLO DE OBLEA DEL ESTADO DE CONNECTICUT
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Ernesto Samper Pizano

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SANTAFE DE BOGOTA, 25 FEB 2003

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

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14 March 2002 (14.03.2002)

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(51) International Patent Classification[7]: C07D 211/60, 211/66, 413/12, 405/12, 401/12, 487/08, 455/02, 207/16, 413/14, A61K 31/5377, A61P 25/28, 9/10, 19/10, 11/06

(21) International Application Number: PCT/US01/08084

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(30) Priority Data:
09/655,351 8 September 2000 (08.09.2000) US

(71) Applicant *(for all designated States except US)*: BOEHRINGER INGELHEIM PHARMACEUTICALS, INC. [US/US]; 900 Ridgebury Road, P.O. Box 368, Ridgefield, CT 06877-0368 (US).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: BEKKALI, Younes [/US]; Unit 34, 60 Padanaram Road, Danbury, CT 06811 (US). HICKEY, Eugene, R. [/US]; 5 Woodbury Drive, Danbury, CT 06811 (US). LIU, Wiemen [CN/US]; 56 Wakelee Avenue, Ext. #12, Shelton, CT 06484 (US). PATEL, Usha, R. [/US]; 20 Dairy Farm Drive, Brookfield, CT 06804 (US). SPERO, Denise, M. [/US]; 18 Limekiln Road, West Redding, CT 06896 (US). SUN, Sanxing [CN/US]; 38 Padanaram Avenue, 21B, Danbury, CT 06811 (US). THOMSON, David, S. [GB/US]; 166 Minuteman Road, Ridgefield, CT 06877 (US). WARD, Yaucey, D. [/US]; 11 Narragansett Trail, Sandy Hook, CT 06482 (US). YOUNG, Erick, R., R. [/US]; 10292 Avalon Valley Drive, Danbury, CT 06811 (US).

(74) Agents: RAYMOND, Robert, P. et al.; Boehringer Ingelheim Pharmaceuticals, Inc., 900 Ridgebury Road, P.O. Box 368, Ridgefield, CT 06877 (US).

(81) Designated States *(national)*: AE, AU, BG, BR, CA, CN, CO, CZ, EE, HR, HU, ID, IL, IN, JP, KR, LT, LV, MX, NO, NZ, PL, RO, SG, SI, SK, TR, UA, US, UZ, VN, YU, ZA.

(84) Designated States *(regional)*: Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR).

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

US 6420364

WO 02/20485 A1

(54) Title: SPIROHETEROCYCLIC NITRILES USEFUL AS REVERSIBLE INHIBITORS OF CYSTEINE PROTEASES

(57) Abstract: Disclosed are novel cathepsin S, K, F, L and B reversible inhibitory compounds of the formula (Ia) and (Ib) where $R_2$, $R_3$, $R_4$, $R_5$, $R_6$, $R_7$, $R_8$, Het and X are defined herein. The compounds are useful for treating autoimmune and other diseases. Also disclosed are processes for making such novel compounds.

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SPIROHETEROCYCLIC NITRILES USEFUL AS REVERSIBLE INHIBITORS OF CYSTEINE PROTEASES

## RELATED APPLICATION DATA

This application is a continuation-in-part of US application serial no. 09/655,351 filed September 8, 2000.

## TECHNICAL FIELD OF THE INVENTION

This invention relates to amidino and guanidino peptidyl compounds active as cysteine protease inhibitors. The compounds are reversible inhibitors of the cysteine protease cathepsin S, K, F, L and B are therefore useful in the treatment of autoimmune and other diseases. The invention also relates to processes for preparing such compounds and pharmaceutical compositions comprising them.

## BACKGROUND OF THE INVENTION

Cathepsin S and cathepsin K are members of the papain family, within the papain superfamily of cysteine proteases. The papain family is the largest group of cysteine proteases and includes proteases such as cathepsins B, H, K, L, O and S. (A.J. Barrett et al., 1996, Perspectives in Drug Discovery and Design, 6, 1). The cysteine proteases have important roles in human biology and diseases including atherosclerosis, emphysema, osteoporosis, chronic inflammation and immune disorders (H.A. Chapman et al., 1997, Ann. Rev. Physiol., 59, 63). Cathepsin S plays a key role in regulating antigen presentation and immunity (H.A. Chapman, 1998, Current Opinion in Immunology, 10, 93; R. J. Riese et al., 1998, J. Clin. Invest., 101, 2351; R.J. Riese et al., 1996, Immunity, 4, 357). Cathepsin S deficient mice have impaired invariant chain degradation resulting in decreased antigen presentation and germinal center formation, and diminished susceptibility to collagen-induced arthritis indicating the therapeutic potential for a cathepsin S inhibitor (G. Shi et al., 1999, Immunity, 10, 197; T.Y. Nakagawa et al, 1999, Immunity, 10, 207)

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The specificity of the immune response relies on processing of foreign protein and presentation of antigenic peptide at the cell surface. Antigenic peptide is presented bound to MHC Class II, a heterodimeric glycoprotein expressed in certain antigen presenting cells of hematopoietic lineage, such as B cells, macrophages and dendritic cells. Presentation of antigen to effector cells, such as T-cells, is a fundamental step in recognition of non-self and thus initiation of the immune response.

Recently MHC Class II heterodimers were shown to associate intracellularly with a third molecule designated invariant chain. Invariant chain facilitates Class II transport to the endosomal compartment and stabilizes the Class II protein prior to loading with antigen. Invariant chain interacts directly with Class II dimers in the antigen-binding groove and therefore must be proteolyzed and removed or antigen cannot be loaded or presented. Current research suggests that invariant chain is selectively proteolyzed by cathepsin S, which is compartmentalized with MHC Class II complexes within the cell. Cathepsin S degrades invariant chain to a small peptide, termed CLIP, which occupies the antigen – binding groove. CLIP is released from MHC Class II by the interaction of MHC Class II with HLA-DM, a MHC-like molecule thus freeing MHC Class II to associate with antigenic peptides. MHC Class II-antigen complexes are then transported to the cell surface for presentation to T-cells, and initiation of the immune response.

Cathepsin S, through proteolytic degradation of invariant chain to CLIP, provides a fundamental step in generation of an immune response. It follows that inhibition of antigen presentation via prevention of invariant chain degradation by cathepsin S could provide a mechanism for immuno-regulation. Control of antigen-specific immune responses has long been desirable as a useful and safe therapy for autoimmune diseases. Such diseases include Crohn's disease and arthritis, as well as other T-cell-mediated immune responses (C. Janeway and P. Travers, 1996, Immunobiology, The Immune System in Health and Disease, Chapter 12). Furthermore, cathepsin S, which has broad pH specificity, has been implicated in a variety of other diseases involving extracellular proteolysis, such as Alzheimer's disease (U. Muller-Ladner et al., 1996, Perspectives in

Drug Discovery and Design, 6, 87), atherosclerosis (G.K. Sukhova et al., 1998, J. Clin. Invest., 102, 576) and endometriosis (WO 9963115, 1999).

A cathepsin S inhibitor has been found to block the rise in IgE titers and eosinophil infiltration in the lung in a mouse model of pulmonary hypersensitivity, suggesting that cathepsin S may be involved in asthma (R.J. Riese et al., J. Clin. Investigation,1998, 101, 2351).

Another cysteine protease, cathepsin F has been found in macrophages and is also involved in antigen processing. It has been postulated that cathepsin F in stimulated lung macrophages and possibly other antigen presenting cells could play a role in airway inflammation (G.-P. Shi et al., J. Exp. Med., 2000, 191, 1177).

Cathepsin K, another cysteine protease has been found to be highly expressed in osteoclasts and to degrade bone collagen and other bone matrix proteins. Inhibitors of cathepsin K have been shown to inhibit bone resorption in mice. Therefore, cathepsin K may play a role in osteoclastic bone resorption and cathepsin K inhibitors may be useful in the treatment of diseases involving bone resorption such as osteoporosis (F. Lazner et al., Human Molecular Genetics, 1999, 8, 1839).

Cysteine proteases are characterized by having a cysteine residue at the active site which serves as a nucleophile. The active site also contains a histidine residue. The imidazole ring on the histidine serves as a base to generate a thiolate anion on the active site cysteine, increasing its nucleophilicity. When a substrate is recognized by the protease, the amide bond to be cleaved is directed to the active site, where the thiolate attacks the carbonyl carbon forming an acyl-enzyme intermediate and cleaving the amide bond, liberating an amine. Subsequently, water cleaves the acyl-enzyme species regenerating the enzyme and liberating the other cleavage product of the substrate, a carboxylic acid.

Inhibitors of cysteine proteases contain a functionality that can react reversibly or irreversibly with the active site cysteine. Examples of reactive functionalities that have

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been described (D. Rasnick, 1996, Perspectives in Drug Discovery and Design, 6, 47) on cysteine protease inhibitors include peptidyl diazomethanes, epoxides, monofluoroalkanes and acyloxymethanes, which irreversibly alkylate the cysteine thiol. Other irreversible inhibitors include Michael acceptors such as peptidyl vinyl esters and other carboxylic acid derivatives (S. Liu et al., J. Med Chem., 1992, 35, 1067) and vinyl sulfones (J.T. Palmer et al., 1995, J. Med Chem., 38, 3193).

Reactive functionalities that form reversible complexes with the active site cysteine include peptidyl aldehydes (R.P. Hanzlik et al., 1991, Biochim. Biophys. Acta., 1073, 33), which are non-selective, inhibiting both cysteine and serine proteases as well as other nucleophiles. Peptidyl nitriles (R.P. Hanzlik et al., 1990, Biochim. Biophys. Acta., 1035, 62) are less reactive than aldehydes and therefore more selective for the more nucleophilic cysteine proteases. Various reactive ketones have also been reported to be reversible inhibitors of cysteine proteases (D. Rasnick, 1996, ibid). In addition to reacting with the nucleophilic cysteine of the active site, reactive ketones may react with water, forming a hemiketal which may act as a transition state inhibitor.

Examples of cathepsin S inhibitors have been reported. J.L. Klaus et al. (WO 9640737) described reversible inhibitors of cysteine proteases including cathepsin S, containing an ethylene diamine. In US Patent No. 5,776,718 to Palmer et al. there is disclosed in it's broadest generic aspect a protease inhibitor comprising a targeting group linked through a two carbon atom chain to an electron withdrawing group (EWG). The compounds of the present application are structurally distinct and thus excluded from the 5,776,718 patent with particular embodiments possessing unexpectedly greater activity than the closest compounds of the prior art. Other examples of cathepsin S inhibitors have been reported by E.T. Altmann et al, (WO 9924460, 1999) which describes dipeptide nitriles asserted to have activity as inhibitors of Cathepsins B, K, L and S. The WO publication does not disclose any compounds possessing a guanidino or amidino structure at the P3 position.

Additional peptidyl nitriles have been reported as protease inhibitors. For example, both nitriles and ketoheterocycles are described by B.A. Rowe et al. (US 5,714,471) as

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protease inhibitors useful in the treatment of neurodegenerative diseases. Peptidyl nitriles are reported by B. Malcolm et al. (WO 9222570) as inhibitors of picornavirus protease. B.J. Gour-Salin (Can. J. Chem., 1991, 69, 1288) and T.C. Liang (Arch. Biochim. Biophys., 1987, 252, 626) described peptidyl nitriles as inhibitors of papain

A reversible inhibitor presents a more attractive therapy than irreversible inhibitors. Even compounds with high specificity for a particular protease can bind non-target enzymes. An irreversible compound could therefore permanently inactivate a non-target enzyme, increasing the likelihood of toxicity. Furthermore, any toxic effects resulting from inactivation of the target enzyme would be mitigated by reversible inhibitors, and could be easily remedied by modified or lower dosing. Finally, covalent modification of an enzyme by an irreversible inhibitor could potentially generate an antibody response by acting as a hapten.

In light of the above, there is a clear need for compounds which reversibly and selectively inhibit cysteine proteases such as cathepsin S and cathepsin K for indications in which these proteases exacerbate disease.

## BRIEF DESCRIPTION OF THE INVENTION

It is therefore an object of this invention to provide novel compounds according to the formulas (Ia) and (Ib) as described herein which reversibly inhibit the cysteine proteases cathepsin S, K, F, L and B. It is a further object of the invention to provide methods for treating diseases and pathological conditions exacerbated by these cysteine proteases such as, but not limited, to rheumatoid arthritis, multiple sclerosis, asthma and osteoporosis. It is yet a further object of the invention to provide novel processes for preparation of the above-mentioned novel compounds.

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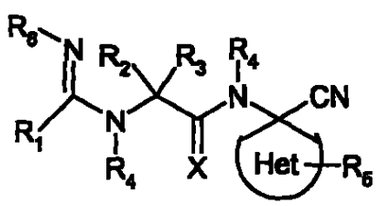
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## DETAILED DESCRIPTION OF THE INVENTION

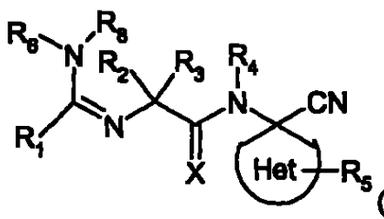
A proposed mechanism of action of the cysteine protease inhibitors of this invention is that the inhibitors contain a functionality that can react (reversibly or irreversibly) with the active site cysteine. The reactive functionality is attached to a peptide or peptide mimic that can be recognized and accommodated by the region of the protease surrounding the active site. The nature of both the reactive functionality and the remaining portion of the inhibitor determine the degree of selectivity and potency toward a particular protease.

Given the similarity of the active sites in cysteine proteases, it may be anticipated that a given class of inhibitors might have activity against more that one cysteine protease. It may also be expected that due to structural differences between individual cysteine proteases, different compounds of the invention may have different inhibitory potencies against different cysteine proteases. Thus some of the compounds of the invention may also be expected to be most effective in treating diseases mediated by cysteine proteases that they inhibit most potently. The activity of particular compounds disclosed herein against cysteine proteases such as cathepsin S, K, F, L and B may be determined by the screens described in the section entitled "Assessment of Biological Properties."

Accordingly, in a first generic aspect of the invention, there are provided compounds of formula (Ia) and (Ib):




(Ia),




(Ib)

wherein:

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Het is

azepanyl, piperidinyl, pyrrolidinyl, azetidinyl, oxepanyl, tetrahydropyranyl, tetrahydrothiopyranyl, tetrahydrofuranyl, oxetanyl, azocanyl, oxocanyl, 1,3-diazocanyl, 1,4-diazocanyl, 1,5-diazocanyl, 1,3-dioxocanyl, 1,4-dioxocanyl, 1,5-dioxocanyl, 1,3-oxazocanyl, 1,4-oxazocanyl, 1,5-oxazocanyl, 1,3-diazepanyl, 1,4-diazepanyl, 1,3-dioxepanyl, 1,4-dioxepanyl, 1,3-oxazepanyl, 1,4-oxazepanyl, 1,2-thiazocanyl-1,1-dioxide, 1,2,8-thiadiazocanyl-1,1-dioxide, 1,2-thiazepanyl-1,1-dioxide, 1,2,7-thiadiazepanyl-1,1-dioxide, tetrahydrothiophenyl, hexahydropyrimidinyl, hexahydropyridazinyl, piperazinyl, 1,4,5,6-tetrahydropyrimidinyl, pyrazolidinyl, dihydro-oxazolyl, dihydrothiazolyl, dihydroimidazolyl, isoxazolinyl, oxazolidinyl, 1,2-thiazinanyl-1,1-dioxide, 1,2,6-thiadiazinanyl-1,1-dioxide, isothiazolidinyl-1,1-dioxide, imidazolidinyl-2,4-dione, imidazolidinyl, morpholinyl, dioxanyl, tetrahydropyridinyl, thiomorpholinyl, thiazolidinyl, dihydropyranyl, dithianyl, decahydro-quinolinyl, decahydro-isoquinolinyl, 1,2,3,4-tetrahydro-quinolinyl, indolinyl, octahydro-quinolizinyl, dihydro-indolizinyl, octahydro-indolizinyl, octahydro-indolyl, decahydroquinazolinyl, decahydroquinoxalinyl, 1,2,3,4-tetrahydroquinazolinyl or 1,2,3,4-tetrahydroquinoxalinyl;

A C6-C10 bridged bicyclo wherein one or more carbon atoms are optionally replaced by a heteroatom chosen from N, O and S;

each being optionally substituted with one or more $R_5$;

$R_1$ is a bond, hydrogen, C1-10 alkyl, C1-10 alkoxy, aryloxy, C3-8 cycloalkyl, C3-8 cycloalkyloxy, aryl, benzyl, tetrahydronaphthyl, indenyl, indanyl, C1-10alkylsulfonylC1-10alkyl, C3-8cycloalkylsulfonylC1-10alkyl, arylsulfonylC1-10alkyl, heterocyclyl selected from azepanyl, azocanyl, pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl, indolinyl, pyranyl, tetrahydropyranyl, tetrahydrothiopyranyl, thiopyranyl, furanyl, tetrahydrofuranyl, thienyl, pyrrolyl, oxazolyl, isoxazolyl, thiazolyl, imidazolyl, pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl,

tetrazolyl, pyrazolyl, indolyl, benzofuranyl, benzothienyl, benzimidazolyl, benzthiazolyl, benzisoxazolyl, quinolinyl, tetrahydroquinolinyl, isoquinolinyl, tetrahydroisoquinolinyl, quinazolinyl, tetrahydroquinazolinyl, benzoxazolyl and quinoxalinyl, heterocyclyloxy wherein the heterocyclyl moiety is selected from those herein described in this paragraph, hydroxy or amino; wherein $R_1$ is optionally substituted by one or more $R_a$;

$R_a$ is a bond, C1-10 alkyl, C3-8 cycloalkyl, aryl, tetrahydronaphthyl, indenyl, indanyl, pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl, indolinyl, furanyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, triazolyl, tetrazolyl, pyridinyl, pyrimidinyl, pyrazinyl, indolyl, benzofuranyl, benzothienyl, benzimidazolyl, benzthiazolyl, benzoxazolyl, benzisoxazolyl, quinolinyl, isoquinolinyl, quinazolinyl, quinoxalinyl, C1-10 alkoxy, C1-10alkanoyl, C1-10alkanoyloxy, aryloxy, benzyloxy, C1-10 alkoxycarbonyl, aryloxycarbonyl, aroyloxy, carbamoyl wherein the nitrogen atom may be independently mono or di-substituted by C1-10 alkyl, aryl, pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl, indolinyl, furanyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, triazolyl, tetrazolyl, pyridinyl, pyrimidinyl, pyrazinyl, indolyl, benzofuranyl, benzothienyl, benzimidazolyl, benzthiazolyl, quinolinyl, isoquinolinyl, quinazolinyl or quinoxalinyl,
or $R_a$ is C1-10 alkanoylamino, aroylamino, C1-10 alkylthio wherein the sulfur atom may be oxidized to a sulfoxide or sulfone, arylthio wherein the sulfur atom may be oxidized to a sulfoxide or sulfone, ureido wherein either nitrogen atom may be independently substituted by C1-10 alkyl, aryl, pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl, indolinyl, furanyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, triazolyl, tetrazolyl, pyridinyl, pyrimidinyl, pyrazinyl, indolyl, benzofuranyl, benzothienyl, benzimidazolyl, benzthiazolyl, quinolinyl, isoquinolinyl, quinazolinyl or quinoxalinyl,
or $R_a$ is C1-10 alkoxycarbonylamino, aryloxycarbonylamino, C1-10 alkylcarbamoyloxy, arylcarbamoyloxy, C1-10 alkylsulfonylamino, arylsulfonylamino, C1-10 alkylaminosulfonyl, arylaminosulfonyl, amino wherein the nitrogen atom may be independently mono or di-substituted by C1-10 alkyl,

aryl, pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl, indolinyl, furanyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, triazolyl, tetrazolyl, pyridinyl, pyrimidinyl, pyrazinyl, indolyl, benzofuranyl, benzothienyl, benzimidazolyl, benzthiazolyl, quinolinyl, isoquinolinyl, quinazolinyl or quinoxalinyl,

or $R_a$ is halogen, hydroxy, oxo, carboxy, cyano, nitro, carboxamide, amidino or guanidino, $R_a$ may be further optionally substituted by one or more $R_b$;

with the proviso that $R_1$ and $R_a$ simultaneously cannot be a bond;

$R_b$ is a C1-6 saturated or unsaturated branched or unbranched carbon chain optionally partially or fully halogenated wherein one or more carbon atoms are optionally replaced by O, N, S(O), $S(O)_2$ or S and wherein said chain is optionally independently substituted with 1-2 oxo groups, $-NH_2$, or one or more C1-4 alkyl, pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl, indolinyl, furanyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, triazolyl, tetrazolyl, pyridinyl, pyrimidinyl, pyrazinyl, indolyl, benzofuranyl, benzothienyl, benzimidazolyl, benzthiazolyl, quinolinyl, isoquinolinyl, quinazolinyl or quinoxalinyl;

or $R_b$ is C3-6 cycloalkyl, aryl, aryloxy, benzyloxy, halogen, hydroxy, oxo, carboxy, cyano, nitro, mono-C1-5alkylamino, di-C1-5alkylamino, carboxamide, amidino or guanidino;

$R_2$ is hydrogen or C1-3 alkyl;

$R_3$ is a bond, hydrogen, C1-10 alkyl, C2-10alkylene, C3-8 cycloalkyl, arylC1-5alkyl or aryl wherein $R_3$ is optionally substituted by one or more $R_c$;

$R_c$ is C1-10 alkyl, C3-8 cycloalkyl, aryl, indanyl, indenyl, bicyclo[2.2.1]heptanyl, bicyclo[2.2.2]octanyl, bicyclo[4.1.0]heptanyl, bicyclo[3.1.0]hexanyl, bicyclo[1.1.1]pentanyl, cubanyl, 1,2,3,4-tetrahydronaphthyl, decahydronaphthyl, pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl, indolinyl,

furanyl, tetrahydrofuranyl, pyranyl, tetrahydropyranyl, tetrahydrothiopyranyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, pyrazolyl, triazolyl, tetrazolyl, pyridinyl, pyrimidinyl, pyrazinyl, indolyl, dihydrobenzofuranyl, octohydrobenzofuranyl, benzofuranyl, benzothienyl, benzimidazolyl, benzthiazolyl, tetrahydroquinolinyl, quinolinyl, tetrahydroisoquinolinyl, isoquinolinyl, quinazolinyl, quinoxalinyl, C1-10 alkoxy, aryloxy, C1-10 alkanoyl, aroyl, C1-10 alkoxycarbonyl, aryloxycarbonyl, C1-10 alkanoyloxy, aroyloxy, carbamoyl wherein the nitrogen atom may be independently mono or di-substituted by C1-10 alkyl, aryl, pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl, indolinyl, furanyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, triazolyl, tetrazolyl, pyridinyl, pyrimidinyl, pyrazinyl, indolyl, benzofuranyl, benzothienyl, benzimidazolyl, benzthiazolyl, quinolinyl, isoquinolinyl, quinazolinyl or quinoxalinyl,

or $R_c$ is C1-10 alkanoylamino, aroylamino, C1-10 alkylthio wherein the sulfur atom may be oxidized to a sulfoxide or sulfone, arylthio wherein the sulfur atom may be oxidized to a sulfoxide or sulfone, ureido wherein either nitrogen atom may be independently substituted by C1-10 alkyl, aryl, pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl, indolinyl, furanyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, triazolyl, tetrazolyl, pyridinyl, pyrimidinyl, pyrazinyl, indolyl, benzofuranyl, benzothienyl, benzimidazolyl, benzthiazolyl, quinolinyl, isoquinolinyl, quinazolinyl or quinoxalinyl,

or $R_c$ is C1-10 alkoxycarbonylamino, aryloxycarbonylamino, C1-10 alkylcarbamoyloxy, arylcarbamoyloxy, C1-10 alkylsulfonylamino, arylsulfonylamino, C1-10 alkylaminosulfonyl, arylaminosulfonyl, amino wherein the nitrogen atom may be independently mono or di-substituted by C1-10 alkyl, aryl, pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl, indolinyl, furanyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, triazolyl, tetrazolyl, pyridinyl, pyrimidinyl, pyrazinyl, indolyl, benzofuranyl, benzothienyl, benzimidazolyl, benzthiazolyl, quinolinyl, isoquinolinyl, quinazolinyl or quinoxalinyl,

or $R_c$ is halogen, hydroxy, oxo, carboxy, cyano, nitro, amidino or guanidino, $R_c$ may be further optionally substituted by one or more $R_d$;

$R_d$ is C1-5 alkyl, C3-6 cycloalkyl, aryl, arylC1-5alkyl, C1-5 alkoxy, aryloxy, arylC1-5alkoxy, aroyl, amino, halogen, hydroxy, oxo, carboxy, cyano, nitro, amidino or guanidino;

$R_2$ and $R_3$ together with the carbon they are attached optionally form a nonaromatic 5-7 membered cycloalkyl or heterocyclic ring;

each $R_4$ is independently hydrogen, hydroxy or C1-3 alkyl;

$R_5$ is a bond, hydrogen, carbonyl, C1-10 alkyl, C1-10alkoxyC1-10alkyl, C1-10alkylaminoC1-10alkyl, C1-10alkylthioC1-10alkyl wherein the sulfur atom may be oxidized to a sulfoxide or sulfone, C1-10 alkoxy, aryloxy, C3-8 cycloalkyl, aryl, benzyl, tetrahydronaphthyl, indenyl, indanyl, C3-7cycloalkylsulfonylC1-5alkyl, arylsulfonylC1-5alkyl, heterocyclyl selected from pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl, indolinyl, pyranyl, tetrahydropyranyl, thiopyranyl, tetrahydrothiopyranyl, furanyl, tetrahydrofuranyl, thienyl, pyrrolyl, oxazolyl, isoxazolyl, thiazolyl, imidazolyl, pyridinyl, pyrimidinyl, pyrazinyl, pyridizinyl, tetrazolyl, triazolyl, pyrazolyl, indolyl, benzofuranyl, benzothienyl, benzimidazolyl, benzthiazolyl, quinolinyl, tetrahydroquinolinyl, isoquinolinyl, tetrahydroisoquinolinyl, quinazolinyl, tetrahydroquinazolinyl, benzoxazolyl and quinoxalinyl, heterocyclyloxy wherein the heterocyclyl moiety is selected from those herein described in this paragraph, C1-10alkanoyl, aroyl, C1-10alkanoyloxy, benzyloxy, C1-10alkoxycarbonyl, arylC1-5alkoxycarbonyl, aryloxycarbonyl, aroyloxy, carbamoyl wherein the nitrogen atom may be independently mono or di-substituted by C1-10 alkyl, aryl, pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl, indolinyl, furanyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, triazolyl, tetrazolyl, pyridinyl, pyrimidinyl, pyrazinyl, indolyl, benzofuranyl, benzothienyl, benzimidazolyl, benzthiazolyl, quinolinyl, isoquinolinyl, quinazolinyl or quinoxalinyl,

or $R_5$ is C1-10 alkanoylamino, aroylamino, C1-10 alkylthio wherein the sulfur atom may be oxidized to a sulfoxide or sulfone, arylthio wherein the sulfur atom may be oxidized to a sulfoxide or sulfone, ureido wherein either nitrogen atom may be independently substituted by C1-10 alkyl, aryl, pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl, indolinyl, furanyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, triazolyl, tetrazolyl, pyridinyl, pyrimidinyl, pyrazinyl, indolyl, benzofuranyl, benzothienyl, benzimidazolyl, benzthiazolyl, quinolinyl, isoquinolinyl, quinazolinyl or quinoxalinyl, or $R_5$ is C1-10 alkoxycarbonylamino, aryloxycarbonylamino, C1-10 alkylcarbamoyloxy, arylcarbamoyloxy, C1-10 alkylsulfonylamino, arylsulfonylamino, C1-10 alkylaminosulfonyl, arylaminosulfonyl, amino wherein the nitrogen atom may be independently mono or di-substituted by C1-10 alkyl, aryl, pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl, indolinyl, furanyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, triazolyl, tetrazolyl, pyridinyl, pyrimidinyl, pyrazinyl, indolyl, benzofuranyl, benzothienyl, benzimidazolyl, benzthiazolyl, quinolinyl, isoquinolinyl, quinazolinyl or quinoxalinyl,
or $R_5$ is halogen, hydroxy, oxy, oxo, carboxy, cyano, nitro, carboxamide, amidino or guanidino, $R_5$ may be further optionally substituted by one or more $R_e$;

$R_e$ is C1-10 alkyl, C1-10alkoxyC1-10alkyl, C1-10alkylaminoC1-10alkyl, C1-10alkylthioC1-10alkyl wherein the sulfur atom may be oxidized to a sulfoxide or sulfone, C1-10 alkoxy, C3-8 cycloalkyl, aryl, tetrahydronaphthyl, indenyl, indanyl, pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl, indolinyl, thiopyranyl, tetrahydrothiopyranyl, pyranyl, tetrahydropyranyl, tetrahydrofuranyl, furanyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, triazolyl, tetrazolyl, pyridinyl, pyrimidinyl, pyrazinyl, indolyl, benzofuranyl, benzothienyl, benzimidazolyl, benzthiazolyl, benzoxazolyl, benzisoxazolyl, quinolinyl, isoquinolinyl, quinazolinyl, quinoxalinyl, C1-10alkanoyl, aroyl, C1-10alkanoyloxy, aryloxy, benzyloxy, C1-10 alkoxycarbonyl, arylC1-3alkoxycarbonyl, aryloxycarbonyl, aroyloxy, carbamoyl wherein the nitrogen atom may be independently mono or di-substituted by C1-10 alkyl, aryl, pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl, indolinyl,

furanyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, triazolyl, tetrazolyl, pyridinyl, pyrimidinyl, pyrazinyl, indolyl, benzofuranyl, benzothienyl, benzimidazolyl, benzthiazolyl, quinolinyl, isoquinolinyl, quinazolinyl or quinoxalinyl,

or $R_e$ is C1-10 alkanoylamino, aroylamino, C1-10 alkylthio wherein the sulfur atom may be oxidized to a sulfoxide or sulfone, arylthio wherein the sulfur atom may be oxidized to a sulfoxide or sulfone, ureido wherein either nitrogen atom may be independently substituted by C1-10 alkyl, aryl, pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl, indolinyl, furanyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, triazolyl, tetrazolyl, pyridinyl, pyrimidinyl, pyrazinyl, indolyl, benzofuranyl, benzothienyl, benzimidazolyl, benzthiazolyl, quinolinyl, isoquinolinyl, quinazolinyl or quinoxalinyl,

or $R_e$ is C1-10 alkoxycarbonylamino, aryloxycarbonylamino, C1-10 alkylcarbamoyloxy, arylcarbamoyloxy, C1-10 alkylsulfonylamino, arylsulfonylamino, C1-10 alkylaminosulfonyl, arylaminosulfonyl, amino wherein the nitrogen atom may be independently mono or di-substituted by C1-10 alkyl, aryl, pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl, indolinyl, furanyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, triazolyl, tetrazolyl, pyridinyl, pyrimidinyl, pyrazinyl, indolyl, benzofuranyl, benzothienyl, benzimidazolyl, benzthiazolyl, quinolinyl, isoquinolinyl, quinazolinyl or quinoxalinyl,

or $R_e$ is halogen, hydroxy, oxo, carboxy, cyano, nitro, carboxamide, amidino or guanidino, $R_e$ may be further optionally substituted by one or more $R_f$;

$R_f$ is C1-5 alkyl, C3-6 cycloalkyl, tolylsulfonyl, C1-5 alkoxy, aryl, aryloxy, benzyloxy, halogen, hydroxy, oxo, carboxy, cyano, nitro, carboxamide, amidino or guanidino;

$R_6$ is

hydrogen, hydroxy, nitrile or

a C1-6 saturated or unsaturated branched or unbranched carbon chain optionally partially or fully halogenated wherein one or more C atoms are optionally replaced by O, NH, S(O), $S(O)_2$ or S and wherein said chain is optionally independently substituted with 1-2 oxo groups, $-NH_2$, one or more $C_{1-4}$ alkyl, pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl, indolinyl, pyranyl, thiopyranyl, furanyl, thienyl, pyrrolyl, oxazolyl, isoxazolyl, thiazolyl, imidazolyl, pyridinyl, pyrimidinyl, pyrazinyl, indolyl, benzofuranyl, benzothienyl, benzimidazolyl, benzthiazolyl, quinolinyl, isoquinolinyl, quinazolinyl, benzoxazolyl or quinoxalinyl;

wherein $R_1$ and $R_6$ in the formulas (Ia) or (Ib) optionally form a 4 to 8 membered mono- or 7-12 membered polycyclo heteroring system, each aromatic or nonaromatic, wherein each heteroring is optionally substituted by one or more $R_7$;

each $R_7$ and $R_8$ are independently:

C1-5 alkyl chain optionally interrupted by one or two N, O or $S(O)_m$ and optionally substituted by 1-2 oxo, amino, hydroxy, halogen, C1-4alkyl, pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl, indolinyl, pyranyl, thiopyranyl, furanyl, thienyl, pyrrolyl, oxazolyl, isoxazolyl, thiazolyl, imidazolyl, pyridinyl, pyrimidinyl, pyrazinyl, indolyl, benzofuranyl, benzothienyl, benzimidazolyl, benzthiazolyl, quinolinyl, isoquinolinyl, quinazolinyl, benzoxazolyl or quinoxalinyl,

aryl, aryloxy, aroyl, furanyl, thienyl, pyrrolyl, imidazolyl, pyridinyl, pyrimidinyl, C1-5 alkanoyl, C1-5 alkoxycarbonyl, aryloxycarbonyl, benzyloxycarbonyl, C1-5 alkanoylamino, aroylamino, C1-5 alkylthio, arylthio C1-5 alkylsulfonylamino, arylsulfonylamino, C1-5 alkylaminosulfonyl, arylaminosulfonyl, C3-6 cycloalkyl and benzyloxy
each of the aforementioned are optionally halogenated,
halogen, hydroxy, oxo, carboxy, nitrile, nitro or $NH_2C(O)$-;

m is 0, 1 or 2;

X is =O, =S or =N-$R_6$ wherein $R_6$ is as defined above, and

pharmaceutically acceptable derivatives thereof.

In another embodiment of the invention, there are provided novel compounds of the formula (Ia) and formula (Ib) as described immediately above, and wherein:

Het is piperidinyl, pyrrolidinyl, tetrahydropyranyl, tetrahydrothiopyranyl, azetidinyl, azepanyl, oxepanyl, tetrahydrofuranyl, oxetanyl, hexahydropyrimidinyl, hexahydropryidazinyl, piperazinyl, 1,4,5,6-tetrahydropyrimidinyl, octahydro-indolizinyl, octahydro-quinolizinyl, decahydro-quinolinyl, 1,2,3,4-tetrahydro-quinolinyl, dihydro-oxazolyl, 1,2-thiazinanyl-1,1-dioxide, 1,2,6-thiadiazinanyl-1,1-dioxide, isothiazolidinyl-1,1-dioxide, imidazolidinyl, pyrazolidinyl or a bridged bicyclo chosen from aza-bicyclo[3.2.1]octane, aza-bicyclo[2.2.1]heptane, aza-bicyclo[2.2.2]octane, aza-bicyclo[3.2.2]nonane, aza-bicyclo[2.1.1]hexane, aza-bicyclo[3.1.1]heptane, aza-bicyclo[3.3.2]decane and 2-oxa or 2-thia-5-aza-bicyclo[2.2.1]heptane;
each ring being substituted with one or more $R_5$;

$R_1$ is a bond, hydrogen, C1-7 alkyl, C1-7 alkoxy, C3-7 cycloalkyl, aryloxy, phenyl, benzyl, naphthyl, tetrahydronaphthyl, C1-7alkylsulfonylC1-7alkyl, C3-7cycloalkylsulfonylC1-7alkyl, arylsulfonylC1-7alkyl, pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl, indolinyl, pyranyl, thiopyranyl, furanyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, pyridinyl, isoxazolyl, pyrimidinyl, pyrazinyl, pyridazinyl, indolyl, quinolinyl, benzofuranyl, benzthienyl, benzimidazolyl, benzthiazolyl, benzoisoxazolyl, benzoxazolyl or amino; wherein $R_1$ is optionally substituted by one or more $R_a$;

$R_a$ is a bond C1-7 alkyl, C3-6 cycloalkyl, phenyl, naphthyl, pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl, furanyl, thienyl, oxazolyl,

thiazolyl, imidazolyl, triazolyl, tetrazolyl, pyridinyl, pyrimidinyl, pyrazinyl, indolyl, benzofuranyl, benzothienyl, benzimidazolyl, benzthiazolyl, benzoxazolyl, quinolinyl, isoquinolinyl, quinazolinyl, quinoxalinyl, C1-7 alkoxy, C1-7alkanoyl, C1-7alkanoyloxy, aryloxy, benzyloxy, C1-7 alkoxycarbonyl, aryloxycarbonyl, aroyloxy, carbamoyl wherein the nitrogen atom may be independently mono or di-substituted by C1-7 alkyl, aryl, pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl, furanyl, thienyl, oxazolyl, thiazolyl, imidazolyl, triazolyl, tetrazolyl, pyridinyl, pyrimidinyl, pyrazinyl, indolyl, benzofuranyl, benzothienyl, benzimidazolyl, benzthiazolyl, quinolinyl, isoquinolinyl, quinazolinyl or quinoxalinyl,

or $R_a$ is C1-7 alkanoylamino, aroylamino, C1-7 alkylthio wherein the sulfur atom may be oxidized to a sulfoxide or sulfone, arylthio wherein the sulfur atom may be oxidized to a sulfoxide or sulfone, ureido wherein either nitrogen atom may be independently substituted by C1-7 alkyl, aryl, pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl, furanyl, thienyl, oxazolyl, thiazolyl, imidazolyl, triazolyl, tetrazolyl, pyridinyl, pyrimidinyl, pyrazinyl, indolyl, benzofuranyl, benzothienyl, benzimidazolyl, benzthiazolyl, quinolinyl, isoquinolinyl, quinazolinyl or quinoxalinyl,

or $R_a$ is C1-7 alkoxycarbonylamino, aryloxycarbonylamino, C1-7 alkylcarbamoyloxy, arylcarbamoyloxy, C1-7 alkylsulfonylamino, arylsulfonylamino, C1-7 alkylaminosulfonyl, arylaminosulfonyl, amino wherein the nitrogen atom may be independently mono or di-substituted by C1-7 alkyl, aryl, pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl, furanyl, thienyl, oxazolyl, thiazolyl, imidazolyl, triazolyl, tetrazolyl, pyridinyl, pyrimidinyl, pyrazinyl, indolyl, benzofuranyl, benzothienyl, benzimidazolyl, benzthiazolyl, quinolinyl, isoquinolinyl, quinazolinyl or quinoxalinyl,

or $R_a$ is halogen, hydroxy, oxo, carboxy, cyano, nitro, carboxamide, amidino or guanidino, $R_a$ may be further optionally substituted by one or more $R_b$;

$R_b$ is C1-5 alkyl, C3-6 cycloalkyl, aryl, C1-5 alkoxy, aryloxy, benzyloxy, halogen, hydroxy, oxo, carboxy, cyano, nitro, carboxamide, amidino or guanidino;

$R_2$ is hydrogen or methyl or ethyl;

$R_3$ is a bond, hydrogen, C1-5 alkyl, C2-5alkylene, C3-7 cycloalkyl, arylC1-3alkyl or aryl wherein $R_3$ is optionally substituted by one or more $R_c$;

$R_c$ is C1-5 alkyl, C3-7 cycloalkyl, aryl, indanyl, indenyl, bicyclo[2.2.1]heptanyl, bicyclo[2.2.2]octanyl, bicyclo[4.1.0]heptanyl, bicyclo[3.1.0]hexanyl, bicyclo[1.1.1]pentanyl, cubanyl, 1,2,3,4-tetrahydronaphthyl, pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl, indolinyl, furanyl, tetrahydrofuranyl, pyranyl, tetrahydropyranyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, pyrazolyl, triazolyl, tetrazolyl, pyridinyl, pyrimidinyl, pyrazinyl, indolyl, benzofuranyl, benzothienyl, benzimidazolyl, benzthiazolyl, quinolinyl, isoquinolinyl, quinazolinyl, quinoxalinyl, C1-5 alkoxy, aryloxy, C1-5 alkanoyl, aroyl, C1-5 alkoxycarbonyl, aryloxycarbonyl, C1-5 alkanoyloxy, aroyloxy, carbamoyl wherein the nitrogen atom may be independently mono or di-substituted by C1-5 alkyl, aryl, pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl, indolinyl, furanyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, triazolyl, tetrazolyl, pyridinyl, pyrimidinyl, pyrazinyl, indolyl, benzofuranyl, benzothienyl, benzimidazolyl, benzthiazolyl, quinolinyl, isoquinolinyl, quinazolinyl or quinoxalinyl,
or $R_c$ is C1-5 alkanoylamino, aroylamino, C1-5 alkylthio wherein the sulfur atom may be oxidized to a sulfoxide or sulfone, arylthio wherein the sulfur atom may be oxidized to a sulfoxide or sulfone, ureido wherein either nitrogen atom may be independently substituted by C1-5 alkyl, aryl, pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl, indolinyl, furanyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, triazolyl, tetrazolyl, pyridinyl, pyrimidinyl,

pyrazinyl, indolyl, benzofuranyl, benzothienyl, benzimidazolyl, benzthiazolyl, quinolinyl, isoquinolinyl, quinazolinyl or quinoxalinyl,
or $R_c$ is C1-5 alkoxycarbonylamino, aryloxycarbonylamino, C1-5 alkylcarbamoyloxy, arylcarbamoyloxy, C1-5 alkylsulfonylamino, arylsulfonylamino, C1-5 alkylaminosulfonyl, arylaminosulfonyl, amino wherein the nitrogen atom may be independently mono or di-substituted by C1-5 alkyl, aryl, pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl, indolinyl, furanyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, triazolyl, tetrazolyl, pyridinyl, pyrimidinyl, pyrazinyl, indolyl, benzofuranyl, benzothienyl, benzimidazolyl, benzthiazolyl, quinolinyl, isoquinolinyl, quinazolinyl or quinoxalinyl,
or $R_c$ is halogen, hydroxy, oxo, carboxy, cyano, nitro, amidino or guanidino, $R_c$ may be further optionally substituted by one or more $R_d$;

$R_d$ is C1-5 alkyl, C3-6 cycloalkyl, aryl, arylC1-4 alkyl, C1-5 alkoxy, aryloxy, arylC1-5alkoxy, aroyl, halogen, hydroxy, oxo or cyano;

$R_4$ is hydrogen or methyl;

$R_5$ is a bond, hydrogen, carbonyl, C1-8 alkyl, C1-8alkoxyC1-8alkyl, C1-8alkylaminoC1-8alkyl, C1-8alkylthioC1-8alkyl wherein the sulfur atom may be oxidized to a sulfoxide or sulfone, C1-8 alkoxy,, aryloxy, C3-7 cycloalkyl, aryl, benzyl, tetrahydronaphthyl, indanyl, heterocyclyl selected from pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl, indolinyl, pyranyl, tetrahydropyranyl, thiopyranyl, tetrahydrothiopyranyl, furanyl, tetrahydrofuranyl, thienyl, oxazolyl, thiazolyl, imidazolyl, pyridinyl, pyrimidinyl, pyrazinyl, tetrazolyl, triazolyl, pyrazolyl, indolyl, benzofuranyl, benzothienyl, benzimidazolyl, benzthiazolyl, quinolinyl, isoquinolinyl, quinazolinyl, benzoxazolyl and quinoxalinyl, heterocyclyloxy wherein the heterocyclyl moiety is selected from those herein described in this paragraph, C1-7alkanoyl, aroyl, C1-7alkanoyloxy, benzyloxy, C1-7 alkoxycarbonyl, arylC1-4alkoxycarbonyl,

aryloxycarbonyl, aroyloxy, carbamoyl wherein the nitrogen atom may be independently mono or di-substituted by C1-7 alkyl, aryl, pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl, furanyl, thienyl, oxazolyl, thiazolyl, imidazolyl, pyridinyl, pyrimidinyl, pyrazinyl, indolyl, benzofuranyl, benzothienyl, benzimidazolyl, benzthiazolyl, quinolinyl, isoquinolinyl, quinazolinyl or quinoxalinyl,
or $R_5$ is C1-7 alkanoylamino, aroylamino, C1-7 alkylthio wherein the sulfur atom may be oxidized to a sulfoxide or sulfone, arylthio wherein the sulfur atom may be oxidized to a sulfoxide or sulfone, ureido wherein either nitrogen atom may be independently substituted by C1-7 alkyl, aryl, pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl, furanyl, thienyl, oxazolyl, thiazolyl, imidazolyl, pyridinyl, pyrimidinyl, pyrazinyl, indolyl, benzofuranyl, benzothienyl, benzimidazolyl, benzthiazolyl, quinolinyl, isoquinolinyl, quinazolinyl or quinoxalinyl,
or $R_5$ is C1-7 alkoxycarbonylamino, aryloxycarbonylamino, C1-7 alkylcarbamoyloxy, arylcarbamoyloxy, C1-7 alkylsulfonylamino, arylsulfonylamino, C1-7 alkylaminosulfonyl, arylaminosulfonyl, amino wherein the nitrogen atom may be independently mono or di-substituted by C1-7 alkyl, aryl, pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl, furanyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, pyridinyl, pyrimidinyl, pyrazinyl, indolyl, benzofuranyl, benzothienyl, benzimidazolyl, benzthiazolyl, quinolinyl, isoquinolinyl, quinazolinyl or quinoxalinyl,
or $R_5$ is halogen, hydroxy, oxy, oxo, carboxy, cyano, nitro or carboxamide, $R_5$ may be further optionally substituted by one or more $R_6$;

$R_6$ is C1-7 alkyl, C1-7alkoxyC1-7alkyl, C1-7alkylaminoC1-7alkyl, C1-7alkylthioC1-7alkyl wherein the sulfur atom may be oxidized to a sulfoxide or sulfone, C1-7 alkoxy, C3-7 cycloalkyl, aryl, tetrahydronaphthyl, indanyl, pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl, thiopyranyl, tetrahydrothiopyranyl, tetrahydropyranyl, tetrahydrofuranyl, furanyl, thienyl, oxazolyl, thiazolyl, imidazolyl, pyridinyl, pyrimidinyl, pyrazinyl, indolyl, benzofuranyl, benzothienyl, benzimidazolyl, benzthiazolyl, benzoxazolyl, quinolinyl, isoquinolinyl, quinazolinyl, quinoxalinyl, C1-5 alkanoyl, aroyl, C1-

5alkanoyloxy, aryloxy, benzyloxy, C1-5 alkoxycarbonyl, aryloxycarbonyl, aroyloxy, carbamoyl wherein the nitrogen atom may be independently mono or di-substituted by C1-5 alkyl, aryl, pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl, furanyl, thienyl, oxazolyl, thiazolyl, imidazolyl, pyridinyl, pyrimidinyl, pyrazinyl, indolyl, benzofuranyl, benzothienyl, benzimidazolyl, benzthiazolyl, quinolinyl, isoquinolinyl, quinazolinyl or quinoxalinyl,

or $R_e$ is C1-5 alkanoylamino, aroylamino, C1-5 alkylthio wherein the sulfur atom may be oxidized to a sulfoxide or sulfone, arylthio wherein the sulfur atom may be oxidized to a sulfoxide or sulfone, ureido wherein either nitrogen atom may be independently substituted by C1-5 alkyl, aryl, pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl, furanyl, thienyl, oxazolyl, thiazolyl, imidazolyl, pyridinyl, pyrimidinyl, pyrazinyl, indolyl, benzofuranyl, benzothienyl, benzimidazolyl, benzthiazolyl, quinolinyl, isoquinolinyl, quinazolinyl or quinoxalinyl,

or $R_e$ is C1-5 alkoxycarbonylamino, aryloxycarbonylamino, C1-5 alkylcarbamoyloxy, arylcarbamoyloxy, C1-5 alkylsulfonylamino, arylsulfonylamino, C1-5 alkylaminosulfonyl, arylaminosulfonyl, amino wherein the nitrogen atom may be independently mono or di-substituted by C1-5 alkyl, aryl, pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl, furanyl, thienyl, oxazolyl, thiazolyl, imidazolyl, pyridinyl, pyrimidinyl, pyrazinyl, indolyl, benzofuranyl, benzothienyl, benzimidazolyl, benzthiazolyl, quinolinyl, isoquinolinyl, quinazolinyl or quinoxalinyl,

or $R_e$ is halogen, hydroxy, oxo, carboxy, cyano, nitro, carboxamide, amidino or guanidino, $R_e$ may be further optionally substituted by one or more $R_f$;

$R_f$ is methyl, ethyl, t-butyl, tolylsulfonyl, C1-3 alkoxy, cyclopropyl, cyclohexyl, phenyl, naphthyl, phenoxy, benzyloxy, fluoro, chloro, bromo, hydroxy, oxo, carboxy, cyano, nitro or carboxamide;

*$R_6$ is*

hydrogen, hydroxy, nitrile or

a C1-6 saturated or unsaturated branched or unbranched carbon chain optionally partially or fully halogenated wherein one or more C atoms are optionally replaced by O, NH, S(O), $S(O)_2$ or S and wherein said chain is optionally independently substituted with 1-2 oxo groups, $-NH_2$, one or more C1-4 alkyl, pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl, indolinyl, pyranyl, thiopyranyl, furanyl, thienyl, pyrrolyl, oxazolyl, isoxazolyl, thiazolyl, imidazolyl, pyridinyl, pyrimidinyl, pyrazinyl, indolyl, benzofuranyl, benzothienyl, benzimidazolyl, benzthiazolyl, quinolinyl, isoquinolinyl, quinazolinyl, benzoxazolyl or quinoxalinyl;

$R_1$ and $R_6$ of the formula (Ia) or formula (Ib) form a monocyclic 5, 6 or 7 membered aromatic or nonaromatic heterocyclic ring optionally substituted by $R_7$;

or a bicyclic ring having one 5, 6 or 7 membered aromatic or nonaromatic heterocyclic ring fused to a second 5-7 membered aromatic or nonaromatic heterocyclic or carbocyclic ring wherein each ring is optionally independently substituted by one or more $R_7$;

$R_7$ and $R_8$ are independently C1-5 alkyl, C3-6 cycloalkyl, aryl, C1-5 alkoxy, aryloxy, benzyloxy each of the aforementioned are optionally halogenated or $R_x$ is halogen, hydroxy, oxo, carboxy, nitrile, nitro or $NH_2C(O)$-;

m is 0, 1 or 2 and

X is O or S.

In yet another embodiment of the invention, there are provided novel compounds of the formulas (Ia) and (Ib) as described immediately above, and wherein:

Het is piperidinyl, pyrrolidinyl, azetidinyl, azepanyl, oxepanyl, tetrahydropyranyl, tetrahydrothiopyranyl, tetrahydrofuranyl, oxetanyl, octahydro-indolizinyl, octahydro-quinolizinyl or aza-bicyclo[3.2.1]octanyl, each ring being optionally substituted with one or more $R_5$;

$R_1$ is a bond, C1-5 alkyl, C1-5 alkoxy, C3-6 cycloalkyl, aryloxy, phenyl, benzyl, naphthyl, C1-3alkylsulfonylC1-3alkyl, C3-6cycloalkylsulfonylC1-3alkyl, arylsulfonylC1-3alkyl, pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl, furanyl, thienyl, oxazolyl, thiazolyl, imidazolyl, pyridinyl, isoxazolyl, pyrimidinyl, pyrazinyl, pyridazinyl, indolyl, quinolinyl, benzofuranyl, benzthienyl, benzimidazolyl, benzthiazolyl, benzoxazolyl or amino; wherein $R_1$ is optionally substituted by one or more $R_a$;

$R_a$ is a bond, C1-3 alkyl, cyclopropyl, cyclopentyl, cyclohexyl, phenyl, naphthyl, pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl, furanyl, thienyl, oxazolyl, thiazolyl, imidazolyl, pyridinyl, pyrimidinyl, benzimidazolyl, benzthiazolyl, benzoxazolyl, C1-3 alkoxy, C1-3alkanoyl, C1-3alkanoyloxy, aryloxy, benzyloxy, C1-3 alkoxycarbonyl, aryloxycarbonyl, aroyloxy, carbamoyl wherein the nitrogen atom may be independently mono or di-substituted by C1-3 alkyl, aryl, pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl, thienyl, oxazolyl, thiazolyl, imidazolyl, pyridinyl, pyrimidinyl, benzimidazolyl or benzthiazolyl,
or $R_a$ is C1-3 alkanoylamino, aroylamino, C1-3 alkylthio wherein the sulfur atom may be oxidized to a sulfoxide or sulfone, arylthio wherein the sulfur atom may be oxidized to a sulfoxide or sulfone, ureido wherein either nitrogen atom may be independently substituted by C1-3 alkyl, aryl, pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl or piperazinyl,
or $R_a$ is C1-3 alkoxycarbonylamino, aryloxycarbonylamino, C1-3 alkylcarbamoyloxy, arylcarbamoyloxy, C1-3 alkylsulfonylamino, arylsulfonylamino, C1-3 alkylaminosulfonyl, arylaminosulfonyl, amino wherein

the nitrogen atom may be independently mono or di-substituted by C1-3 alkyl, aryl, pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl or piperazinyl, or $R_a$ is halogen, hydroxy, oxo, carboxy, cyano, nitro, carboxamide, amidino or guanidino, $R_a$ may be further optionally substituted by one or more $R_b$;

$R_b$ is C1-3 alkyl, C3-6 cycloalkyl, aryl, C1-3 alkoxy, aryloxy, benzyloxy, halogen, hydroxy, oxo, carboxy, cyano, nitro, carboxamide, amidino or guanidino;

$R_2$ is hydrogen or methyl;

$R_3$ is a bond, hydrogen, C1-5 alkyl, C2-5alkylene, C4-6 cycloalkyl or arylC1-2alkyl wherein $R_3$ is optionally substituted by one or more $R_c$;

$R_c$ is C1-4 alkyl, C5-6 cycloalkyl, phenyl, naphthyl, indanyl, bicyclo[2.2.1]heptanyl, bicyclo[2.2.2]octanyl, bicyclo[4.1.0]heptanyl, bicyclo[3.1.0]hexanyl, bicyclo[1.1.1]pentanyl, cubanyl, 1,2,3,4-tetrahydronaphthyl, pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, indolinyl, furanyl, tetrahydrofuranyl, pyranyl, tetrahydropyranyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, pyrazolyl, pyridinyl, pyrimidinyl, pyrazinyl, indolyl, benzofuranyl, benzothienyl, benzimidazolyl, benzthiazolyl, quinolinyl, isoquinolinyl, quinazolinyl, quinoxalinyl, C1-4 alkoxy, phenoxy, naphthyloxy, C1-3 alkanoyl, benzoyl, C1-3 alkoxycarbonyl, phenoxycarbonyl, C1-3 alkanoyloxy, benzoyloxy, carbamoyl wherein the nitrogen atom may be independently mono or di-substituted by C1-5 alkyl or aryl, or $R_c$ is C1-3 alkanoylamino, benzoylamino, C1-3 alkylthio wherein the sulfur atom may be oxidized to a sulfoxide or sulfone, phenylthio wherein the sulfur atom may be oxidized to a sulfoxide or sulfone, ureido wherein either nitrogen atom may be independently substituted by C1-5 alkyl or aryl, or $R_c$ is C1-3 alkoxycarbonylamino, aryloxycarbonylamino, C1-3 alkylcarbamoyloxy, arylcarbamoyloxy, C1-3 alkylsulfonylamino,

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arylsulfonylamino, C1-3 alkylaminosulfonyl, arylaminosulfonyl, amino wherein the nitrogen atom may be independently mono or di-substituted by C1-5 alkyl or aryl,

or $R_c$ is halogen, hydroxy, oxo, carboxy, cyano, nitro, amidino or guanidino, $R_c$ may be further optionally substituted by one or more $R_d$;

$R_d$ is C1-3 alkyl, C3-6 cycloalkyl, phenyl, benzyl, C1-3 alkoxy, phenoxy, phenylC1-3alkoxy, benzoyl, halogen, hydroxy, oxo or cyano;

$R_4$ is hydrogen;

$R_5$ is a bond, hydrogen, carbonyl, C1-6 alkyl, C1-6alkoxyC1-6alkyl, C1-6alkylaminoC1-6alkyl, C1-6alkylthioC1-6alkyl wherein the sulfur atom may be oxidized to a sulfoxide or sulfone, C1-6 alkoxy, , phenoxy, naphthyloxy, C3-6 cycloalkyl, phenyl, naphthyl, benzyl, indanyl, heterocyclyl selected from pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl, tetrahydropyranyl, tetrahydrothiopyranyl, furanyl, tetrahydrofuranyl, thienyl, oxazolyl, thiazolyl, imidazolyl, pyridinyl, pyrimidinyl, pyrazolyl, benzofuranyl, benzothienyl, benzimidazolyl, benzthiazolyl, quinolinyl, isoquinolinyl and benzoxazolyl, heterocyclyloxy wherein the heterocyclyl moiety is selected from those herein described in this paragraph, C1-3alkanoyl, benzoyl, naphthoyl, C1-4alkanoyloxy, benzyloxy, C1-4 alkoxycarbonyl, arylC1-2alkoxycarbonyl, phenoxycarbonyl, benzoyloxy, carbamoyl wherein the nitrogen atom may be independently mono or di-substituted by C1-3 alkyl, phenyl, pyrrolidinyl, piperidinyl, morpholinyl, piperazinyl, oxazolyl, thiazolyl, imidazolyl, pyridinyl or pyrimidinyl, or $R_5$ is C1-4 alkanoylamino, aroylamino, C1-4 alkylthio wherein the sulfur atom may be oxidized to a sulfoxide or sulfone, arylthio wherein the sulfur atom may be oxidized to a sulfoxide or sulfone, ureido wherein either nitrogen atom may be independently substituted by C1-3 alkyl, phenyl, naphthyl, pyrrolidinyl, piperidinyl, morpholinyl, piperazinyl, oxazolyl, thiazolyl, imidazolyl, pyridinyl, pyrimidinyl, pyrazinyl, indolyl, benzofuranyl, benzothienyl, benzimidazolyl or benzthiazolyl,

or $R_5$ is C1-4 alkoxycarbonylamino, phenoxycarbonylamino, C1-4 alkylcarbamoyloxy, phenylcarbamoyloxy, C1-4 alkylsulfonylamino, phenylsulfonylamino, C1-3 alkylaminosulfonyl, phenylaminosulfonyl, amino wherein the nitrogen atom may be independently mono or di-substituted by C1-4 alkyl, aryl, pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl, furanyl, thienyl, oxazolyl, thiazolyl, imidazolyl, pyridinyl, pyrimidinyl, benzimidazolyl or benzthiazolyl,
or $R_5$ is halogen, hydroxy, oxo, carboxy, cyano, nitro or carboxamide, $R_5$ may be further optionally substituted by one or more $R_6$;

$R_6$ is C1-4 alkyl, C1-4 alkoxy, C3-7 cycloalkyl, phenyl, naphthyl, indanyl, pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl, tetrahydrothiopyranyl, tetrahydropyranyl, tetrahydrofuranyl, thienyl, oxazolyl, thiazolyl, imidazolyl, pyridinyl, pyrimidinyl, pyrazinyl, indolyl, benzimidazolyl, benzthiazolyl, benzoxazolyl, quinolinyl, isoquinolinyl, quinazolinyl, quinoxalinyl, C1-4 alkanoyl, aroyl, C1-4alkanoyloxy, phenoxy, naphthyloxy, benzyloxy, C1-4 alkoxycarbonyl, phenoxycarbonyl, benzoyloxy, carbamoyl wherein the nitrogen atom may be independently mono or di-substituted by C1-3 alkyl, phenyl, naphthyl, pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl, furanyl, thienyl, oxazolyl, thiazolyl, imidazolyl, pyridinyl, pyrimidinyl, benzimidazolyl, or benzthiazolyl,
or $R_6$ is C1-4 alkanoylamino, benzoylamino, C1-4 alkylthio wherein the sulfur atom may be oxidized to a sulfoxide or sulfone, phenylthio wherein the sulfur atom may be oxidized to a sulfoxide or sulfone, ureido wherein either nitrogen atom may be independently substituted by C1-3 alkyl, phenyl, naphthyl, pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl, furanyl, thienyl, oxazolyl, thiazolyl, imidazolyl, pyridinyl, pyrimidinyl, benzimidazolyl or benzthiazolyl,
or $R_6$ is C1-4 alkoxycarbonylamino, phenoxycarbonylamino, C1-4 alkylcarbamoyloxy, phenylcarbamoyloxy, C1-4 alkylsulfonylamino, phenylsulfonylamino, C1-4 alkylaminosulfonyl, phenylaminosulfonyl, amino wherein the nitrogen atom may be independently mono or di-substituted by C1-3

alkyl, phenyl, naphthyl, pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl, furanyl, thienyl, oxazolyl, thiazolyl, imidazolyl, pyridinyl, pyrimidinyl, benzimidazolyl or benzthiazolyl,
or $R_e$ is halogen, hydroxy, oxo, carboxy, cyano, nitro or carboxamide, $R_e$ may be further optionally substituted by one or more $R_f$;

$R_f$ is methyl, ethyl, t-butyl, tolylsulfonyl, methoxy, cyclopropyl, phenyl, phenoxy, benzyloxy, fluoro, chloro, bromo, hydroxy, oxo, carboxy or carboxamide.

$R_1$ and $R_6$ of the formula (Ia) or Formula (Ib) optionally form a monocyclic 5 or 6 membered aromatic or nonaromatic heterocyclic ring optionally substituted by $R_7$;

or a bicyclic ring having one 5, 6 or 7 membered aromatic or nonaromatic heterocyclic ring fused to a second 5-6 membered aromatic or nonaromatic heterocyclic or carbocyclic ring wherein each ring is optionally independently substituted by one or more $R_7$;

$R_7$ and $R_8$ are independently C1-4 alkyl, C5-6 cycloalkyl, C1-4 alkoxy, halogen, hydroxy, oxo, carboxy, nitrile, nitro or $NH_2C(O)$-;
and
X is O.

In yet still another embodiment of the invention, there are provided novel compounds of the formulas (Ia) and (Ib) as described immediately above, and wherein:

Het is piperidinyl, pyrrolidinyl, azetidinyl, azepanyl, oxepanyl, tetrahydropyranyl, oxetanyl or tetrahydrothiopyranyl each ring being optionally substituted with one or more $R_5$;

$R_1$ is a bond, C1-5 alkyl, C1-5 alkoxy, C3-6 cycloalkyl, aryloxy, phenyl, benzyl, naphthyl, pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl, furanyl, thienyl, oxazolyl, thiazolyl, imidazolyl, pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, indolyl, quinolinyl, benzofuranyl, benzthienyl, benzimidazolyl, benzthiazolyl, benzoxazolyl or amino; wherein $R_1$ is optionally substituted by one or more $R_a$;

$R_a$ is a bond, C1-3 alkyl, cyclopropyl, cyclohexyl, phenyl, pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl, thienyl, imidazolyl, C1-3 alkoxy, C1-3alkanoyl, C1-3alkanoyloxy, aryloxy, benzyloxy, C1-3 alkoxycarbonyl, aryloxycarbonyl, aroyloxy, carbamoyl wherein the nitrogen atom may be independently mono or di-substituted by C1-3 alkyl, aryl, pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl or piperazinyl,
or $R_a$ is C1-3 alkanoylamino, aroylamino, C1-3 alkylthio wherein the sulfur atom may be oxidized to a sulfoxide or sulfone, arylthio wherein the sulfur atom may be oxidized to a sulfoxide or sulfone, ureido wherein either nitrogen atom may be independently substituted by C1-3 alkyl, aryl, pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl or piperazinyl,
or $R_a$ is C1-3 alkoxycarbonylamino, aryloxycarbonylamino, C1-3 alkylcarbamoyloxy, arylcarbamoyloxy, C1-3 alkylsulfonylamino, arylsulfonylamino, C1-3 alkylaminosulfonyl, arylaminosulfonyl, amino wherein the nitrogen atom may be independently mono or di-substituted by C1-3 alkyl, aryl, pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl or piperazinyl,
or $R_a$ is halogen, hydroxy, oxo, carboxy, cyano, nitro, carboxamide, amidino or guanidino, $R_a$ may be further optionally substituted by one or more $R_b$;

$R_b$ is methyl, ethyl, n-propyl, i-propyl, cyclopropyl, cyclopentyl, cyclohexyl, phenyl, methoxy, ethoxy, n-propoxy, i-propoxy, phenoxy, benzyloxy, fluoro, chloro, bromo, iodo, hydroxy, oxo, carboxy, cyano, nitro or carboxamide;

$R_2$ is hydrogen;

$R_3$ is a bond, C1-3 alkyl, C2-4alkylene, C5-6 cycloalkyl, benzyl or naphthylmethyl wherein $R_3$ is optionally substituted by one or more $R_c$;

$R_c$ is C1-3 alkyl, C5-6 cycloalkyl, phenyl, naphthyl, indanyl, bicyclo[2.2.1]heptanyl, bicyclo[2.2.2]octanyl, bicyclo[4.1.0]heptanyl, bicyclo[3.1.0]hexanyl, bicyclo[1.1.1]pentanyl, cubanyl, 1,2,3,4-tetrahydronaphthyl, furanyl, tetrahydropyranyl, thienyl, oxazolyl, thiazolyl, imidazolyl, pyrimidinyl, indolyl, benzofuranyl, benzothienyl, benzthiazolyl, C1-3 alkoxy, phenoxy, naphthyloxy, C1-2 alkanoyl, benzoyl, C1-2 alkoxycarbonyl, phenoxycarbonyl, C1-2alkanoyloxy, benzoyloxy, carbamoyl wherein the nitrogen atom may be independently mono or di-substituted by C1-3 alkyl or aryl, or $R_c$ is C1-2 alkanoylamino, benzoylamino, C1-2 alkylthio wherein the sulfur atom may be oxidized to a sulfoxide or sulfone, phenylthio wherein the sulfur atom may be oxidized to a sulfoxide or sulfone, ureido wherein either nitrogen atom may be independently substituted by C1-3 alkyl or aryl, or $R_c$ is C1-2 alkoxycarbonylamino, phenoxycarbonylamino, C1-2 alkylcarbamoyloxy, arylcarbamoyloxy, C1-2 alkylsulfonylamino, phenylsulfonylamino, C1-2alkylaminosulfonyl, phenylaminosulfonyl, amino wherein the nitrogen atom may be independently mono or di-substituted by C1-3 alkyl or phenyl, or $R_c$ is halogen, hydroxy, oxo, carboxy or cyano, $R_c$ may be further optionally substituted by one or more $R_d$;

$R_d$ is methyl, cyclopropyl, cyclohexyl, phenyl, benzyl, methoxy, phenoxy, benzyloxy, benzoyl, fluoro, chloro, oxo or cyano;

$R_5$ is a bond, hydrogen, carbonyl, C1-5 alkyl, C1-5alkoxyC1-5alkyl, C1-5alkylaminoC1-5alkyl, C1-5alkylthioC1-5alkyl wherein the sulfur atom may be oxidized to a sulfoxide or sulfone, C1-5 alkoxy, phenoxy, C3-6 cycloalkyl, phenyl, naphthyl, benzyl, indanyl, heterocyclyl selected from pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl,

piperazinyl, tetrahydropyranyl, oxazolyl, thiazolyl, imidazolyl, pyridinyl, pyrimidinyl, benzimidazolyl and benzthiazolyl, heterocyclyloxy wherein the heterocyclyl moiety is selected from those herein described in this paragraph, C1-3alkanoyl, benzoyl, naphthoyl, C1-3alkanoyloxy, benzyloxy, C1-3 alkoxycarbonyl, benzyloxycarbonyl, phenoxycarbonyl, benzoyloxy, carbamoyl wherein the nitrogen atom may be independently mono or di-substituted by C1-3 alkyl, phenyl, pyrrolidinyl, piperidinyl, morpholinyl, piperazinyl, oxazolyl, thiazolyl, imidazolyl, pyridinyl or pyrimidinyl, or $R_5$ is C1-3 alkanoylamino, aroylamino, C1-3 alkylthio wherein the sulfur atom may be oxidized to a sulfoxide or sulfone, phenylthio wherein the sulfur atom may be oxidized to a sulfoxide or sulfone, ureido wherein either nitrogen atom may be independently substituted by C1-3 alkyl, phenyl, pyrrolidinyl, piperidinyl, morpholinyl, piperazinyl, oxazolyl, thiazolyl, imidazolyl, pyridinyl, pyrimidinyl, benzofuranyl, benzothienyl, benzimidazolyl or benzthiazolyl, or $R_5$ is C1-3 alkoxycarbonylamino, phenoxycarbonylamino, C1-3 alkylcarbamoyloxy, phenylcarbamoyloxy, C1-3 alkylsulfonylamino, phenylsulfonylamino, C1-3 alkylaminosulfonyl, phenylaminosulfonyl, amino wherein the nitrogen atom may be independently mono or di-substituted by C1-3 alkyl, phenyl, pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl, oxazolyl, thiazolyl, imidazolyl, pyridinyl, pyrimidinyl, benzimidazolyl or benzthiazolyl, or $R_5$ is halogen, hydroxy, oxo, carboxy, cyano or carboxamide, $R_5$ may be further optionally substituted by one or more $R_e$;

$R_e$ is C1-3 alkyl, C1-3 alkoxy, C3-7 cycloalkyl, phenyl, naphthyl, indanyl, pyrrolidinyl, piperidinyl, morpholinyl, piperazinyl, tetrahydropyranyl, indolyl, thienyl, oxazolyl, thiazolyl, imidazolyl, pyridinyl, pyrimidinyl, benzimidazolyl, benzthiazolyl, benzoxazolyl, C1-3 alkanoyl, aroyl, C1-3alkanoyloxy, phenoxy, benzyloxy, C1-3 alkoxycarbonyl, phenoxycarbonyl, benzoyloxy, carbamoyl wherein the nitrogen atom may be independently mono or di-substituted by C1-3 alkyl, phenyl, pyrrolidinyl, piperidinyl, morpholinyl, piperazinyl, oxazolyl, thiazolyl, imidazolyl, pyridinyl, pyrimidinyl, benzimidazolyl or benzthiazolyl,

or $R_e$ is C1-3 alkanoylamino, benzoylamino, C1-3 alkylthio wherein the sulfur atom may be oxidized to a sulfoxide or sulfone, phenylthio wherein the sulfur atom may be oxidized to a sulfoxide or sulfone, ureido wherein either nitrogen atom may be independently substituted by C1-3 alkyl, phenyl, pyrrolidinyl, piperidinyl, morpholinyl, piperazinyl, oxazolyl, thiazolyl, imidazolyl, pyridinyl, pyrimidinyl, benzimidazolyl or benzthiazolyl,
or $R_e$ is C1-3 alkoxycarbonylamino, phenoxycarbonylamino, C1-3 alkylcarbamoyloxy, phenylcarbamoyloxy, C1-3 alkylsulfonylamino, phenylsulfonylamino, C1-3 alkylaminosulfonyl, phenylaminosulfonyl, amino wherein the nitrogen atom may be independently mono or di-substituted by C1-3 alkyl, phenyl, naphthyl, pyrrolidinyl, piperidinyl, morpholinyl, piperazinyl, oxazolyl, thiazolyl, imidazolyl, pyridinyl, pyrimidinyl, benzimidazolyl or benzthiazolyl,
or $R_e$ is halogen, hydroxy, oxo, carboxy, cyano or carboxamide, $R_e$ may be further optionally substituted by one or more $R_f$;
and

$R_f$ is methyl, phenyl, tolylsulfonyl, methoxy, phenoxy, benzyloxy, fluoro, chloro, bromo, hydroxy, oxo, carboxy or carboxamide;

$R_1$ and $R_6$ of the formula (Ia) or Formula (Ib) form a bicyclic ring having one 5 or 6 membered aromatic or nonaromatic heterocyclic ring fused to a second 5-6 membered heteroaryl, heterocycle or phenyl ring;
wherein each ring is optionally independently substituted by one or two $R_7$.

In yet a further embodiment of the invention, there are provided novel compounds of the formulas (Ia) and (Ib) as described immediately above, and wherein:

Het is piperidinyl, pyrrolidinyl, azetidinyl, azepanyl or tetrahydropyranyl each ring being substituted with one or more $R_5$;

$R_1$ is a bond, methyl, ethyl, i-propyl, methoxy, ethoxy, cyclopropyl, cyclopentyl, cyclohexyl, phenoxy, phenyl, benzyl, naphthyl, pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl, furanyl, thienyl, thiazolyl, imidazolyl, pyridinyl, pyrazinyl or amino; wherein $R_1$ is optionally substituted by one or more $R_a$;

$R_a$ is a bond, methyl, ethyl, cyclopropyl, phenyl, pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl, thienyl, imidazolyl, methoxy, acetyl, acetoxy, phenoxy, benzyloxy, methoxycarbonyl, phenoxycarbonyl, benzoyloxy, carbamoyl wherein the nitrogen atom may be independently mono or di-substituted by methyl, ethyl or phenyl,
or $R_a$ is acetylamino, benzoylamino, methylthio, phenylthio wherein the sulfur atom may be oxidized to a sulfoxide or sulfone, ureido wherein either nitrogen atom may be independently substituted by methyl, ethyl or phenyl,
or $R_a$ is methoxycarbonylamino, phenoxycarbonylamino, methylcarbamoyloxy, phenylcarbamoyloxy, methylsulfonylamino, phenylsulfonylamino, methylaminosulfonyl, phenylaminosulfonyl, amino wherein the nitrogen atom may be independently mono or di-substituted by methyl or phenyl,
or $R_a$ is fluoro, chloro, bromo, iodo, hydroxy, oxo, carboxy, cyano, nitro or carboxamide, $R_a$ may be further optionally substituted by one or more $R_b$;

$R_b$ is methyl, cyclopropyl, phenyl, methoxy, phenoxy, benzyloxy, fluoro, chloro, hydroxy, oxo, carboxy or carboxamide;

$R_3$ is a bond, C1-3 alkyl, C2-4alkylene, C5-6 cycloalkyl, benzyl or naphthylmethyl wherein $R_3$ is optionally substituted by one or more $R_c$;

$R_c$ is methyl, ethyl, n-propyl, i-propyl, C5-6 cycloalkyl, indanyl, bicyclo[2.2.1]heptanyl, bicyclo[2.2.2]octanyl, bicyclo[4.1.0]heptanyl, bicyclo[3.1.0]hexanyl, bicyclo[1.1.1]pentanyl, cubanyl, 1,2,3,4-tetrahydronaphthyl, thienyl, oxazolyl, thiazolyl, indolyl, benzofuranyl,

benzothienyl, benzthiazolyl, methoxy, ethoxy, phenoxy, acetyl, benzoyl, methoxycarbonyl, phenoxycarbonyl, acetoxy, benzoyloxy, carbamoyl wherein the nitrogen atom may be independently mono or di-substituted by methyl, ethyl or aryl,

or $R_c$ is acetylamino, benzoylamino, methylthio wherein the sulfur atom may be oxidized to a sulfoxide or sulfone, phenylthio wherein the sulfur atom may be oxidized to a sulfoxide or sulfone, ureido wherein either nitrogen atom may be independently substituted by methyl, ethyl or aryl,

or $R_c$ is methoxycarbonylamino, phenoxycarbonylamino, methylcarbamoyloxy, phenylcarbamoyloxy, methylsulfonylamino, phenylsulfonylamino, methylaminosulfonyl, phenylaminosulfonyl, amino wherein the nitrogen atom may be independently mono or di-substituted by methyl, ethyl or phenyl,

or $R_c$ is fluoro, chloro or oxo, $R_c$ may be further optionally substituted by one or more $R_d$;

$R_d$ is methyl, cyclopropyl, phenyl, methoxy, fluoro, chloro or oxo;

$R_5$ is a bond, hydrogen, carbonyl, C1-4 alkyl, C1-4alkoxyC1-4alkyl, C1-4alkylaminoC1-4alkyl, C1-4alkylthioC1-4alkyl wherein the sulfur atom may be oxidized to a sulfoxide or sulfone, C1-4 alkoxy,phenoxy, cyclopropyl, cyclopentyl, cyclohexyl, phenyl, naphthyl, benzyl, indanyl, heterocyclyl selected from pyrrolidinyl, piperidinyl, morpholinyl, piperazinyl, tetrahydropyranyl, oxazolyl, thiazolyl, imidazolyl, pyridinyl, pyrimidinyl, benzimidazolyl and benzthiazolyl, heterocyclyloxy wherein the heterocyclyl moiety is selected from those herein described in this paragraph, C1-2alkanoyl, benzoyl, naphthoyl, C1-2alkanoyloxy, benzyloxy, C1-2 alkoxycarbonyl, benzyloxycarbonyl, phenoxycarbonyl, benzoyloxy, carbamoyl wherein the nitrogen atom may be independently mono or di-substituted by C1-2 alkyl, phenyl, pyrrolidinyl, piperidinyl, morpholinyl, piperazinyl, oxazolyl, thiazolyl, imidazolyl, pyridinyl or pyrimidinyl,

or $R_5$ is C1-2 alkanoylamino, benzoylamino, C1-2 alkylthio wherein the sulfur atom may be oxidized to a sulfoxide or sulfone, phenylthio wherein the sulfur atom may be oxidized to a sulfoxide or sulfone, ureido wherein either nitrogen atom may be

independently substituted by C1-2 alkyl, phenyl, pyrrolidinyl, piperidinyl, morpholinyl, piperazinyl, oxazolyl, thiazolyl, imidazolyl, pyridinyl, pyrimidinyl, benzimidazolyl or benzthiazolyl,

or $R_5$ is C1-2 alkoxycarbonylamino, phenoxycarbonylamino, C1-2 alkylcarbamoyloxy, phenylcarbamoyloxy, C1-2 alkylsulfonylamino, phenylsulfonylamino, C1-2 alkylaminosulfonyl, phenylaminosulfonyl, amino wherein the nitrogen atom may be independently mono or di-substituted by C1-2 alkyl, phenyl, pyrrolidinyl, piperidinyl, morpholinyl, piperazinyl, oxazolyl, thiazolyl, imidazolyl, pyridinyl or pyrimidinyl,

or $R_5$ is fluoro, chloro, bromo, hydroxy, oxo, carboxy or carboxamide, $R_5$ may be further optionally substituted by one or more $R_6$;

$R_6$ is C1-3 alkyl, C1-2 alkoxy, C3-6 cycloalkyl, phenyl, naphthyl, indanyl, pyrrolidinyl, piperidinyl, morpholinyl, piperazinyl, tetrahydropyranyl, indolyl, thienyl, oxazolyl, thiazolyl, imidazolyl, pyridinyl, pyrimidinyl, benzimidazolyl, benzthiazolyl, benzoxazolyl, C1-2 alkanoyl, aroyl, C1-2alkanoyloxy, phenoxy, benzyloxy, C1-2 alkoxycarbonyl, phenoxycarbonyl, benzoyloxy, carbamoyl wherein the nitrogen atom may be independently mono or di-substituted by C1-2 alkyl, phenyl, pyrrolidinyl, piperidinyl, morpholinyl, piperazinyl, oxazolyl, thiazolyl, imidazolyl, pyridinyl or pyrimidinyl,

or $R_6$ is C1-2 alkanoylamino, benzoylamino, C1-2 alkylthio wherein the sulfur atom may be oxidized to a sulfoxide or sulfone, phenylthio wherein the sulfur atom may be oxidized to a sulfoxide or sulfone, ureido wherein either nitrogen atom may be independently substituted by C1-2 alkyl, phenyl, pyrrolidinyl, piperidinyl, morpholinyl, piperazinyl, oxazolyl, thiazolyl, imidazolyl, pyridinyl or pyrimidinyl,

or $R_6$ is C1-2 alkoxycarbonylamino, phenoxycarbonylamino, C1-2 alkylcarbamoyloxy, phenylcarbamoyloxy, C1-2 alkylsulfonylamino, phenylsulfonylamino, C1-2 alkylaminosulfonyl, phenylaminosulfonyl, amino wherein the nitrogen atom may be independently mono or di-substituted by C1-2 alkyl, phenyl, naphthyl, pyrrolidinyl, piperidinyl, morpholinyl, piperazinyl, oxazolyl, thiazolyl, imidazolyl, pyridinyl or pyrimidinyl,

or $R_e$ is fluoro, chloro, bromo, hydroxy, oxo, carboxy or carboxamide, $R_e$ may be further optionally substituted by one or more $R_f$;

$R_f$ is methyl, phenyl, tolylsulfonyl, methoxy, phenoxy, benzyloxy, fluoro, chloro, hydroxy, oxo, carboxy or carboxamide and

$R_1$ and $R_6$ of the formula (Ia) or Formula (Ib) form a bicyclic ring having one 5-6 membered aromatic or nonaromatic heterocyclic ring fused to a phenyl ring; wherein each ring is optionally independently substituted by one or two $R_7$.

In yet still a further embodiment of the invention, there are provided novel compounds of the formula (Ia) or formula (Ib) as described immediately above, and wherein:

Het is piperidin-4-yl, piperidin-3-yl, pyrrolidin-3-yl, azetidin-3-yl, azepan-3-yl, azepan-4-yl or tetrahydropyran-4-yl, each ring being optionally substituted with one or more $R_5$;

$R_1$ is a bond, methyl, ethyl, i-propyl, methoxy, cyclopropyl, cyclohexyl, phenoxy, phenyl, benzyl, naphthyl, pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl, furanyl, thienyl, thiazolyl, imidazolyl, pyridinyl, pyrazinyl or amino; wherein $R_1$ is optionally substituted by one or more $R_a$;

$R_a$ is methyl, phenyl, thienyl, methoxy, acetyl, acetoxy, phenoxy, benzyloxy, methoxycarbonyl, benzoyloxy, carbamoyl wherein the nitrogen atom may be independently mono or di-substituted by methyl or phenyl,
or $R_a$ is acetylamino, methylthio, phenylthio wherein the sulfur atom may be oxidized to a sulfoxide or sulfone, ureido wherein either nitrogen atom may be independently substituted by methyl or phenyl,

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or $R_a$ is methoxycarbonylamino, methylcarbamoyloxy, phenylcarbamoyloxy, methylsulfonylamino, phenylsulfonylamino, amino wherein the nitrogen atom may be independently mono or di-substituted by methyl or phenyl, or $R_a$ is fluoro, chloro, hydroxy, oxo, carboxy, cyano or carboxamide;

$R_3$ is a bond, methyl, ethyl, n-propyl, propenyl, butenyl, i-butenyl, cyclohexyl, benzyl or naphthylmethyl wherein $R_3$ is optionally substituted by one or more $R_c$;

$R_c$ is methyl, ethyl, n-propyl, i-propyl, cyclohexyl, cyclopentyl, indanyl, bicyclo[2.2.1]heptanyl, bicyclo[2.2.2]octanyl, bicyclo[4.1.0]heptanyl, bicyclo[3.1.0]hexanyl, bicyclo[1.1.1]pentanyl, cubanyl, 1,2,3,4-tetrahydronaphthyl, methoxy, phenoxy, acetyl, benzoyl, methoxycarbonyl, phenoxycarbonyl, acetoxy, benzoyloxy, methylthio wherein the sulfur atom may be oxidized to a sulfoxide or sulfone, phenylthio wherein the sulfur atom may be oxidized to a sulfoxide or sulfone, fluoro, chloro or oxo;

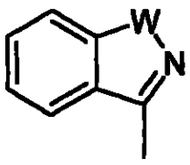
$R_5$ is a bond, hydrogen, carbonyl, C1-4 alkyl, C1-2alkoxyC1-2alkyl, C1-2alkylaminoC1-2alkyl, C1-2alkylthioC1-2alkyl wherein the sulfur atom may be oxidized to a sulfoxide or sulfone, C1-2 alkoxy, phenoxy, cyclopropyl, cyclopentyl, cyclohexyl, phenyl, benzyl, heterocyclyl selected from pyrrolidinyl, piperidinyl, morpholinyl, tetrahydropyranyl, pyridinyl, and pyrimidinyl, heterocyclyloxy wherein the heterocyclyl moiety is selected from those herein described in this paragraph, acetyl, benzoyl, acetyloxy, benzyloxy, methoxycarbonyl, ethoxycarbonyl, benzyloxycarbonyl, benzoyloxy, carbamoyl wherein the nitrogen atom may be independently mono or di-substituted by methyl, ethyl or phenyl,
or $R_5$ is acetylamino, benzoylamino, methylthio wherein the sulfur atom may be oxidized to a sulfoxide or sulfone, phenylthio wherein the sulfur atom may be oxidized to a sulfoxide or sulfone, ureido wherein either nitrogen atom may be independently substituted by methyl, ethyl or phenyl,
or $R_5$ is methoxycarbonylamino, ethoxycarbonylamino, phenoxycarbonylamino, methylcarbamoyloxy, phenylcarbamoyloxy, methylsulfonylamino, phenylsulfonylamino,

methylaminosulfonyl, phenylaminosulfonyl, amino wherein the nitrogen atom may be independently mono or di-substituted by methyl, ethyl or phenyl,
or $R_5$ is fluoro, chloro, hydroxy, oxo, carboxy or carboxamide, $R_5$ may be further optionally substituted by one or more $R_e$;

$R_e$ is methyl, methoxy, ethoxy, cyclopropyl, cyclopentyl, cyclohexyl, phenyl; naphthyl, indanyl, piperidinyl, morpholinyl, indolyl, thienyl, pyridinyl, acetyl, benzoyl, acetyloxy, phenoxy, benzyloxy, methoxycarbonyl, ethoxycarbonyl, carbamoyl wherein the nitrogen atom may be independently mono or di-substituted by methyl, ethyl or phenyl,
or $R_e$ is acetylamino, benzoylamino, methylthio wherein the sulfur atom may be oxidized to a sulfoxide or sulfone, phenylthio wherein the sulfur atom may be oxidized to a sulfoxide or sulfone, ureido wherein either nitrogen atom may be independently substituted by methyl, ethyl or phenyl,
or $R_e$ is methoxycarbonylamino, ethoxycarbonylamino, phenoxycarbonylamino, methylcarbamoyloxy, phenylcarbamoyloxy, methylsulfonylamino, phenylsulfonylamino, methylaminosulfonyl, phenylaminosulfonyl, amino wherein the nitrogen atom may be independently mono or di-substituted by methyl, ethyl or phenyl,
or $R_e$ is fluoro, chloro, hydroxy, oxo, carboxy or carboxamide, $R_e$ may be further optionally substituted by one or more $R_f$;
and

$R_f$ is methyl, phenyl, tolylsulfonyl, phenoxy, benzyloxy, fluoro, chloro or oxo;

$R_1$ and $R_6$ of the formula (Ia) or Formula (Ib) form the bicyclic ring



; wherein W is $-S(O)_n-$, -O-C(O)- or -N-C(O)-, n is 0, 1 or 2 and wherein each ring is optionally independently substituted by one or two $R_7$.

In a further embodiment of the invention, there are provided novel compounds of the formulas (Ia) and (Ib) as described immediately above, and wherein:

Het is piperidin-4-yl, piperidin-3-yl, pyrrolidin-3-yl, azetidin-3-yl or tetrahydropyran-4-yl, each ring being substituted with one or more $R_5$;

$R_1$ is i-propyl, benzyloxy, cyclohexyl, phenyl, 4-(acetylamino)-phenyl, 4-(methanesulfonylamino)-phenyl, 4-methoxyphenyl, 3-phenoxyphenyl, 4-chlorophenyl, 4-fluorophenyl, 2-fluorophenyl, 2-fluoro-4-chlorophenyl, naphthyl, thienylmethyl, piperidinyl, morpholinyl, pyrrolidinyl, piperazinyl, furanyl, thienyl, 5-chlorothienyl, pyridin-4-yl, pyrazinyl, methylamino, ethylamino, dimethylamino or diethylamino;

$R_3$ is ethyl, n-propyl,propenyl, butenyl, i-butenyl, benzyl or naphthylmethyl wherein $R_3$ is optionally substituted by one or more $R_6$;

$R_6$ is methyl, cyclohexyl, cyclopentyl, indanyl, 1,2,3,4-tetrahydronaphthyl, methoxy, methylthio wherein the sulfur atom may be oxidized to a sulfoxide or sulfone, fluoro or chloro;

$R_5$ is a bond, carbonyl, methyl, ethyl, n-propyl, n-butyl, t-butyl, i-propyl, i-butyl, cyclopropyl, cyclopentyl, cyclohexyl, phenyl, benzyl, piperidinyl, tetrahydropyranyl, pyrimidinyl, acetyl, benzoyl, ethoxycarbonyl, benzyloxycarbonyl, methylsulfonylamino, phenylsulfonylamino, methylamino, dimethylamino, fluoro, oxo or carboxy, $R_5$ may be further optionally substituted by one or more $R_6$;

$R_e$ is methyl, cyclopropyl, cyclopentyl, cyclohexyl, phenyl, naphthyl, indanyl, thienyl, 5-methylthienyl, methoxy, phenoxy, benzyloxy, piperidinyl, pyridinyl, indolyl, 1-(tolyl-sulfonyl)-indolyl, carbamoyl wherein the nitrogen atom may be independently mono or di-substituted by methyl, phenyl or benzyl, or $R_e$ is hydroxy, fluoro, chloro, oxo, dimethylamino or trifluoromethyl;

and

n is 2.

In another embodiment of the invention, there are provided novel compounds of the formulas (Ia) and (Ib) as described for the broadest generic aspect above and wherein:

$R_1$ and $R_6$ remain acyclic,

Het is piperidinyl, pyrrolidinyl, azetidinyl, azepanyl, oxepanyl, tetrahydropyranyl, oxetanyl or tetrahydrothiopyranyl each ring being optionally substituted with one or more $R_5$;

$R_1$ is a bond, C1-5 alkyl, C1-5 alkoxy, C3-6 cycloalkyl, aryloxy, phenyl, benzyl, naphthyl, pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl, furanyl, thienyl, oxazolyl, thiazolyl, imidazolyl, pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, indolyl, quinolinyl, benzofuranyl, benzthienyl, benzimidazolyl, benzthiazolyl, benzoxazolyl or amino; wherein $R_1$ is optionally substituted by one or more $R_4$;

$R_4$ is a bond, C1-3 alkyl, cyclopropyl, cyclohexyl, phenyl, pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl, thienyl, imidazolyl, C1-3 alkoxy, C1-3alkanoyl, C1-3alkanoyloxy, aryloxy, benzyloxy, C1-3 alkoxycarbonyl, aryloxycarbonyl, aroyloxy, carbamoyl wherein the nitrogen atom

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may be independently mono or di-substituted by C1-3 alkyl, aryl, pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl or piperazinyl,
or $R_a$ is C1-3 alkanoylamino, aroylamino, C1-3 alkylthio wherein the sulfur atom may be oxidized to a sulfoxide or sulfone, arylthio wherein the sulfur atom may be oxidized to a sulfoxide or sulfone, ureido wherein either nitrogen atom may be independently substituted by C1-3 alkyl, aryl, pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl or piperazinyl,
or $R_a$ is C1-3 alkoxycarbonylamino, aryloxycarbonylamino, C1-3 alkylcarbamoyloxy, arylcarbamoyloxy, C1-3 alkylsulfonylamino, arylsulfonylamino, C1-3 alkylaminosulfonyl, arylaminosulfonyl, amino wherein the nitrogen atom may be independently mono or di-substituted by C1-3 alkyl, aryl, pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl or piperazinyl,
or $R_a$ is halogen, hydroxy, oxo, carboxy, cyano, nitro, carboxamide, amidino or guanidino, $R_a$ may be further optionally substituted by one or more $R_b$;

$R_b$ is methyl, ethyl, n-propyl, i-propyl, cyclopropyl, cyclopentyl, cyclohexyl, phenyl, methoxy, ethoxy, n-propoxy, i-propoxy, phenoxy, benzyloxy, fluoro, chloro, bromo, iodo, hydroxy, oxo, carboxy, cyano, nitro or carboxamide;

$R_2$ is hydrogen;

$R_3$ is a bond, C1-3 alkyl, C2-4alkylene, C5-6 cycloalkyl, benzyl or naphthylmethyl wherein $R_3$ is optionally substituted by one or more $R_c$;

$R_c$ is C1-3 alkyl, C5-6 cycloalkyl, phenyl, naphthyl, indanyl, bicyclo[2.2.1]heptanyl, bicyclo[2.2.2]octanyl, bicyclo[4.1.0]heptanyl, bicyclo[3.1.0]hexanyl, bicyclo[1.1.1]pentanyl, cubanyl, 1,2,3,4-tetrahydronaphthyl, furanyl, tetrahydropyranyl, thienyl, oxazolyl, thiazolyl, imidazolyl, pyrimidinyl, indolyl, benzofuranyl, benzothienyl, benzthiazolyl, C1-3 alkoxy, phenoxy, naphthyloxy, C1-2 alkanoyl, benzoyl, C1-2 alkoxycarbonyl,

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phenoxycarbonyl, C1-2alkanoyloxy, benzoyloxy, carbamoyl wherein the nitrogen atom may be independently mono or di-substituted by C1-3 alkyl or aryl, or $R_c$ is C1-2 alkanoylamino, benzoylamino, C1-2 alkylthio wherein the sulfur atom may be oxidized to a sulfoxide or sulfone, phenylthio wherein the sulfur atom may be oxidized to a sulfoxide or sulfone, ureido wherein either nitrogen atom may be independently substituted by C1-3 alkyl or aryl, or $R_c$ is C1-2 alkoxycarbonylamino, phenoxycarbonylamino, C1-2 alkylcarbamoyloxy, arylcarbamoyloxy, C1-2 alkylsulfonylamino, phenylsulfonylamino, C1-2alkylaminosulfonyl, phenylaminosulfonyl, amino wherein the nitrogen atom may be independently mono or di-substituted by C1-3 alkyl or phenyl, or $R_c$ is halogen, hydroxy, oxo, carboxy or cyano, $R_c$ may be further optionally substituted by one or more $R_d$;

$R_d$ is methyl, cyclopropyl, cyclohexyl, phenyl, benzyl, methoxy, phenoxy, benzyloxy, benzoyl, fluoro, chloro, oxo or cyano;

$R_4$ is hydrogen;

$R_5$ is a bond, hydrogen, carbonyl, C1-5 alkyl, C1-5alkoxyC1-5alkyl, C1-5alkylaminoC1-5alkyl, C1-5alkylthioC1-5alkyl wherein the sulfur atom may be oxidized to a sulfoxide or sulfone, C1-5 alkoxy, phenoxy, C3-6 cycloalkyl, phenyl, naphthyl, benzyl, indanyl, heterocyclyl selected from pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl, tetrahydropyranyl, oxazolyl, thiazolyl, imidazolyl, pyridinyl, pyrimidinyl, benzimidazolyl and benzthiazolyl, heterocyclyloxy wherein the heterocyclyl moiety is selected from those herein described in this paragraph, C1-3alkanoyl, benzoyl, naphthoyl, C1-3alkanoyloxy, benzyloxy, C1-3 alkoxycarbonyl, benzyloxycarbonyl, phenoxycarbonyl, benzoyloxy, carbamoyl wherein the nitrogen atom may be independently mono or di-substituted by C1-3 alkyl, phenyl, pyrrolidinyl, piperidinyl, morpholinyl, piperazinyl, oxazolyl, thiazolyl, imidazolyl, pyridinyl or pyrimidinyl,

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or $R_5$ is C1-3 alkanoylamino, aroylamino, C1-3 alkylthio wherein the sulfur atom may be oxidized to a sulfoxide or sulfone, phenylthio wherein the sulfur atom may be oxidized to a sulfoxide or sulfone, ureido wherein either nitrogen atom may be independently substituted by C1-3 alkyl, phenyl, pyrrolidinyl, piperidinyl, morpholinyl, piperazinyl, oxazolyl, thiazolyl, imidazolyl, pyridinyl, pyrimidinyl, benzofuranyl, benzothienyl, benzimidazolyl or benzthiazolyl,

or $R_5$ is C1-3 alkoxycarbonylamino, phenoxycarbonylamino, C1-3 alkylcarbamoyloxy, phenylcarbamoyloxy, C1-3 alkylsulfonylamino, phenylsulfonylamino, C1-3 alkylaminosulfonyl, phenylaminosulfonyl, amino wherein the nitrogen atom may be independently mono or di-substituted by C1-3 alkyl, phenyl, pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl, oxazolyl, thiazolyl, imidazolyl, pyridinyl, pyrimidinyl, benzimidazolyl or benzthiazolyl,

or $R_5$ is halogen, hydroxy, oxo, carboxy, cyano or carboxamide, $R_5$ may be further optionally substituted by one or more $R_6$;

$R_6$ is C1-3 alkyl, C1-3 alkoxy, C3-7 cycloalkyl, phenyl, naphthyl, indanyl, pyrrolidinyl, piperidinyl, morpholinyl, piperazinyl, tetrahydropyranyl, indolyl, thienyl, oxazolyl, thiazolyl, imidazolyl, pyridinyl, pyrimidinyl, benzimidazolyl, benzthiazolyl, benzoxazolyl, C1-3 alkanoyl, aroyl, C1-3alkanoyloxy, phenoxy, benzyloxy, C1-3 alkoxycarbonyl, phenoxycarbonyl, benzoyloxy, carbamoyl wherein the nitrogen atom may be independently mono or di-substituted by C1-3 alkyl, phenyl, pyrrolidinyl, piperidinyl, morpholinyl, piperazinyl, oxazolyl, thiazolyl, imidazolyl, pyridinyl, pyrimidinyl, benzimidazolyl or benzthiazolyl,

or $R_6$ is C1-3 alkanoylamino, benzoylamino, C1-3 alkylthio wherein the sulfur atom may be oxidized to a sulfoxide or sulfone, phenylthio wherein the sulfur atom may be oxidized to a sulfoxide or sulfone, ureido wherein either nitrogen atom may be independently substituted by C1-3 alkyl, phenyl, pyrrolidinyl, piperidinyl, morpholinyl, piperazinyl, oxazolyl, thiazolyl, imidazolyl, pyridinyl, pyrimidinyl, benzimidazolyl or benzthiazolyl,

or $R_6$ is C1-3 alkoxycarbonylamino, phenoxycarbonylamino, C1-3 alkylcarbamoyloxy, phenylcarbamoyloxy, C1-3 alkylsulfonylamino,

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phenylsulfonylamino, C1-3 alkylaminosulfonyl, phenylaminosulfonyl, amino wherein the nitrogen atom may be independently mono or di-substituted by C1-3 alkyl, phenyl, naphthyl, pyrrolidinyl, piperidinyl, morpholinyl, piperazinyl, oxazolyl, thiazolyl, imidazolyl, pyridinyl, pyrimidinyl, benzimidazolyl or benzthiazolyl,

or $R_e$ is halogen, hydroxy, oxo, carboxy, cyano or carboxamide, $R_e$ may be further optionally substituted by one or more $R_f$;

$R_f$ is methyl, phenyl, tolylsulfonyl, methoxy, phenoxy, benzyloxy, fluoro, chloro, bromo, hydroxy, oxo, carboxy or carboxamide;

$R_6$ is

hydroxy, nitrile or

a C1-5 saturated or unsaturated branched or unbranched carbon chain optionally partially or fully halogenated wherein one or more C atoms are optionally replaced by O, NH, or $S(O)_2$ and wherein said chain is optionally independently substituted with 1-2 oxo groups, $-NH_2$, one or more C1-4 alkyl, pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl, indolinyl, pyranyl, thiopyranyl, furanyl, thienyl, pyrrolyl, oxazolyl, isoxazolyl, thiazolyl, imidazolyl, pyridinyl, pyrimidinyl, pyrazinyl, indolyl, benzofuranyl, benzothienyl, benzimidazolyl, benzthiazolyl, quinolinyl, isoquinolinyl, quinazolinyl, benzoxazolyl or quinoxalinyl;

and

X is O.

In another embodiment of the invention, there are provided novel compounds of the formula (Ia) and (Ib) as described immediately above, and wherein:

$R_1$ is a bond, methyl, ethyl, i-propyl, methoxy, ethoxy, cyclopropyl, cyclopentyl, cyclohexyl, phenoxy, phenyl, benzyl, naphthyl, pyrrolidinyl, piperidinyl, morpholinyl,

thiomorpholinyl, piperazinyl, furanyl, thienyl, thiazolyl, imidazolyl, pyridinyl, pyrazinyl or amino; wherein $R_1$ is optionally substituted by one or more $R_a$;

$R_a$ is a bond, methyl, ethyl, cyclopropyl, phenyl, pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl, thienyl, imidazolyl, methoxy, acetyl, acetoxy, phenoxy, benzyloxy, methoxycarbonyl, phenoxycarbonyl, benzoyloxy, carbamoyl wherein the nitrogen atom may be independently mono or di-substituted by methyl, ethyl or phenyl,
or $R_a$ is acetylamino, benzoylamino, methylthio, phenylthio wherein the sulfur atom may be oxidized to a sulfoxide or sulfone, ureido wherein either nitrogen atom may be independently substituted by methyl, ethyl or phenyl,
or $R_a$ is methoxycarbonylamino, phenoxycarbonylamino, methylcarbamoyloxy, phenylcarbamoyloxy, methylsulfonylamino, phenylsulfonylamino, methylaminosulfonyl, phenylaminosulfonyl, amino wherein the nitrogen atom may be independently mono or di-substituted by methyl or phenyl,
or $R_a$ is fluoro, chloro, bromo, iodo, hydroxy, oxo, carboxy, cyano, nitro or carboxamide, $R_a$ may be further optionally substituted by one or more $R_b$;

$R_b$ is methyl, cyclopropyl, phenyl, methoxy, phenoxy, benzyloxy, fluoro, chloro, hydroxy, oxo, carboxy or carboxamide;

$R_3$ is a bond, C1-3 alkyl, C2-4alkylene, C5-6 cycloalkyl, benzyl or naphthylmethyl wherein $R_3$ is optionally substituted by one or more $R_c$;

$R_c$ is methyl, ethyl, n-propyl, i-propyl, C5-6 cycloalkyl, indanyl, bicyclo[2.2.1]heptanyl, bicyclo[2.2.2]octanyl, bicyclo[4.1.0]heptanyl, bicyclo[3.1.0]hexanyl, bicyclo[1.1.1]pentanyl, cubanyl, 1,2,3,4-tetrahydronaphthyl, thienyl, oxazolyl, thiazolyl, indolyl, benzofuranyl, benzothienyl, benzthiazolyl, methoxy, ethoxy, phenoxy, acetyl, benzoyl, methoxycarbonyl, phenoxycarbonyl, acetoxy, benzoyloxy, carbamoyl wherein the nitrogen atom may be independently mono or di-substituted by methyl, ethyl or aryl,

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or $R_c$ is acetylamino, benzoylamino, methylthio wherein the sulfur atom may be oxidized to a sulfoxide or sulfone, phenylthio wherein the sulfur atom may be oxidized to a sulfoxide or sulfone, ureido wherein either nitrogen atom may be independently substituted by methyl, ethyl or aryl,

or $R_c$ is methoxycarbonylamino, phenoxycarbonylamino, methylcarbamoyloxy, phenylcarbamoyloxy, methylsulfonylamino, phenylsulfonylamino, methylaminosulfonyl, phenylaminosulfonyl, amino wherein the nitrogen atom may be independently mono or di-substituted by methyl, ethyl or phenyl,

or $R_c$ is fluoro, chloro or oxo, $R_c$ may be further optionally substituted by one or more $R_d$;

$R_d$ is methyl, cyclopropyl, phenyl, methoxy, fluoro, chloro or oxo;

$R_5$ is a bond, hydrogen, carbonyl, C1-4 alkyl, C1-4alkoxyC1-4alkyl, C1-4alkylaminoC1-4alkyl, C1-4alkylthioC1-4alkyl wherein the sulfur atom may be oxidized to a sulfoxide or sulfone, C1-4 alkoxy,phenoxy, cyclopropyl, cyclopentyl, cyclohexyl, phenyl, naphthyl, benzyl, indanyl, heterocyclyl selected from pyrrolidinyl, piperidinyl, morpholinyl, piperazinyl, tetrahydropyranyl, oxazolyl, thiazolyl, imidazolyl, pyridinyl, pyrimidinyl, benzimidazolyl and benzthiazolyl, heterocyclyloxy wherein the heterocyclyl moiety is selected from those herein described in this paragraph, C1-2alkanoyl, benzoyl, naphthoyl, C1-2alkanoyloxy, benzyloxy, C1-2 alkoxycarbonyl, benzyloxycarbonyl, phenoxycarbonyl, benzoyloxy, carbamoyl wherein the nitrogen atom may be independently mono or di-substituted by C1-2 alkyl, phenyl, pyrrolidinyl, piperidinyl, morpholinyl, piperazinyl, oxazolyl, thiazolyl, imidazolyl, pyridinyl or pyrimidinyl,

or $R_5$ is C1-2 alkanoylamino, benzoylamino, C1-2 alkylthio wherein the sulfur atom may be oxidized to a sulfoxide or sulfone, phenylthio wherein the sulfur atom may be oxidized to a sulfoxide or sulfone, ureido wherein either nitrogen atom may be independently substituted by C1-2 alkyl, phenyl, pyrrolidinyl, piperidinyl, morpholinyl, piperazinyl, oxazolyl, thiazolyl, imidazolyl, pyridinyl, pyrimidinyl, benzimidazolyl or benzthiazolyl,

or $R_5$ is C1-2 alkoxycarbonylamino, phenoxycarbonylamino, C1-2 alkylcarbamoyloxy, phenylcarbamoyloxy, C1-2 alkylsulfonylamino, phenylsulfonylamino, C1-2 alkylaminosulfonyl, phenylaminosulfonyl, amino wherein the nitrogen atom may be independently mono or di-substituted by C1-2 alkyl, phenyl, pyrrolidinyl, piperidinyl, morpholinyl, piperazinyl, oxazolyl, thiazolyl, imidazolyl, pyridinyl or pyrimidinyl, or $R_5$ is fluoro, chloro, bromo, hydroxy, oxo, carboxy or carboxamide, $R_5$ may be further optionally substituted by one or more $R_e$;

$R_e$ is C1-3 alkyl, C1-2 alkoxy, C3-6 cycloalkyl, phenyl, naphthyl, indanyl, pyrrolidinyl, piperidinyl, morpholinyl, piperazinyl, tetrahydropyranyl, indolyl, thienyl, oxazolyl, thiazolyl, imidazolyl, pyridinyl, pyrimidinyl, benzimidazolyl, benzthiazolyl, benzoxazolyl, C1-2 alkanoyl, aroyl, C1-2alkanoyloxy, phenoxy, benzyloxy, C1-2 alkoxycarbonyl, phenoxycarbonyl, benzoyloxy, carbamoyl wherein the nitrogen atom may be independently mono or di-substituted by C1-2 alkyl, phenyl, pyrrolidinyl, piperidinyl, morpholinyl, piperazinyl, oxazolyl, thiazolyl, imidazolyl, pyridinyl or pyrimidinyl,
or $R_e$ is C1-2 alkanoylamino, benzoylamino, C1-2 alkylthio wherein the sulfur atom may be oxidized to a sulfoxide or sulfone, phenylthio wherein the sulfur atom may be oxidized to a sulfoxide or sulfone, ureido wherein either nitrogen atom may be independently substituted by C1-2 alkyl, phenyl, pyrrolidinyl, piperidinyl, morpholinyl, piperazinyl, oxazolyl, thiazolyl, imidazolyl, pyridinyl or pyrimidinyl,
or $R_e$ is C1-2 alkoxycarbonylamino, phenoxycarbonylamino, C1-2 alkylcarbamoyloxy, phenylcarbamoyloxy, C1-2 alkylsulfonylamino, phenylsulfonylamino, C1-2 alkylaminosulfonyl, phenylaminosulfonyl, amino wherein the nitrogen atom may be independently mono or di-substituted by C1-2 alkyl, phenyl, naphthyl, pyrrolidinyl, piperidinyl, morpholinyl, piperazinyl, oxazolyl, thiazolyl, imidazolyl, pyridinyl or pyrimidinyl,
or $R_e$ is fluoro, chloro, bromo, hydroxy, oxo, carboxy or carboxamide, $R_e$ may be further optionally substituted by one or more $R_f$;

$R_f$ is methyl, phenyl, tolylsulfonyl, methoxy, phenoxy, benzyloxy, fluoro, chloro, hydroxy, oxo, carboxy or carboxamide and

$R_6$ is

nitrile or

a C1-5 saturated or unsaturated branched or unbranched carbon chain optionally partially or fully halogenated wherein one or more C atoms are optionally replaced by O, NH, or $S(O)_2$ and wherein said chain is optionally independently substituted with oxo, $-NH_2$, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl, pyridinyl, pyrimidinyl or pyrazinyl.

In yet another embodiment of the invention, there are provided novel compounds of the formula (Ia) or formula (Ib) as described immediately above, and wherein:

Het is piperidin-4-yl, piperidin-3-yl, pyrrolidin-3-yl, azetidin-3-yl, azepan-3-yl, azepan-4-yl or tetrahydropyran-4-yl, each ring being optionally substituted with one or more $R_5$;

$R_1$ is a bond, methyl, ethyl, i-propyl, methoxy, cyclopropyl, cyclohexyl, phenoxy, phenyl, benzyl, naphthyl, pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl, furanyl, thienyl, thiazolyl, imidazolyl, pyridinyl, pyrazinyl or amino; wherein $R_1$ is optionally substituted by one or more $R_a$;

$R_a$ is methyl, phenyl, thienyl, methoxy, acetyl, acetoxy, phenoxy, benzyloxy, methoxycarbonyl, benzoyloxy, carbamoyl wherein the nitrogen atom may be independently mono or di-substituted by methyl or phenyl,
or $R_a$ is acetylamino, methylthio, phenylthio wherein the sulfur atom may be oxidized to a sulfoxide or sulfone, ureido wherein either nitrogen atom may be independently substituted by methyl or phenyl,

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or $R_a$ is methoxycarbonylamino, methylcarbamoyloxy, phenylcarbamoyloxy, methylsulfonylamino, phenylsulfonylamino, amino wherein the nitrogen atom may be independently mono or di-substituted by methyl or phenyl,
or $R_a$ is fluoro, chloro, hydroxy, oxo, carboxy, cyano or carboxamide;

$R_3$ is a bond, methyl, ethyl, n-propyl, propenyl, butenyl, i-butenyl, cyclohexyl, benzyl or naphthylmethyl wherein $R_3$ is optionally substituted by one or more $R_c$;

$R_c$ is methyl, ethyl, n-propyl, i-propyl, cyclohexyl, cyclopentyl, indanyl, bicyclo[2.2.1]heptanyl, bicyclo[2.2.2]octanyl, bicyclo[4.1.0]heptanyl, bicyclo[3.1.0]hexanyl, bicyclo[1.1.1]pentanyl, cubanyl, 1,2,3,4-tetrahydronaphthyl, methoxy, phenoxy, acetyl, benzoyl, methoxycarbonyl, phenoxycarbonyl, acetoxy, benzoyloxy, methylthio wherein the sulfur atom may be oxidized to a sulfoxide or sulfone, phenylthio wherein the sulfur atom may be oxidized to a sulfoxide or sulfone, fluoro, chloro or oxo;

and

wherein the configuration at the stereocenter defined by $R_2$ and $R_3$ when they are different and the carbon they are attached to is defined as L; and

$R_5$ is a bond, hydrogen, carbonyl, C1-4 alkyl, C1-2alkoxyC1-2alkyl, C1-2alkylaminoC1-2alkyl, C1-2alkylthioC1-2alkyl wherein the sulfur atom may be oxidized to a sulfoxide or sulfone, C1-2 alkoxy, phenoxy, cyclopropyl, cyclopentyl, cyclohexyl, phenyl, benzyl, heterocyclyl selected from pyrrolidinyl, piperidinyl, morpholinyl, tetrahydropyranyl, pyridinyl, and pyrimidinyl, heterocyclyloxy wherein the heterocyclyl moiety is selected from those herein described in this paragraph, acetyl, benzoyl, acetyloxy, benzyloxy, methoxycarbonyl, ethoxycarbonyl, benzyloxycarbonyl, benzoyloxy, carbamoyl wherein the nitrogen atom may be independently mono or di-substituted by methyl, ethyl or phenyl,
or $R_5$ is acetylamino, benzoylamino, methylthio wherein the sulfur atom may be oxidized to a sulfoxide or sulfone, phenylthio wherein the sulfur atom may be oxidized to a

sulfoxide or sulfone, ureido wherein either nitrogen atom may be independently substituted by methyl, ethyl or phenyl,
or $R_5$ is methoxycarbonylamino, ethoxycarbonylamino, phenoxycarbonylamino, methylcarbamoyloxy, phenylcarbamoyloxy, methylsulfonylamino, phenylsulfonylamino, methylaminosulfonyl, phenylaminosulfonyl, amino wherein the nitrogen atom may be independently mono or di-substituted by methyl, ethyl or phenyl,
or $R_5$ is fluoro, chloro, hydroxy, oxo, carboxy or carboxamide, $R_5$ may be further optionally substituted by one or more $R_e$;

$R_e$ is methyl, methoxy, ethoxy, cyclopropyl, cyclopentyl, cyclohexyl, phenyl, naphthyl, indanyl, piperidinyl, morpholinyl, indolyl, thienyl, pyridinyl, acetyl, benzoyl, acetyloxy, phenoxy, benzyloxy, methoxycarbonyl, ethoxycarbonyl, carbamoyl wherein the nitrogen atom may be independently mono or di-substituted by methyl, ethyl or phenyl,
or $R_e$ is acetylamino, benzoylamino, methylthio wherein the sulfur atom may be oxidized to a sulfoxide or sulfone, phenylthio wherein the sulfur atom may be oxidized to a sulfoxide or sulfone, ureido wherein either nitrogen atom may be independently substituted by methyl, ethyl or phenyl,
or $R_e$ is methoxycarbonylamino, ethoxycarbonylamino, phenoxycarbonylamino, methylcarbamoyloxy, phenylcarbamoyloxy, methylsulfonylamino, phenylsulfonylamino, methylaminosulfonyl, phenylaminosulfonyl, amino wherein the nitrogen atom may be independently mono or di-substituted by methyl, ethyl or phenyl,
or $R_e$ is fluoro, chloro, hydroxy, oxo, carboxy or carboxamide, $R_e$ may be further optionally substituted by one or more $R_f$;

$R_f$ is methyl, phenyl, tolylsulfonyl, phenoxy, benzyloxy, fluoro, chloro or oxo;

$R_6$ is
nitrile or
a C1-5 saturated or unsaturated branched or unbranched carbon chain optionally partially or fully halogenated wherein one or more C atoms are optionally replaced by O, NH, or

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$S(O)_2$ and wherein said chain is optionally independently substituted with oxo, $-NH_2$, morpholinyl or piperazinyl.

In yet still another embodiment of the invention, there are provided novel compounds of the formulas (Ia) and (Ib) as described immediately above, and wherein:

Het is piperidin-4-yl, piperidin-3-yl, pyrrolidin-3-yl, azetidin-3-yl or tetrahydropyran-4-yl, each ring being substituted with one or more $R_5$;

$R_1$ is i-propyl, benzyloxy, cyclohexyl, phenyl, 4-(acetylamino)-phenyl, 4-(methanesulfonylamino)-phenyl, 4-methoxyphenyl, 3-phenoxyphenyl, 4-chlorophenyl, 4-fluorophenyl, 2-fluorophenyl, 2-fluoro-4-chlorophenyl, naphthyl, thienylmethyl, piperidinyl, morpholinyl, pyrrolidinyl, piperazinyl, furanyl, thienyl, 5-chlorothienyl, pyridin-4-yl, pyrazinyl, methylamino, ethylamino, dimethylamino or diethylamino;

$R_3$ is ethyl, n-propyl,propenyl, butenyl, i-butenyl, benzyl or naphthylmethyl wherein $R_3$ is optionally substituted by one or more $R_c$;

$R_c$ is methyl, cyclohexyl, cyclopentyl, indanyl, 1,2,3,4-tetrahydronaphthyl, methoxy, methylthio wherein the sulfur atom may be oxidized to a sulfoxide or sulfone, fluoro or chloro;

$R_5$ is a bond, carbonyl, methyl, ethyl, n-propyl, n-butyl, t-butyl, i-propyl, i-butyl, cyclopropyl, cyclopentyl, cyclohexyl, phenyl, benzyl, piperidinyl, tetrahydropyranyl, pyrimidinyl, acetyl, benzoyl, ethoxycarbonyl, benzyloxycarbonyl, methylsulfonylamino, phenylsulfonylamino, methylamino, dimethylamino, fluoro, oxo or carboxy, $R_5$ may be further optionally substituted by one or more $R_e$;

$R_e$ is methyl, cyclopropyl, cyclopentyl, cyclohexyl, phenyl, naphthyl, indanyl, thienyl, 5-methylthienyl, methoxy, phenoxy, benzyloxy, piperidinyl, pyridinyl,

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indolyl, 1-(tolyl-sulfonyl)-indolyl, carbamoyl wherein the nitrogen atom may be independently mono or di-substituted by methyl, phenyl or benzyl,
or $R_6$ is hydroxy, fluoro, chloro, oxo, dimethylamino or trifluoromethyl;

and

$R_6$ is acetyl, C1-3alkylaminocarbonyl or C1-3alkoxycarbonyl.

In yet a further embodiment of the invention, there are provided novel compounds of the formulas (Ia) and (Ib) as described immediately above, and wherein:

Het is piperidin-4-yl or pyrrolidin-3-yl;

$R_1$ is morpholin-4-yl, p-fluorophenyl or p-methoxyphenyl;

$R_5$ is methyl, propyl, n-pentyl or cyclohexyl
and

$R_6$ is acetyl, ethylaminocarbonyl or ethoxycarbonyl.

The activity of particular compounds disclosed herein against cathepsin K may be determined without undue experimentation by one of ordinary skill in the art in view of the art, the guidance provided throughout this specification and by the screens described in the section entitled "Assessment of Biological Properties."

The following subgeneric aspect of the compounds of the formulas (Ia) and (Ib) is postulated to possess Cathepsin K activity:

The broadest embodiment of the formula (Ia) and (Ib) as described hereinabove and wherein

Het is piperidinyl, pyrrolidinyl, azetidinyl, azepanyl, oxepanyl, tetrahydropyranyl, oxetanyl or tetrahydrothiopyranyl each ring being optionally substituted with one or more $R_5$;

$R_1$ is a bond, C1-4 alkyl, C1-4 alkoxy, cyclopropyl, cyclohexyl, phenoxy, naphthyloxy, phenyl, benzyl, naphthyl, pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl, furanyl, thienyl, oxazolyl, thiazolyl, imidazolyl, pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, indolyl, quinolinyl, benzofuranyl, benzthienyl, benzimidazolyl, benzthiazolyl, benzoxazolyl or amino; wherein $R_1$ is optionally substituted by one or more $R_a$;

$R_a$ is methyl, ethyl, propyl, i-propyl, cyclopropyl, cyclohexyl, phenyl, pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl, thienyl, imidazolyl, methoxy, ethoxy, acetyl, acetoxy, phenoxy, naphthyloxy, benzyloxy, methoxycarbonyl, ethoxycarbonyl, phenoxycarbonyl, naphthyloxycarbonyl, benzoyloxy, carbamoyl wherein the nitrogen atom may be independently mono or di-substituted by methyl, ethyl, phenyl, naphthyl, pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl or piperazinyl,
or $R_a$ is acetylamino, benzoylamino, methylthio wherein the sulfur atom may be oxidized to a sulfoxide or sulfone, ethylthio wherein the sulfur atom may be oxidized to a sulfoxide or sulfone, phenylthio wherein the sulfur atom may be oxidized to a sulfoxide or sulfone, ureido wherein either nitrogen atom may be independently substituted by methyl, ethyl, phenyl, naphthyl, pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl or piperazinyl,
or $R_a$ is methoxycarbonylamino, ethoxycarbonylamino, phenoxycarbonylamino, C1-2 alkylcarbamoyloxy, phenylcarbamoyloxy, naphthylcarbamoyloxy, C1-2 alkylsulfonylamino, phenylsulfonylamino, naphthylsulfonylamino, C1-2 alkylaminosulfonyl, phenylaminosulfonyl, naphthylaminosulfonyl, amino wherein the nitrogen atom may be independently mono or di-substituted by methyl, ethyl, phenyl, naphthyl, pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl or piperazinyl,

or $R_a$ is halogen, hydroxy, oxo, carboxy, cyano, nitro, carboxamide, amidino or guanidino, $R_a$ may be further optionally substituted by one or more $R_b$;

$R_b$ is methyl, ethyl, cyclopropyl, cyclohexyl, phenyl, methoxy, ethoxy, phenoxy, benzyloxy, fluoro, chloro, bromo, hydroxy, oxo, carboxy, cyano, nitro or carboxamide;

$R_2$ is hydrogen or methyl;

$R_3$ is a bond, methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, n-pentyl, propenyl, i-butenyl, cyclohexyl, benzyl or naphthylmethyl wherein $R_3$ is optionally substituted by one or more $R_c$;

$R_c$ is methyl, ethyl, cyclohexyl, cyclopentyl, phenyl, naphthyl, bicyclo[3.1.0]hexanyl, bicyclo[1.1.1]pentanyl, cubanyl, furanyl, tetrahydropyranyl, thienyl, oxazolyl, thiazolyl, imidazolyl, pyrimidinyl, methoxy, ethoxy, phenoxy, acetyl, benzoyl, methoxycarbonyl, phenoxycarbonyl, acetoxy, benzoyloxy, carbamoyl wherein the nitrogen atom may be independently mono or di-substituted by methyl or phenyl,
or $R_c$ is acetylamino, benzoylamino, methylthio wherein the sulfur atom may be oxidized to a sulfoxide or sulfone, phenylthio wherein the sulfur atom may be oxidized to a sulfoxide or sulfone, ureido wherein either nitrogen atom may be independently substituted by methyl or phenyl,
or $R_c$ is methoxycarbonylamino, phenoxycarbonylamino, methylcarbamoyloxy, phenylcarbamoyloxy, methylsulfonylamino, phenylsulfonylamino, methylaminosulfonyl, phenylaminosulfonyl, amino wherein the nitrogen atom may be independently mono or di-substituted by methyl or phenyl,
or $R_c$ is chloro, fluoro, hydroxy, oxo, carboxy or cyano;

$R_2$ and $R_3$ together with the carbon they are attached optionally form a ring selected from cyclopentyl, cyclohexyl, cycloheptyl, tetrahydropyranyl, tetrahydrothiopyranyl,

tetrahydrofuranyl, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl or tetrahydrothiophenyl;

$R_4$ is hydrogen;

$R_5$ is a bond, hydrogen, carbonyl, C1-5 alkyl, C1-5alkoxyC1-5alkyl, C1-5alkylaminoC1-5alkyl, C1-5alkylthioC1-5alkyl wherein the sulfur atom may be oxidized to a sulfoxide or sulfone, C1-5 alkoxy, phenoxy, naphthyloxy, cyclopropyl, cyclopentyl, cyclohexyl, phenyl, benzyl, heterocyclyl selected from pyrrolidinyl, piperidinyl, morpholinyl, tetrahydropyranyl, pyridinyl, and pyrimidinyl, heterocyclyloxy wherein the heterocyclyl moiety is selected from those herein described in this paragraph, acetyl, benzoyl, acetyloxy, benzyloxy, methoxycarbonyl, ethoxycarbonyl, benzyloxycarbonyl, benzoyloxy, carbamoyl wherein the nitrogen atom may be independently mono or di-substituted by methyl, ethyl or phenyl,
or $R_5$ is acetylamino, benzoylamino, phenylthio wherein the sulfur atom may be oxidized to a sulfoxide or sulfone, ureido wherein either nitrogen atom may be independently substituted by methyl, ethyl or phenyl,
or $R_5$ is methoxycarbonylamino, ethoxycarbonylamino, phenoxycarbonylamino, methylcarbamoyloxy, phenylcarbamoyloxy, phenylsulfonylamino, phenylaminosulfonyl, amino wherein the nitrogen atom may be independently mono or di-substituted by methyl, ethyl or phenyl,
or $R_5$ is fluoro, chloro, hydroxy, oxo, carboxy or carboxamide, $R_5$ may be further optionally substituted by one or more $R_6$;

$R_6$ is methyl ethyl, methoxy, ethoxy, cyclopropyl, cyclopentyl, cyclohexyl, phenyl, naphthyl, indanyl, piperidinyl, morpholinyl, indolyl, thienyl, pyridinyl, methoxy, ethoxy, acetyl, benzoyl, acetyloxy, phenoxy, benzyloxy, methoxycarbonyl, ethoxycarbonyl, carbamoyl wherein the nitrogen atom may be independently mono or di-substituted by methyl, ethyl or phenyl,
or $R_6$ is acetylamino, benzoylamino, methylthio wherein the sulfur atom may be oxidized to a sulfoxide or sulfone, phenylthio methylthio wherein the sulfur atom

may be oxidized to a sulfoxide or sulfone, ureido wherein either nitrogen atom may be independently substituted by methyl, ethyl or phenyl,
or $R_e$ is methoxycarbonylamino, ethoxycarbonylamino, phenoxycarbonylamino, methylcarbamoyloxy, phenylcarbamoyloxy, methylsulfonylamino, phenylsulfonylamino, methylaminosulfonyl, phenylaminosulfonyl, amino wherein the nitrogen atom may be independently mono or di-substituted by methyl, ethyl or phenyl,
or $R_e$ is fluoro, chloro, hydroxy, oxo, carboxy or carboxamide, $R_e$ may be further optionally substituted by one or more $R_f$;

$R_f$ is methyl, phenyl, tolylsulfonyl, phenoxy, benzyloxy, fluoro, chloro or oxo.

Preferred cathepsin K inhibitors are those as described immediately above and wherein:

$R_1$ is a bond, methyl, ethyl, n-propyl, i-propyl, methoxy, ethoxy, benzyloxy, cyclopropyl, cyclohexyl, phenoxy, naphthyloxy, phenyl, benzyl, naphthyl, pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl, furanyl, thienyl, oxazolyl, thiazolyl, imidazolyl, pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, indolyl, quinolinyl, benzofuranyl, benzthienyl, benzimidazolyl, benzthiazolyl, benzoxazolyl or amino; wherein $R_1$ is optionally substituted by one or more $R_e$;

$R_e$ is methyl, cyclopropyl, phenyl, halogen, hydroxy, oxo, carboxy, cyano, nitro or carboxamide;

$R_3$ is a bond, methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, n-pentyl, propenyl, i-butenyl, benzyl or naphthylmethyl wherein $R_3$ is optionally substituted by one or more $R_c$;

$R_c$ is methyl, ethyl, cyclohexyl, cyclopentyl, phenyl, furanyl, tetrahydropyranyl, thienyl, oxazolyl, thiazolyl, methoxy, phenoxy, acetyl, benzoyl, methoxycarbonyl,

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carbamoyl wherein the nitrogen atom may be independently mono or di-substituted by methyl or phenyl,
or $R_6$ is acetylamino, benzoylamino, methylthio, methoxycarbonylamino, methylcarbamoyloxy, methylsulfonylamino, methylaminosulfonyl, amino wherein the nitrogen atom may be independently mono or di-substituted by methyl,
or $R_6$ is fluoro or oxo;

$R_2$ and $R_3$ together with the carbon they are attached optionally form a ring selected from cyclopentyl, cyclohexyl, cycloheptyl, tetrahydropyranyl, tetrahydrothiopyranyl, tetrahydrofuranyl, pyrrolidinyl or piperidinyl;

$R_5$ is methyl, ethyl, n-propyl, n-butyl, n-pentyl, 2-pentyl, 3-pentyl, phenethyl, phenpropyl, 2,2-dimethylpropyl, t-butyl, i-propyl, i-butyl, cyclopropyl, cyclopentyl, cyclohexyl, cyclopropylmethyl, cyclopentylmethyl, cyclohexylmethyl, phenyl, benzyl, 2-methylbenzyl, 3-methylbenzyl, 4-methylbenzyl, 2,6-dimethylbenzyl, 2,5-dimethylbenzyl, 2,4-dimethylbenzyl, 2,3-dimethylbenzyl, 3,4-dimethylbenzyl, 3,5-dimethylbenzyl, 2,4,6-trimethylbenzyl, 2-methoxybenzyl, 3-methoxybenzyl, 4-methoxybenzyl, 2-phenoxybenzyl, 3-phenoxybenzyl, 4-phenoxybenzyl, 2-benzyloxybenzyl,3-benzyloxybenzyl, 4-benzyloxybenzyl, 2-fluorobenzyl, 3-fluorobenzyl, 4-fluorobenzyl, 2,6-difluorobenzyl, 2,5-difluorobenzyl, 2,4-difluorobenzyl, 2,3-difluorobenzyl, 3,4-difluorobenzyl, 3,5-difluorobenzyl, 2,4,6-triflurobenzyl, 2-trifluoromethylbenzyl, 3-trifluoromethylbenzyl, 4-trifluoromethylbenzyl, naphthylmethyl, indanylmethyl, pyridinylmethyl, indolylmethyl, thienylmethyl, 5-methylthienylmethyl, piperidinyl, piperidinylcarbonyl, pyridinylcarbonyl, tetrahydropyranyl, pyrimidinyl, acetyl, benzoyl, ethoxycarbonyl, benzyloxycarbonyl, t-butoxycarbonyl, methylcarbamoyl, phenylcarbamoyl, benzylcarbamoyl, methylsulfonylamino, phenylsulfonylamino, methylamino, dimethylamino, fluoro, oxo or carboxy.

Most preferred cathepsin K inhibitors are those as described immediately above and wherein:

$R_1$ is methoxy, benzyloxy, cyclohexyl, phenoxy, naphthyloxy, phenyl, benzyl, naphthyl, pyrrolidinyl, pipecidinyl, morpholinyl, thiomorpholinyl, piperazinyl, furanyl, thienyl, oxazolyl, thiazolyl, imidazolyl, pyridinyl, pyrimidinyl, pyrazinyl, indolyl, quinolinyl, benzofuranyl, benzthienyl, benzimidazolyl, benzthiazolyl, benzoxazolyl or amino; wherein $R_1$ is optionally substituted by one or more $R_a$;

$R_a$ is methyl, phenyl, fluoro, chloro, hydroxy, oxo, carboxy or carboxamide;

$R_3$ is a bond, methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, n-pentyl, propenyl, i-butenyl or benzyl wherein $R_3$ is optionally substituted by one or more $R_c$;

$R_c$ is methyl, ethyl, cyclohexyl, cyclopentyl, phenyl, furanyl, tetrahydropyranyl, thienyl, oxazolyl, thiazolyl, methoxy, phenoxy, acetyl, benzoyl, methoxycarbonyl, acetylamino, methylthio, methylsulfonylamino or fluoro;

$R_2$ and $R_3$ together with the carbon they are attached optionally form a ring selected from cyclopentyl, cyclohexyl, cycloheptyl, tetrahydropyranyl, tetrahydrothiopyranyl or tetrahydrofuranyl;

$R_5$ is methyl, ethyl, n-propyl, n-butyl, phenethyl, phenpropyl, t-butyl, i-propyl, i-butyl, cyclopropyl, cyclohexyl, cyclopropylmethyl, cyclohexylmethyl, phenyl, benzyl, 2-methoxybenzyl, 3-methoxybenzyl, 4-methoxybenzyl 4-fluorobenzyl, 3,5-difluorobenzyl, 4-trifluoromethylbenzyl, naphthylmethyl, pyridinylmethyl, indolylmethyl, thienylmethyl, acetyl, benzoyl, ethoxycarbonyl, benzyloxycarbonyl, t-butoxycarbonyl, phenylcarbamoyl, phenylsulfonylamino or fluoro.

Most preferred cathepsin K inhibitors are those as described immediately above and wherein:

Het is pyrrolidinyl, piperidinyl or tetrahydropyranyl;

$R_1$ is benzyloxy, phenoxy, naphthyloxy, phenyl, naphthyl, pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl, pyridinyl, indolyl, quinolinyl, benzofuranyl, benzthienyl, benzimidazolyl, benzthiazolyl, benzoxazolyl or phenylamino;

$R_3$ is n-propyl, i-butyl, propenyl, i-butenyl or 2,2-dimethylpropyl;

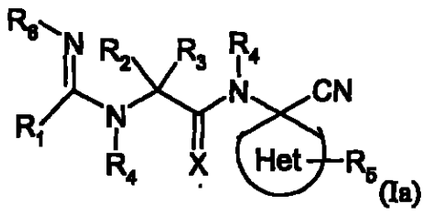
$R_2$ and $R_3$ together with the carbon they are attached optionally form a ring selected from cyclopentyl, cyclohexyl, or cycloheptyl;

$R_5$ is methyl, ethyl, n-propyl, phenethyl, t-butyl, i-propyl, i-butyl, cyclohexyl, cyclohexylmethyl, benzyl, 4-fluorobenzyl, naphthylmethyl, acetyl, benzoyl or benzyloxycarbonyl.

Further compounds of Formula (Ia), made up of components A, B, and C are provided in the following Table I. Any and all combinations of A, B, and C components within the structural limitations of Formula (Ia), comprise a compound of the invention, and their pharmaceutically acceptable derivatives. These compounds can be synthesized by the General schemes, methods described in the experimental section of this document and analogous methods known to those skilled in the art without undue experimentation. Preferred compounds will possess desirable inhibition activity of Cathepsin S in a cell based assay as described in Riese, R.J. et al., Immunity, 1996, 4, 357-366, incorporated herein by reference.

FORMULA (Ia)

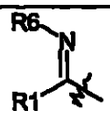
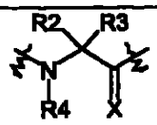
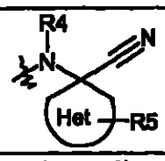
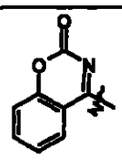
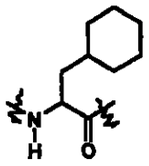
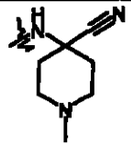
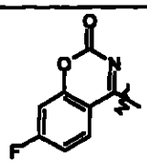
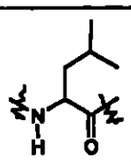
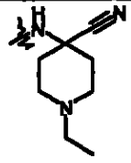
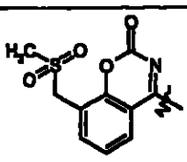
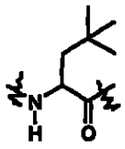
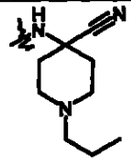
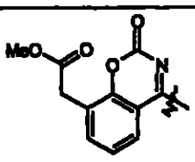
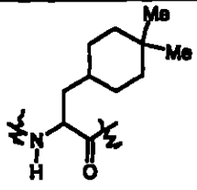
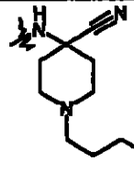
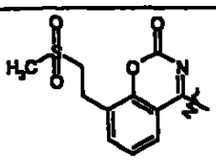
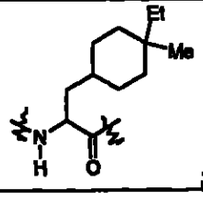
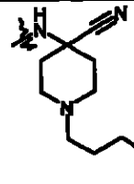
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(Ia)

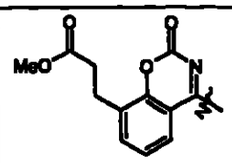
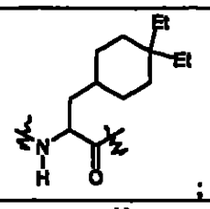
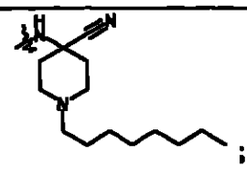
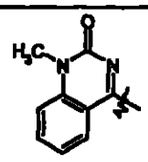
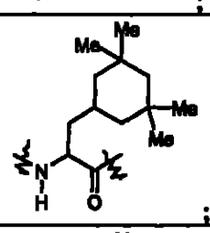
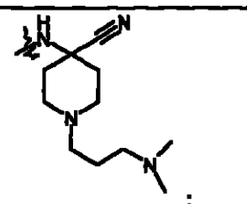
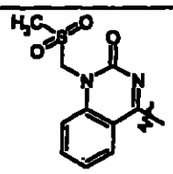
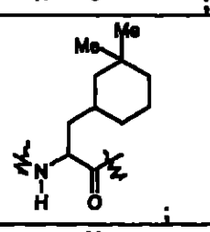
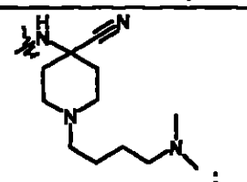
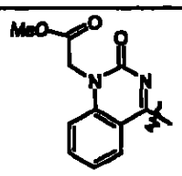
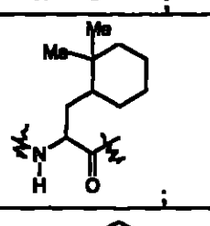
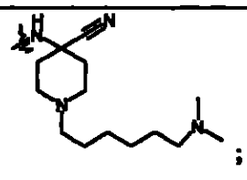
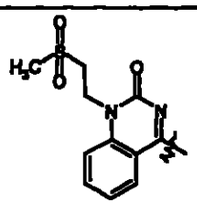
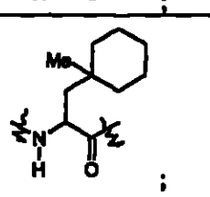
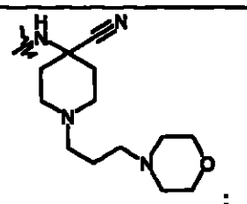
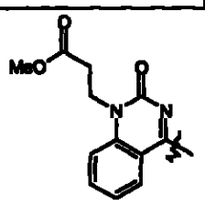
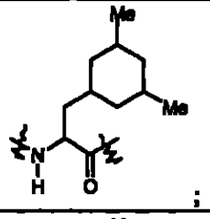
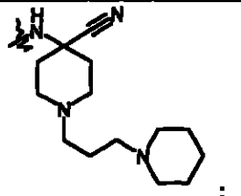
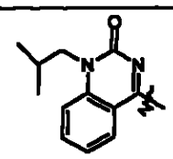
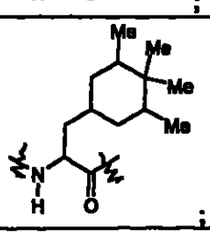
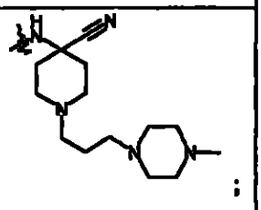
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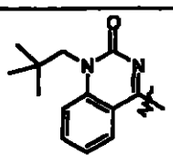
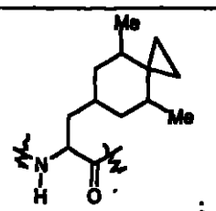
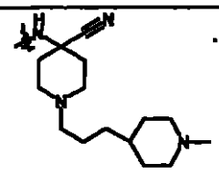
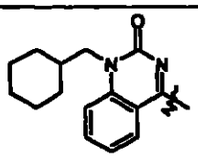
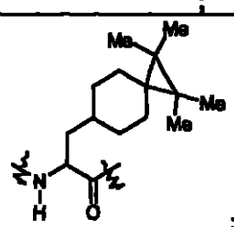
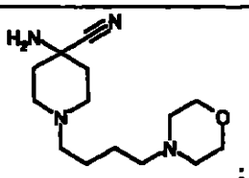
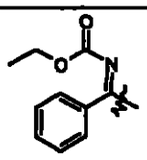
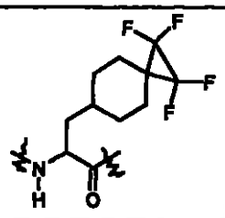
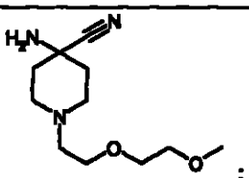
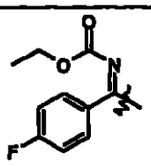
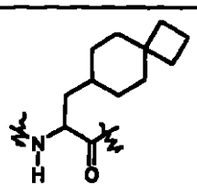
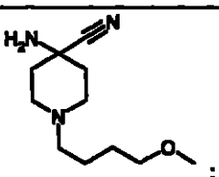
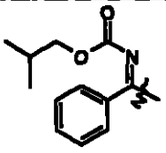
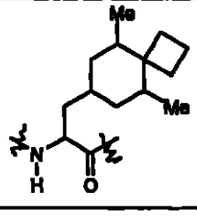
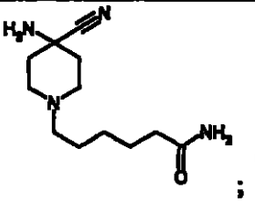
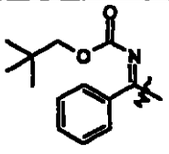
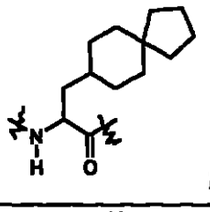
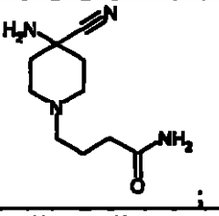
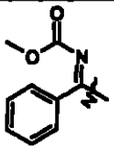
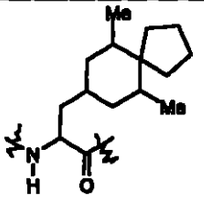
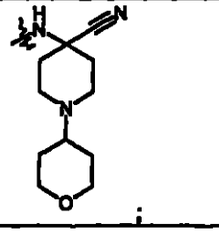
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| A3 |  ; | B3 |  ; | C3 |  ; |
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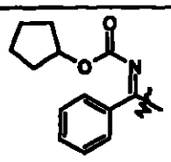
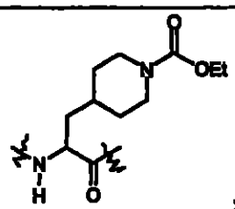
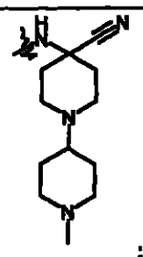
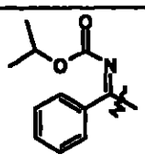
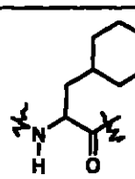
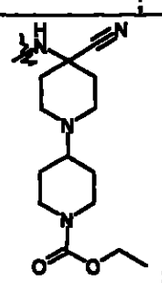
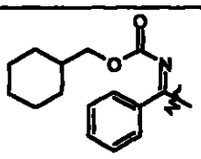
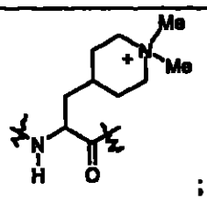
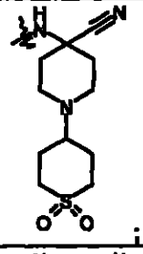
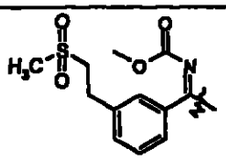
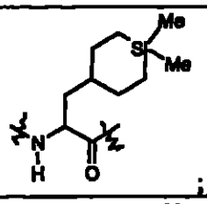
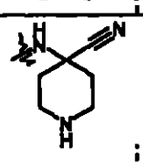
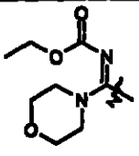
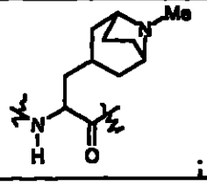
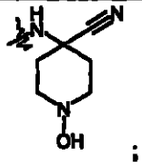
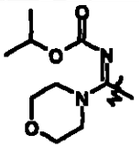
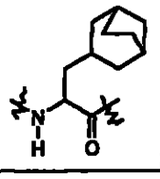
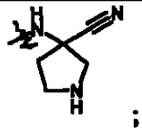
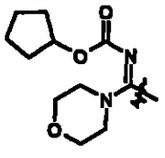
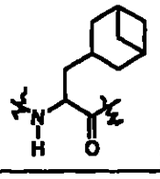
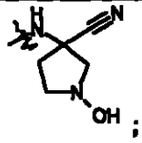
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| A8 |  ; | B8 |  ; | C8 |  ; |
| A9 |  ; | B9 |  ; | C9 |  ; |
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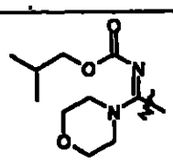
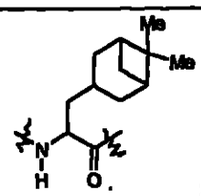
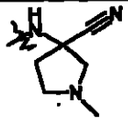
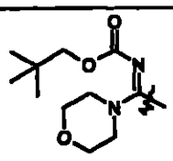
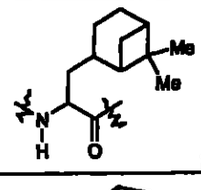
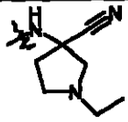
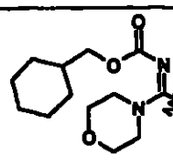
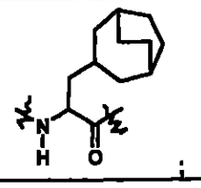
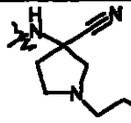
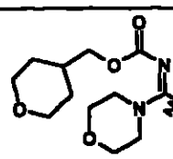
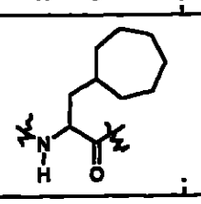
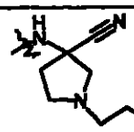
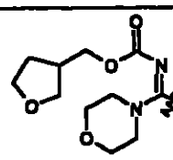
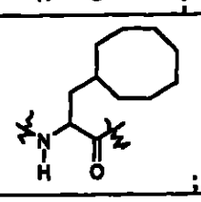
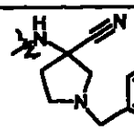
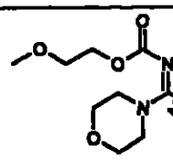
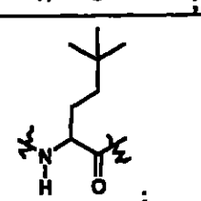
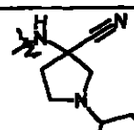
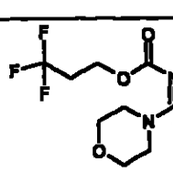
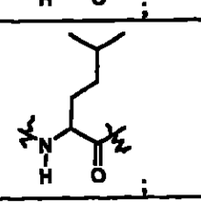
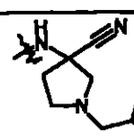
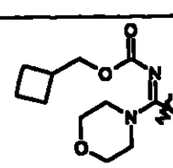
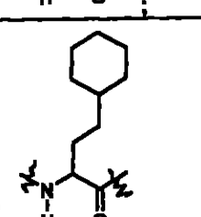
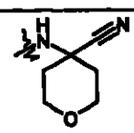
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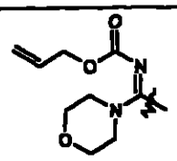
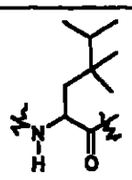
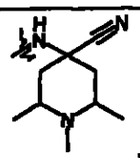
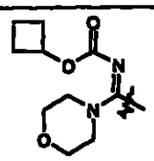
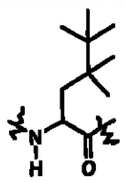
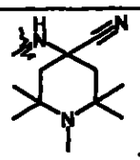
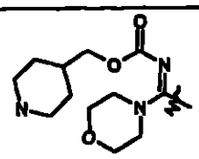
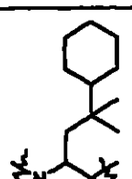
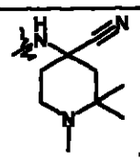
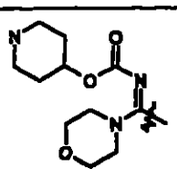
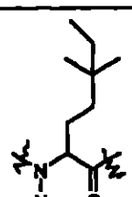
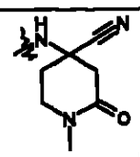
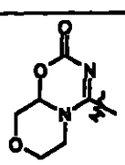
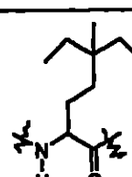
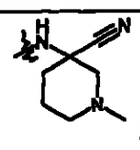
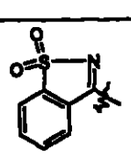
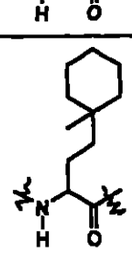
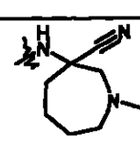
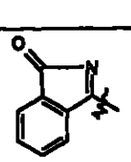
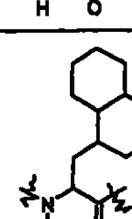
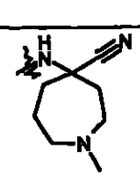
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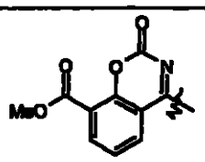
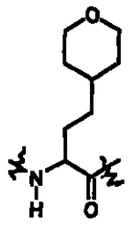
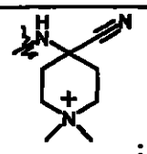
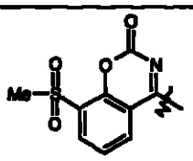
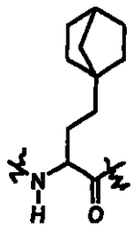
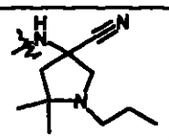
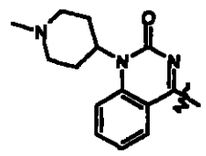
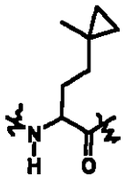
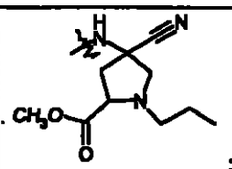
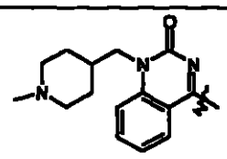
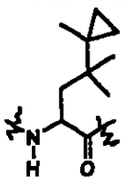
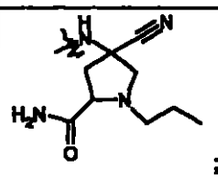
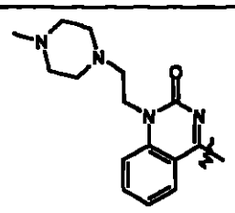
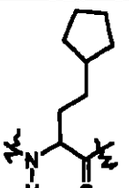
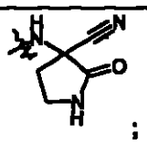
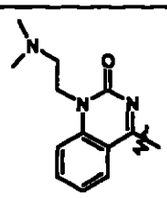
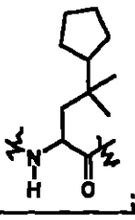
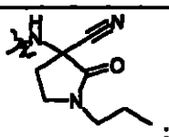
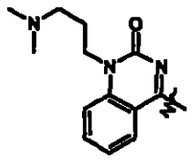
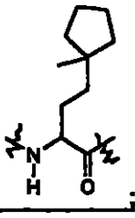
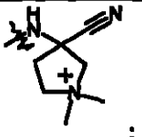
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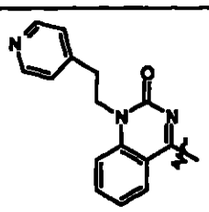
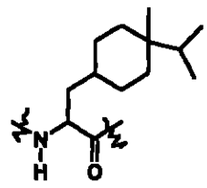
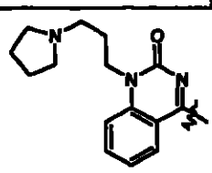
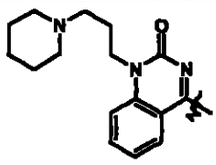
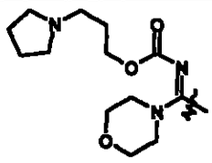
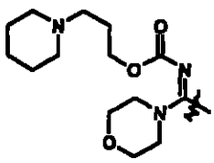
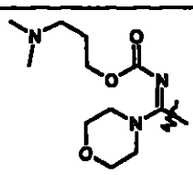
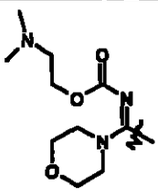
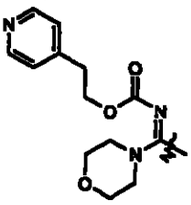
| | | | | | |
|---|---|---|---|---|---|
| A20 |  ; | B20 |  ; | C20 |  ; |
| A21 |  ; | B21 |  ; | C21 |  ; |
| A22 |  ; | B22 |  ; | C22 |  ; |
| A23 |  ; | B23 |  ; | C23 |  ; |
| A24 |  ; | B24 |  ; | C24 |  ; |
| A25 |  ; | B25 |  ; | C25 |  ; |
| A26 |  ; | B26 |  ; | C26 |  ; |

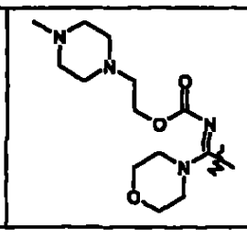
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| A27 |  | B27 |  | C27 |  |
| A28 |  | B28 |  | C28 |  |
| A29 |  | B29 |  | C29 |  |
| A30 |  | B30 |  | C30 |  |
| A31 |  | B31 |  | C31 |  |
| A32 |  | B32 |  | C32 |  |
| A33 |  | B33 |  | C33 |  |
| A34 |  | B34 |  | C34 |  |

| | | | | | |
|---|---|---|---|---|---|
| A35 |  ; | B35 |  ; | C35 |  ; |
| A36 |  ; | B35 |  ; | C36 |  ; |
| A37 |  ; | B37 |  ; | C37 |  ; |
| A38 |  ; | B38 |  ; | C38 |  ; |
| A39 |  ; | B39 |  ; | C39 |  ; |
| A40 |  ; | B40 |  ; | C40 |  ; |
| A41 |  ; | B41 |  ; | C41 |  ; |

| | | | | | |
|---|---|---|---|---|---|
| A42 |  | B42 |  | C42 |  |
| A43 |  | B43 |  | C43 |  |
| A44 |  | B44 |  | C44 |  |
| A45 |  | B45 |  | C45 |  |
| A46 |  | B46 |  | C46 |  |
| A47 |  | B47 |  | C47 |  |
| A48 |  | B48 |  | C48 |  |

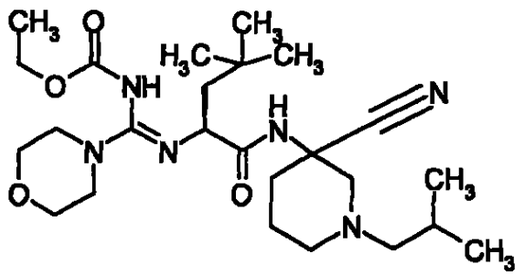
123

| | | | | | |
|---|---|---|---|---|---|
| A49 |  ; | B49 |  ; | | |
| A50 |  ; | | | | |
| A51 |  ; | | | | |
| A52 |  ; | | | | |
| A53 |  ; | | | | |
| A54 |  ; | | | | |
| A55 |  ; | | | | |
| A56 |  ; | | | | |

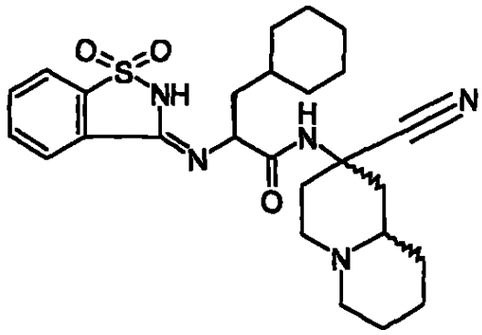
| | | | | | |
|---|---|---|---|---|---|
| A57 |  | | | | |

and the pharmaceutically acceptable derivates thereof.

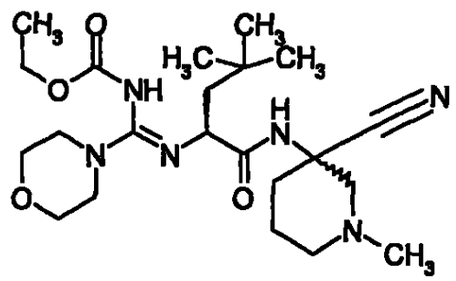
In another embodiment of the invention there are provided the following compounds of the Formulas (Ia) and (Ib) which have been synthesized using the General schemes, methods described in the experimental section of this document and analogous methods known to those skilled in the art without undue experimentation. The compound possess desirable inhibition activity of Cathepsin S in the cell based assay referenced above.



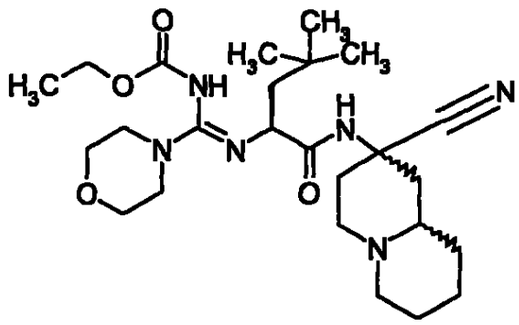
{[1-(3-cyano-1-isobutyl-piperdin-3-yl carbamoyl)-3,3-dimethyl-butylamino]-morpholin-4-yl-methylene}-carbamic acid ethyl ester; MS: 493 (M+1)



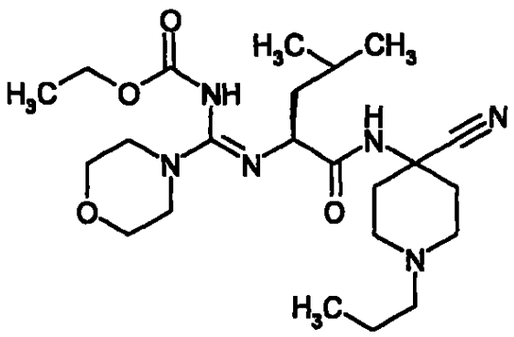
N-(2Cyano-octahydro-quinolizin-2-yl)-3-cyclohexyl-2-(1,1-dioxo-1H-1λ-benzo-3-ylamino)-propionamide; MS: 498 (M+1)



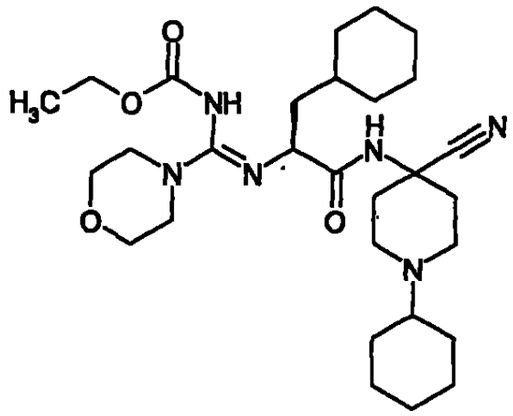
{[1-3-Cyano-1-methyl-piperidin-3-ylcarbamoyl)-3,3-dimethyl-butylamino]-morpholin-4-yl-methylene}-carbamic acid ethyl ester; MS: 451 (M+1)



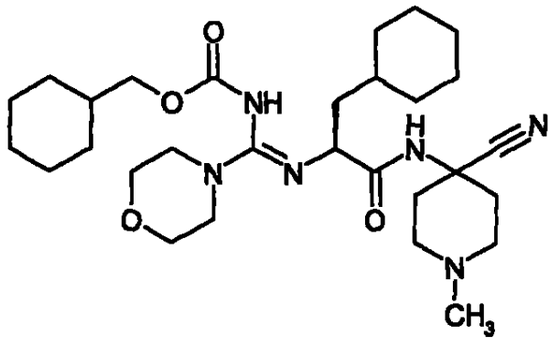
{[1-(2-cyano-octahydro-quinolizin-2-ylcarbamoyl)-3,3-dimethyl-butylamino]-morpholin-4-yl-methylene}-carbamic acid ethyl ester; MS: 491 (M+1)



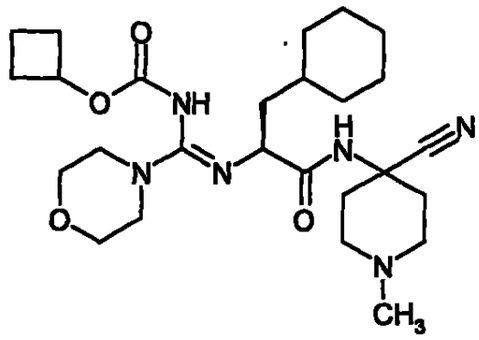
{[1-(4-Cyano-1-propyl-piperidin-4-ylcarbamoyl)-3-methyl-butylamino]-morpholin-4-yl-methylene}-carbamic acid ethyl ester; MS: 465 (M+1)



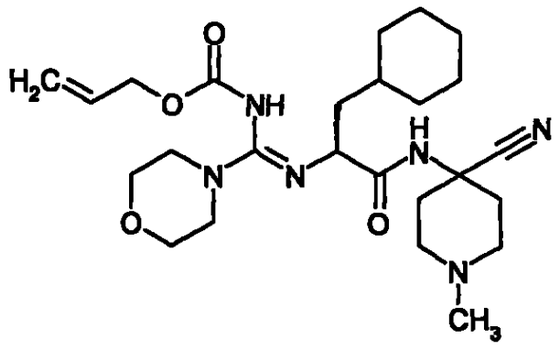
{[1-(4-cyano-1-cyclohexyl-piperidin-4-ylcarbamoyl)-2-cyclohexyl-ethylamino]-morpholin-4-yl-methylene}-carbamic acid ethyl ester; MS: 545 (M+1)



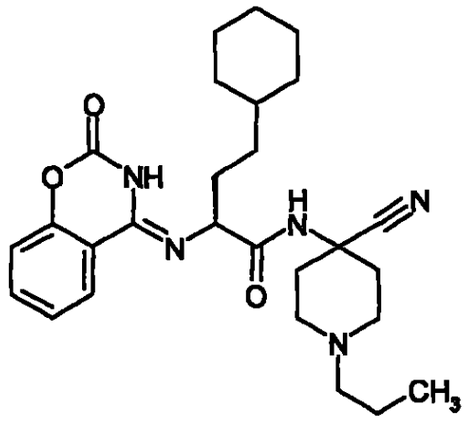
{[1-(4-cyano-1-methyl-piperidin-4-ylcarbamoyl)-2-cyclohexyl-ethylamino]-morpholin-4-yl-methylene}-carbamic acid cyclohexylmethyl ester; MS: 545 (M+1)



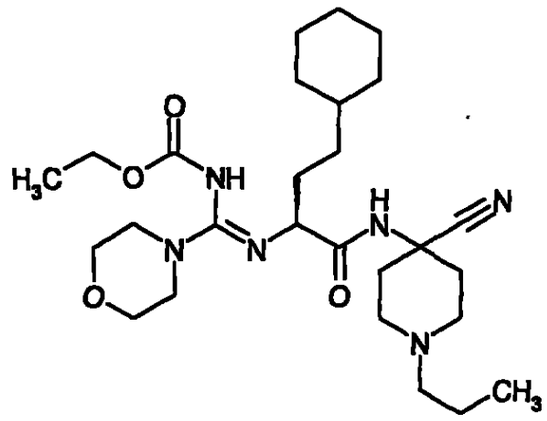
{[-1-(4-cyano-1-methyl-piperidin-4-ylcarbamoyl)-2-cyclohexyl-ethylamino]-morpholin-4-yl-methylene}-carbamic acid cyclobutyl ester; MS: 503 (M+1)



{[1-(4-cyano-1-methyl-piperidin-4-ylcarbamoyl)-2-cyclohexyl-ethylamino]-morpholin-4-yl-methylene}-carbamic acid allyl ester; MS: 489 (M+1)



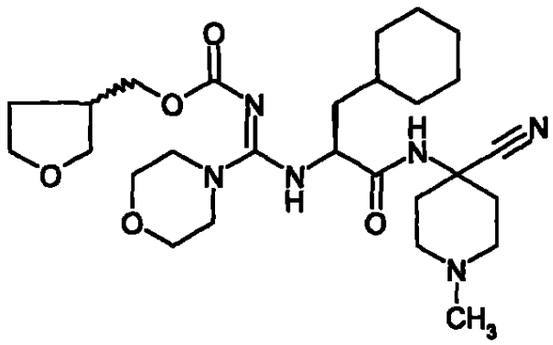
N-(4-Cyano-1-propyl-piperidin-4-yl)-4-cyclohexyl-2-(2-oxo-2,3-dihydro-benzo[e][1,3]oxazin-4-ylideneamino)-butyramide; MS: 480 (M+1)



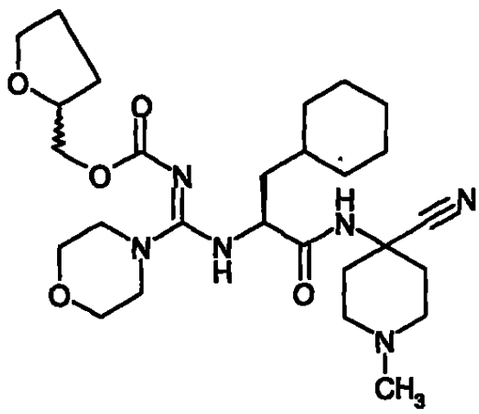
{[1-(4-cyano-1-propyl-piperidin-4-ylcarbamoyl)-3-cyclohexyl-propylamino]-morpholin-4-yl-methylene}-carbamic acid ester; MS: 519 (M+1)

127

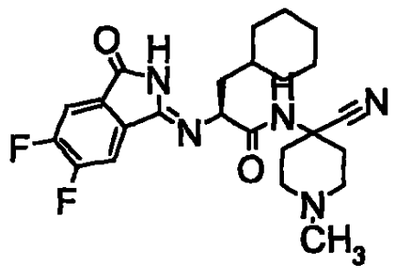
128



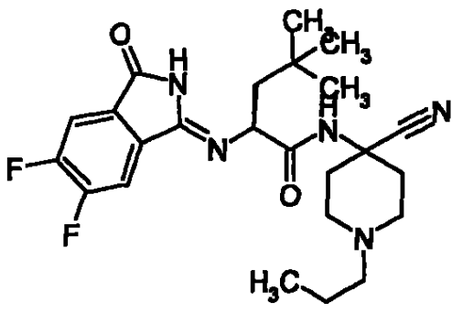
{[ 1-(4-cyano-1-methyl-piperidin-4-ylcarbamoyl)-2-cyclohexyl-ethylamino]-morpholin-4-yl-methylene}-carbamic acid tetrahydro-furan-3ylmethyl ester; MS: 533 (M+1)



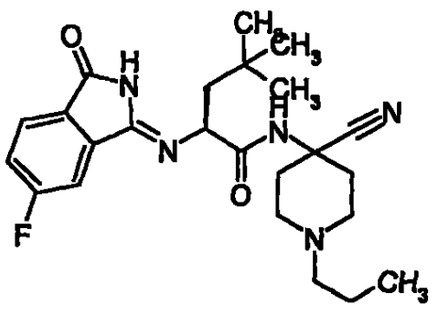
{[1-(4-cyano-1-methy-piperidin-4-ylcarbamoyl)-2-cyclohexyl-ethyl amino]-morpholin-4-yl-methylene}-carbamic acid tetrahydro-furan-2-ylmethyl ester; MS: 533 (M+1)



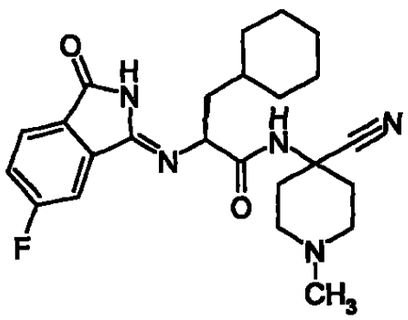
*N*-(4-Cyano-1-methyl-piperidin-4-yl)-3-cyclohexyl-2-(5,6-difluoro-3-oxo-2,3-dihydro-isoindol-1-ylideneamino)-propionamide; MS: 458 (M+1)



2-(5,6-Difluoro-3-oxo-2,3-dihydro-isoindol-1-ylideneamino)-4,4-dimethyl-pentanoic acid (4-cyano-1-propyl-piperidin-4-yl)-amide; MS: 460 (M+1)

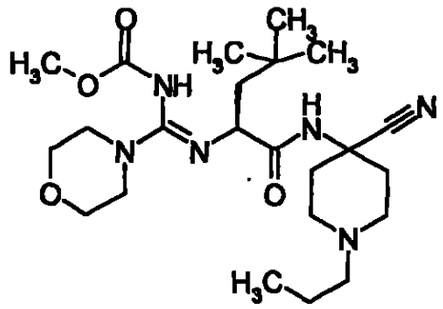


2-(6-Fluoro-3-oxo-2,3-dihydro-isoindol-1-ylideneamino)-4,4-dimethyl-pentanoic acid (4-cyano-1-propyl-piperidin-4-yl)-amide; MS: 442 (M+1)

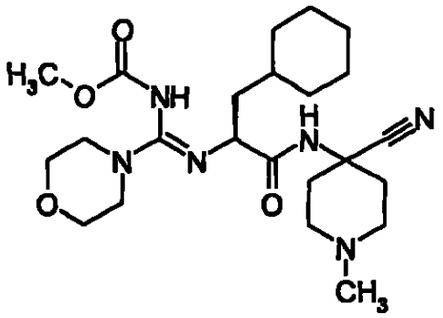


*N*-(4-Cyano-1-methyl-piperidin-4-yl)-3-cyclohexyl-2-(6-fluoro-3-oxo-2,3-dihydro-isoindol-1-ylideneamino)-propionamide; MS: 440 (M+1)

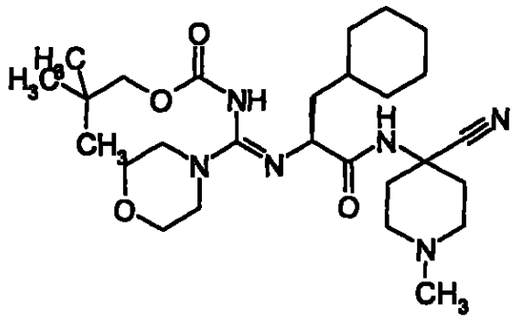
129
130



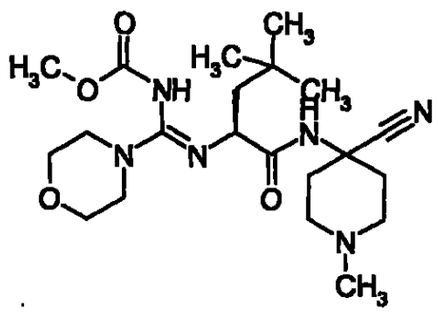
{[1-(4-Cyano-1-propyl-piperidin-4-ylcarbamoyl)-3,3-dimethyl-butylimino]-morpholin-4-yl-methyl}-carbamic acid methyl ester; MS: 465 (M+1)



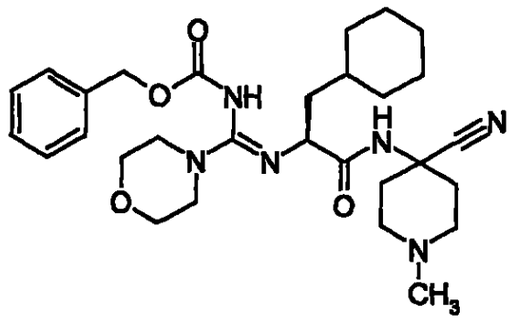
{[1-(4-Cyano-1-methyl-piperidin-4-ylcarbamoyl)-2-cyclohexyl-ethylimino]-morpholin-4-yl-methyl}-carbamic acid methyl ester; MS: 463 (M+1)



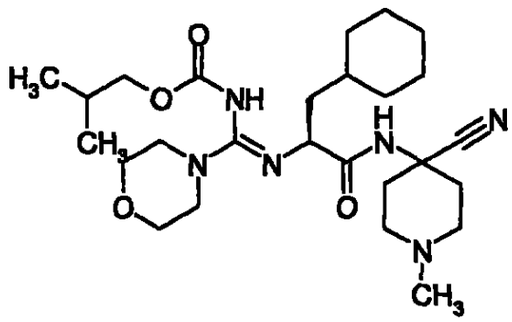
{[1-(4-Cyano-1-methyl-piperidin-4-ylcarbamoyl)-2-cyclohexyl-ethylimino]-morpholin-4-yl-methyl}-carbamic acid 2,2-dimethyl-propyl ester; MS: 519 (M+1)



{[1-(4-Cyano-1-methyl-piperidin-4-ylcarbamoyl)-3,3-dimethyl-butylimino]-morpholin-4-yl-methyl}-carbamic acid methyl ester; MS: 437 (M+1)

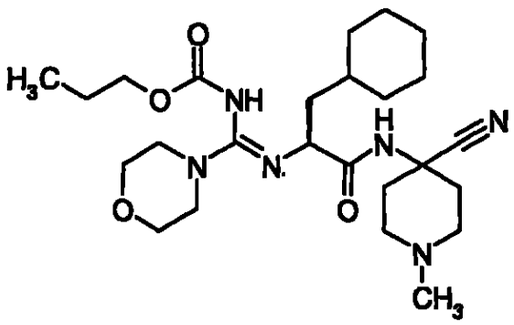


{[1-(4-Cyano-1-methyl-piperidin-4-ylcarbamoyl)-2-cyclohexyl-ethylimino]-morpholin-4-yl-methyl}-carbamic acid benzyl ester; MS: 539 (M+1)

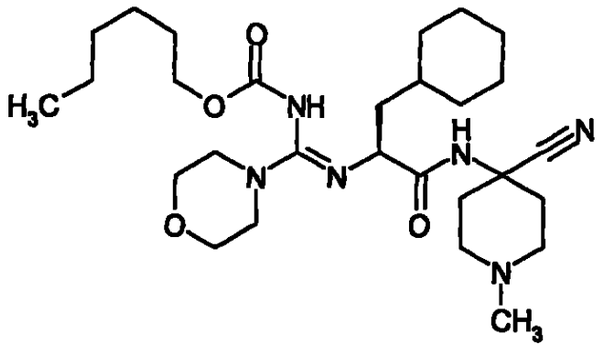


{[1-(4-Cyano-1-methyl-piperidin-4-ylcarbamoyl)-2-cyclohexyl-ethylimino]-morpholin-4-yl-methyl}-carbamic acid isobutyl ester; MS: 505 (M+1)

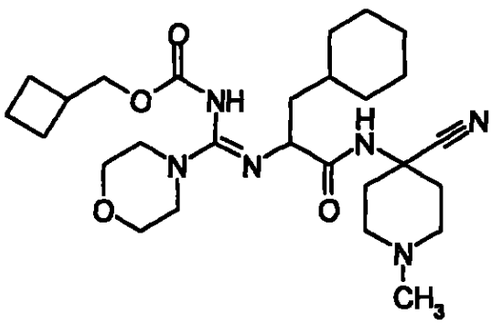
132



{[1-(4-Cyano-1-methyl-piperidin-4-ylcarbamoyl)-2-cyclohexyl-ethylimino]-morpholin-4-yl-methyl}-carbamic acid propyl ester; MS: 491 (M+1)



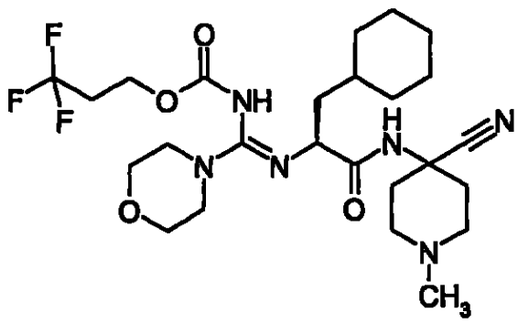
{[1-(4-Cyano-1-methyl-piperidin-4-ylcarbamoyl)-2-cyclohexyl-ethylimino]-morpholin-4-yl-methyl}-carbamic acid hexyl ester; MS: 533 (M+1)



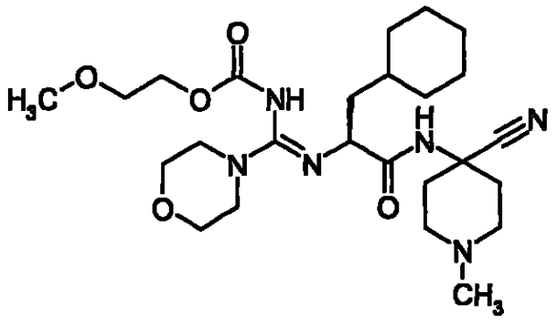
{[1-(4-Cyano-1-methyl-piperidin-4-ylcarbamoyl)-2-cyclohexyl-ethylimino]-morpholin-4-yl-methyl}-carbamic acid cyclobutylmethyl ester; MS: 517 (M+1)

132

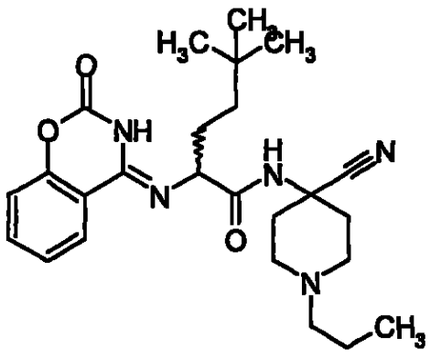
133



{[1-(4-Cyano-1-methyl-piperidin-4-ylcarbamoyl)-2-cyclohexyl-ethylimino]-morpholin-4-yl-methyl}-carbamic acid 3,3,3-trifluoro-propyl ester; MS: 545 (M+1)



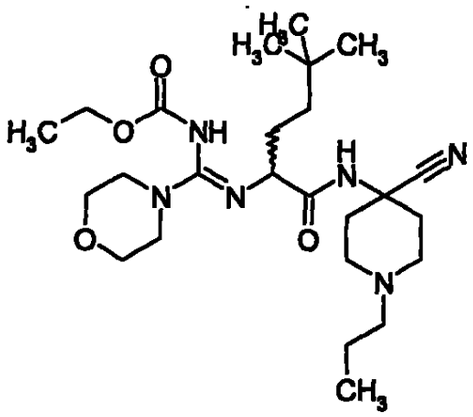
{[1-(4-Cyano-1-methyl-piperidin-4-ylcarbamoyl)-2-cyclohexyl-ethylimino]-morpholin-4-yl-methyl}-carbamic acid 2-methoxy-ethyl ester; MS: 507 (M+1)



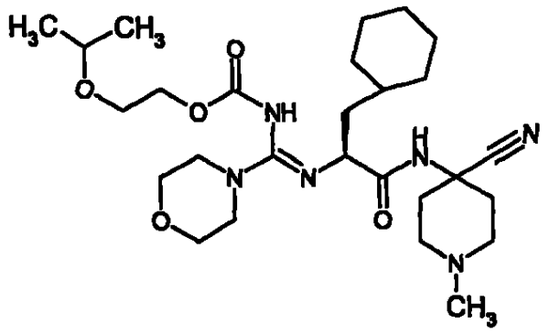
5,5-Dimethyl-2-(2-oxo-2,3-dihydro-benzo[*e*][1,3]oxazin-4-ylideneamino)-hexanoic acid (4-cyano-1-propyl-piperidin-4-yl)-amide; MS: 454 (M+1)

133

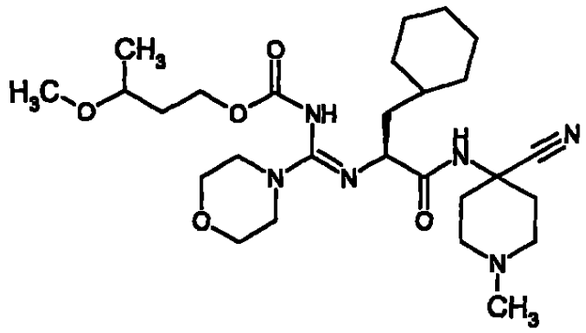
134



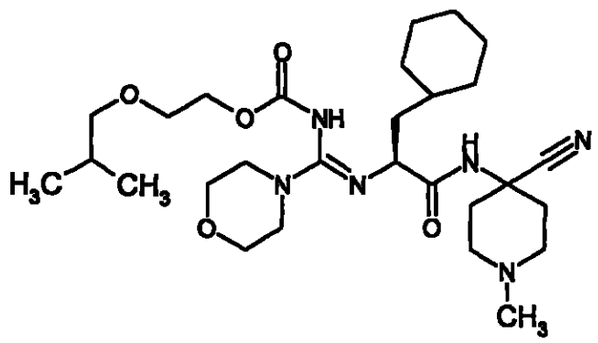
{[1-(4-Cyano-1-propyl-piperidin-4-ylcarbamoyl)-4,4-dimethyl-pentylimino]-morpholin-4-yl-methyl}-carbamic acid ethyl ester; MS: 493 (M+1)



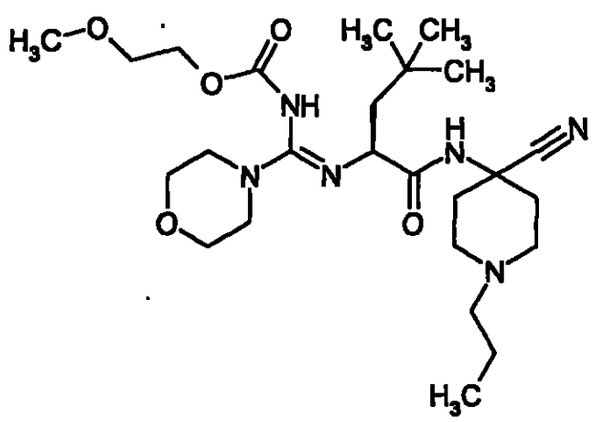
{[1-(4-Cyano-1-methyl-piperidin-4-ylcarbamoyl)-2-cyclohexyl-ethylimino]-morpholin-4-yl-methyl}-carbamic acid 2-isopropoxy-ethyl ester; MS: 534 (M+1)



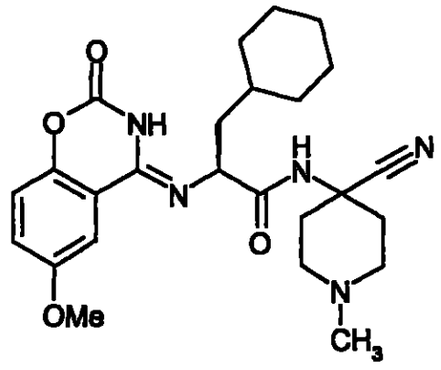
{[1-(4-Cyano-1-methyl-piperidin-4-ylcarbamoyl)-2-cyclohexyl-ethylimino]-morpholin-4-yl-methyl}-carbamic acid 3-methoxy-butyl ester; MS: 534 (M+1)



{[1-(4-Cyano-1-methyl-piperidin-4-ylcarbamoyl)-2-cyclohexyl-ethylimino]-morpholin-4-yl-methyl}-carbamic acid 2-isobutoxy-ethyl ester; MS: 549 (M+1)

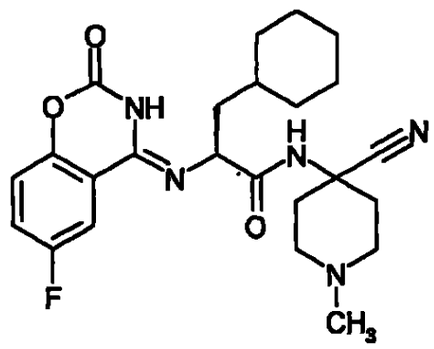


{[1-(4-Cyano-1-propyl-piperidin-4-ylcarbamoyl)-3,3-dimethyl-butylimino]-morpholin-4-yl-methyl}-carbamic acid 2-methoxy-ethyl ester; MS: 509 (M+1)

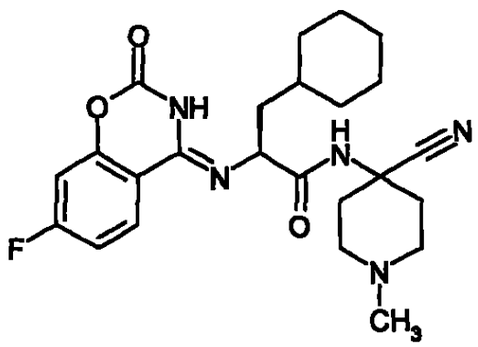


N-(4-Cyano-1-methyl-piperidin-4-yl)-4-cyclohexyl-2-(6-methoxy-2-oxo-2,3-dihydro-benzo[e][1,3]oxazin-4-ylideneamino)-butyramide; MS: 468 (M+1)

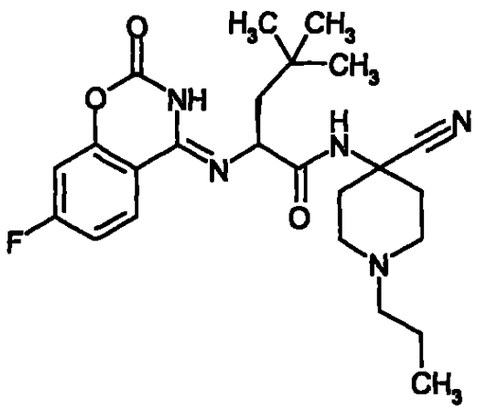
135
136



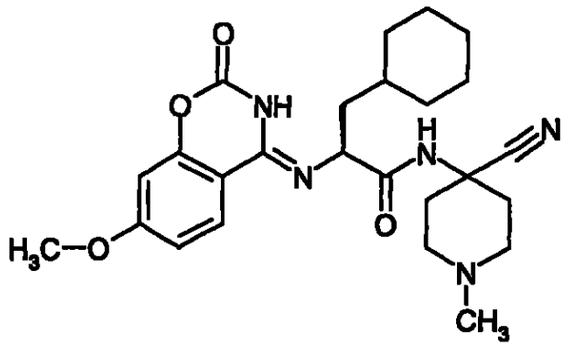
N-(4-Cyano-1-methyl-piperidin-4-yl)-4-cyclohexyl-2-(6-fluoro-2-oxo-2,3-dihydro-benzo[e][1,3]oxazin-4-ylideneamino)-butyramide; MS: 456 (M+1)



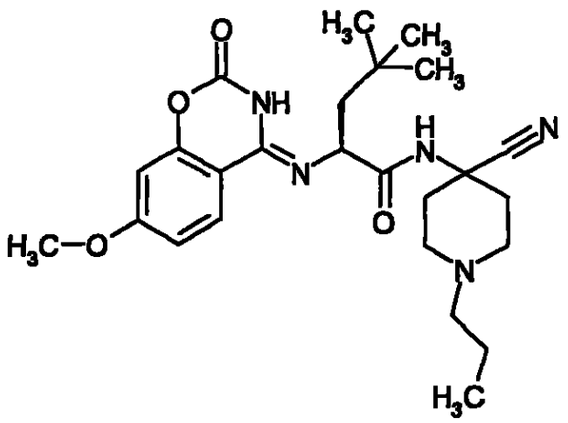
N-(4-Cyano-1-methyl-piperidin-4-yl)-4-cyclohexyl-2-(7-fluoro-2-oxo-2,3-dihydro-benzo[e][1,3]oxazin-4-ylideneamino)-butyramide; MS: 456 (M+1)



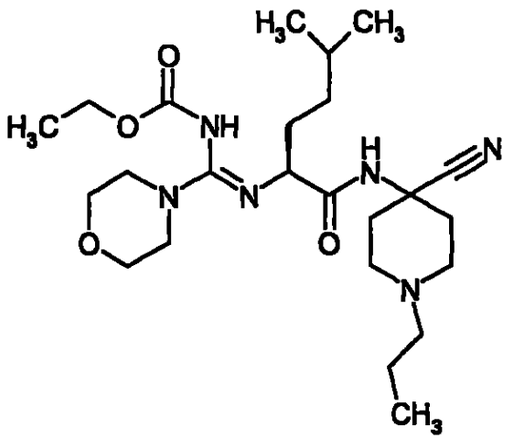
2-(7-Fluoro-2-oxo-2,3-dihydro-benzo[e][1,3]oxazin-4-yldeneamino)-5,5-dimethyl-hexanoic acid(4-cyano-1-propyl-piperidin-4-yl)-amide; MS: 458 (M+1)



N-(4-Cyano-1-methyl-piperidin-4-yl)-4-cyclohexyl-2-(7-methoxy-2-oxo-2,3-dihydro-benzo[e][1,3]oxazin-4-ylideneamino)-butyramide; MS: 468 (M+1)



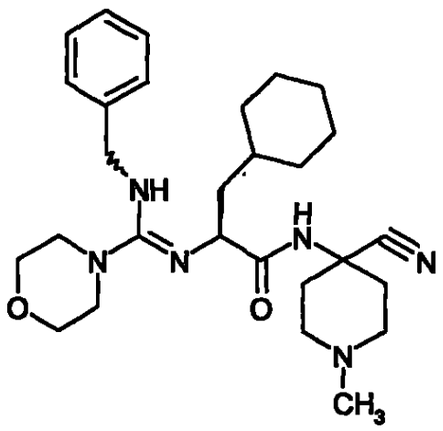
2-(7-Methoxy-2-oxo-2,3-dihydro-benzo[e][1,3]oxazin-4-yldeneamino)-5,5-dimethyl-hexanoic acid(4-cyano-1-propyl-piperidin-4-yl)-amide; MS: 470 (M+1)



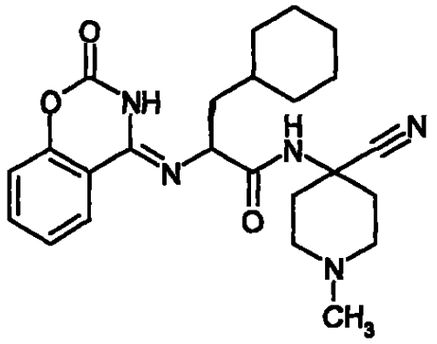
{[1-(4-Cyano-1-propyl-piperidin-4-ylcarbamoyl)-5-methyl-hexylimino]-morpholin-4-yl-methyl}-carbamic acid ethyl ester; MS: 479 (M+1)

137

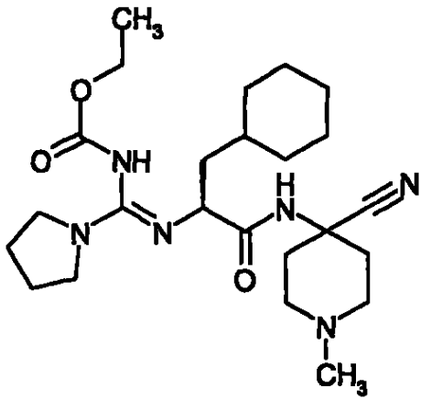
138



2-[(*N*-Benzyl-morpholine-4-carboximidoyl)-amino]-*N*-(4-cyano-1-methyl-piperidin-4-yl)-3-cyclohexyl-propionamide; MS: 495 (M+1).



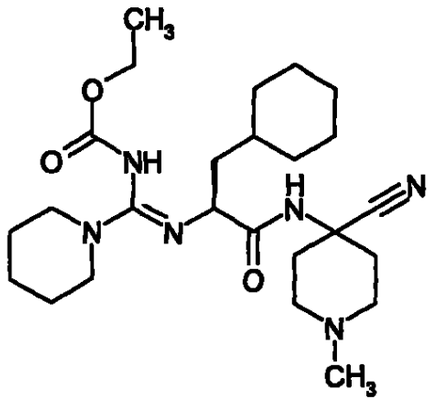
*N*-(4-Cyano-1-methyl-piperidin-4-yl)-3-cyclohexyl-2-(2-oxo-2,3-dihydro-benzo[*e*][1,3]oxazin-4-ylideneamino)-propionamide; MS: 438 (M+1).



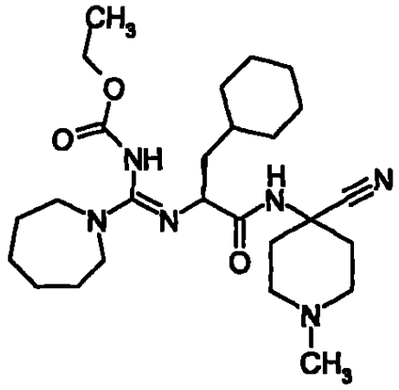
{[1-(4-Cyano-1-methyl-piperidin-4-ylcarbamoyl)-2-cyclohexyl-ethylimino]-pyrrolidin-1-yl-methyl}-carbamic acid ethyl ester; MS: 461 (M+1).

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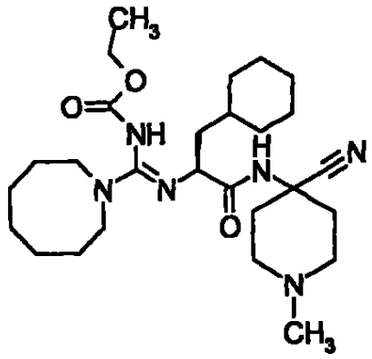
139



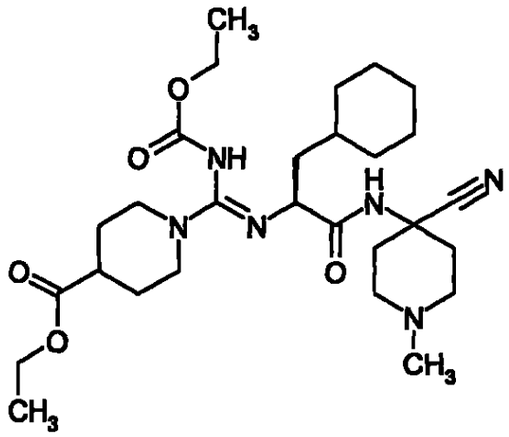
{[1-(4-Cyano-1-methyl-piperidin-4-ylcarbamoyl)-2-cyclohexyl-ethylimino]-piperidin-1-yl-methyl}-carbamic acid ethyl ester; MS: 475 (M+1).



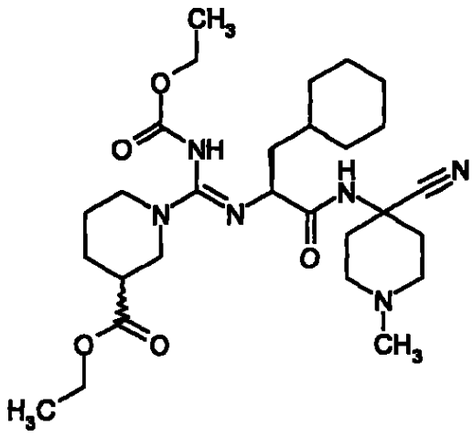
{Azepan-1-yl-[1-(4-cyano-1-methyl-piperidin-4-ylcarbamoyl)-2-cyclohexyl-ethylimino]-methyl}-carbamic acid ethyl ester; MS: 489 (M+1).



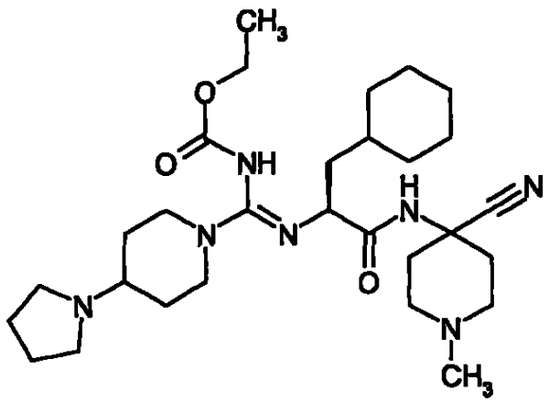
{Azocan-1-yl-[1-(4-cyano-1-methyl-piperidin-4-ylcarbamoyl)-2-cyclohexyl-ethylimino]-methyl}-carbamic acid ethyl ester; MS: 503 (M+1).



1 {[1-(4-Cyano-1 methyl piperidin-4-ylcarbamoyl)-2-cyclohexyl ethylimino] ethoxycarbonylamino-methyl} piperidine-4-carboxylic acid ethyl ester MS 547 (M+1)

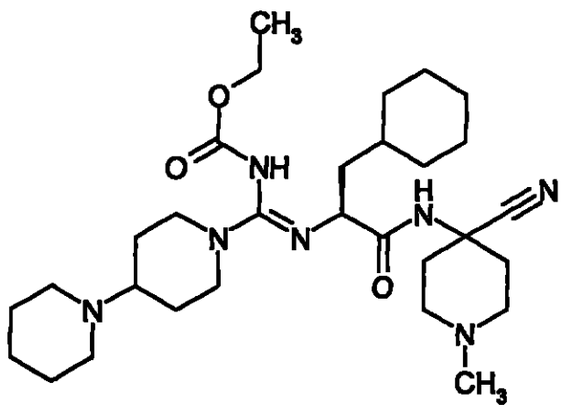


1 {[1 (4-Cyano-1 methyl piperidin-4-ylcarbamoyl) 2-cyclohexyl ethylimino] ethoxycarbonylamino-methyl} piperidine-3-carboxylic acid ethyl ester MS 547 (M+1)

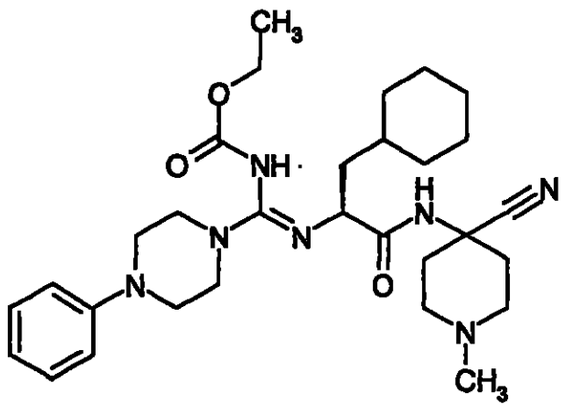


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[[1-(4-Cyano-1-methyl-piperidin-4-ylcarbamoyl)-2-cyclohexyl-ethylimino]-(4-pyrrolidin-1-yl-piperidin-1-yl)-methyl]-carbamic acid ethyl ester; MS: 544 (M+1).



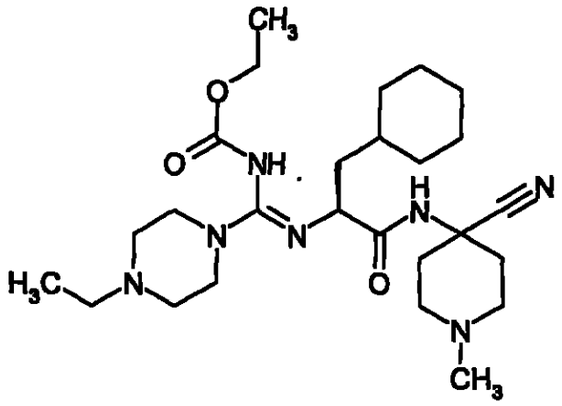
{[1,4']Bipiperidinyl-1'-yl-[1-(4-cyano-1-methyl-piperidin-4-ylcarbamoyl)-2-cyclohexyl-ethylimino]-methyl}-carbamic acid ethyl ester; MS: 558 (M+1).



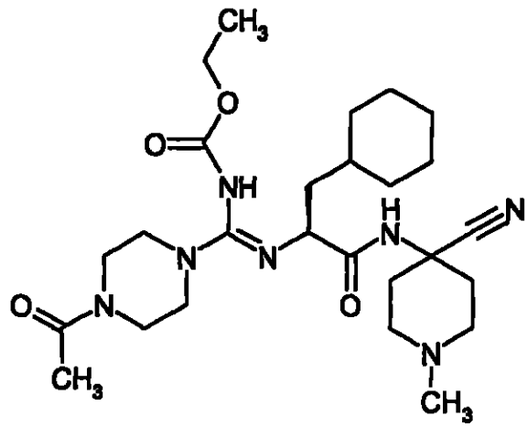
[[1-(4-Cyano-1-methyl-piperidin-4-ylcarbamoyl)-2-cyclohexyl-ethylimino]-(4-phenyl-piperazin-1-yl)-methyl]-carbamic acid ethyl ester; MS: 552 (M+1).

141

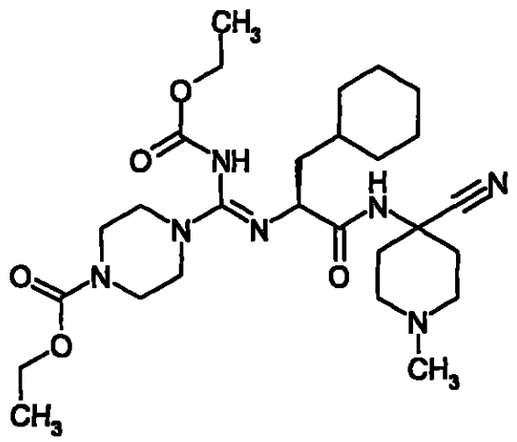
142



[[1-(4-Cyano-1-methyl-piperidin-4-ylcarbamoyl)-2-cyclohexyl-ethylimino]-(4-ethyl-piperazin-1-yl)-methyl]-carbamic acid ethyl ester; MS: 504 (M+1).



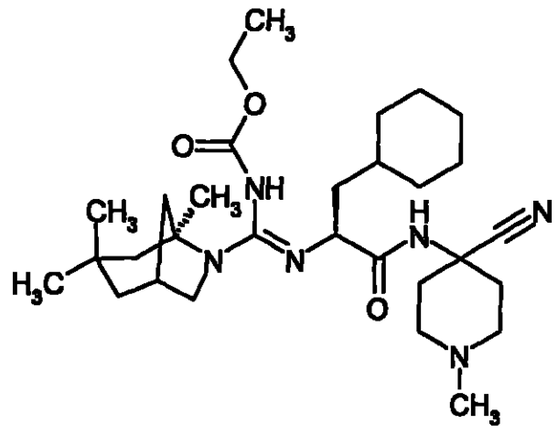
{(4-Acetyl-piperazin-1-yl)-[1-(4-cyano-1-methyl-piperidin-4-ylcarbamoyl)-2-cyclohexyl-ethylimino]-methyl}-carbamic acid ethyl ester; MS: 518 (M+1).



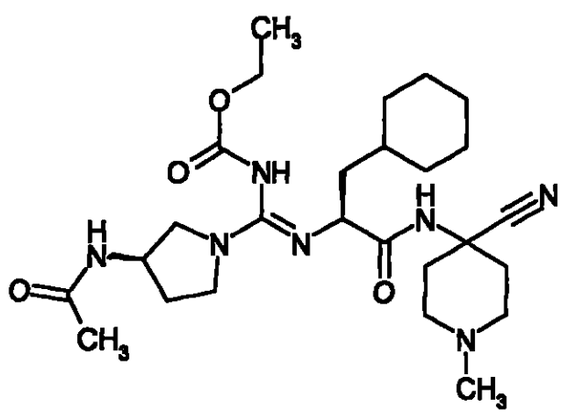
4-{[1-(4-Cyano-1-methyl-piperidin-4-ylcarbamoyl)-2-cyclohexyl-ethylimino]-ethoxycarbonylamino-methyl}-piperazine-1-carboxylic acid ethyl ester; MS: 548 (M+1).

142

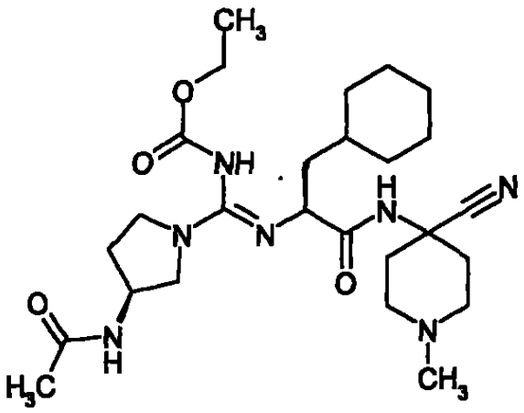
143



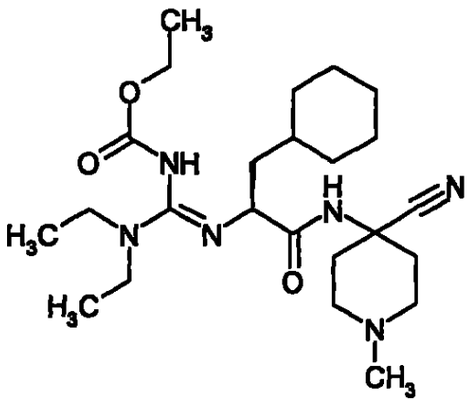
[[1-(4-Cyano-1-methyl-piperidin-4-ylcarbamoyl)-2-cyclohexyl-ethylimino]-(3,3,5-trimethyl-6-aza-bicyclo[3.2.1]oct-6-yl)-methyl]-carbamic acid ethyl ester; MS: 543 (M+1).



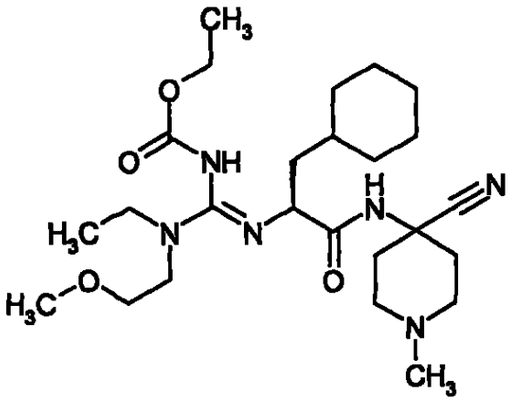
{(3-Acetylamino-pyrrolidin-1-yl)-[1-(4-cyano-1-methyl-piperidin-4-ylcarbamoyl)-2-cyclohexyl-ethylimino]-methyl}-carbamic acid ethyl ester; MS: 518 (M+1).



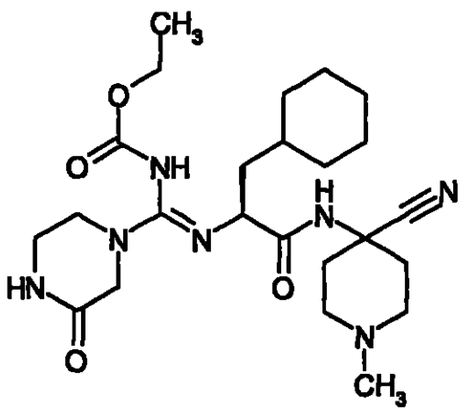
{(3-Acetylamino-pyrrolidin-1-yl)-[1-(4-cyano-1-methyl-piperidin-4-ylcarbamoyl)-2-cyclohexyl-ethylimino]-methyl}-carbamic acid ethyl ester; MS: 518 (M+1).



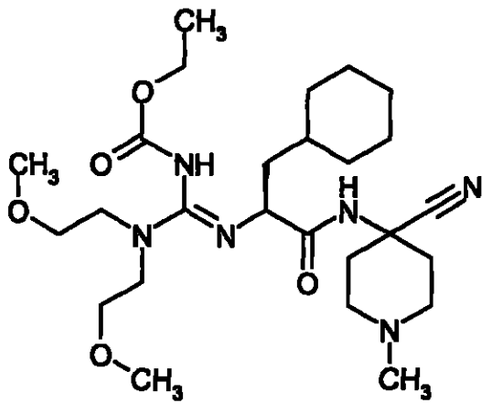
{(3-Azapent-3-yl)-[1-(4-cyano-1-methyl-piperidin-4-ylcarbamoyl)-2-cyclohexyl-ethylimino]-methyl}-carbamic acid ethyl ester; MS: 463 (M+1).



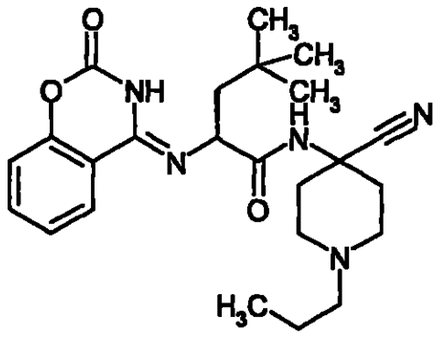
{(1-Methoxy-3-azapent-3-yl)-[1-(4-cyano-1-methyl-piperidin-4-ylcarbamoyl)-2-cyclohexyl-ethylimino]-methyl}-carbamic acid ethyl ester; MS: 493 (M+1).



[[1-(4-Cyano-1-methyl-piperidin-4-ylcarbamoyl)-2-cyclohexyl-ethylimino]-(3-oxo-piperazin-1-yl)-methyl]-carbamic acid ethyl ester; MS: 490 (M+1).

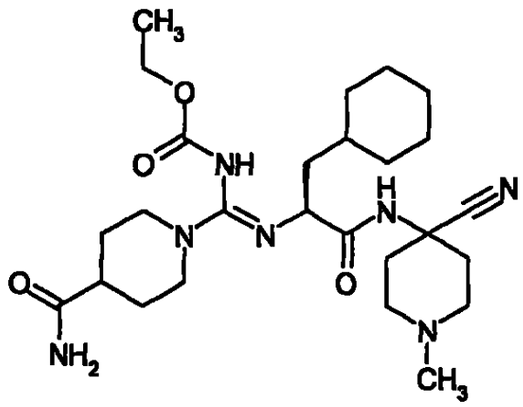


{(1,5-Dimethoxy-3-azapent-3-yl)-[1-(4-cyano-1-methyl-piperidin-4-ylcarbamoyl)-2-cyclohexyl-ethylimino]-methyl}-carbamic acid ethyl ester; MS: 523 (M+1).

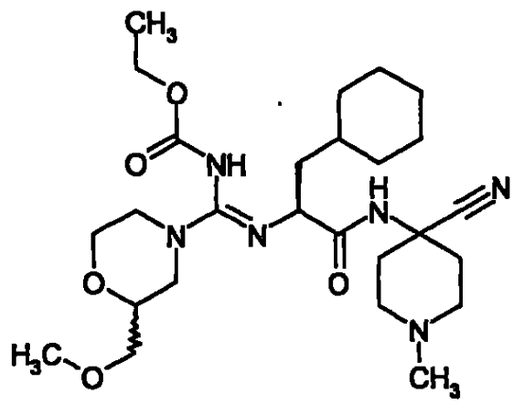


4,4-Dimethyl-2-(2-oxo-2,3-dihydro-benzo[e][1,3]oxazin-4-ylidencamino)-pentanoic acid (4-cyano-1-propyl-piperidin-4-yl)-amide; MS: 440 (M+1)

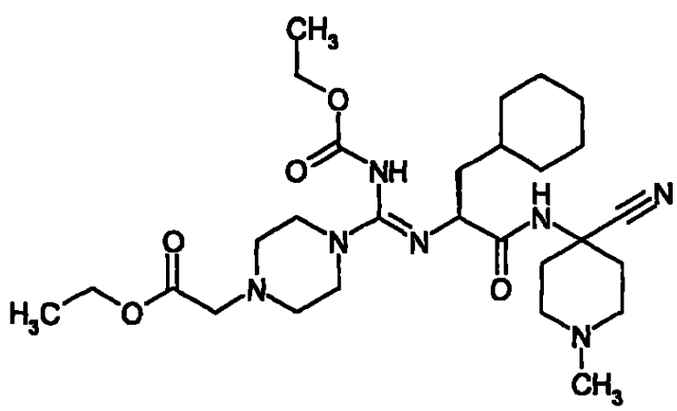
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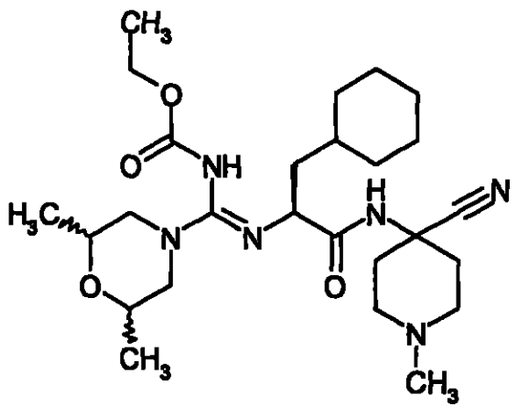
{(4-Carbamoyl-piperidin-1-yl)-[1-(4-cyano-1-methyl-piperidin-4-ylcarbamoyl)-2-cyclohexyl-ethylimino]-methyl}-carbamic acid ethyl ester; MS: 518 (M+1)



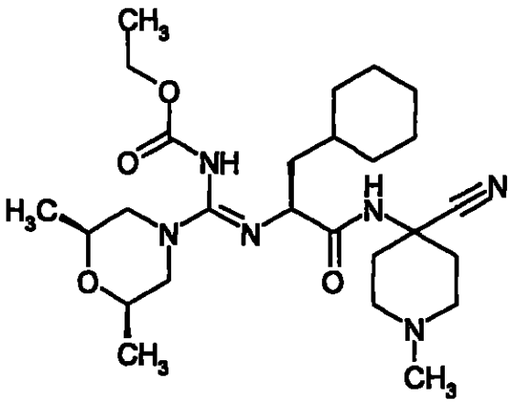
[[1-(4-Cyano-1-methyl-piperidin-4-ylcarbamoyl)-2-cyclohexyl-ethylimino]-(2-methoxymethyl-morpholin-4-yl)-methyl]-carbamic acid ethyl ester; MS: 521 (M+1)



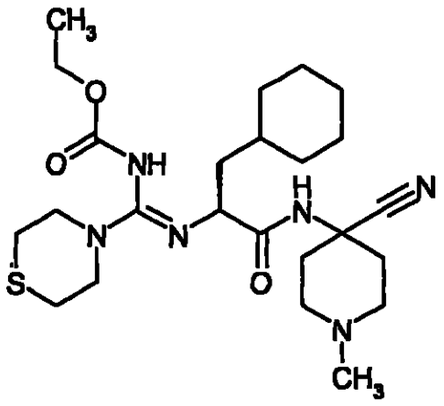
(4-{[1-(4-Cyano-1-methyl-piperidin-4-ylcarbamoyl)-2-cyclohexyl-ethylimino]-ethoxycarbonylamino-methyl}-piperazin-1-yl)-acetic acid ethyl ester; MS: 562 (M+1)



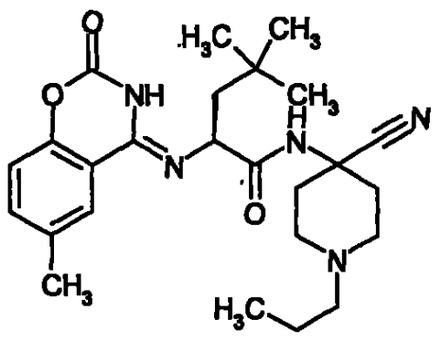
[[1-(4-Cyano-1-methyl-piperidin-4-ylcarbamoyl)-2-cyclohexyl-ethylimino]-(2,6-dimethyl-morpholin-4-yl)-methyl]-carbamic acid ethyl ester; MS: 505 (M+1)



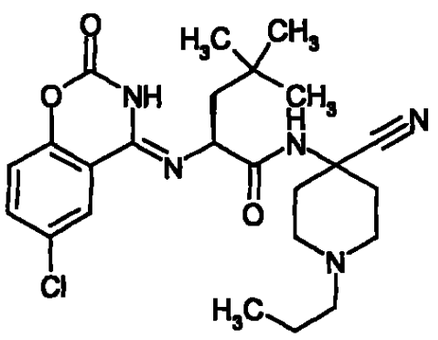
[[1-(4-Cyano-1-methyl-piperidin-4-ylcarbamoyl)-2-cyclohexyl-ethylimino]-(2,6-dimethyl-morpholin-4-yl)-methyl]-carbamic acid ethyl ester; MS: 505 (M+1)



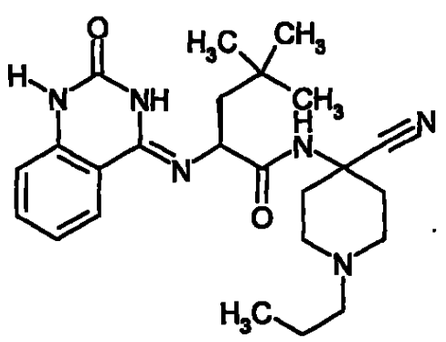
{[1-(4-Cyano-1-methyl-piperidin-4-ylcarbamoyl)-2-cyclohexyl-ethylimino]-thiomorpholin-4-yl-methyl}-carbamic acid ethyl ester; MS: 493 (M+1)



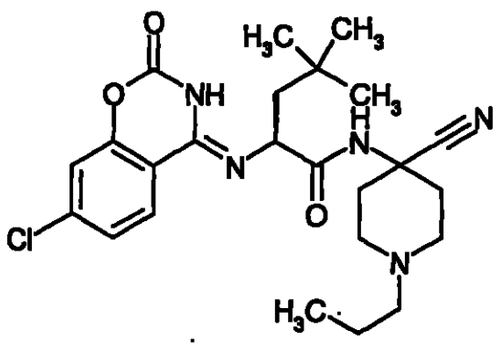
4,4-Dimethyl-2-(6-methyl-2-oxo-2,3-dihydro-benzo[*e*][1,3]oxazin-4-ylideneamino)-pentanoic acid (4-cyano-1-propyl-piperidin-4-yl)-amide; MS: 454 (M+1)



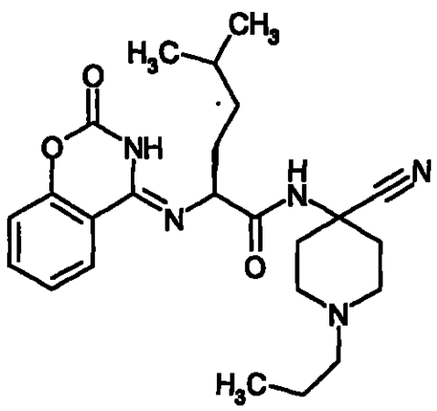
2-(6-Chloro-2-oxo-2,3-dihydro-benzo[*e*][1,3]oxazin-4-ylideneamino)-4,4-dimethyl-pentanoic acid (4-cyano-1-propyl-piperidin-4-yl)-amide; MS: 475 (M+1)



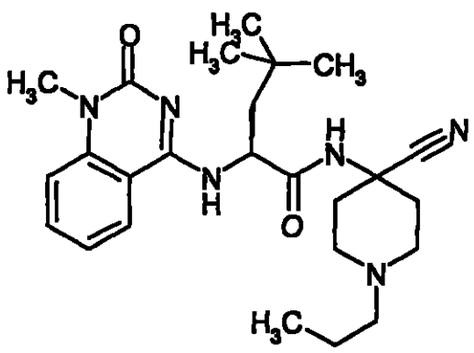
4,4-Dimethyl-2-(2-oxo-2,3-dihydro-1*H*-quinazolin-4-ylideneamino)-pentanoic acid (4-cyano-1-propyl-piperidin-4-yl)-amide; MS: 439 (M+1)



2-(7-Chloro-2-oxo-2,3-dihydro-benzo[*e*][1,3]oxazin-4-ylideneamino)-4,4-dimethyl-pentanoic acid (4-cyano-1-propyl-piperidin-4-yl)-amide; MS: 475 (M+1)



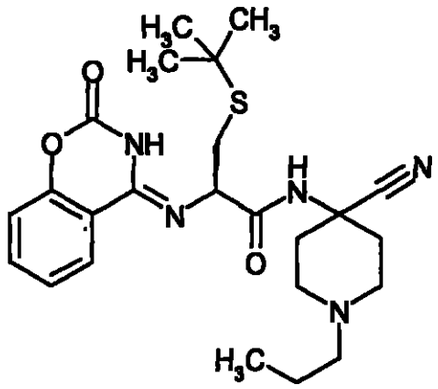
5-Methyl-2-(2-oxo-2,3-dihydro-benzo[*e*][1,3]oxazin-4-ylideneamino)-hexanoic acid (4-cyano-1-propyl-piperidin-4-yl)-amide; MS: 440 (M+1)



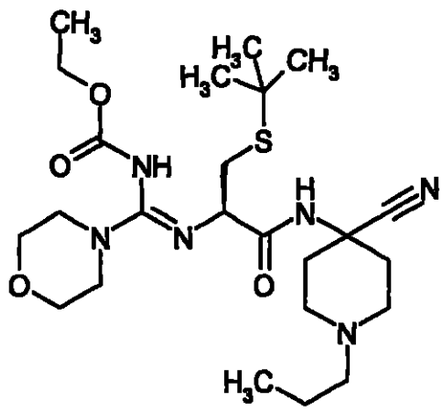
4,4-Dimethyl-2-(1-methyl-2-oxo-1,2-dihydro-quinazolin-4-ylamino)-pentanoic acid (4-cyano-1-propyl-piperidin-4-yl)-amide; MS: 453 (M+1)

149

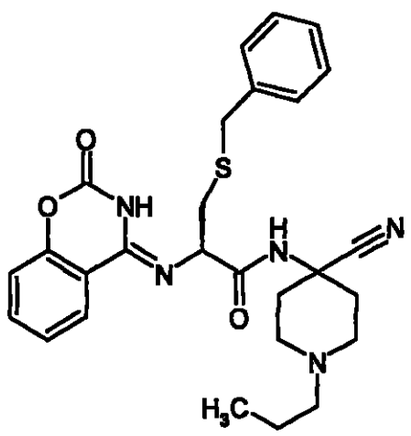
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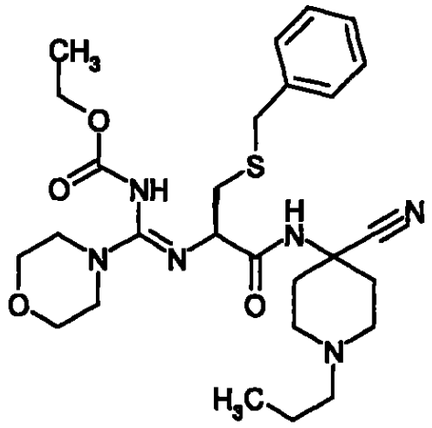
3-*tert*-Butylsulfanyl-*N*-(4-cyano-1-propyl-piperidin-4-yl)-2-(2-oxo-2,3-dihydro-benzo[*e*][1,3]oxazin-4-ylideneamino)-propionamide; MS: 472 (M+1)



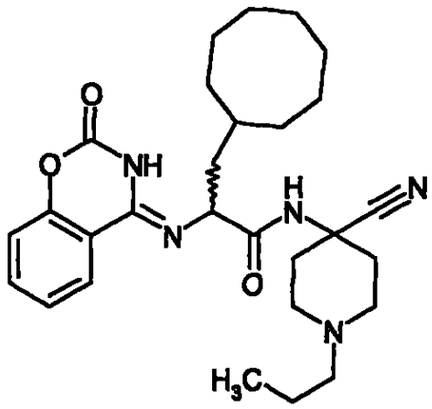
{[2-*tert*-Butylsulfanyl-1-(4-cyano-1-propyl-piperidin-4-ylcarbamoyl)-ethylimino]-morpholin-4-yl-methyl}-carbamic acid ethyl ester; MS: 511 (M+1)



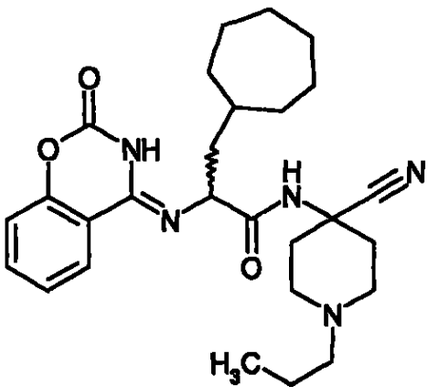
3-Benzylsulfanyl-*N*-(4-cyano-1-propyl-piperidin-4-yl)-2-(2-oxo-2,3-dihydro-benzo[*e*][1,3]oxazin-4-ylideneamino)-propionamide; MS: 506 (M+1)



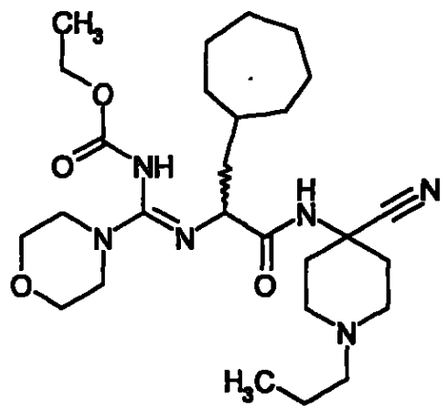
{[2-Benzylsulfanyl-1-(4-cyano-1-propyl-piperidin-4-ylcarbamoyl)-ethylimino]-morpholin-4-yl-methyl}-carbamic acid ethyl ester; MS: 545 (M+1)



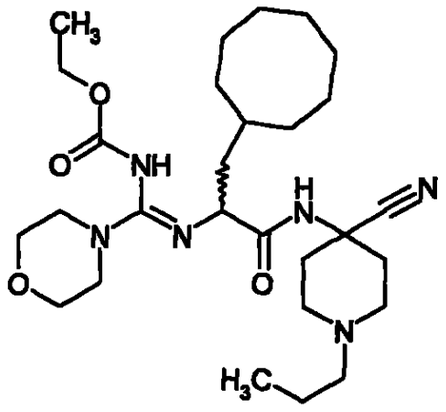
*N*-(4-Cyano-1-propyl-piperidin-4-yl)-3-cyclooctyl-2-(2-oxo-2,3-dihydro-benzo[*e*][1,3]oxazin-4-ylideneamino)-propionamide; MS: 494 (M+1)



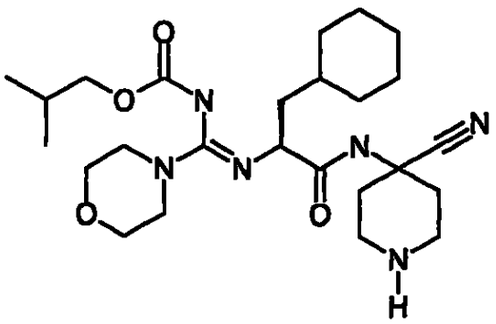
*N*-(4-Cyano-1-propyl-piperidin-4-yl)-3-cycloheptyl-2-(2-oxo-2,3-dihydro-benzo[*e*][1,3]oxazin-4-ylideneamino)-propionamide; MS: 480 (M+1)



{[1-(4-Cyano-1-propyl-piperidin-4-ylcarbamoyl)-2-cycloheptyl-ethylimino]-morpholin-4-yl-methyl}-carbamic acid ethyl ester; MS: 519 (M+1)

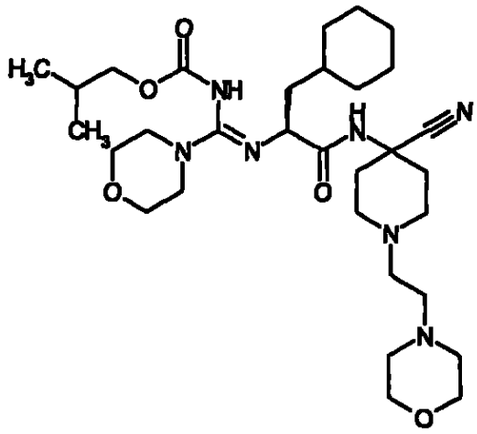


{[1-(4-Cyano-1-propyl-piperidin-4-ylcarbamoyl)-2-cyclooctyl-ethylimino]-morpholin-4-yl-methyl}-carbamic acid ethyl ester; MS: 533 (M+1)

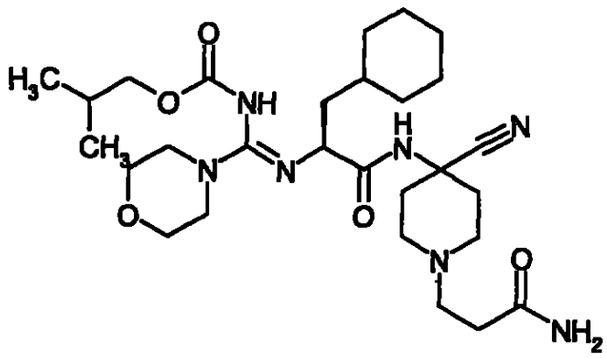


{[1-(4-Cyano-piperidin-4-ylcarbamoyl)-2-cyclohexyl-ethylamino]-morpholin-4-yl-methylene}-carbamic acid isobutyl ester; MS: 491 (M+1)

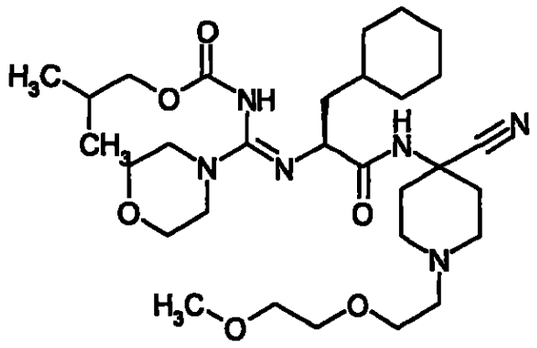
153



({1-[4-Cyano-1-(2-morpholin-4-yl-ethyl)-piperidin-4-ylcarbamoyl]-2-cyclohexyl-ethylamino}-morpholin-4-yl-methylene)-carbamic acid isobutyl ester; MS: 604 (M+1)



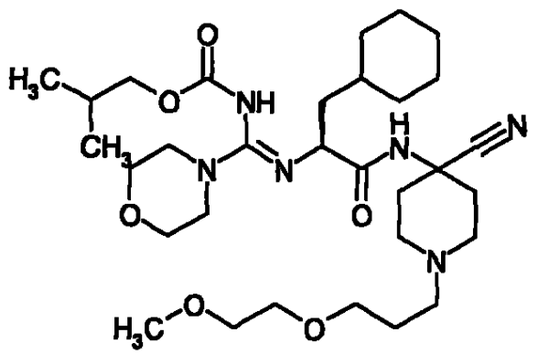
({1-[1-2-Carbamoyl-ethyl)-4-cyano-piperidin-4-ylcarbamoyl]-2-cyclohexyl-ethylamino}-morpholin-4-yl-methylene)-carbamic acid isobutyl ester; MS: 562 (M+1)



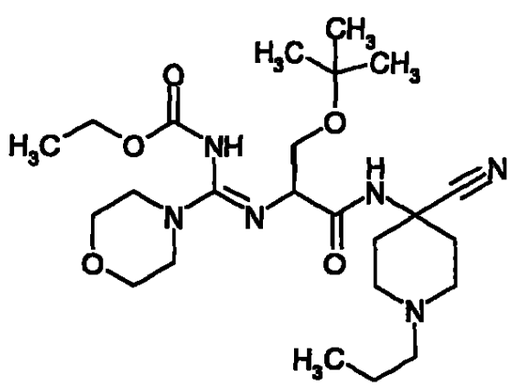
[(1-{4-Cyano-1-[2-(2-methoxyl-ethoxy)-ethyl]-piperidin-4-ylcarbamoyl}-2-cyclohexyl-ethylamino)-morpholin-4-yl-methylene]-carbamic acid isobutyl ester; MS: 593 (M+1)

153

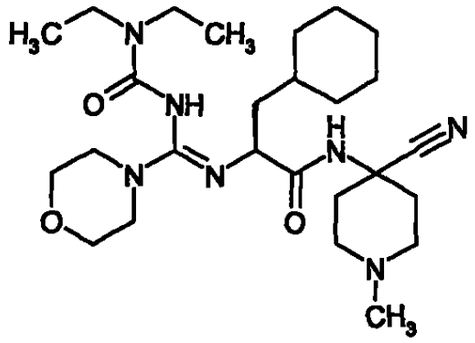
154



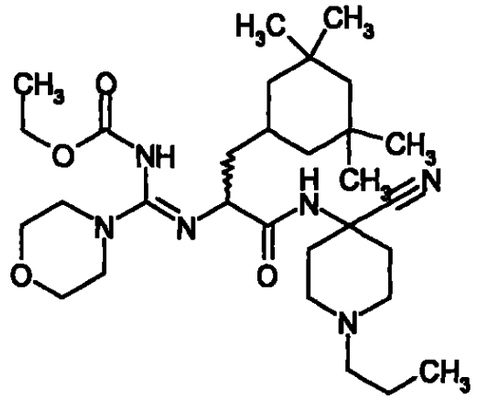
[(1-{4-Cyano-1-[3-(2-methoxyl-ethoxy)-propyl]-piperidin-4-ylcarbamoyl}-2-cyclohexyl-ethylamino)-morpholin-4-yl-methylene]-carbamic acid isobutyl ester; MS: 607 (M+1)



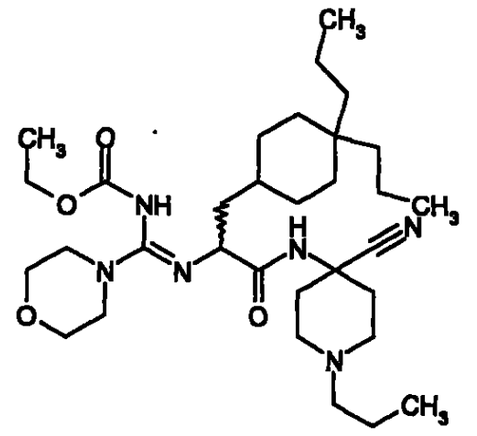
{[2-tert-Butoxy-1-(4-cyano-1-propyl-piperidin-4-ylcarbamoly)-ethylamino]-morpholin-4-yl-methylene}-carbamic acid ethyl ester; MS: 495 (M+1)



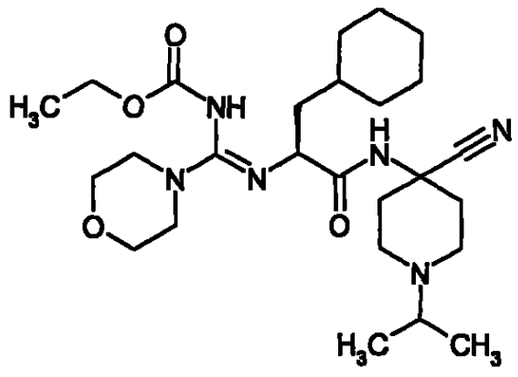
N-(4-Cyano-1-methyl-piperidin-4-yl)-3-cyclohexyl-2-{[diethyl-carbamoylimino)-morpholin-4-yl-methyl]-amino}-propionamide; MS: 504 (M+1)



{[1-(4-Cyano-1-propyl-piperidin-4-ylcarbamoyl)-2-(3,3,5,5-tetramethyl-cyclohexyl)-ethylamino]-morpholin-4-yl-methylene}-carbamic acid ethyl ester; MS: 561 (M+1)

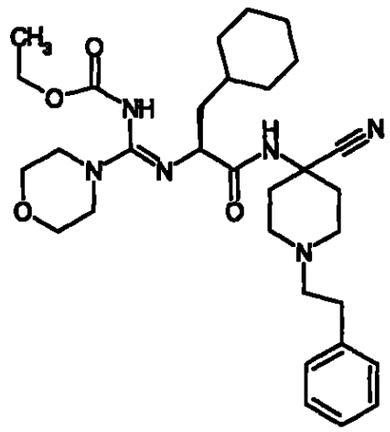


{[1-(4-Cyano-1-propyl-piperidin-4-ylcarbamoyl)-2-(4,4-dipropyl-cyclohexyl)-ethylamino]-morpholin-4-yl-methylene}-carbamic acid ethyl ester; MS: 589 (M+1)

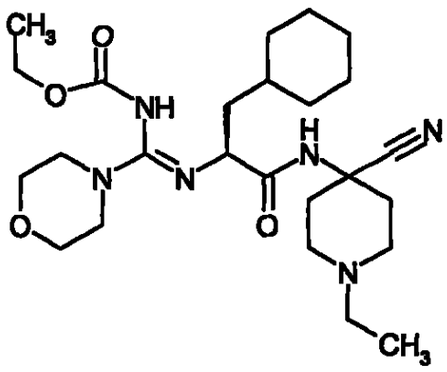


{[1-(4-Cyano-1-isopropyl-piperidin-4-ylcarbamoyl)-2-cyclohexyl-ethylamino]-morpholin-4-yl-methylene}-carbamic acid ethyl ester; MS: 505 (M+1)

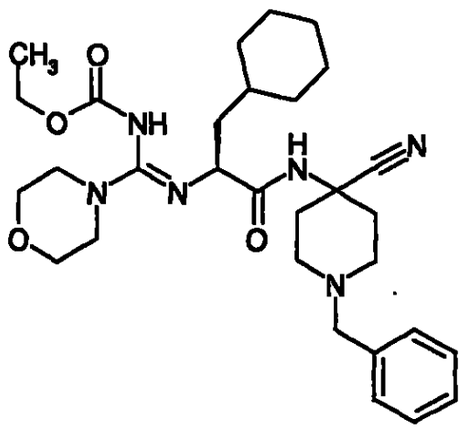
156



{[1-(4-Cyano-1-phenethyl-piperidin-4-ylcarbamoyl)-2-cyclohexyl-ethylamino]-morpholin-4-yl-methylene}-carbamic acid ethyl ester; MS: 567 (M+1)

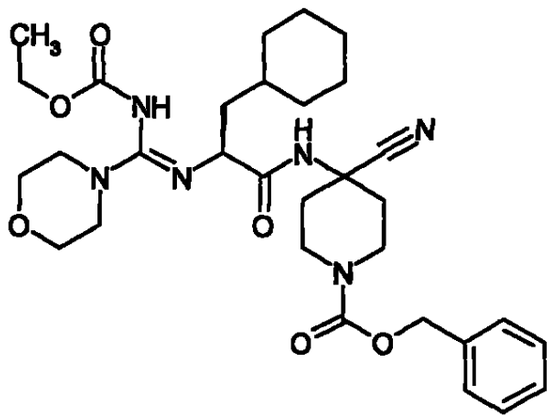


{[1-(4-Cyano-1-ethyl-piperidin-4-ylcarbamoyl)-2-cyclohexyl-ethylamino]-morpholin-4-yl-methylene}-carbamic acid ethyl ester; MS: 491 (M+1)

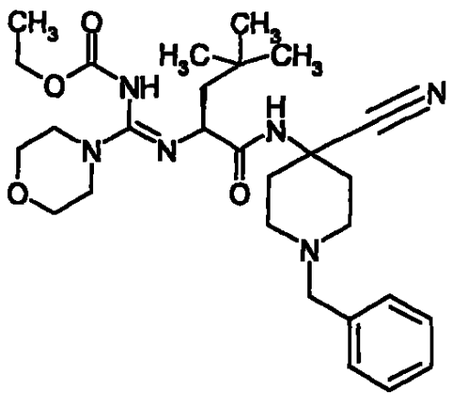


{[1-(1-Benzyl-4-cyano-piperidin-4-ylcarbamoyl)-2-cyclohexyl-ethylamino]-morpholin-4-yl-methylene}-carbamic acid ethyl ester; MS: 553 (M+1)

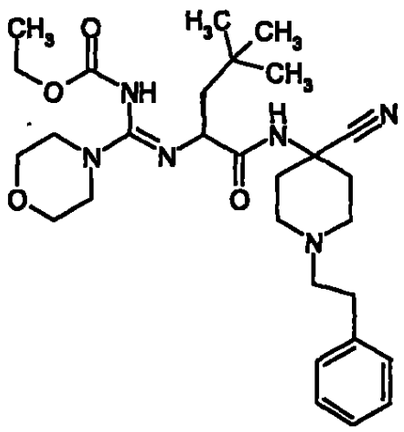
157



4-Cyano-4-{3-cyclohexyl-2-[(ethoxycarbonylimino-morpholin-4-yl-methyl)-amino]-propionylamino}-piperidine-1-carboxylic acid benzyl ester; MS: 597 (M+1)

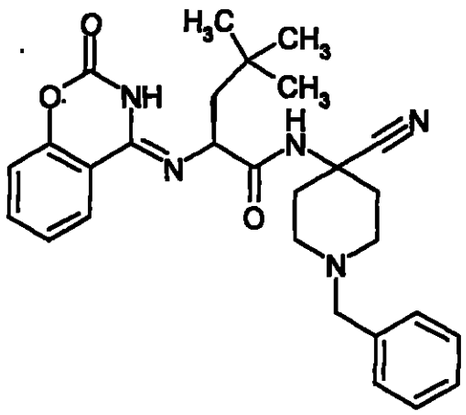


{[1-(1-Benzyl-4-cyano-piperidin-4-ylcarbamoyl)-3,3-dimethyl-butylamino]-morpholin-4-yl-methylene}-carbamic acid ethyl ester; MS: 527 (M+1)

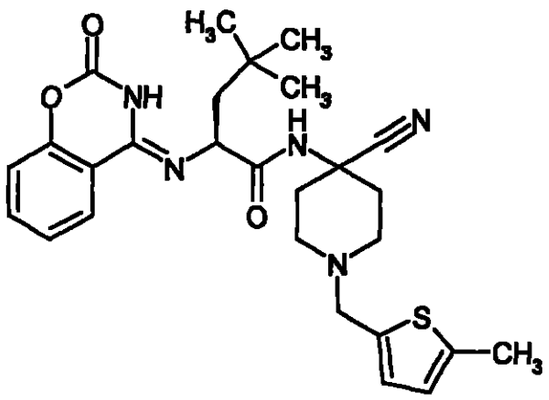


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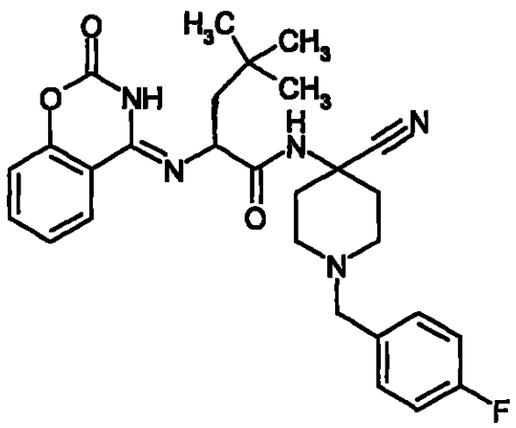
{[1-(4-cyano-1-phenethyl-piperidin-4-ylcarbamoyl)-3,3-dimethyl-butylamino]-morpholin-4-yl-methylene}-carbamic acid ethyl ester; MS: 541 (M+1)



4,4-Dimethyl-2-(2-oxo-2H-benzo[e][1,3]oxazin-4-ylamino)-pentanoic acid (1-benzyl-4-cyano-piperidin-4-yl)-amide; MS: 488 (M+1)

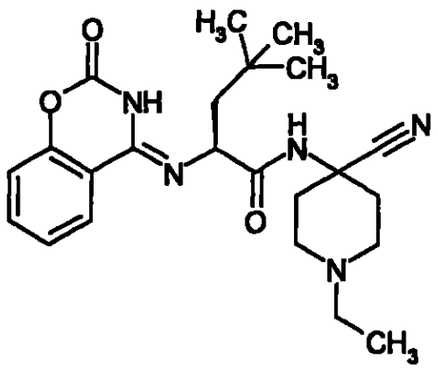


4,4-Dimethyl-2-(2-oxo-2H-benzo[e][1,3]oxazin-4-ylamino)-pentanoic acid [4-cyano-1-(5-methyl-thiophen-2-ylmethyl)-piperidin-4-yl]-amide; MS: 508 (M+1)

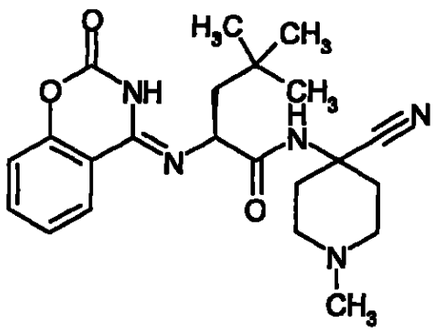


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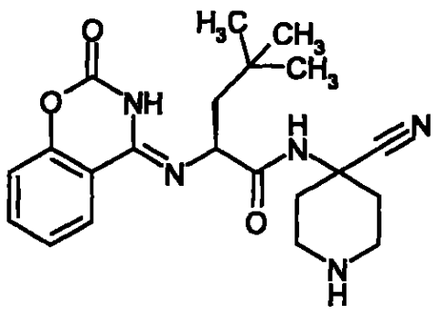
4,4-Dimethyl-2-(2-oxo-2H-benzo[e][1,3]oxazin-4-ylamino)-pentanoic acid [4-cyano-1-(4-fluoro-benzyl)-piperidin-4-yl]-amide; MS: 506 (M+1)



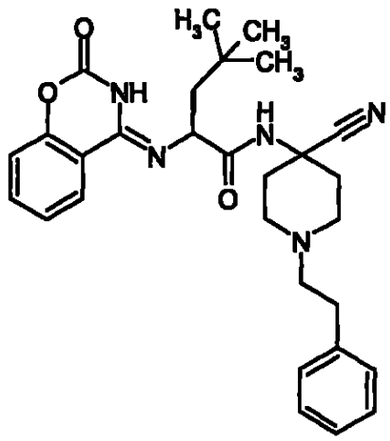
4,4-Dimethyl-2-(2-oxo-2H-benzo[e][1,3]oxazin-4-ylamino)-pentanoic acid (4-cyano-1-ethyl-piperidin-4-yl)-amide; MS: 426 (M+1)



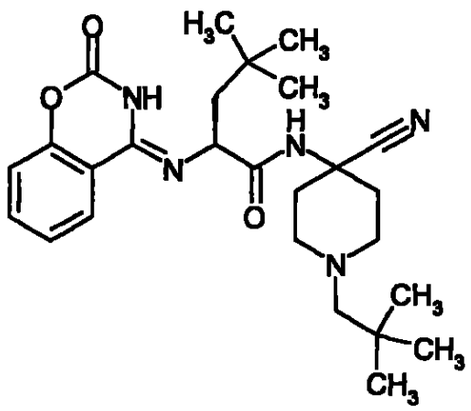
4,4-Dimethyl-2-(2-oxo-2H-benzo[e][1,3]oxazin-4-ylamino)-pentanoic acid (4-cyano-1-methyl-piperidin-4-yl)-amide; MS: 412 (M+1)



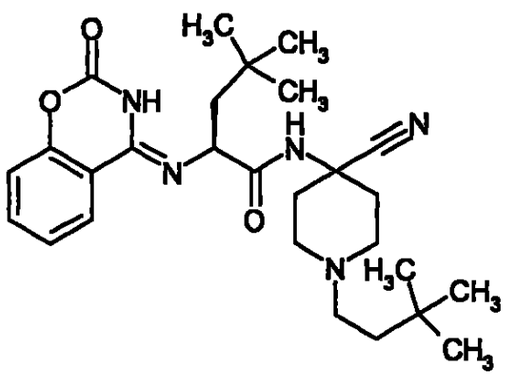
4,4-Dimethyl-2-(2-oxo-2H-benzo[e][1,3]oxazin-4-ylamino)-pentanoic acid (4-cyano-piperidin-4-yl)-amide; MS: 398 (M+1)



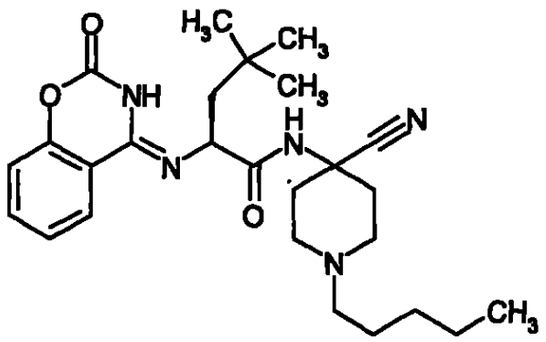
4,4-Dimethyl-2-(2-oxo-2H-benzo[e][1,3]oxazin-4-ylamino)-pentanoic acid (4-cyano-1-phenethyl-piperidin-4-yl)-amide; MS: 502 (M+1)



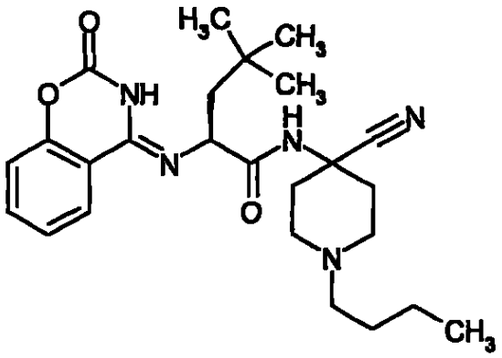
4,4-Dimethyl-2-(2-oxo-2H-benzo[e][1,3]oxazin-4-ylamino)-pentanoic acid [4-cyano-1-(2,2-dimethyl-propyl)-piperidin-4-yl]-amide; MS: 468 (M+1)



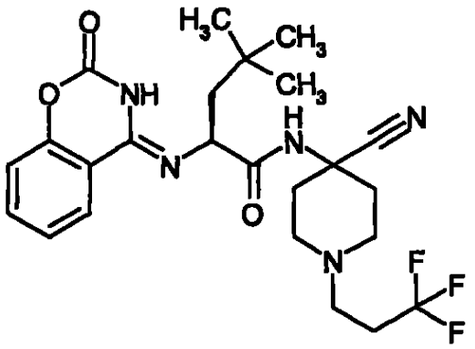
4,4-Dimethyl-2-(2-oxo-2H-benzo[e][1,3]oxazin-4-ylamino)-pentanoic acid [4-cyano-1-(3,3-dimethyl-butyl)-piperidin-4-yl]-amide; MS: 482 (M+1)



4,4-Dimethyl-2-(2-oxo-2H-benzo[e][1,3]oxazin-4-ylamino)-pentanoic acid (4-cyano-1-pentyl-piperidin-4-yl)-amide; MS: 468 (M+1)



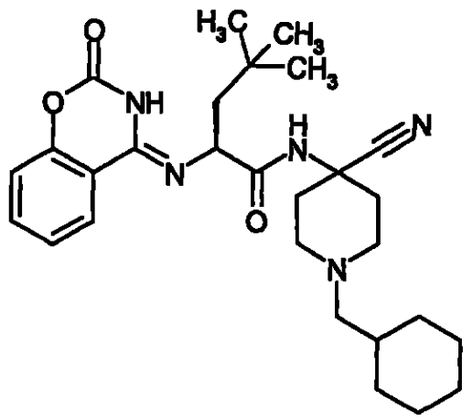
4,4-Dimethyl-2-(2-oxo-2H-benzo[e][1,3]oxazin-4-ylamino)-pentanoic acid (1-butyl-4-cyano-piperidin-4-yl)-amide; MS: 454(M+1)



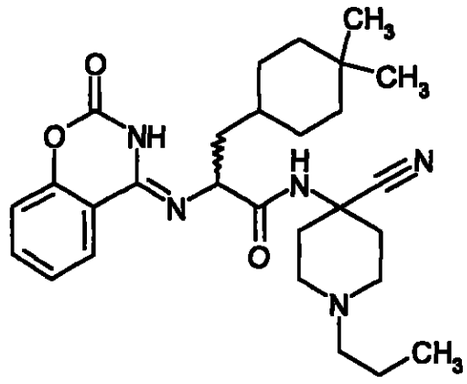
4,4-Dimethyl-2-(2-oxo-2H-benzo[e][1,3]oxazin-4-ylamino)-pentanoic acid [4-cyano-1-(3,3,3-trifluoro-propyl)-piperidin-4-yl]-amide; MS: 494 (M+1)

161

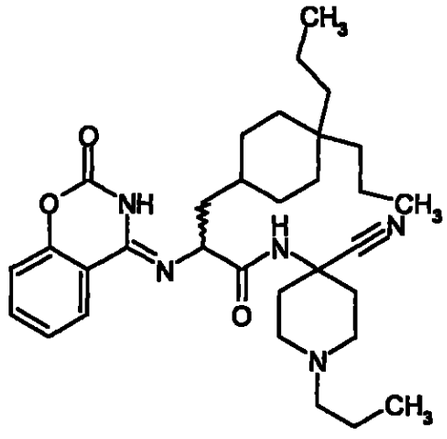
162



4,4-Dimethyl-2-(2-oxo-2H-benzo[e][1,3]oxazin-4-ylamino)-pentanoic acid (4-cyano-1-cyclohexylmethyl-piperidin-4-yl)-amide; MS: 494 (M+1)

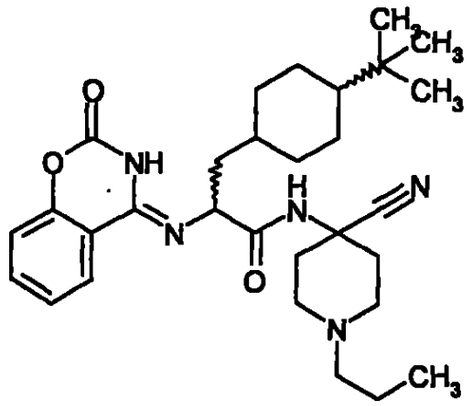


N-(4-Cyano-1-propyl-piperidin-4-yl)-3-(4,4-dimethyl-cyclohexyl)-2-(2-oxo-2H-benzo[e][1,3]oxazin-4-ylamino)-propionamide; MS: 494 (M+1)

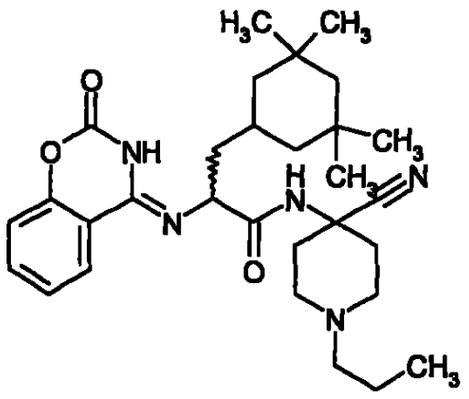


N-(4-Cyano-1-propyl-piperidin-4-yl)-3-(4,4-dipropyl-cyclohexyl)-2-(2-oxo-

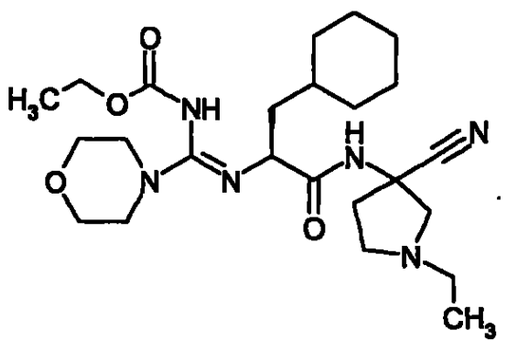
2H-benzo[e][1,3]oxazin-4-ylamino)-propionamide; MS: 550 (M+1)



N-(4-Cyano-1-propyl-piperidin-4-yl)-3-(4-tert-butyl-cyclohexyl)-2-(2-oxo-
2H-benzo[e][1,3]oxazin-4-ylamino)-propionamide; MS: 522 (M+1)

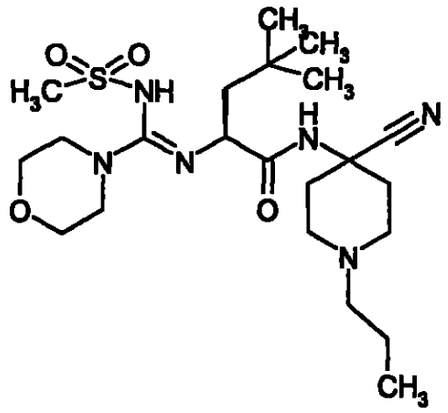


N-(4-Cyano-1-propyl-piperidin-4-yl)-3-(3,3,5,5-tetramethyl-cyclohexyl)-2-(2-oxo-
2H-benzo[e][1,3]oxazin-4-ylamino)-propionamide; MS: 522 (M+1)

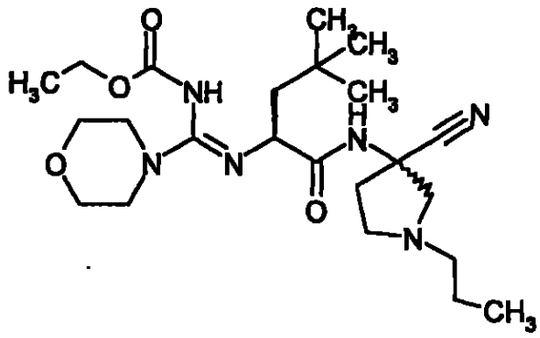


164

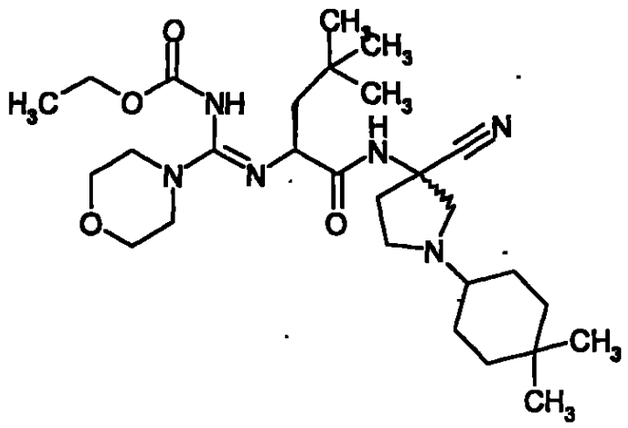
{[1-(3-Cyano-1-ethyl-pyrrolidin-3-ylcarbamoyl)-2-cyclohexyl-ethylamino]-morpholin-4-yl-methylene}-carbamic acid ethyl ester. MS: 477 (M+1).



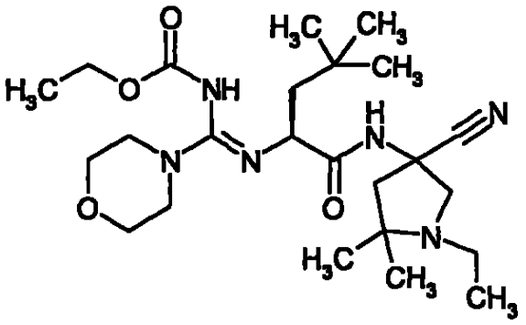
2-[(Methanesulfonylimino-morpholin-4-yl-methyl)-amino]-4,4-dimethyl-pentanoic acid (4-cyano-1-propyl-piperidin-4-yl)-amide. MS: 485 (M+1).



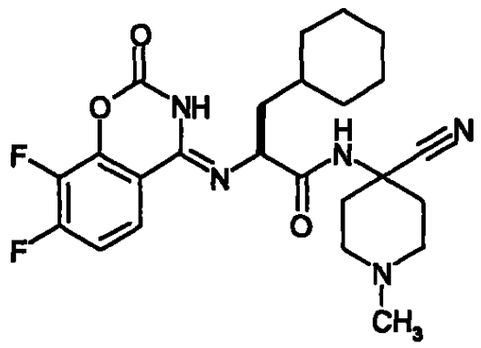
{[1-(3-Cyano-1-propyl-pyrrolidin-3-ylcarbamoyl)-3,3-dimethyl-butylamino]-morpholin-4-yl-methylene}-carbamic acid ethyl ester. MS: 465 (M+1).



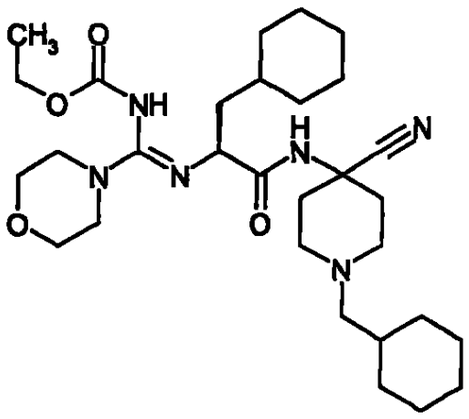
({1-[3-Cyano-1-(4,4-dimethyl-cyclohexyl)-pyrrolidin-3-ylcarbamoyl]-3,3-dimethyl-butylamino}-morpholin-4-yl-methylene)-carbamic acid ethyl ester. MS: 533 (M+1).



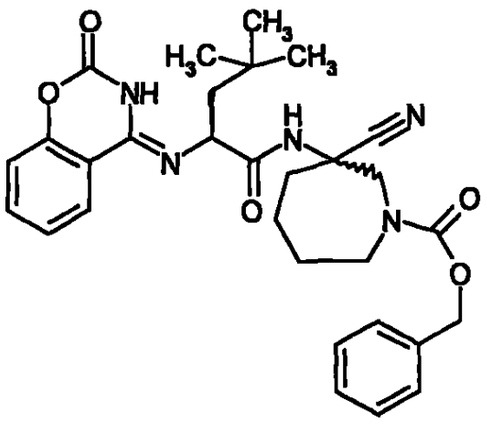
{[1-(3-Cyano-1-ethyl-5,5-dimethyl-pyrrolidin-3-ylcarbamoyl)-3,3-dimethyl-butylamino]-morpholin-4-yl-methylene}-carbamic acid ethyl ester. MS: 479 (M+1).



N-(4-Cyano-1-methyl-piperidin-4-yl)-3-cyclohexyl-2-(7,8-difluoro-2-oxo-2H-benzo[e][1,3]oxazin-4-ylamino)-propionamide; MS: 474 (M+1)



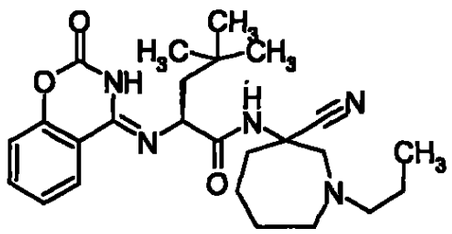
{[1-(4-Cyano-1-cyclohexylmethyl-piperidin-4-ylcarbamoyl)-2-cyclohexyl-ethylamino]-morpholin-4-yl-methylene}-carbamic acid ethyl ester; MS: 559 (M+1)



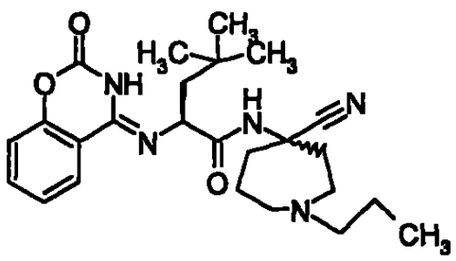
166

167

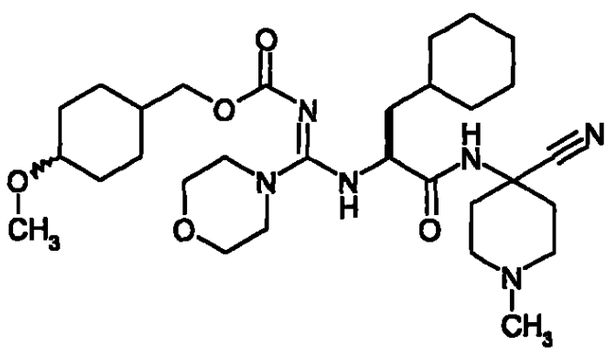
3-Cyano-3-[4,4-dimethyl-2-(2-oxo-2*H*-benzo[*e*][1,3]oxazin-4-ylamino)-pentanoylamino]-azepane-1-carboxylic acid benzyl ester; MS: 546 (M+1)



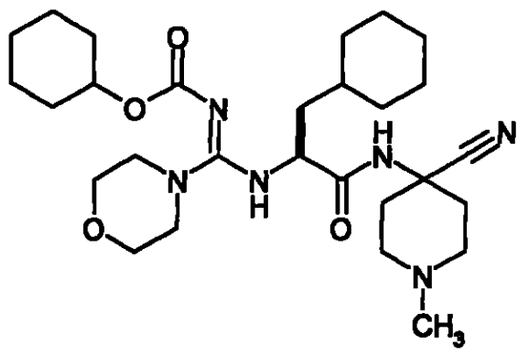
4,4-Dimethyl-2-(2-oxo-2*H*-benzo[*e*][1,3]oxazin-4-ylamino)-pentanoic acid (3-cyano-1-propyl-azepan-3-yl)-amide; MS: 454 (M+1)



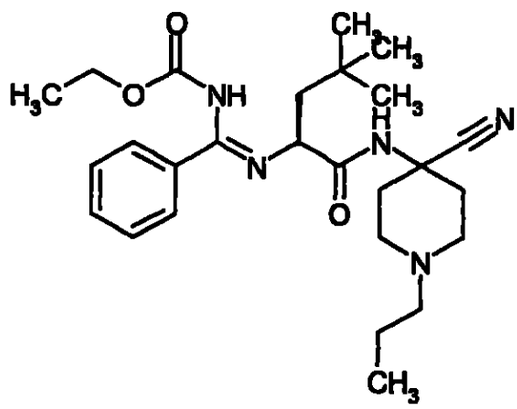
4,4-Dimethyl-2-(2-oxo-2*H*-benzo[*e*][1,3]oxazin-4-ylamino)-pentanoic acid (4-cyano-1-propyl-azepan-4-yl)-amide; MS: 454 (M+1)



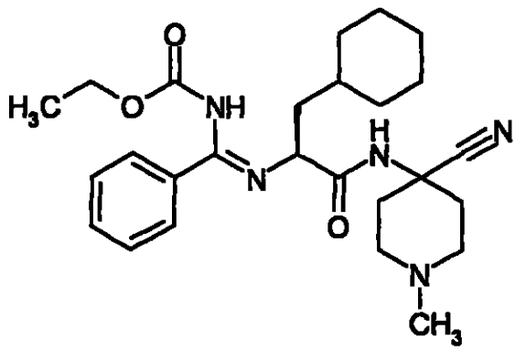
{[1-(4-Cyano-1-methyl-piperidin-4-ylcarbamoyl)-2-cyclohexyl-ethylamino]-morpholin-4-yl-methylene}-carbamic acid 4-methoxy-cyclohexylmethyl ester; MS: 575 (M+1)



{[1-(4-Cyano-1-methyl-piperidin-4-ylcarbamoyl)-2-cyclohexyl-ethylamino]-morpholin-4-yl-methylene}-carbamic acid cyclohexyl ester; MS: 531 (M+1)



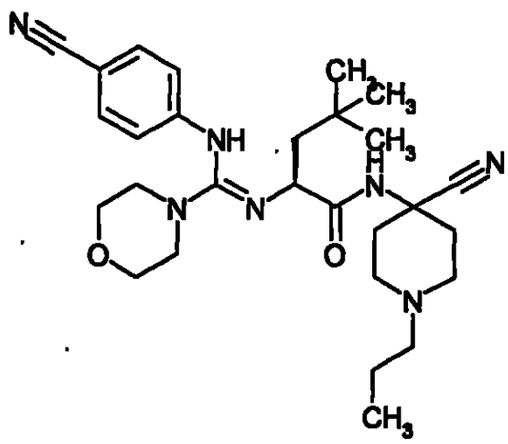
{[1-(4-Cyano-1-propyl-piperidin-4-ylcarbamoyl)-3,3-dimethyl-butylamino]-phenyl-methylene}-carbamic acid ethyl ester; MS: 470 (M+1)



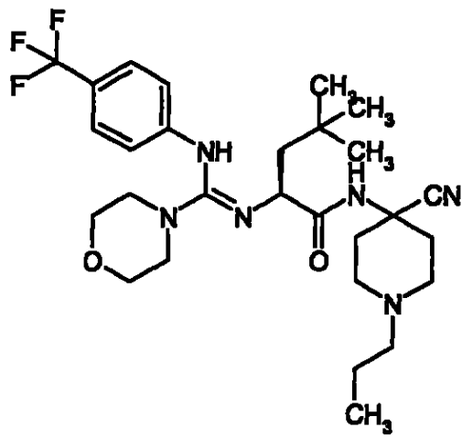
{[1-(4-Cyano-1-methyl-piperidin-4-ylcarbamoyl)-2-cyclohexyl-ethylamino]-phenyl-methylene}-carbamic acid ethyl ester; MS: 468 (M+1)

168

169

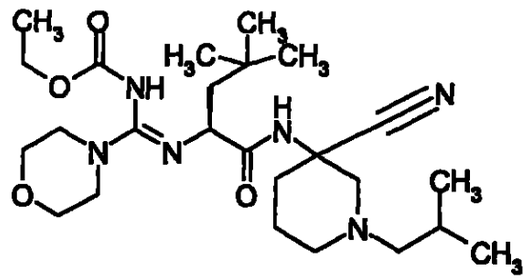


2-{[N-(4-Cyano-phenyl)-morpholine-4-carboximidoyl]-amino}-4,4-dimethyl-pentanoic acid (4-cyano-1-propyl-piperidin-4-yl)-amide; MS: 508 (M+1)

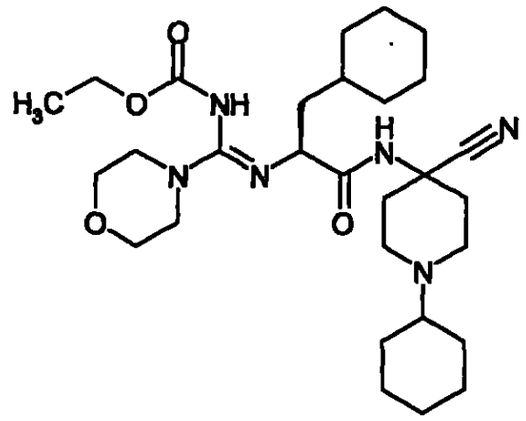


4,4-Dimethyl-2-{[N-(4-trifluoromethyl-phenyl)-morpholine-4-carboximidoyl]-amino}-pentanoic acid (4-cyano-1-propyl-piperidin-4-yl)-amide; MS: 551 (M+1)

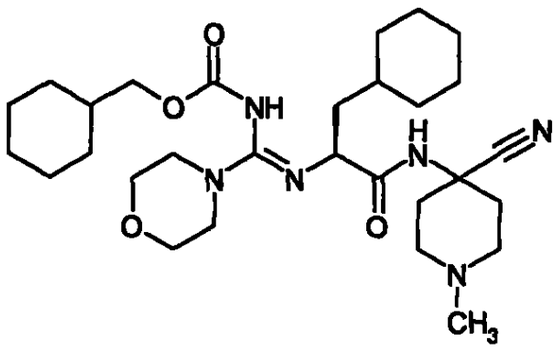
The following are preferred compounds of the Formulas (Ia) and (Ib):



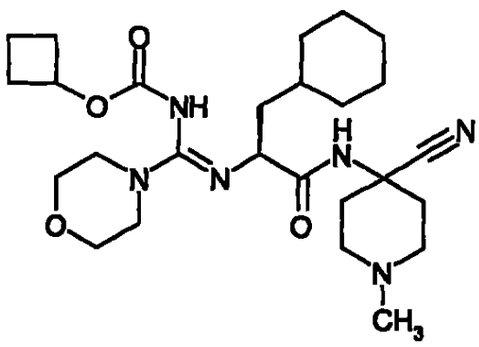
{[1-(3-cyano-1-isobutyl-piperdin-3-yl carbamoyl)-3,3-dimethyl-butylamino]-morpholin-4-yl-methylene}-carbamic acid ethyl ester; MS: 493 (M+1)



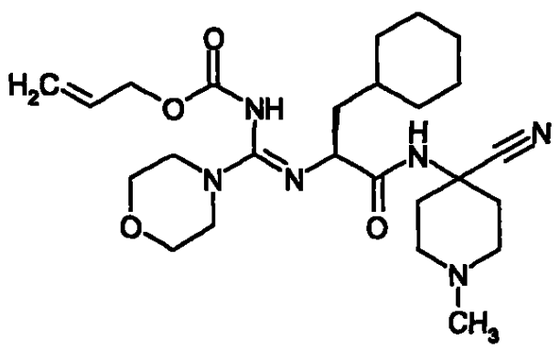
{[1-(4-cyano-1-cyclohexyl-piperidin-4-ylcarbamoyl)-2-cyclohexyl-ethylamino]-morpholin-4-yl-methylene}-carbamic acid ethyl ester; MS: 545 (M+1)



{[1-(4-cyano-1-methyl-piperidin-4-ylcarbamoyl)-2-cyclohexyl-ethylamino]-morpholin-4-yl-methylene}-carbamic acid cyclohexylmethyl ester; MS: 545 (M+1)

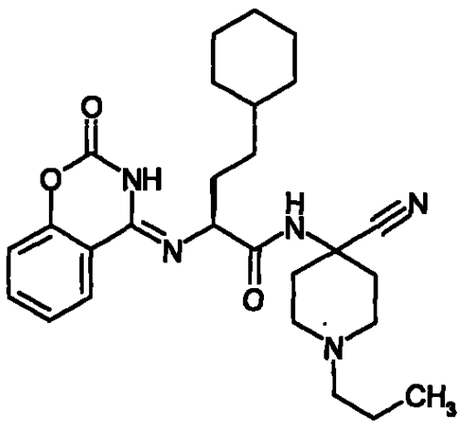


{[-1-(4-cyano-1-methyl-piperidin-4-ylcarbamoyl)-2-cyclohexyl-ethylamino]-morpholin-4-yl-methylene}-carbamic acid cyclobutyl ester; MS: 503 (M+1)

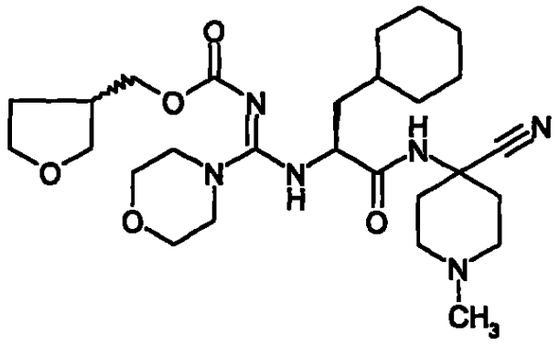


{[1-(4-cyano-1-methyl-piperidin-4-ylcarbamoyl)-2-cyclohexyl-ethylamino]-morpholin-4-yl-methylene}-carbamic acid allyl ester; MS: 489 (M+1)

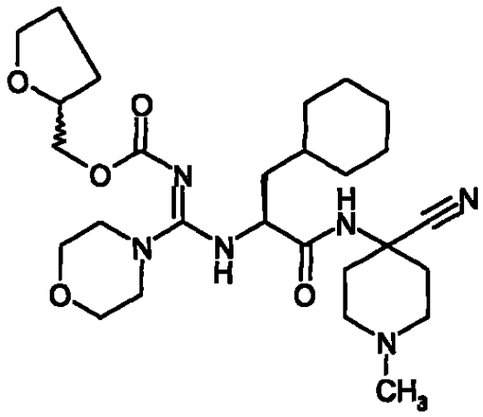
172



N-(4-Cyano-1-propyl-piperidin-4-yl)-4-cyclohexyl-2-(2-oxo-2,3-dihydro-benzo[e][1,3]oxazin-4-ylideneamino)-butyramide; MS: 480 (M+1)

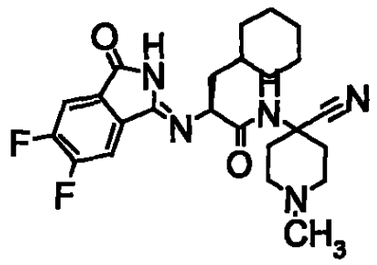


{[ 1-(4-cyano-1-methyl-piperidin-4-ylcarbamoyl)-2-cyclohexyl-ethylamino]-morpholin-4-yl-methylene}-carbamic acid tetrahydro-furan-3ylmethyl ester; MS: 533 (M+1)

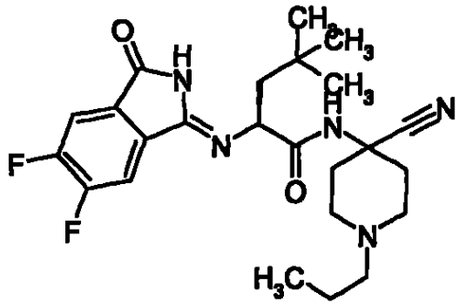


{[1-(4-cyano-1-methy-piperidin-4-ylcarbamoyl)-2-cyclohexyl-ethyl amino]-morpholin-4-yl-methylene}-carbamic acid tetrahydro-furan-2-ylmethyl ester; MS: 533 (M+1)

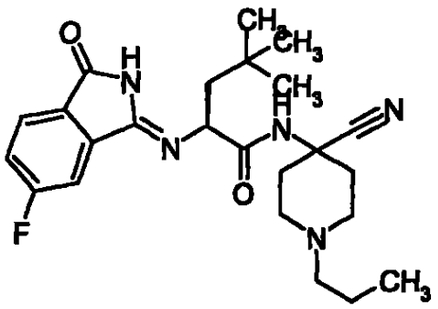
172
173



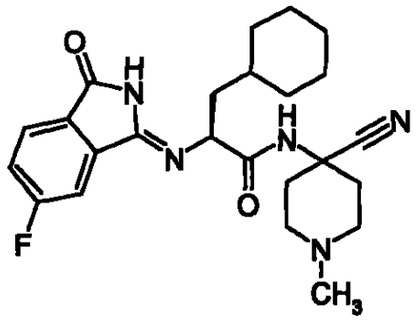
*N*-(4-Cyano-1-methyl-piperidin-4-yl)-3-cyclohexyl-2-(5,6-difluoro-3-oxo-2,3-dihydro-isoindol-1-ylideneamino)-propionamide; MS: 458 (M+1)



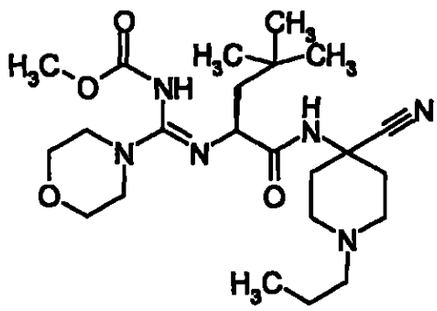
2-(5,6-Difluoro-3-oxo-2,3-dihydro-isoindol-1-ylideneamino)-4,4-dimethyl-pentanoic acid (4-cyano-1-propyl-piperidin-4-yl)-amide; MS: 460 (M+1)



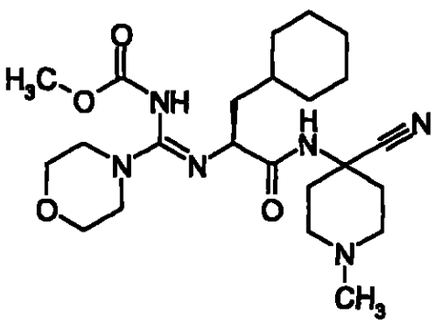
2-(6-Fluoro-3-oxo-2,3-dihydro-isoindol-1-ylideneamino)-4,4-dimethyl-pentanoic acid (4-cyano-1-propyl-piperidin-4-yl)-amide; MS: 442 (M+1)



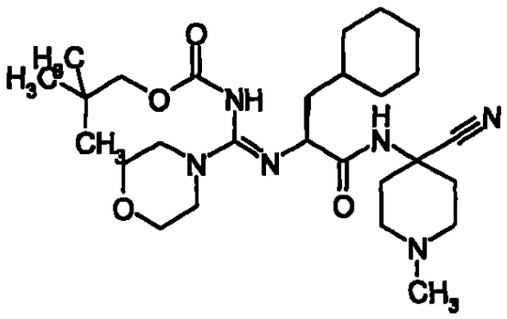
*N*-(4-Cyano-1-methyl-piperidin-4-yl)-3-cyclohexyl-2-(6-fluoro-3-oxo-2,3-dihydro-isoindol-1-ylideneamino)-propionamide; MS: 440 (M+1)



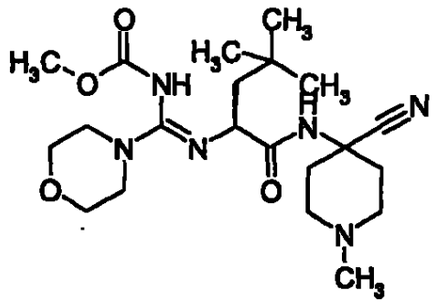
{[1-(4-Cyano-1-propyl-piperidin-4-ylcarbamoyl)-3,3-dimethyl-butylimino]-morpholin-4-yl-methyl}-carbamic acid methyl ester; MS: 465 (M+1)



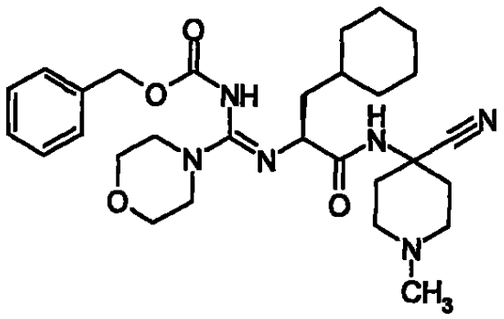
{[1-(4-Cyano-1-methyl-piperidin-4-ylcarbamoyl)-2-cyclohexyl-ethylimino]-morpholin-4-yl-methyl}-carbamic acid methyl ester; MS: 463 (M+1)



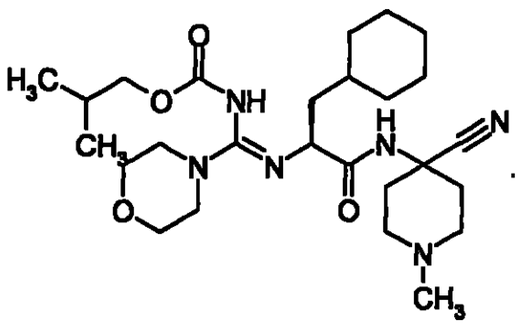
{[1-(4-Cyano-1-methyl-piperidin-4-ylcarbamoyl)-2-cyclohexyl-ethylimino]-morpholin-4-yl-methyl}-carbamic acid 2,2-dimethyl-propyl ester; MS: 519 (M+1)



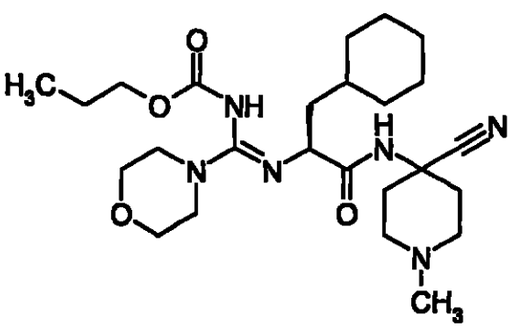
{[1-(4-Cyano-1-methyl-piperidin-4-ylcarbamoyl)-3,3-dimethyl-butylimino]-morpholin-4-yl-methyl}-carbamic acid methyl ester; MS: 437 (M+1)



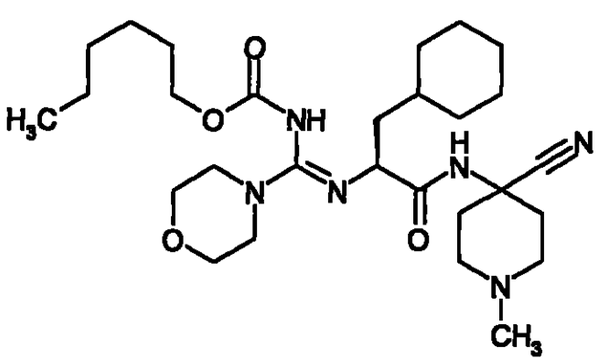
{[1-(4-Cyano-1-methyl-piperidin-4-ylcarbamoyl)-2-cyclohexyl-ethylimino]-morpholin-4-yl-methyl}-carbamic acid benzyl ester; MS: 539 (M+1)



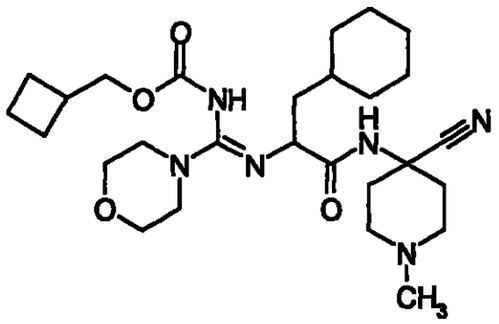
{[1-(4-Cyano-1-methyl-piperidin-4-ylcarbamoyl)-2-cyclohexyl-ethylimino]-morpholin-4-yl-methyl}-carbamic acid isobutyl ester; MS: 505 (M+1)



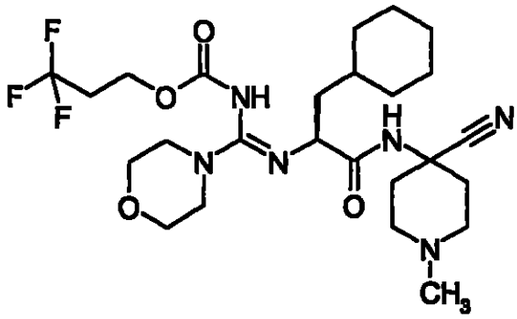
{[1-(4-Cyano-1-methyl-piperidin-4-ylcarbamoyl)-2-cyclohexyl-ethylimino]-morpholin-4-yl-methyl}-carbamic acid propyl ester; MS: 491 (M+1)



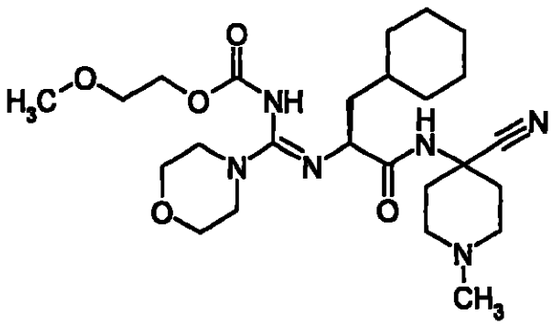
{[1-(4-Cyano-1-methyl-piperidin-4-ylcarbamoyl)-2-cyclohexyl-ethylimino]-morpholin-4-yl-methyl}-carbamic acid hexyl ester; MS: 533 (M+1)



{[1-(4-Cyano-1-methyl-piperidin-4-ylcarbamoyl)-2-cyclohexyl-ethylimino]-morpholin-4-yl-methyl}-carbamic acid cyclobutylmethyl ester; MS: 517 (M+1)

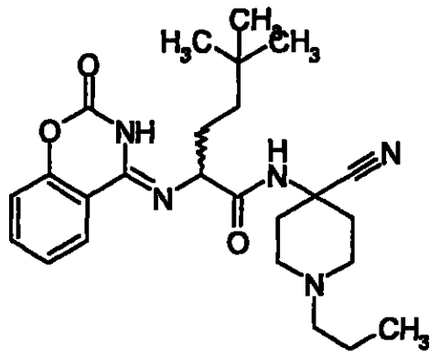


{[1-(4-Cyano-1-methyl-piperidin-4-ylcarbamoyl)-2-cyclohexyl-ethylimino]-morpholin-4-yl-methyl}-carbamic acid 3,3,3-trifluoro-propyl ester; MS: 545 (M+1)

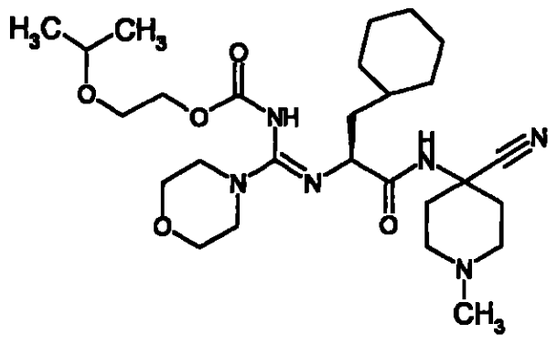


{[1-(4-Cyano-1-methyl-piperidin-4-ylcarbamoyl)-2-cyclohexyl-ethylimino]-morpholin-4-yl-methyl}-carbamic acid 2-methoxy-ethyl ester; MS: 507 (M+1)

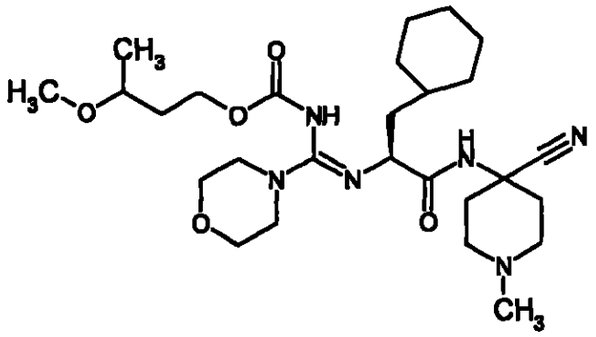
178



5,5-Dimethyl-2-(2-oxo-2,3-dihydro-benzo[*e*][1,3]oxazin-4-ylideneamino)-hexanoic acid (4-cyano-1-propyl-piperidin-4-yl)-amide; MS: 454 (M+1)



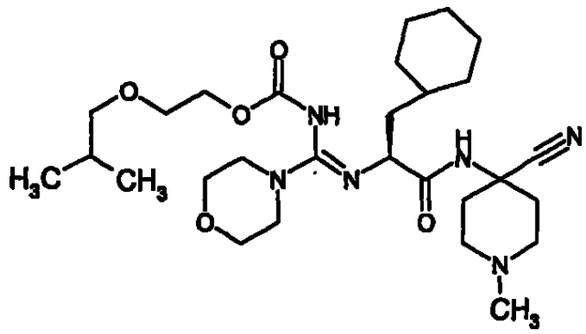
{[1-(4-Cyano-1-methyl-piperidin-4-ylcarbamoyl)-2-cyclohexyl-ethylimino]-morpholin-4-yl-methyl}-carbamic acid 2-isopropoxy-ethyl ester; MS: 534 (M+1)



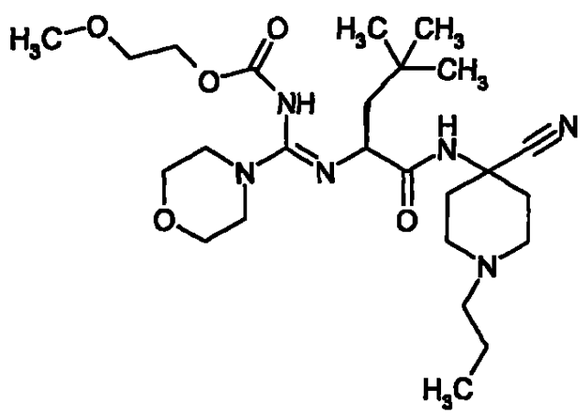
{[1-(4-Cyano-1-methyl-piperidin-4-ylcarbamoyl)-2-cyclohexyl-ethylimino]-morpholin-4-yl-methyl}-carbamic acid 3-methoxy-butyl ester; MS: 534 (M+1)

178

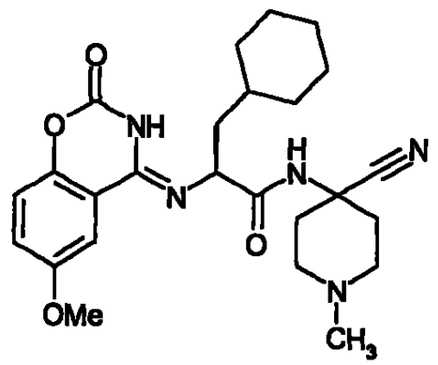
179



{[1-(4-Cyano-1-methyl-piperidin-4-ylcarbamoyl)-2-cyclohexyl-ethylimino]-morpholin-4-yl-methyl}-carbamic acid 2-isobutoxy-ethyl ester; MS: 549 (M+1)

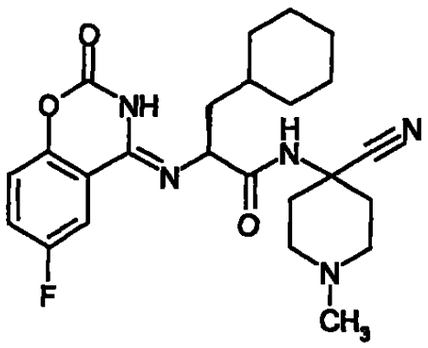


{[1-(4-Cyano-1-propyl-piperidin-4-ylcarbamoyl)-3,3-dimethyl-butylimino]-morpholin-4-yl-methyl}-carbamic acid 2-methoxy-ethyl ester; MS: 509 (M+1)

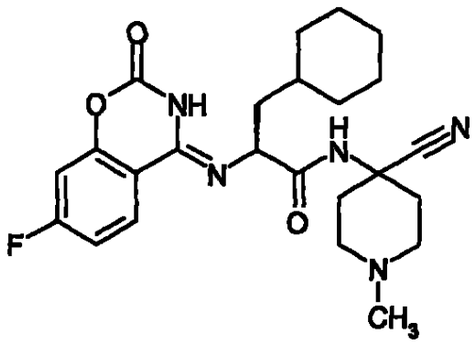


N-(4-Cyano-1-methyl-piperidin-4-yl)-4-cyclohexyl-2-(6-methoxy-2-oxo-2,3-dihydro-benzo[e][1,3]oxazin-4-ylideneamino)-butyramide; MS: 468 (M+1)

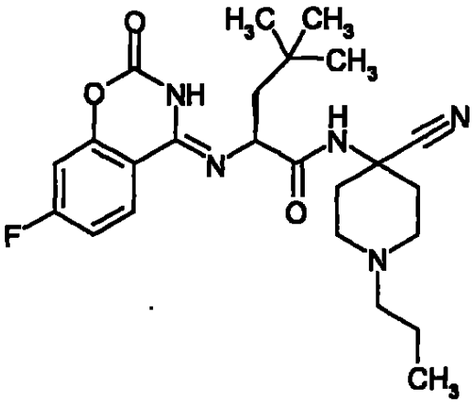
180



N-(4-Cyano-1-methyl-piperidin-4-yl)-4-cyclohexyl-2-(6-fluoro-2-oxo-2,3-dihydro-benzo[e][1,3]oxazin-4-ylideneamino)-butyramide; MS: 456 (M+1)

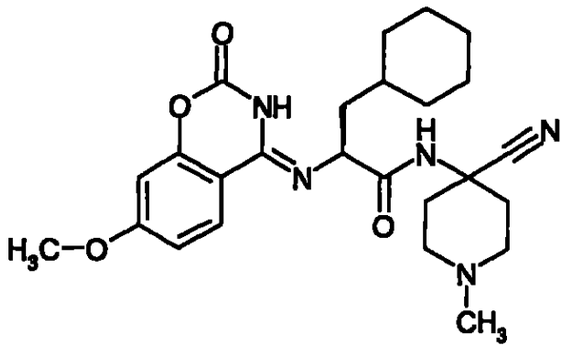


N-(4-Cyano-1-methyl-piperidin-4-yl)-4-cyclohexyl-2-(7-fluoro-2-oxo-2,3-dihydro-benzo[e][1,3]oxazin-4-ylideneamino)-butyramide; MS: 456 (M+1)

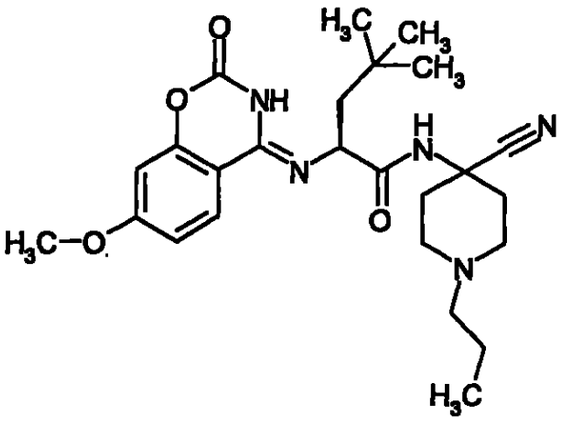


2-(7-Fluoro-2-oxo-2,3-dihydro-benzo[e][1,3]oxazin-4-yldeneamino)-5,5-dimethyl-hexanoic acid(4-cyano-1-propyl-piperidin-4-yl)-amide; MS: 458 (M+1)

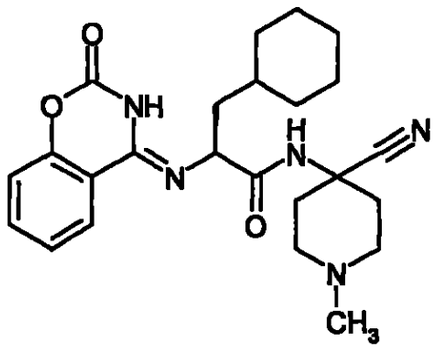
181



N-(4-Cyano-1-methyl-piperidin-4-yl)-4-cyclohexyl-2-(7-methoxy-2-oxo-2,3-dihydro-benzo[e][1,3]oxazin-4-ylideneamino)-butyramide; MS: 468 (M+1)

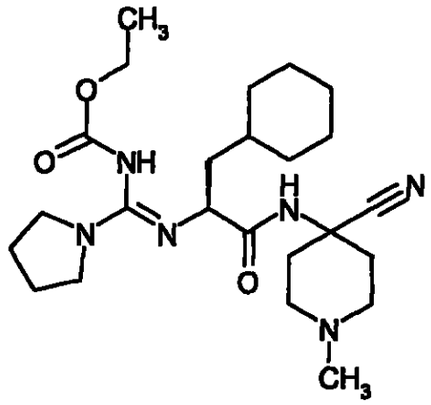


2-(7-Methoxy-2-oxo-2,3-dihydro-benzo[e][1,3]oxazin-4-yldeneamino)-5,5-dimethyl-hexanoic acid(4-cyano-1-propyl-piperidin-4-yl)-amide; MS: 470 (M+1)

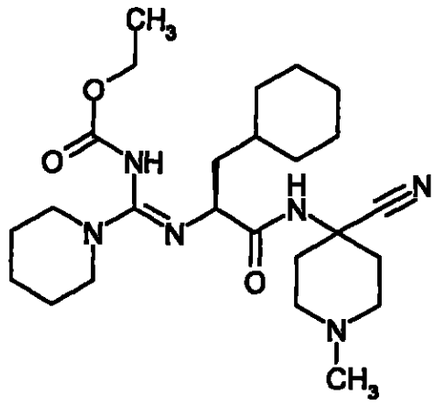


*N*-(4-Cyano-1-methyl-piperidin-4-yl)-3-cyclohexyl-2-(2-oxo-2,3-dihydro-benzo[*e*][1,3]oxazin-4-ylideneamino)-propionamide; MS: 438 (M+1).

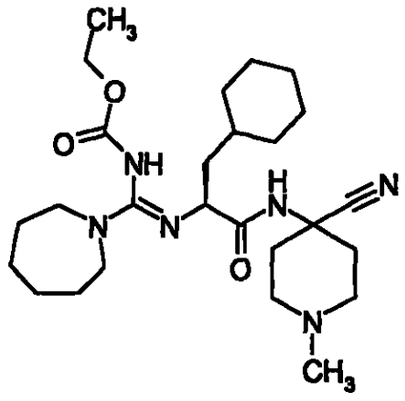
182



{[1-(4-Cyano-1-methyl-piperidin-4-ylcarbamoyl)-2-cyclohexyl-ethylimino]-pyrrolidin-1-yl-methyl}-carbamic acid ethyl ester; MS: 461 (M+1).



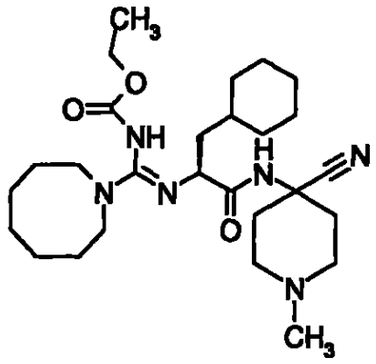
{[1-(4-Cyano-1-methyl-piperidin-4-ylcarbamoyl)-2-cyclohexyl-ethylimino]-piperidin-1-yl-methyl}-carbamic acid ethyl ester; MS: 475 (M+1).



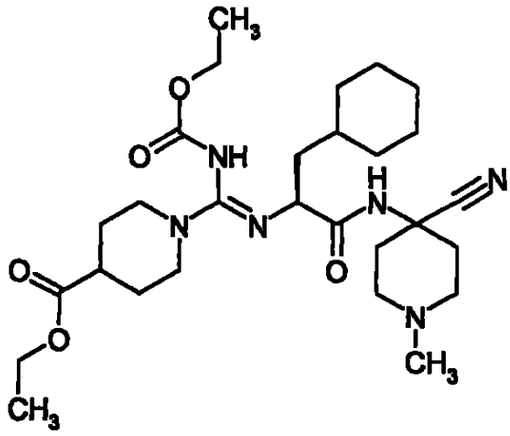
{Azepan-1-yl-[1-(4-cyano-1-methyl-piperidin-4-ylcarbamoyl)-2-cyclohexyl-ethylimino]-methyl}-carbamic acid ethyl ester; MS: 489 (M+1).

182

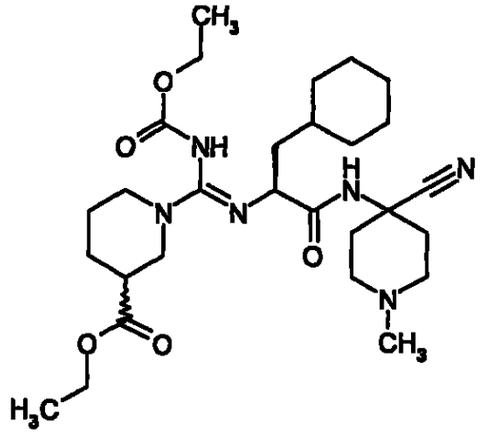
183



{Azocan-1-yl-[1-(4-cyano-1-methyl-piperidin-4-ylcarbamoyl)-2-cyclohexyl-ethylimino]-methyl}-carbamic acid ethyl ester; MS: 503 (M+1).



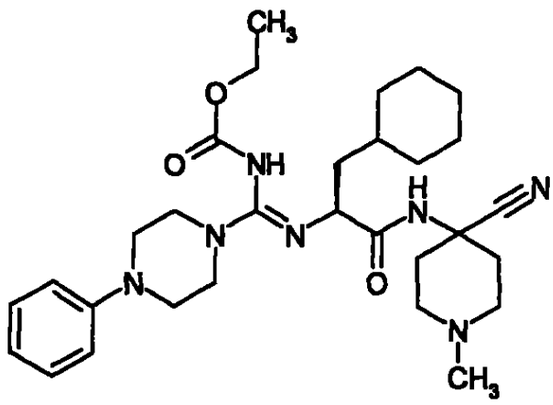
1-{[1-(4-Cyano-1-methyl-piperidin-4-ylcarbamoyl)-2-cyclohexyl-ethylimino]-ethoxycarbonylamino-methyl}-piperidine-4-carboxylic acid ethyl ester; MS: 547 (M+1).



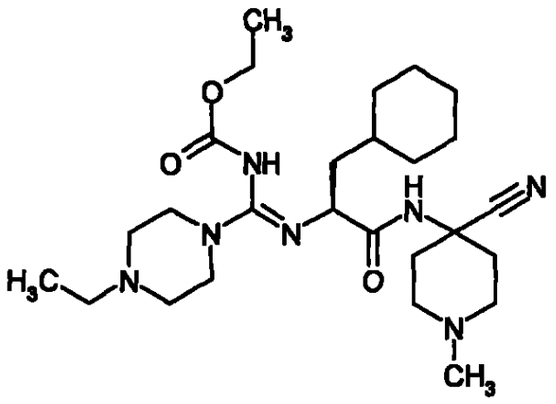
1-{[1-(4-Cyano-1-methyl-piperidin-4-ylcarbamoyl)-2-cyclohexyl-ethylimino]-ethoxycarbonylamino-methyl}-piperidine-3-carboxylic acid ethyl ester; MS: 547 (M+1).

183

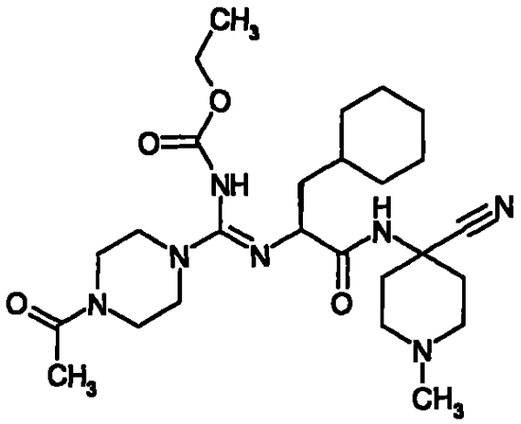
184



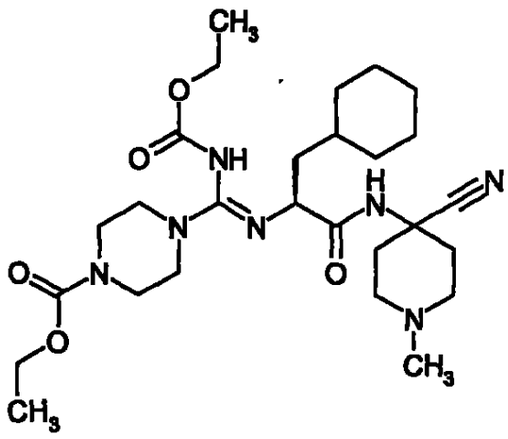
[[1-(4-Cyano-1-methyl-piperidin-4-ylcarbamoyl)-2-cyclohexyl-ethylimino]-(4-phenyl-piperazin-1-yl)-methyl]-carbamic acid ethyl ester; MS: 552 (M+1).



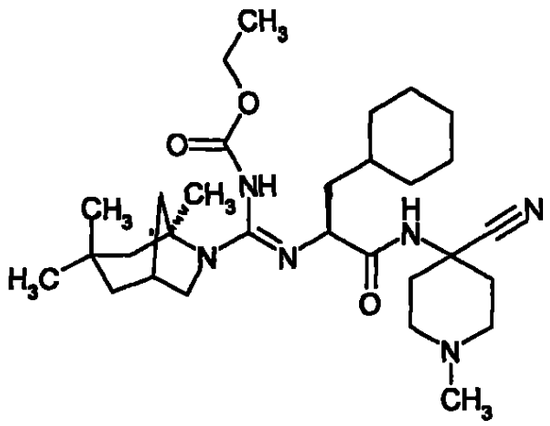
[[1-(4-Cyano-1-methyl-piperidin-4-ylcarbamoyl)-2-cyclohexyl-ethylimino]-(4-ethyl-piperazin-1-yl)-methyl]-carbamic acid ethyl ester; MS: 504 (M+1).



{(4-Acetyl-piperazin-1-yl)-[1-(4-cyano-1-methyl-piperidin-4-ylcarbamoyl)-2-cyclohexyl-ethylimino]-methyl}-carbamic acid ethyl ester; MS: 518 (M+1).



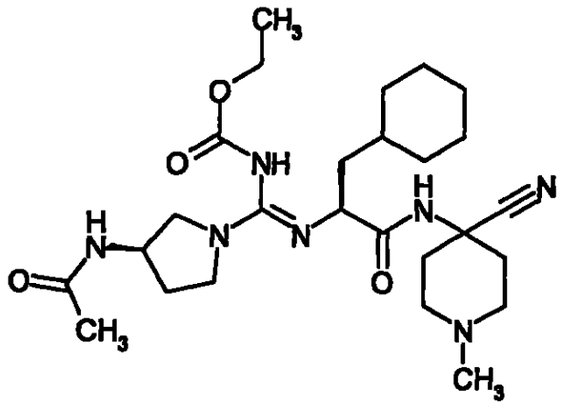
4-{[1-(4-Cyano-1-methyl-piperidin-4-ylcarbamoyl)-2-cyclohexyl-ethylimino]-ethoxycarbonylamino-methyl}-piperazine-1-carboxylic acid ethyl ester; MS: 548 (M+1).



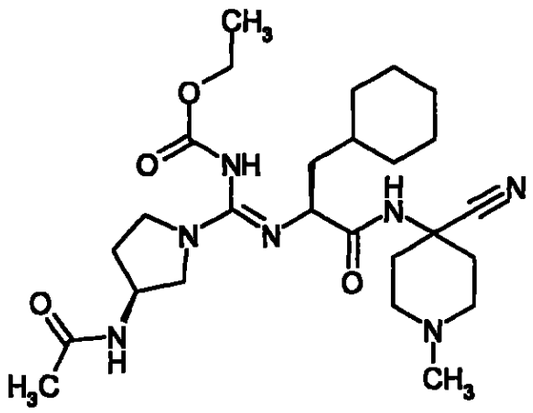
[[1-(4-Cyano-1-methyl-piperidin-4-ylcarbamoyl)-2-cyclohexyl-ethylimino]-(3,3,5-trimethyl-6-aza-bicyclo[3.2.1]oct-6-yl)-methyl]-carbamic acid ethyl ester; MS: 543 (M+1).

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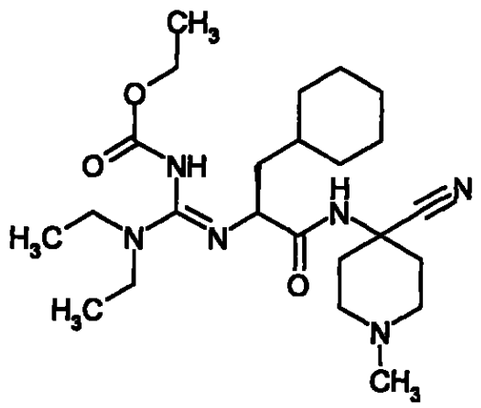
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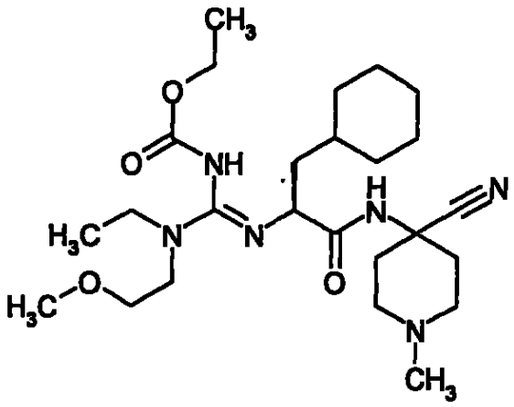
{(3-Acetylamino-pyrrolidin-1-yl)-[1-(4-cyano-1-methyl-piperidin-4-ylcarbamoyl)-2-cyclohexyl-ethylimino]-methyl}-carbamic acid ethyl ester; MS: 518 (M+1).



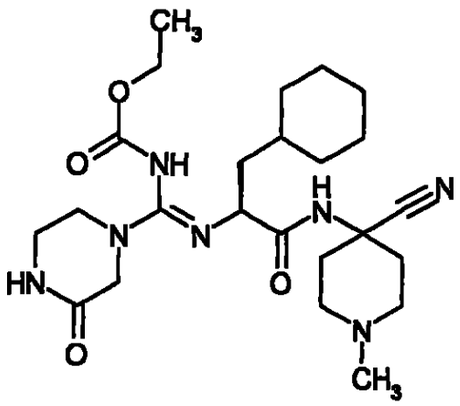
{(3-Acetylamino-pyrrolidin-1-yl)-[1-(4-cyano-1-methyl-piperidin-4-ylcarbamoyl)-2-cyclohexyl-ethylimino]-methyl}-carbamic acid ethyl ester; MS: 518 (M+1).



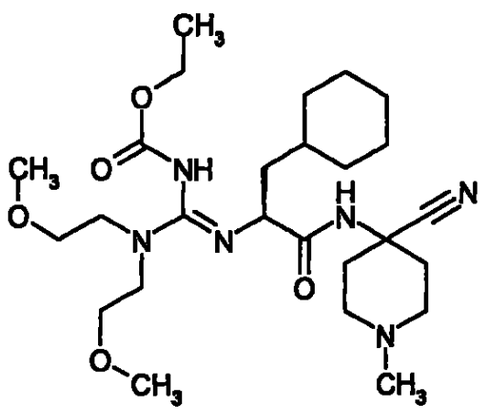
{(3-Azapent-3-yl)-[1-(4-cyano-1-methyl-piperidin-4-ylcarbamoyl)-2-cyclohexyl-ethylimino]-methyl}-carbamic acid ethyl ester; MS: 463 (M+1).



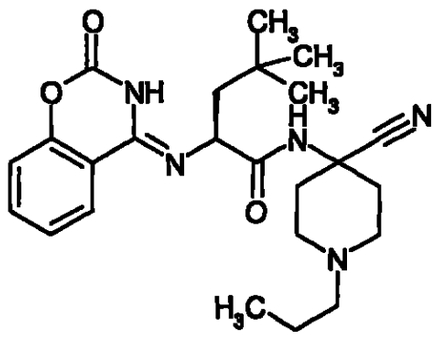
{(1-Methoxy-3-azapent-3-yl)-[1-(4-cyano-1-methyl-piperidin-4-ylcarbamoyl)-2-cyclohexyl-ethylimino]-methyl}-carbamic acid ethyl ester; MS: 493 (M+1).



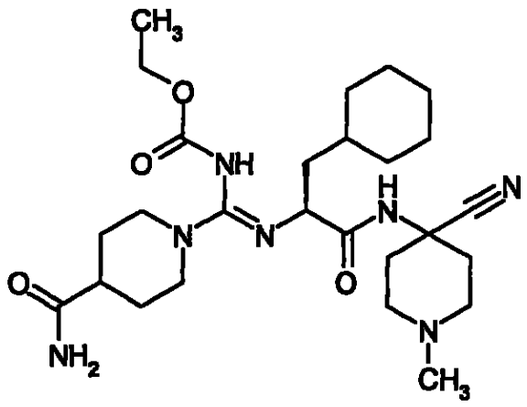
[[1-(4-Cyano-1-methyl-piperidin-4-ylcarbamoyl)-2-cyclohexyl-ethylimino]-(3-oxo-piperazin-1-yl)-methyl]-carbamic acid ethyl ester; MS: 490 (M+1).



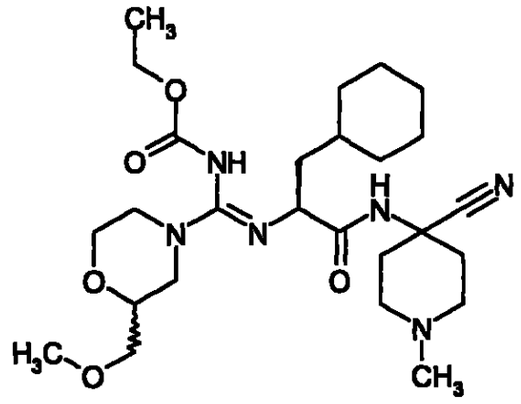
{(1,5-Dimethoxy-3-azapent-3-yl)-[1-(4-cyano-1-methyl-piperidin-4-ylcarbamoyl)-2-cyclohexyl-ethylimino]-methyl}-carbamic acid ethyl ester; MS: 523 (M+1).



4,4-Dimethyl-2-(2-oxo-2,3-dihydro-benzo[e][1,3]oxazin-4-ylideneamino)-pentanoic acid (4-cyano-1-propyl-piperidin-4-yl)-amide; MS: 440 (M+1)

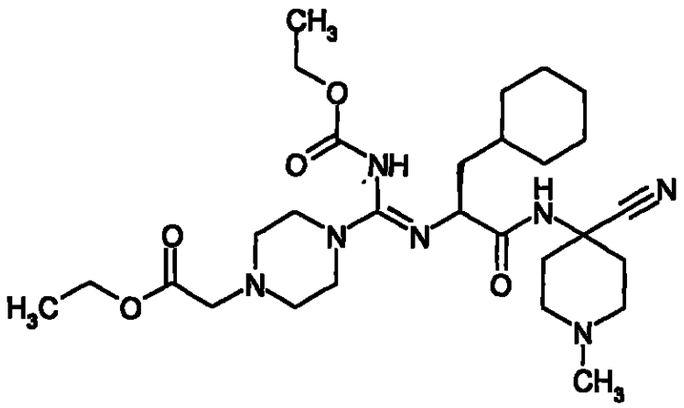


{(4-Carbamoyl-piperidin-1-yl)-[1-(4-cyano-1-methyl-piperidin-4-ylcarbamoyl)-2-cyclohexyl-ethylimino]-methyl}-carbamic acid ethyl ester; MS: 518 (M+1)

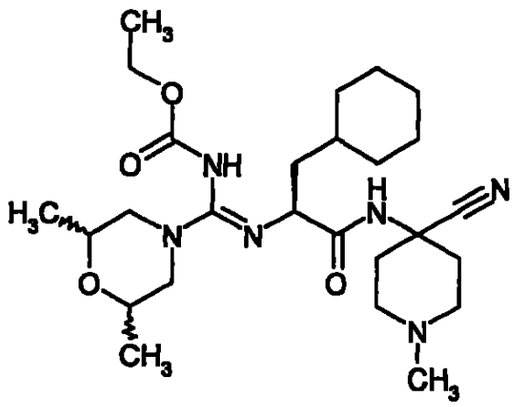


[[1-(4-Cyano-1-methyl-piperidin-4-ylcarbamoyl)-2-cyclohexyl-ethylimino]-(2-methoxymethyl-morpholin-4-yl)-methyl]-carbamic acid ethyl ester; MS: 521 (M+1)

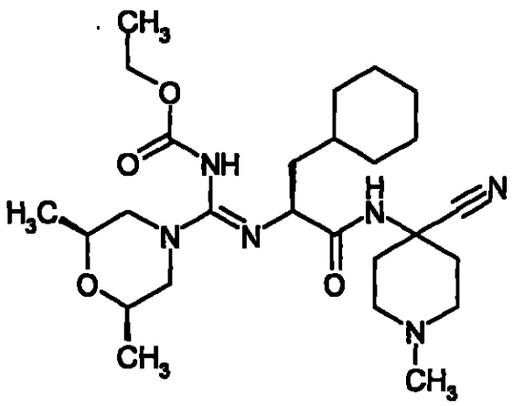
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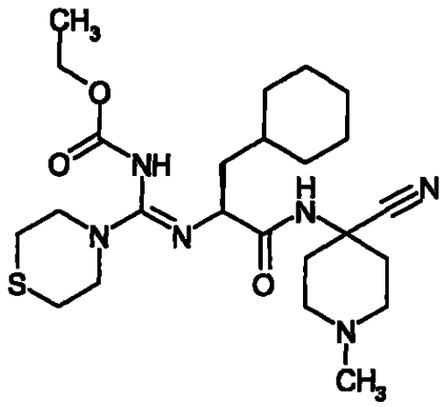
(4-{[1-(4-Cyano-1-methyl-piperidin-4-ylcarbamoyl)-2-cyclohexyl-ethylimino]-ethoxycarbonylamino-methyl}-piperazin-1-yl)-acetic acid ethyl ester; MS: 562 (M+1)



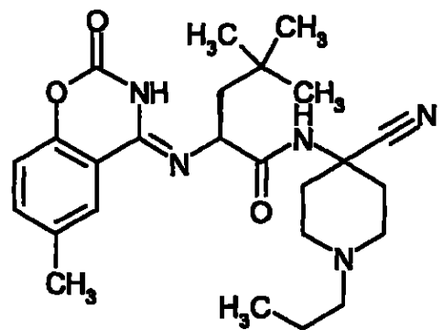
[[1-(4-Cyano-1-methyl-piperidin-4-ylcarbamoyl)-2-cyclohexyl-ethylimino]-(2,6-dimethyl-morpholin-4-yl)-methyl]-carbamic acid ethyl ester; MS: 505 (M+1)



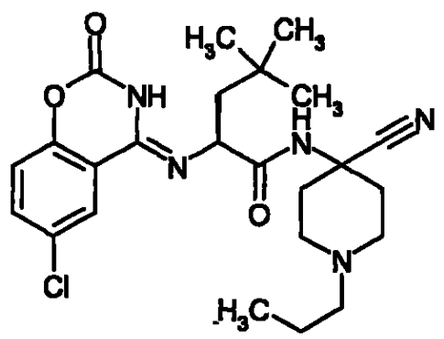
[[1-(4-Cyano-1-methyl-piperidin-4-ylcarbamoyl)-2-cyclohexyl-ethylimino]-(2,6-dimethyl-morpholin-4-yl)-methyl]-carbamic acid ethyl ester; MS: 505 (M+1)



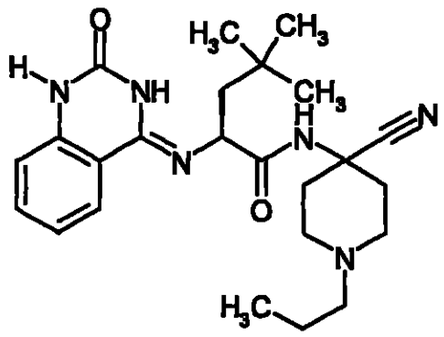
{[1-(4-Cyano-1-methyl-piperidin-4-ylcarbamoyl)-2-cyclohexyl-ethylimino]-thiomorpholin-4-yl-methyl}-carbamic acid ethyl ester; MS: 493 (M+1)



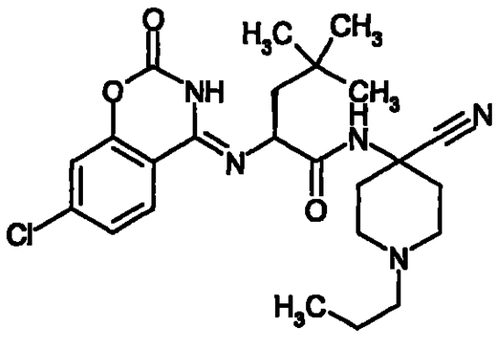
4,4-Dimethyl-2-(6-methyl-2-oxo-2,3-dihydro-benzo[*e*][1,3]oxazin-4-ylideneamino)-pentanoic acid (4-cyano-1-propyl-piperidin-4-yl)-amide; MS: 454 (M+1)



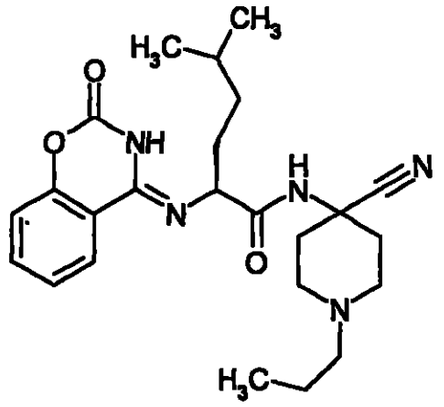
2-(6-Chloro-2-oxo-2,3-dihydro-benzo[*e*][1,3]oxazin-4-ylideneamino)-4,4-dimethyl-pentanoic acid (4-cyano-1-propyl-piperidin-4-yl)-amide; MS: 475 (M+1)



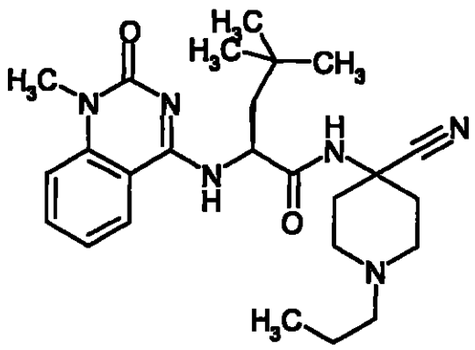
4,4-Dimethyl-2-(2-oxo-2,3-dihydro-1*H*-quinazolin-4-ylideneamino)-pentanoic acid (4-cyano-1-propyl-piperidin-4-yl)-amide; MS: 439 (M+1)



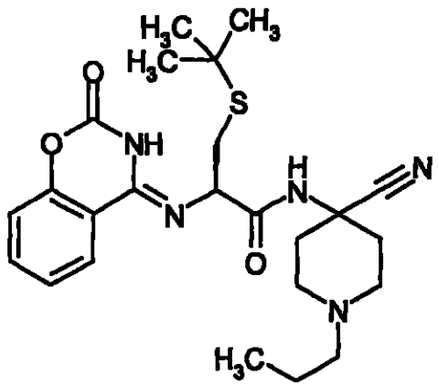
2-(7-Chloro-2-oxo-2,3-dihydro-benzo[*e*][1,3]oxazin-4-ylideneamino)-4,4-dimethyl-pentanoic acid (4-cyano-1-propyl-piperidin-4-yl)-amide; MS: 475 (M+1)



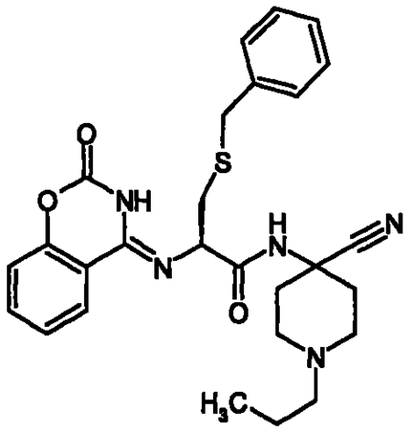
5-Methyl-2-(2-oxo-2,3-dihydro-benzo[*e*][1,3]oxazin-4-ylideneamino)-hexanoic acid (4-cyano-1-propyl-piperidin-4-yl)-amide; MS: 440 (M+1)



4,4-Dimethyl-2-(1-methyl-2-oxo-1,2-dihydro-quinazolin-4-ylamino)-pentanoic acid (4-cyano-1-propyl-piperidin-4-yl)-amide; MS: 453 (M+1)

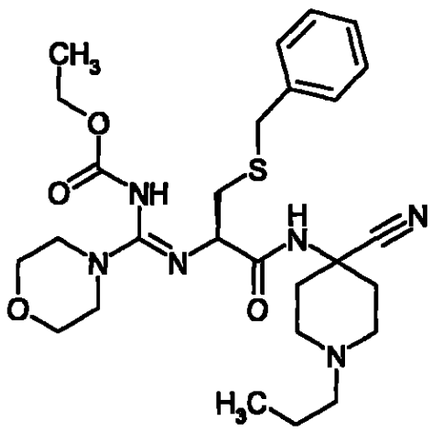


3-*tert*-Butylsulfanyl-*N*-(4-cyano-1-propyl-piperidin-4-yl)-2-(2-oxo-2,3-dihydro-benzo[*e*][1,3]oxazin-4-ylideneamino)-propionamide; MS: 472 (M+1)

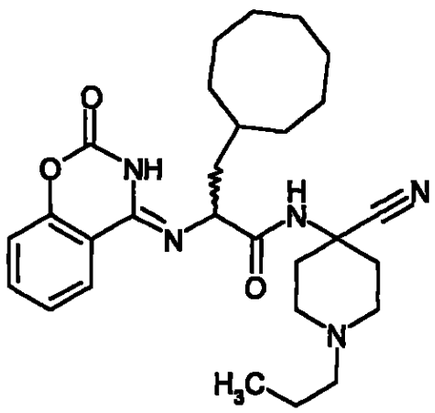


3-Benzylsulfanyl-*N*-(4-cyano-1-propyl-piperidin-4-yl)-2-(2-oxo-2,3-dihydro-benzo[*e*][1,3]oxazin-4-ylideneamino)-propionamide; MS: 506 (M+1)

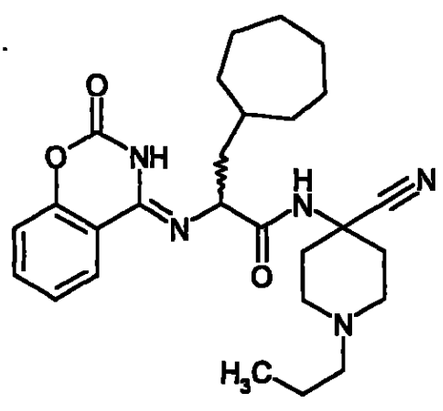
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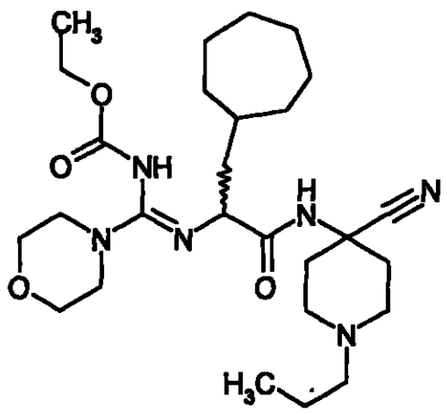
{[2-Benzylsulfanyl-1-(4-cyano-1-propyl-piperidin-4-ylcarbamoyl)-ethylimino]-morpholin-4-yl-methyl}-carbamic acid ethyl ester; MS: 545 (M+1)



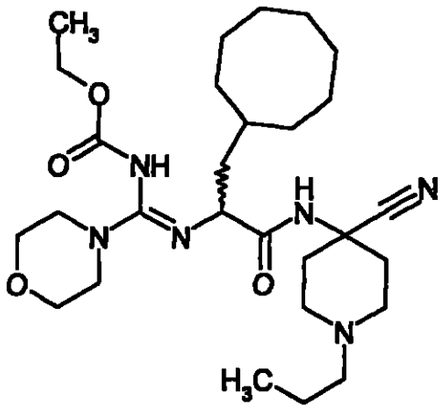
*N*-(4-Cyano-1-propyl-piperidin-4-yl)-3-cyclooctyl-2-(2-oxo-2,3-dihydro-benzo[*e*][1,3]oxazin-4-ylideneamino)-propionamide; MS: 494 (M+1)



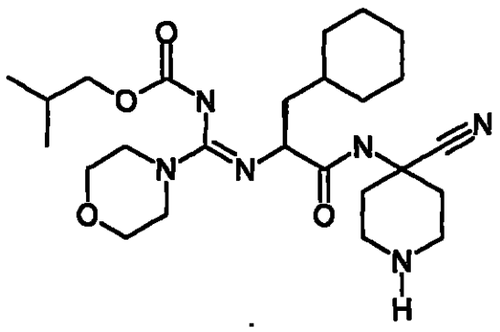
*N*-(4-Cyano-1-propyl-piperidin-4-yl)-3-cycloheptyl-2-(2-oxo-2,3-dihydro-benzo[*e*][1,3]oxazin-4-ylideneamino)-propionamide; MS: 480 (M+1)



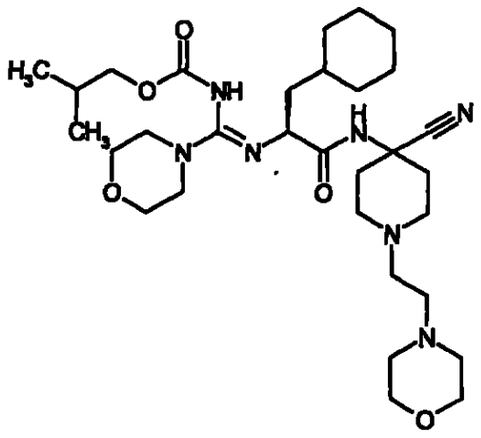
{[1-(4-Cyano-1-propyl-piperidin-4-ylcarbamoyl)-2-cycloheptyl-ethylimino]-morpholin-4-yl-methyl}-carbamic acid ethyl ester; MS: 519 (M+1)



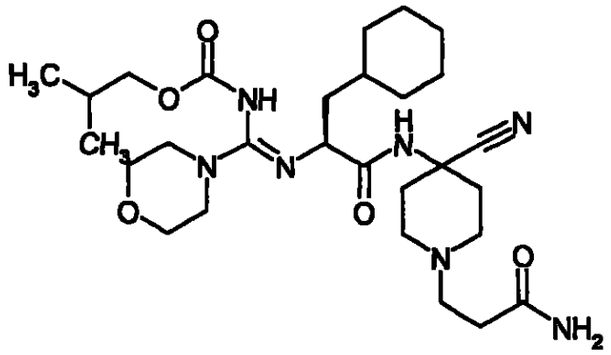
{[1-(4-Cyano-1-propyl-piperidin-4-ylcarbamoyl)-2-cyclooctyl-ethylimino]-morpholin-4-yl-methyl}-carbamic acid ethyl ester; MS: 533 (M+1)



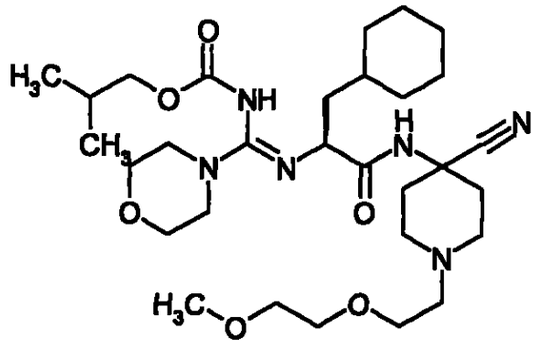
{[1-(4-Cyano-piperidin-4-ylcarbamoyl)-2-cyclohexyl-ethylamino]-morpholin-4-yl-methylene}-carbamic acid isobutyl ester; MS: 491 (M+1)



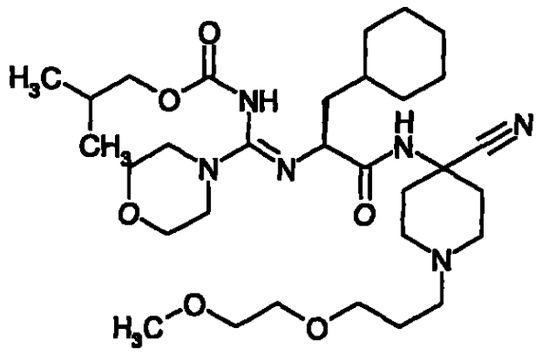
({1-[4-Cyano-1-(2-morpholin-4-yl-ethyl)-piperidin-4-ylcarbamoyl]-2-cyclohexyl-ethylamino}-morpholin-4-yl-methylene)-carbamic acid isobutyl ester; MS: 604 (M+1)



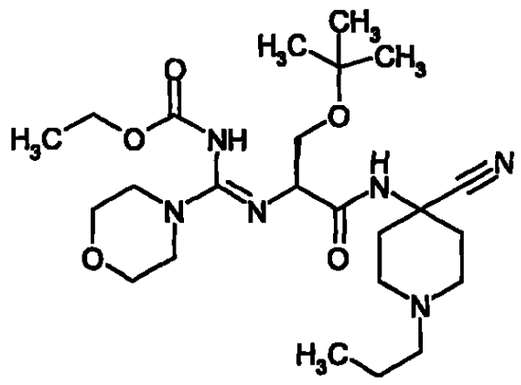
({1-[1-2-Carbamoyl-ethyl)-4-cyano-piperidin-4-ylcarbamoyl]-2-cyclohexyl-ethylamino}-morpholin-4-yl-methylene)-carbamic acid isobutyl ester; MS: 562 (M+1)



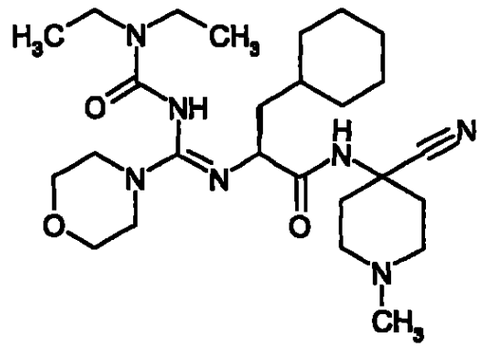
[(1-{4-Cyano-1-[2-(2-methoxyl-ethoxy)-ethyl]-piperidin-4-ylcarbamoyl}-2-cyclohexyl-ethylamino)-morpholin-4-yl-methylene]-carbamic acid isobutyl ester; MS: 593 (M+1)



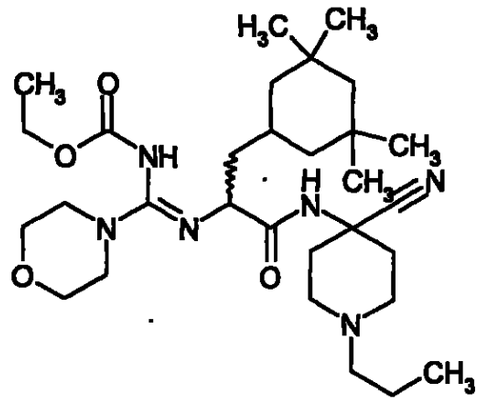
[(1-{4-Cyano-1-[3-(2-methoxyl-ethoxy)-propyl]-piperidin-4-ylcarbamoyl}-2-cyclohexyl-ethylamino)-morpholin-4-yl-methylene]-carbamic acid isobutyl ester; MS: 607 (M+1)



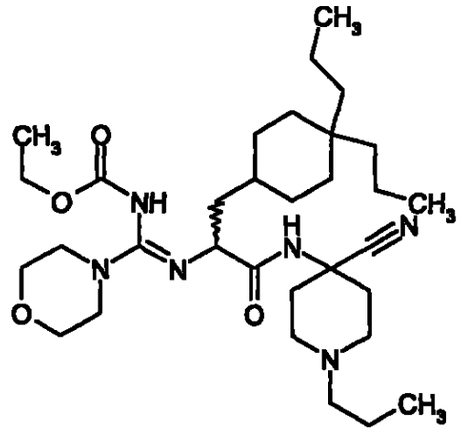
{[2-tert-Butoxy-1-(4-cyano-1-propyl-piperidin-4-ylcarbamoly)-ethylamino]-morpholin-4-yl-methylene}-carbamic acid ethyl ester; MS: 495 (M+1)



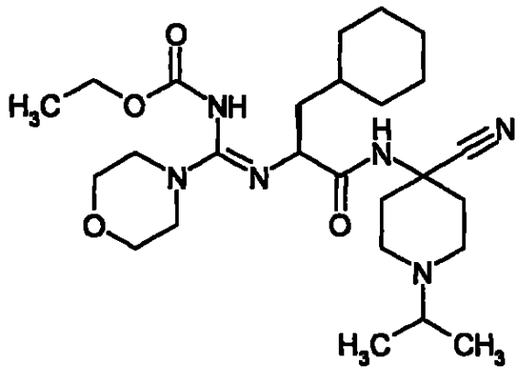
N-(4-Cyano-1-methyl-piperidin-4-yl)-3-cyclohexyl-2-{[diethyl-carbamoylimino)-morpholin-4-yl-methyl]-amino}-propionamide; MS: 504 (M+1)



{[1-(4-Cyano-1-propyl-piperidin-4-ylcarbamoyl)-2-(3,3,5,5-tetramethyl-cyclohexyl)-ethylamino]-morpholin-4-yl-methylene}-carbamic acid ethyl ester; MS: 561 (M+1)

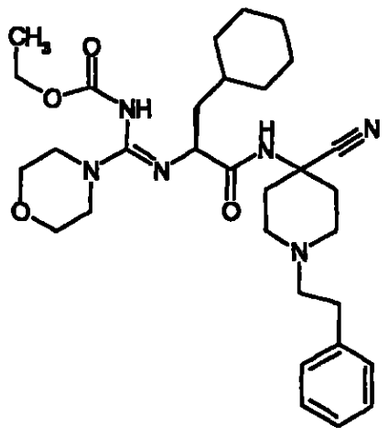


{[1-(4-Cyano-1-propyl-piperidin-4-ylcarbamoyl)-2-(4,4-dipropyl-cyclohexyl)-ethylamino]-morpholin-4-yl-methylene}-carbamic acid ethyl ester; MS: 589 (M+1)

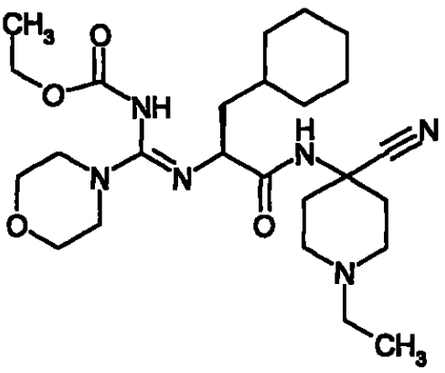


{[1-(4-Cyano-1-isopropyl-piperidin-4-ylcarbamoyl)-2-cyclohexyl-ethylamino]-morpholin-4-yl-methylene}-carbamic acid ethyl ester; MS: 505 (M+1)

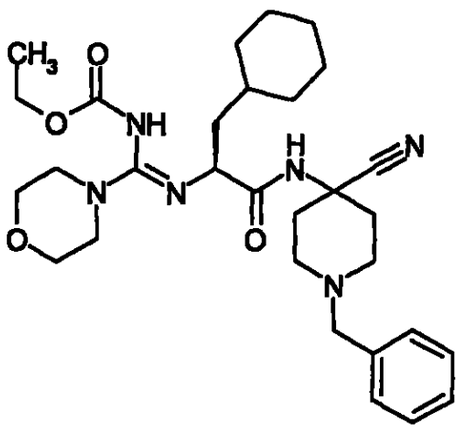
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198



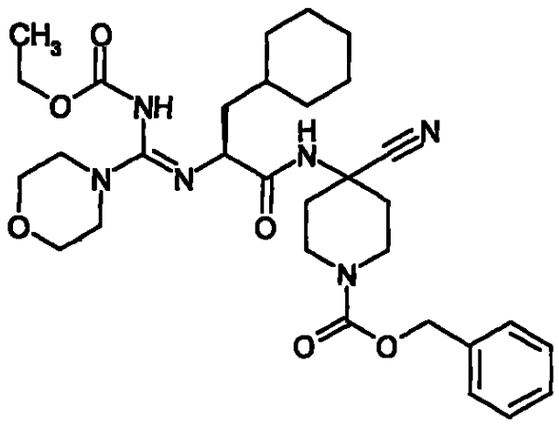
{[1-(4-Cyano-1-phenethyl-piperidin-4-ylcarbamoyl)-2-cyclohexyl-ethylamino]-morpholin-4-yl-methylene}-carbamic acid ethyl ester; MS: 567 (M+1)



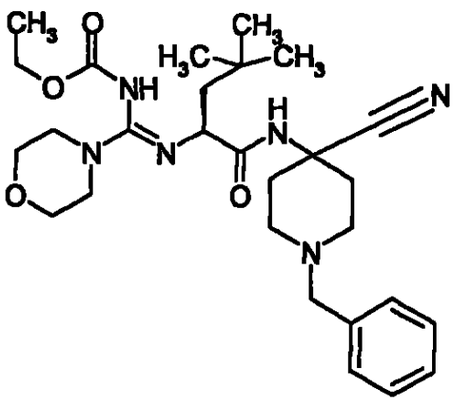
{[1-(4-Cyano-1-ethyl-piperidin-4-ylcarbamoyl)-2-cyclohexyl-ethylamino]-morpholin-4-yl-methylene}-carbamic acid ethyl ester; MS: 491 (M+1)



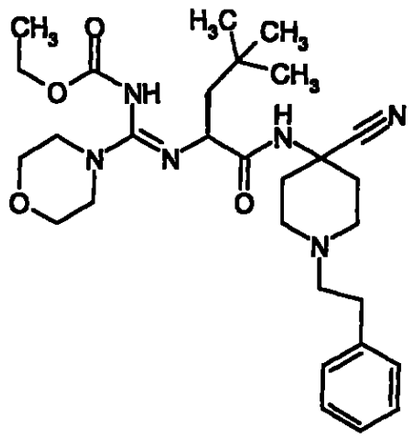
{[1-(1-Benzyl-4-cyano-piperidin-4-ylcarbamoyl)-2-cyclohexyl-ethylamino]-morpholin-4-yl-methylene}-carbamic acid ethyl ester; MS: 553 (M+1)



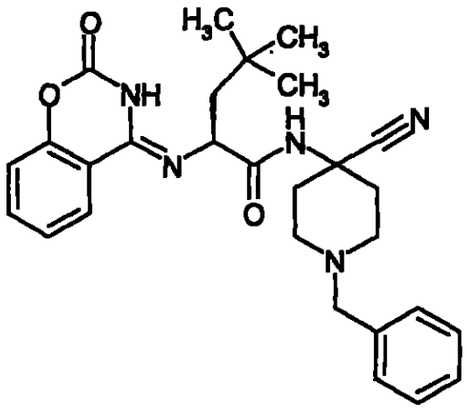
4-Cyano-4-{3-cyclohexyl-2-[(ethoxycarbonylimino-morpholin-4-yl-methyl)-amino]-propionylamino}-piperidine-1-carboxylic acid benzyl ester; MS: 597 (M+1)



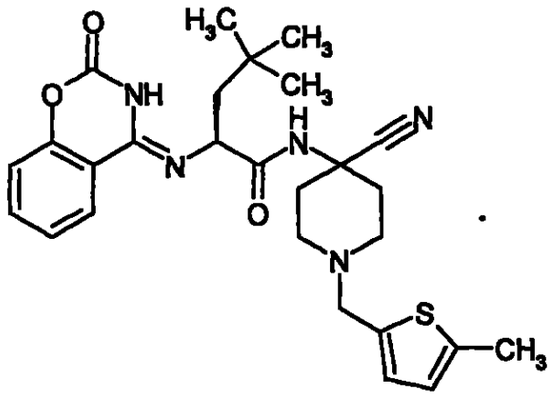
{[1-(1-Benzyl-4-cyano-piperidin-4-ylcarbamoyl)-3,3-dimethyl-butylamino]-morpholin-4-yl-methylene}-carbamic acid ethyl ester; MS: 527 (M+1)



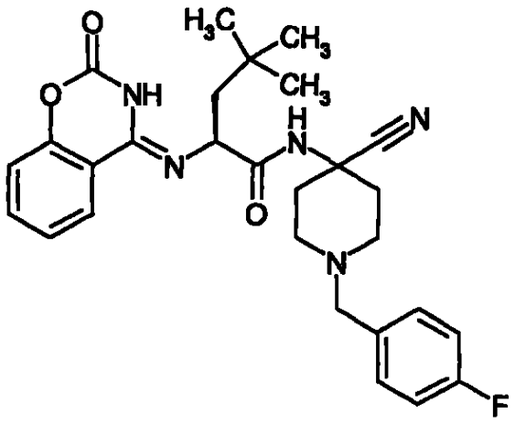
{[1-(4-cyano-1-phenethyl-piperidin-4-ylcarbamoyl)-3,3-dimethyl-butylamino]-morpholin-4-yl-methylene}-carbamic acid ethyl ester; MS: 541 (M+1)



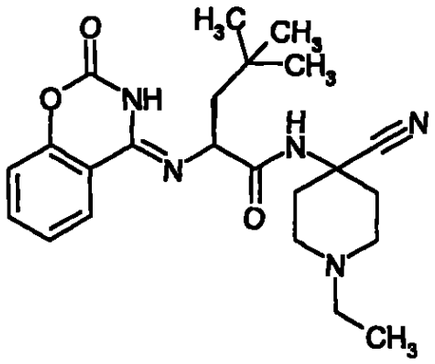
4,4-Dimethyl-2-(2-oxo-2H-benzo[e][1,3]oxazin-4-ylamino)-pentanoic acid (1-benzyl-4-cyano-piperidin-4-yl)-amide; MS: 488 (M+1)



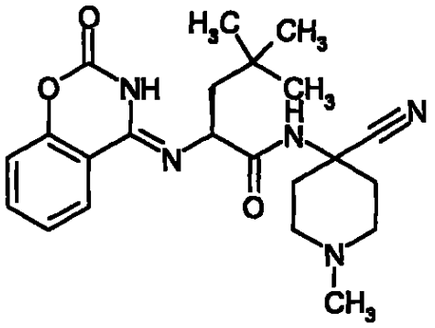
4,4-Dimethyl-2-(2-oxo-2H-benzo[e][1,3]oxazin-4-ylamino)-pentanoic acid [4-cyano-1-(5-methyl-thiophen-2-ylmethyl)-piperidin-4-yl]-amide; MS: 508 (M+1)



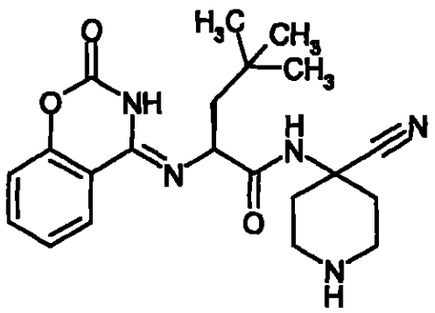
4,4-Dimethyl-2-(2-oxo-2H-benzo[e][1,3]oxazin-4-ylamino)-pentanoic acid [4-cyano-1-(4-fluoro-benzyl)-piperidin-4-yl]-amide; MS: 506 (M+1)



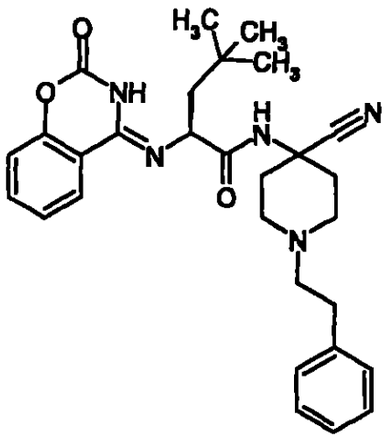
4,4-Dimethyl-2-(2-oxo-2H-benzo[e][1,3]oxazin-4-ylamino)-pentanoic acid (4-cyano-1-ethyl-piperidin-4-yl)-amide; MS: 426 (M+1)



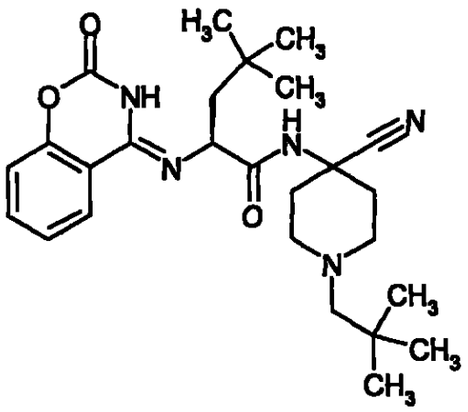
4,4-Dimethyl-2-(2-oxo-2H-benzo[e][1,3]oxazin-4-ylamino)-pentanoic acid (4-cyano-1-methyl-piperidin-4-yl)-amide; MS: 412 (M+1)



4,4-Dimethyl-2-(2-oxo-2H-benzo[e][1,3]oxazin-4-ylamino)-pentanoic acid (4-cyano-piperidin-4-yl)-amide; MS: 398 (M+1)

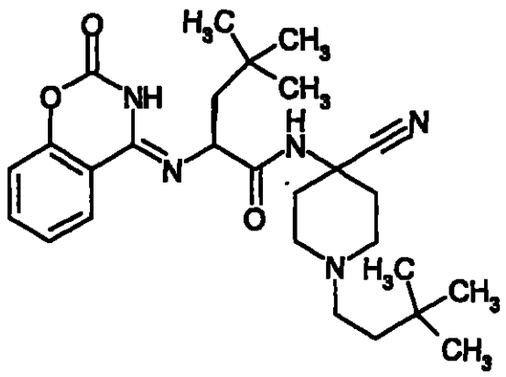


4,4-Dimethyl-2-(2-oxo-2H-benzo[e][1,3]oxazin-4-ylamino)-pentanoic acid (4-cyano-1-phenethyl-piperidin-4-yl)-amide; MS: 502 (M+1)

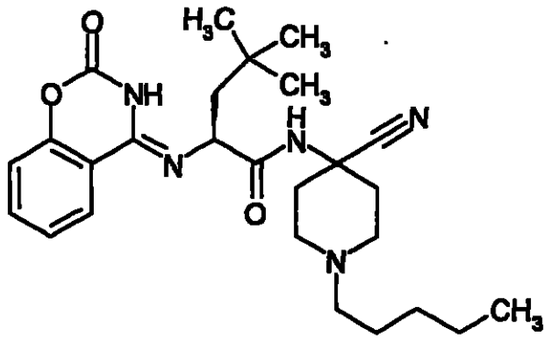


4,4-Dimethyl-2-(2-oxo-2H-benzo[e][1,3]oxazin-4-ylamino)-pentanoic acid [4-cyano-1-(2,2-dimethyl-propyl)-piperidin-4-yl]-amide; MS: 468 (M+1)

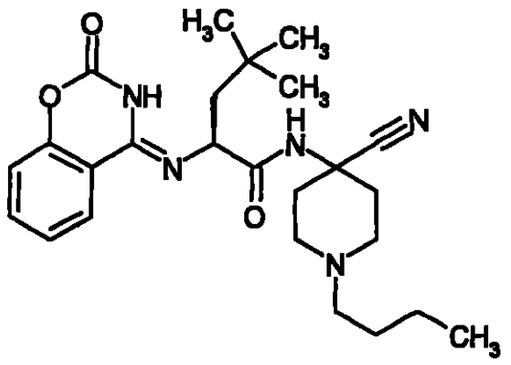
202
203



4,4-Dimethyl-2-(2-oxo-2H-benzo[e][1,3]oxazin-4-ylamino)-pentanoic acid [4-cyano-1-(3,3-dimethyl-butyl)-piperidin-4-yl]-amide; MS: 482 (M+1)

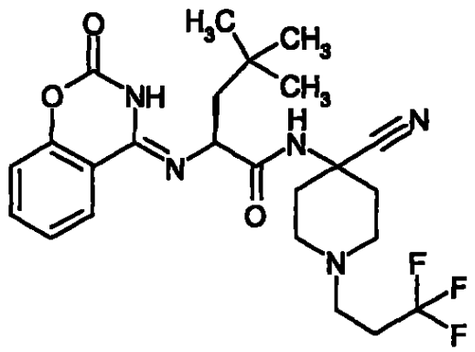


4,4-Dimethyl-2-(2-oxo-2H-benzo[e][1,3]oxazin-4-ylamino)-pentanoic acid (4-cyano-1-pentyl-piperidin-4-yl)-amide; MS: 468 (M+1)

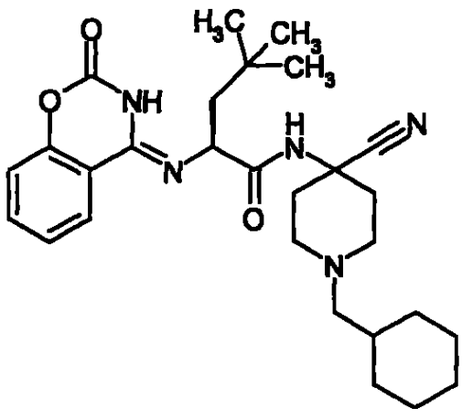


4,4-Dimethyl-2-(2-oxo-2H-benzo[e][1,3]oxazin-4-ylamino)-pentanoic acid (1-butyl-4-cyano-piperidin-4-yl)-amide; MS: 454(M+1)

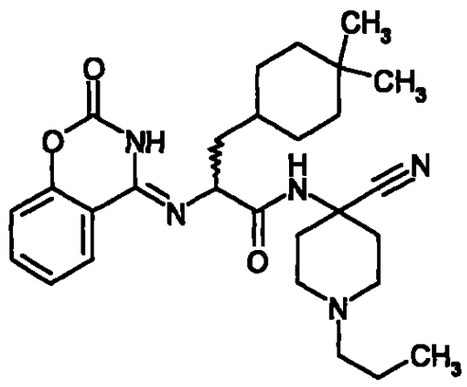
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204



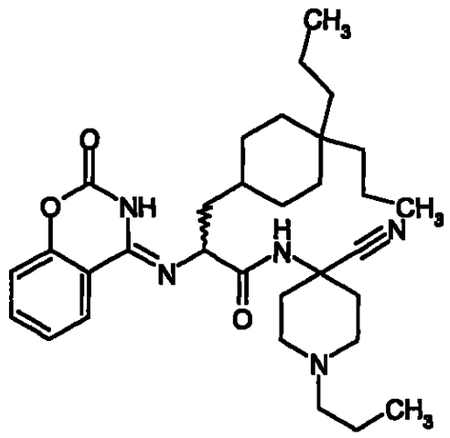
4,4-Dimethyl-2-(2-oxo-2H-benzo[e][1,3]oxazin-4-ylamino)-pentanoic acid [4-cyano-1-(3,3,3-trifluoro-propyl)-piperidin-4-yl]-amide; MS: 494 (M+1)



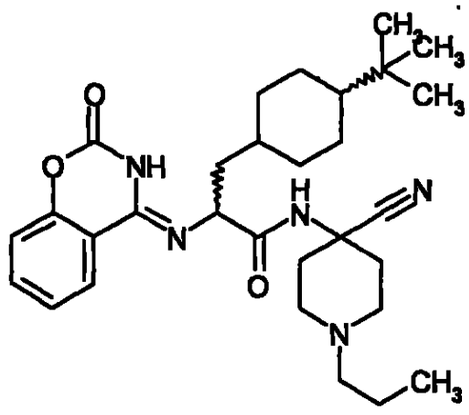
4,4-Dimethyl-2-(2-oxo-2H-benzo[e][1,3]oxazin-4-ylamino)-pentanoic acid (4-cyano-1-cyclohexylmethyl-piperidin-4-yl)-amide; MS: 494 (M+1)



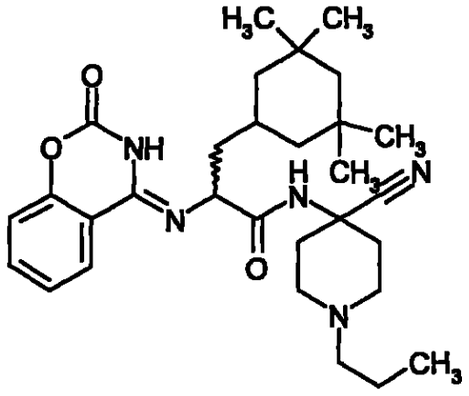
N-(4-Cyano-1-propyl-piperidin-4-yl)-3-(4,4-dimethyl-cyclohexyl)-2-(2-oxo-2H-benzo[e][1,3]oxazin-4-ylamino)-propionamide; MS: 494 (M+1)



N-(4-Cyano-1-propyl-piperidin-4-yl)-3-(4,4-dipropyl-cyclohexyl)-2-(2-oxo-2H-benzo[e][1,3]oxazin-4-ylamino)-propionamide; MS: 550 (M+1)

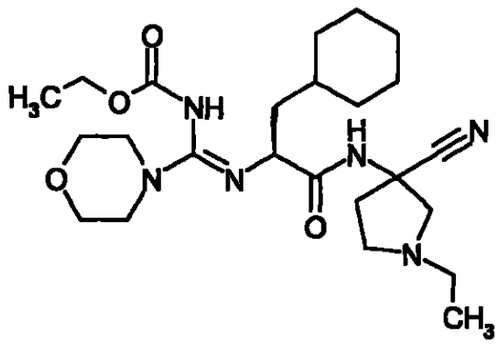


N-(4-Cyano-1-propyl-piperidin-4-yl)-3-(4-tert-butyl-cyclohexyl)-2-(2-oxo-2H-benzo[e][1,3]oxazin-4-ylamino)-propionamide; MS: 522 (M+1)

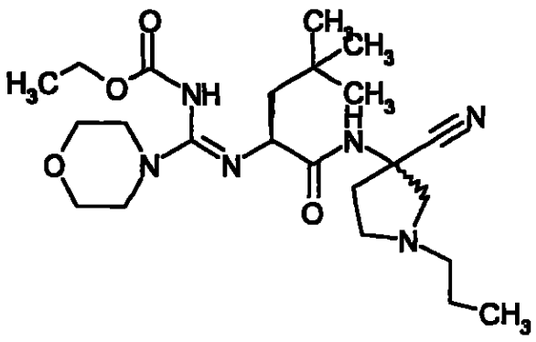


205
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N-(4-Cyano-1-propyl-piperidin-4-yl)-3-(3,3,5,5-tetramethyl-cyclohexyl)-2-(2-oxo-2H-benzo[e][1,3]oxazin-4-ylamino)-propionamide; MS: 522 (M+1)

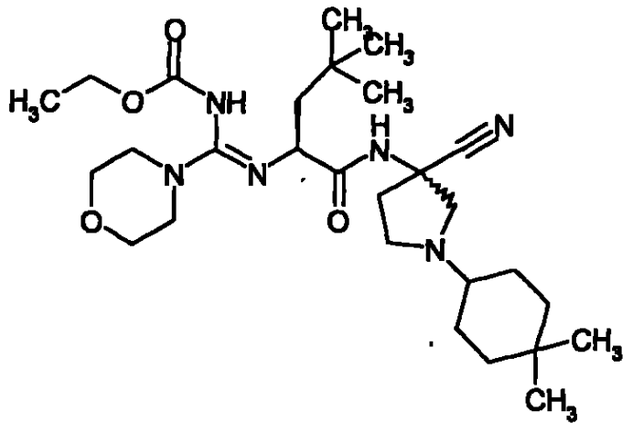


{[1-(3-Cyano-1-ethyl-pyrrolidin-3-ylcarbamoyl)-2-cyclohexyl-ethylamino]-morpholin-4-yl-methylene}-carbamic acid ethyl ester. MS: 477 (M+1).

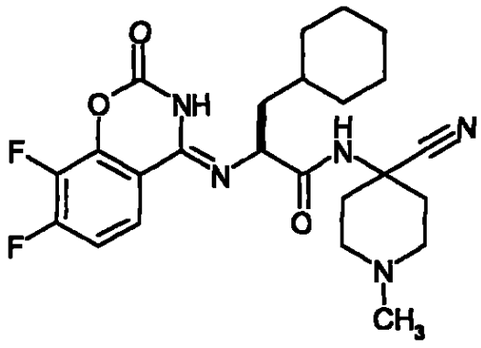


{[1-(3-Cyano-1-propyl-pyrrolidin-3-ylcarbamoyl)-3,3-dimethyl-butylamino]-morpholin-4-yl-methylene}-carbamic acid ethyl ester. MS: 465 (M+1).

206
207

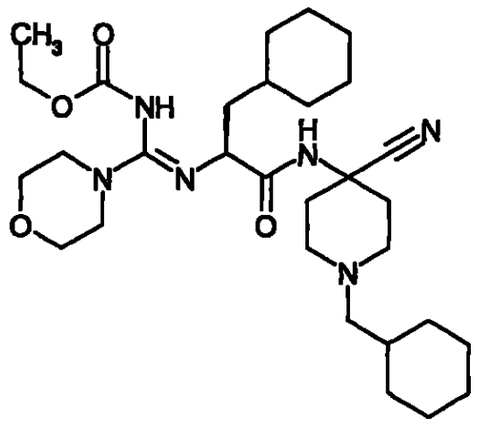


({1-[3-Cyano-1-(4,4-dimethyl-cyclohexyl)-pyrrolidin-3-ylcarbamoyl]-3,3-dimethyl-butylamino}-morpholin-4-yl-methylene)-carbamic acid ethyl ester. MS: 533 (M+1).

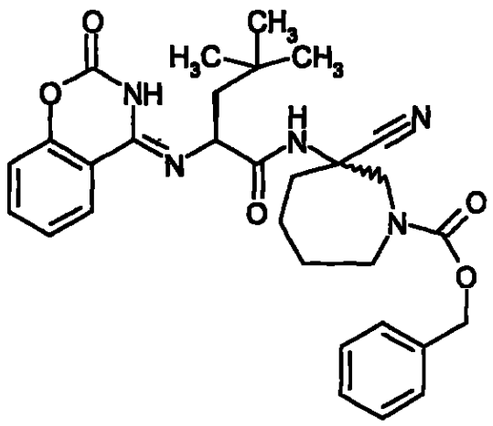


N-(4-Cyano-1-methyl-piperidin-4-yl)-3-cyclohexyl-2-(7,8-difluoro-2-oxo-2H-benzo[e][1,3]oxazin-4-ylamino)-propionamide; MS: 474 (M+1)

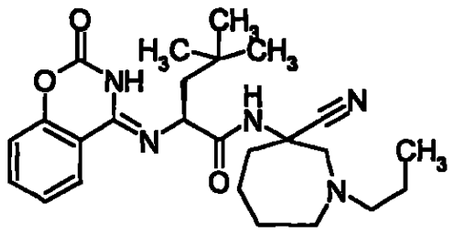
207
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{[1-(4-Cyano-1-cyclohexylmethyl-piperidin-4-ylcarbamoyl)-2-cyclohexyl-ethylamino]-morpholin-4-yl-methylene}-carbamic acid ethyl ester; MS: 559 (M+1)



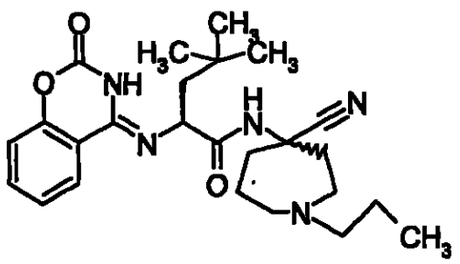
3-Cyano-3-[4,4-dimethyl-2-(2-oxo-2*H*-benzo[*e*][1,3]oxazin-4-ylamino)-pentanoylamino]-azepane-1-carboxylic acid benzyl ester; MS: 546 (M+1)



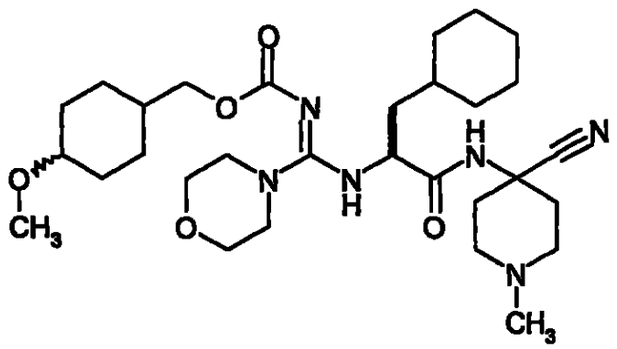
4,4-Dimethyl-2-(2-oxo-2*H*-benzo[*e*][1,3]oxazin-4-ylamino)-pentanoic acid (3-cyano-1-propyl-azepan-3-yl)-amide; MS: 454 (M+1)

208

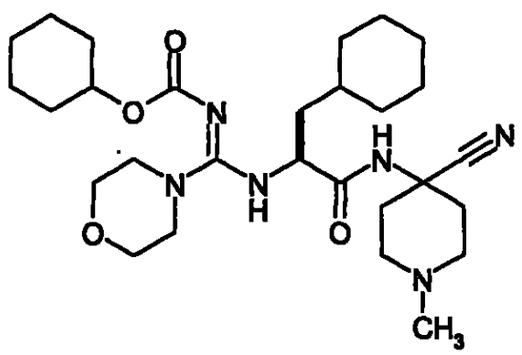
209



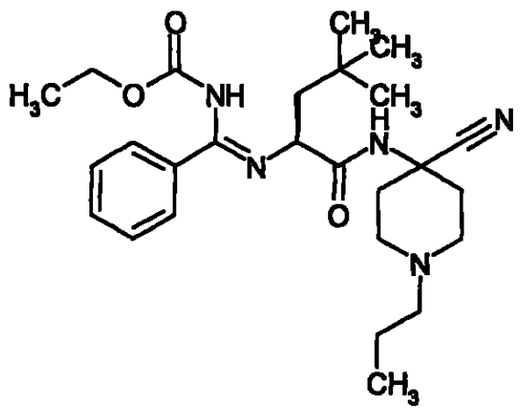
4,4-Dimethyl-2-(2-oxo-2*H*-benzo[*e*][1,3]oxazin-4-ylamino)-pentanoic acid (4-cyano-1-propyl-azepan-4-yl)-amide; MS: 454 (M+1)



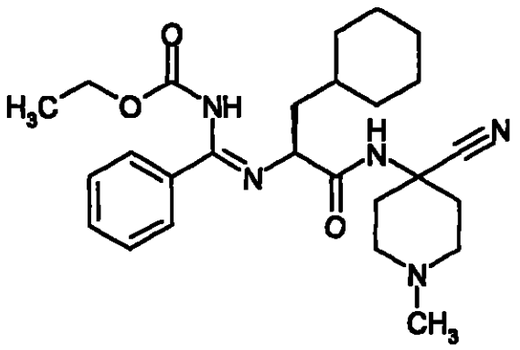
{[1-(4-Cyano-1-methyl-piperidin-4-ylcarbamoyl)-2-cyclohexyl-ethylamino]-morpholin-4-yl-methylene}-carbamic acid 4-methoxy-cyclohexylmethyl ester; MS: 575 (M+1)



{[1-(4-Cyano-1-methyl-piperidin-4-ylcarbamoyl)-2-cyclohexyl-ethylamino]-morpholin-4-yl-methylene}-carbamic acid cyclohexyl ester; MS: 531 (M+1)

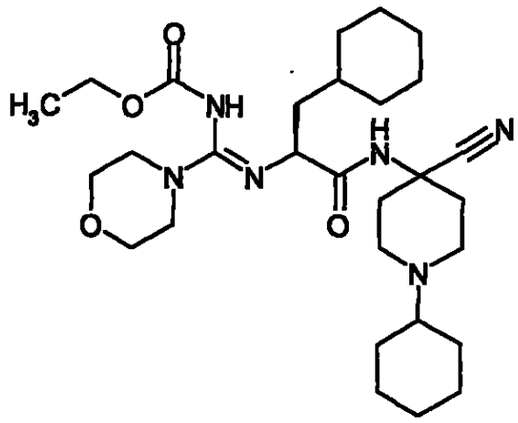


{[1-(4-Cyano-1-propyl-piperidin-4-ylcarbamoyl)-3,3-dimethyl-butylamino]-phenyl-methylene}-carbamic acid ethyl ester; MS: 470 (M+1)

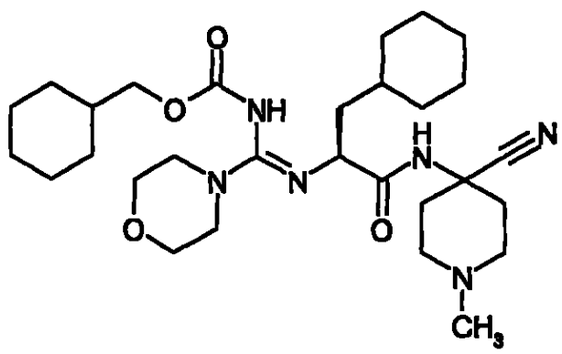


{[1-(4-Cyano-1-methyl-piperidin-4-ylcarbamoyl)-2-cyclohexyl-ethylamino]-phenyl-methylene}-carbamic acid ethyl ester; MS: 468 (M+1)

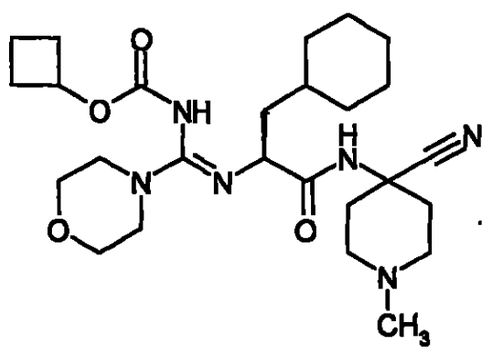
More preferred compounds of the formulas (Ia) and (Ib) are chosen from the following:



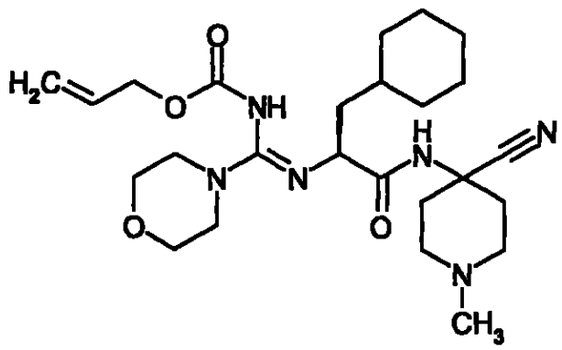
{[1-(4-cyano-1-cyclohexyl-piperidin-4-ylcarbamoyl)-2-cyclohexyl-ethylamino]-morpholin-4-yl-methylene}-carbamic acid ethyl ester; MS: 545 (M+1)



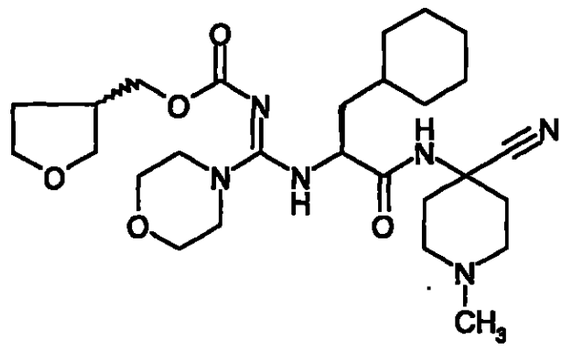
{[1-(4-cyano-1-methyl-piperidin-4-ylcarbamoyl)-2-cyclohexyl-ethylamino]-morpholin-4-yl-methylene}-carbamic acid cyclohexylmethyl ester; MS: 545 (M+1)



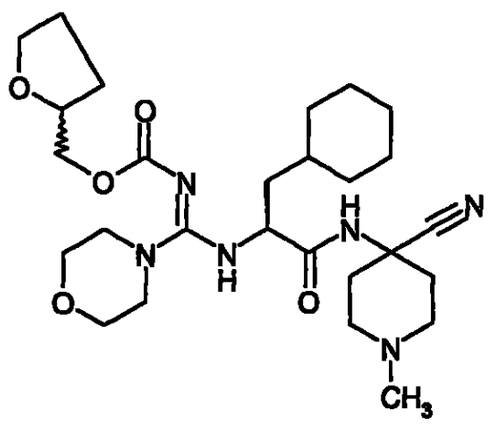
{[-1-(4-cyano-1-methyl-piperidin-4-ylcarbamoyl)-2-cyclohexyl-ethylamino]-morpholin-4-yl-methylene}-carbamic acid cyclobutyl ester; MS: 503 (M+1)



{[1-(4-cyano-1-methyl-piperidin-4-ylcarbamoyl)-2-cyclohexyl-ethylamino]-morpholin-4-yl-methylene}-carbamic acid allyl ester; MS: 489 (M+1)



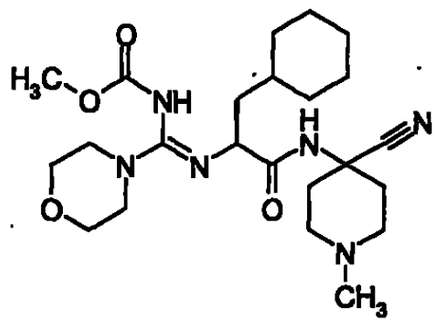
{[ 1-(4-cyano-1-methyl-piperidin-4-ylcarbamoyl)-2-cyclohexyl-ethylamino]-morpholin-4-yl-methylene}-carbamic acid tetrahydro-furan-3ylmethyl ester; MS: 533 (M+1)



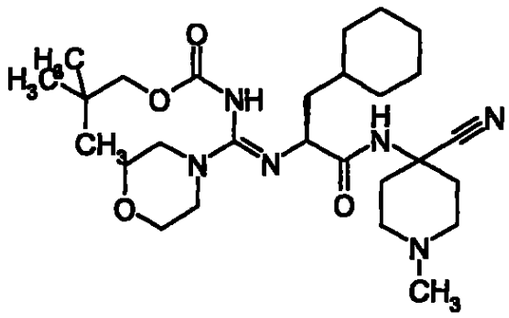
{[1-(4-cyano-1-methy-piperidin-4-ylcarbamoyl)-2-cyclohexyl-ethyl amino]-morpholin-4-yl-methylene}-carbamic acid tetrahydro-furan-2-ylmethyl ester; MS: 533 (M+1)

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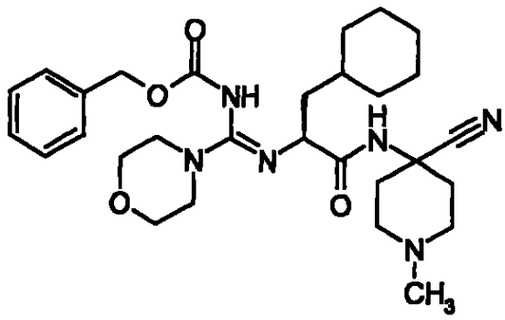
213



{[1-(4-Cyano-1-methyl-piperidin-4-ylcarbamoyl)-2-cyclohexyl-ethylimino]-morpholin-4-yl-methyl}-carbamic acid methyl ester; MS: 463 (M+1)

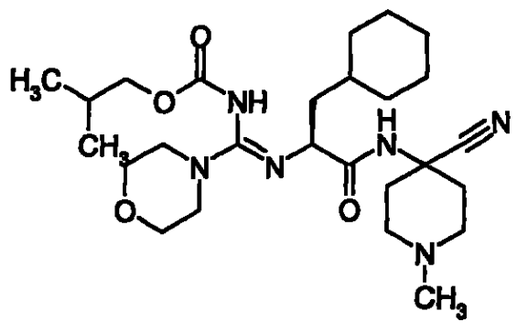


{[1-(4-Cyano-1-methyl-piperidin-4-ylcarbamoyl)-2-cyclohexyl-ethylimino]-morpholin-4-yl-methyl}-carbamic acid 2,2-dimethyl-propyl ester; MS: 519 (M+1)

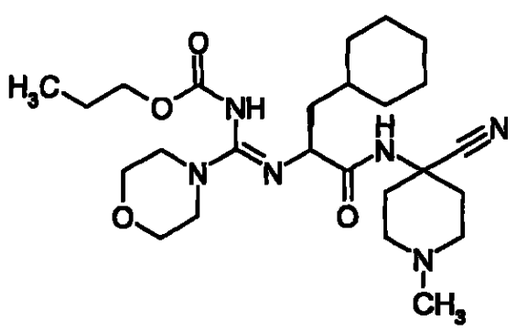


{[1-(4-Cyano-1-methyl-piperidin-4-ylcarbamoyl)-2-cyclohexyl-ethylimino]-morpholin-4-yl-methyl}-carbamic acid benzyl ester; MS: 539 (M+1)

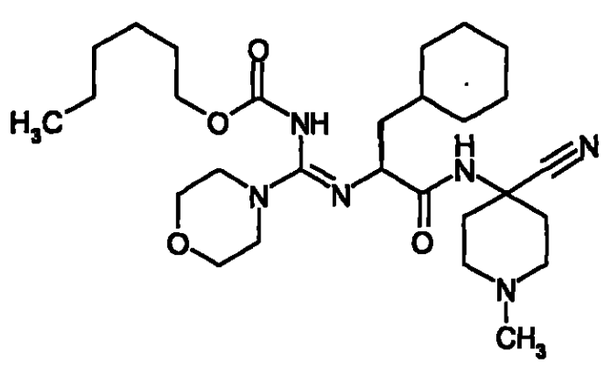
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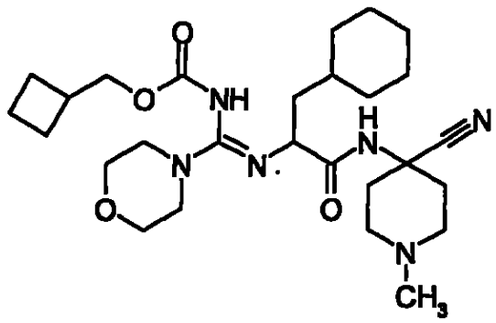
{[1-(4-Cyano-1-methyl-piperidin-4-ylcarbamoyl)-2-cyclohexyl-ethylimino]-morpholin-4-yl-methyl}-carbamic acid isobutyl ester; MS: 505 (M+1)



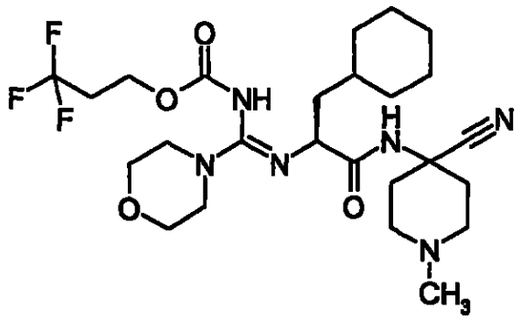
{[1-(4-Cyano-1-methyl-piperidin-4-ylcarbamoyl)-2-cyclohexyl-ethylimino]-morpholin-4-yl-methyl}-carbamic acid propyl ester; MS: 491 (M+1)



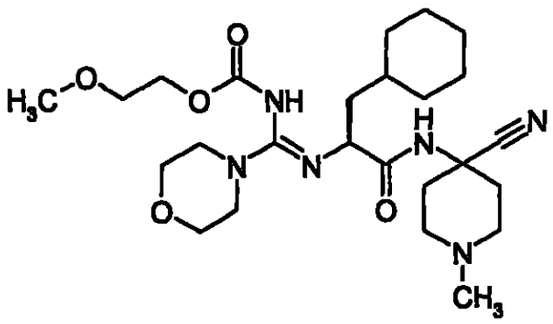
{[1-(4-Cyano-1-methyl-piperidin-4-ylcarbamoyl)-2-cyclohexyl-ethylimino]-morpholin-4-yl-methyl}-carbamic acid hexyl ester; MS: 533 (M+1)



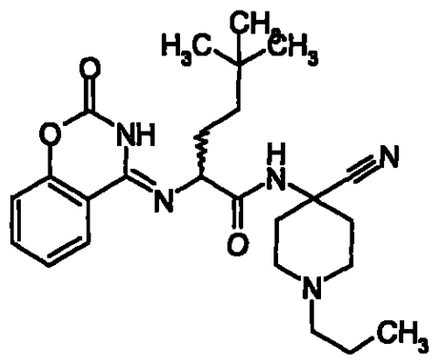
{[1-(4-Cyano-1-methyl-piperidin-4-ylcarbamoyl)-2-cyclohexyl-ethylimino]-morpholin-4-yl-methyl}-carbamic acid cyclobutylmethyl ester; MS: 517 (M+1)



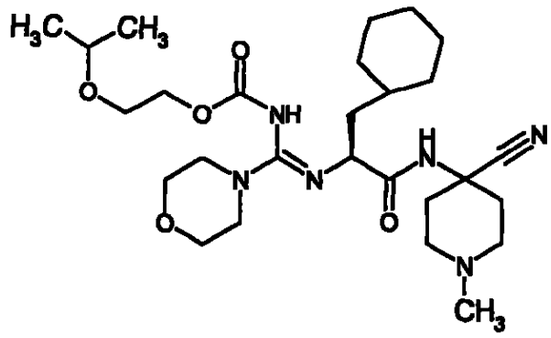
{[1-(4-Cyano-1-methyl-piperidin-4-ylcarbamoyl)-2-cyclohexyl-ethylimino]-morpholin-4-yl-methyl}-carbamic acid 3,3,3-trifluoro-propyl ester; MS: 545 (M+1)



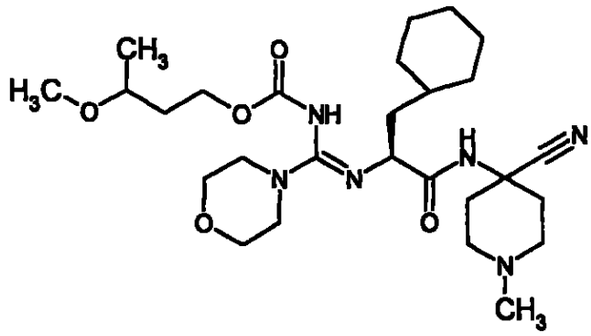
{[1-(4-Cyano-1-methyl-piperidin-4-ylcarbamoyl)-2-cyclohexyl-ethylimino]-morpholin-4-yl-methyl}-carbamic acid 2-methoxy-ethyl ester; MS: 507 (M+1)



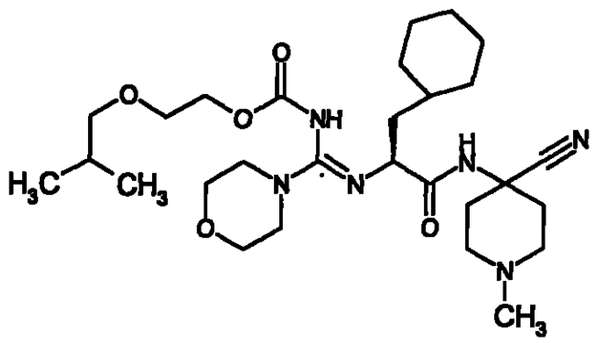
5,5-Dimethyl-2-(2-oxo-2,3-dihydro-benzo[*e*][1,3]oxazin-4-ylideneamino)-hexanoic acid (4-cyano-1-propyl-piperidin-4-yl)-amide; MS: 454 (M+1)



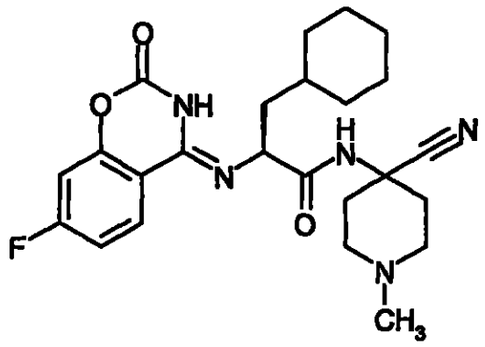
{[1-(4-Cyano-1-methyl-piperidin-4-ylcarbamoyl)-2-cyclohexyl-ethylimino]-morpholin-4-yl-methyl}-carbamic acid 2-isopropoxy-ethyl ester; MS: 534 (M+1)



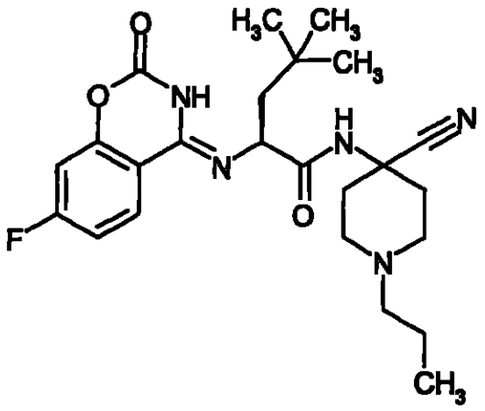
{[1-(4-Cyano-1-methyl-piperidin-4-ylcarbamoyl)-2-cyclohexyl-ethylimino]-morpholin-4-yl-methyl}-carbamic acid 3-methoxy-butyl ester; MS: 534 (M+1)



{[1-(4-Cyano-1-methyl-piperidin-4-ylcarbamoyl)-2-cyclohexyl-ethylimino]-morpholin-4-yl-methyl}-carbamic acid 2-isobutoxy-ethyl ester; MS: 549 (M+1)



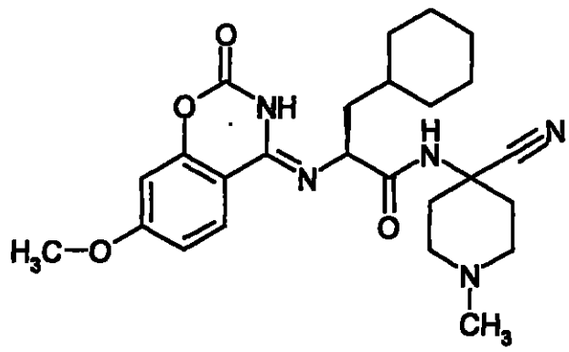
N-(4-Cyano-1-methyl-piperidin-4-yl)-4-cyclohexyl-2-(7-fluoro-2-oxo-2,3-dihydro-benzo[e][1,3]oxazin-4-ylideneamino)-butyramide; MS: 456 (M+1)



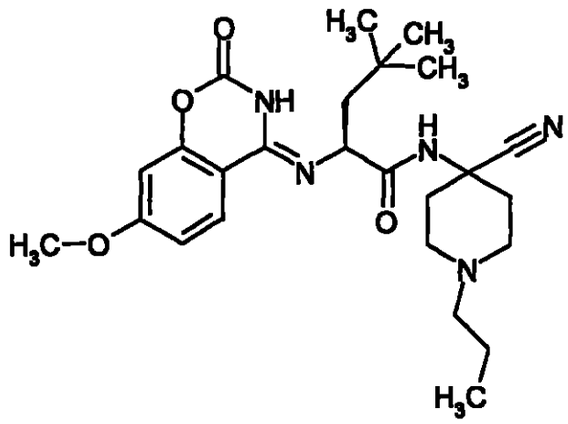
2-(7-Fluoro-2-oxo-2,3-dihydro-benzo[e][1,3]oxazin-4-yldeneamino)-5,5-dimethyl-hexanoic acid(4-cyano-1-propyl-piperidin-4-yl)-amide; MS: 458 (M+1)

217

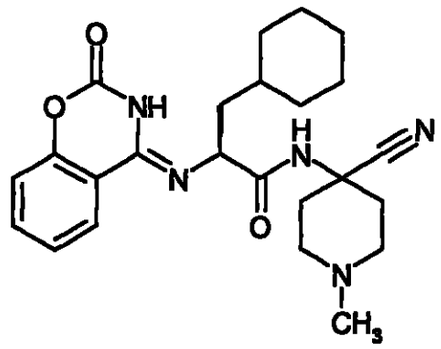
218



N-(4-Cyano-1-methyl-piperidin-4-yl)-4-cyclohexyl-2-(7-methoxy-2-oxo-2,3-dihydro-benzo[e][1,3]oxazin-4-ylideneamino)-butyramide; MS: 468 (M+1)

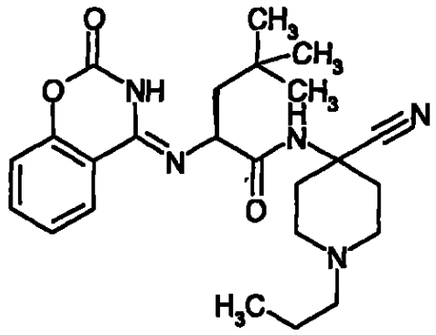


2-(7-Methoxy-2-oxo-2,3-dihydro-benzo[e][1,3]oxazin-4-yldeneamino)-5,5-dimethyl-hexanoic acid(4-cyano-1-propyl-piperidin-4-yl)-amide; MS: 470 (M+1)

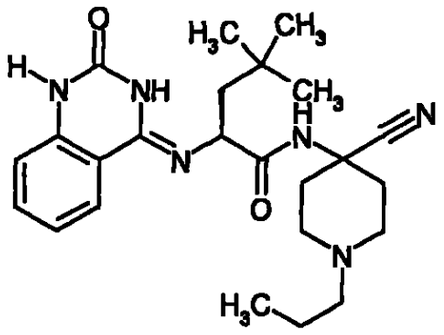


*N*-(4-Cyano-1-methyl-piperidin-4-yl)-3-cyclohexyl-2-(2-oxo-2,3-dihydro-benzo[*e*][1,3]oxazin-4-ylideneamino)-propionamide; MS: 438 (M+1).

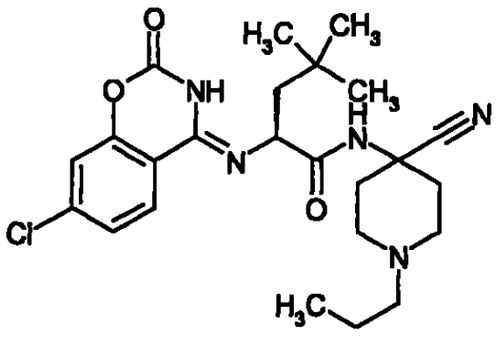
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219



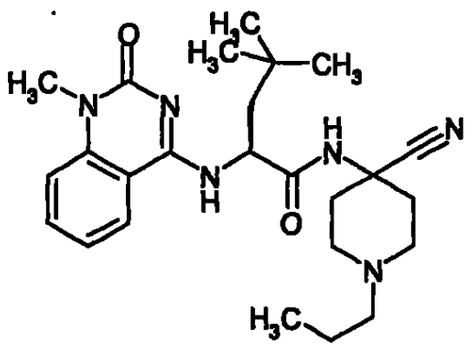
4,4-Dimethyl-2-(2-oxo-2,3-dihydro-benzo[e][1,3]oxazin-4-ylideneamino)-pentanoic acid (4-cyano-1-propyl-piperidin-4-yl)-amide; MS: 440 (M+1)



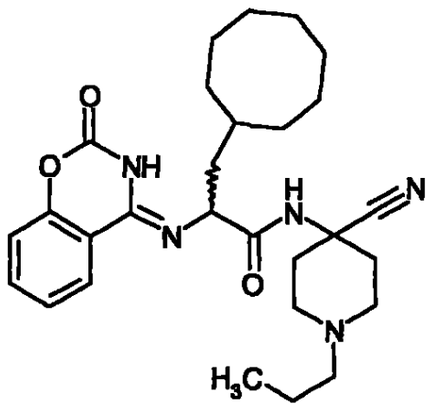
4,4-Dimethyl-2-(2-oxo-2,3-dihydro-1*H*-quinazolin-4-ylideneamino)-pentanoic acid (4-cyano-1-propyl-piperidin-4-yl)-amide; MS: 439 (M+1)



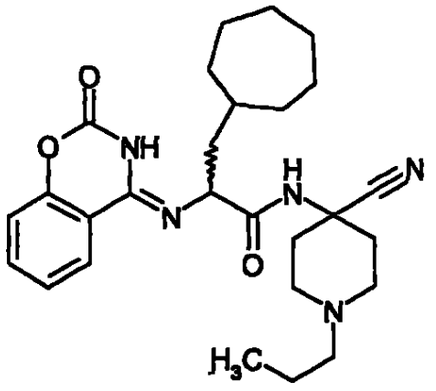
2-(7-Chloro-2-oxo-2,3-dihydro-benzo[*e*][1,3]oxazin-4-ylideneamino)-4,4-dimethyl-pentanoic acid (4-cyano-1-propyl-piperidin-4-yl)-amide; MS: 475 (M+1)



4,4-Dimethyl-2-(1-methyl-2-oxo-1,2-dihydro-quinazolin-4-ylamino)-pentanoic acid (4-cyano-1-propyl-piperidin-4-yl)-amide; MS: 453 (M+1)



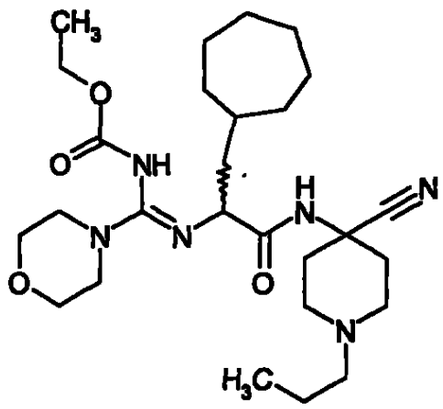
*N*-(4-Cyano-1-propyl-piperidin-4-yl)-3-cyclooctyl-2-(2-oxo-2,3-dihydro-benzo[*e*][1,3]oxazin-4-ylideneamino)-propionamide; MS: 494 (M+1)



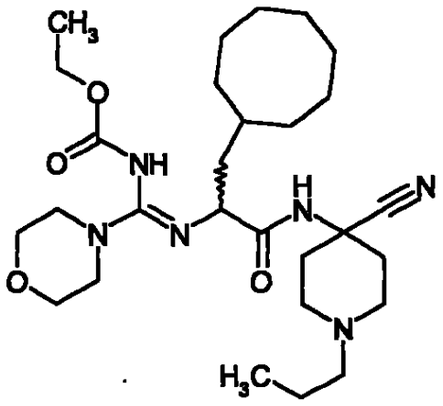
*N*-(4-Cyano-1-propyl-piperidin-4-yl)-3-cycloheptyl-2-(2-oxo-2,3-dihydro-benzo[*e*][1,3]oxazin-4-ylideneamino)-propionamide; MS: 480 (M+1)

220

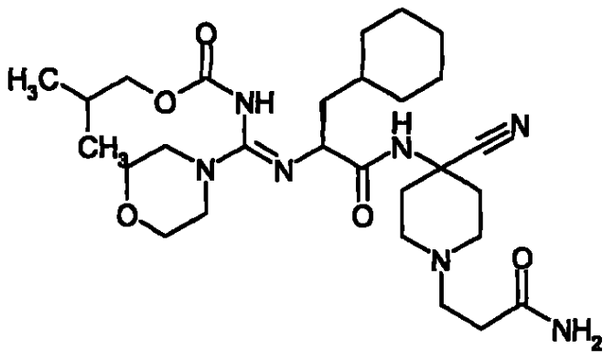
221



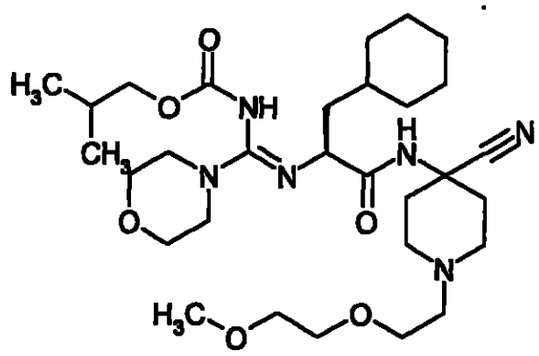
{[1-(4-Cyano-1-propyl-piperidin-4-ylcarbamoyl)-2-cycloheptyl-ethylimino]-morpholin-4-yl-methyl}-carbamic acid ethyl ester; MS: 519 (M+1)



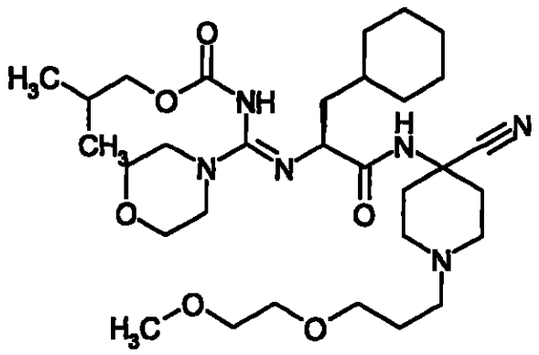
{[1-(4-Cyano-1-propyl-piperidin-4-ylcarbamoyl)-2-cyclooctyl-ethylimino]-morpholin-4-yl-methyl}-carbamic acid ethyl ester; MS: 533 (M+1)



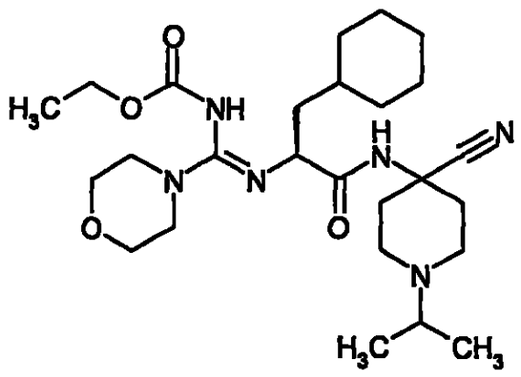
({1-[1-2-Carbamoyl-ethyl)-4-cyano-piperidin-4-ylcarbamoyl]-2-cyclohexyl-ethylamino}-morpholin-4-yl-methylene)-carbamic acid isobutyl ester; MS: 562 (M+1)



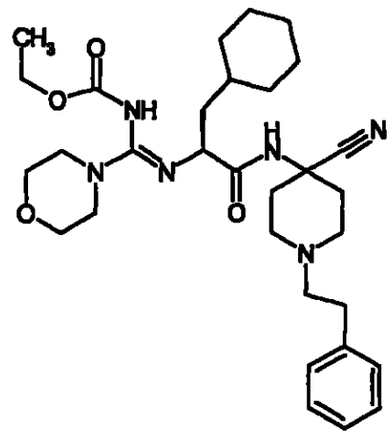
[(1-{4-Cyano-1-[2-(2-methoxyl-ethoxy)-ethyl]-piperidin-4-ylcarbamoyl}-2-cyclohexyl-ethylamino)-morpholin-4-yl-methylene]-carbamic acid isobutyl ester; MS: 593 (M+1)



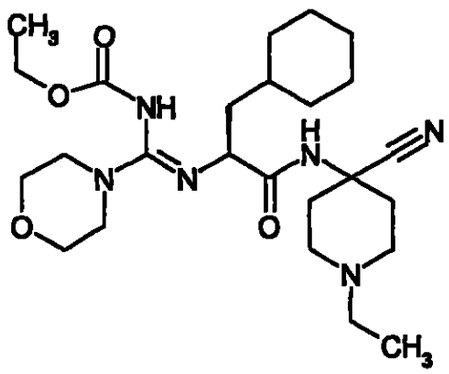
[(1-{4-Cyano-1-[3-(2-methoxyl-ethoxy)-propyl]-piperidin-4-ylcarbamoyl}-2-cyclohexyl-ethylamino)-morpholin-4-yl-methylene]-carbamic acid isobutyl ester; MS: 607 (M+1)



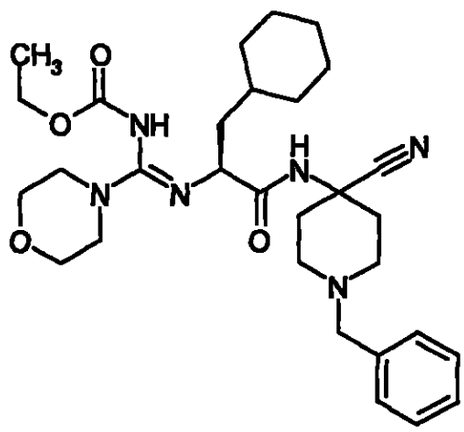
{[1-(4-Cyano-1-isopropyl-piperidin-4-ylcarbamoyl)-2-cyclohexyl-ethylamino]-morpholin-4-yl-methylene}-carbamic acid ethyl ester; MS: 505 (M+1)



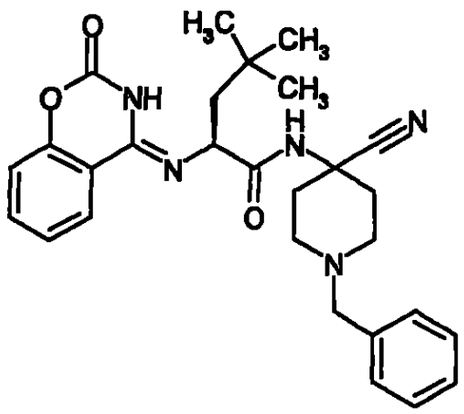
{[1-(4-Cyano-1-phenethyl-piperidin-4-ylcarbamoyl)-2-cyclohexyl-ethylamino]-morpholin-4-yl-methylene}-carbamic acid ethyl ester; MS: 567 (M+1)



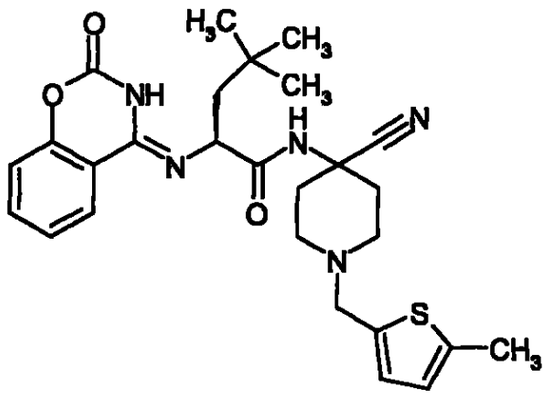
{[1-(4-Cyano-1-ethyl-piperidin-4-ylcarbamoyl)-2-cyclohexyl-ethylamino]-morpholin-4-yl-methylene}-carbamic acid ethyl ester; MS: 491 (M+1)



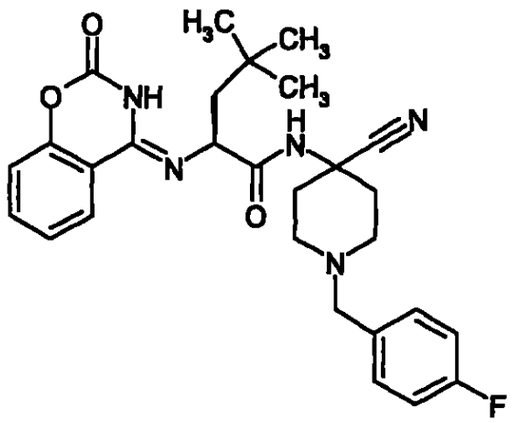
{[1-(1-Benzyl-4-cyano-piperidin-4-ylcarbamoyl)-2-cyclohexyl-ethylamino]-morpholin-4-yl-methylene}-carbamic acid ethyl ester; MS: 553 (M+1)



4,4-Dimethyl-2-(2-oxo-2H-benzo[e][1,3]oxazin-4-ylamino)-pentanoic acid (1-benzyl-4-cyano-piperidin-4-yl)-amide; MS: 488 (M+1)



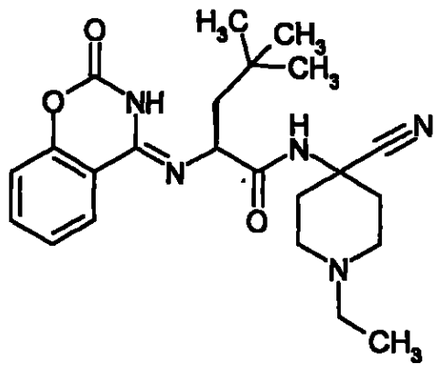
4,4-Dimethyl-2-(2-oxo-2H-benzo[e][1,3]oxazin-4-ylamino)-pentanoic acid [4-cyano-1-(5-methyl-thiophen-2-ylmethyl)-piperidin-4-yl]-amide; MS: 508 (M+1)



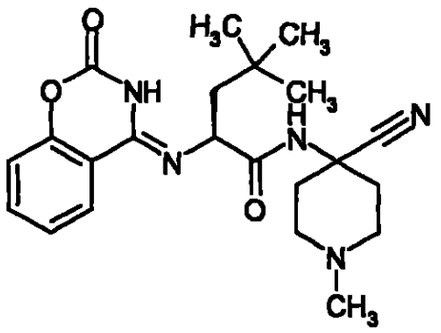
4,4-Dimethyl-2-(2-oxo-2H-benzo[e][1,3]oxazin-4-ylamino)-pentanoic acid [4-cyano-1-(4-fluoro-benzyl)-piperidin-4-yl]-amide; MS: 506 (M+1)

224

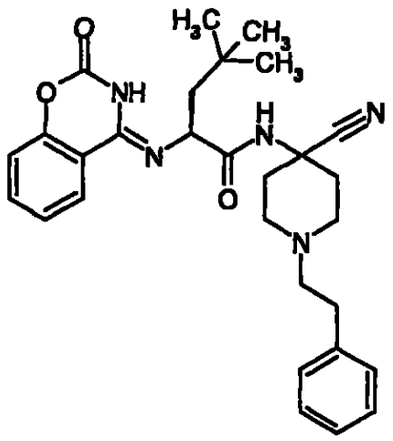
225



4,4-Dimethyl-2-(2-oxo-2H-benzo[e][1,3]oxazin-4-ylamino)-pentanoic acid (4-cyano-1-ethyl-piperidin-4-yl)-amide; MS: 426 (M+1)

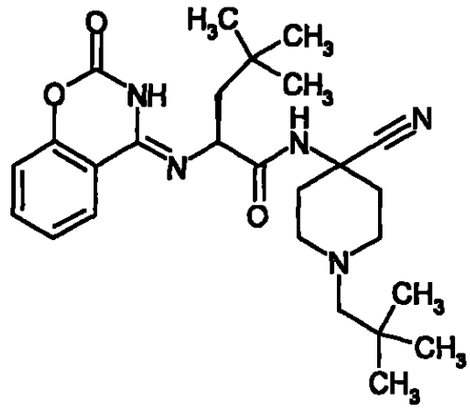


4,4-Dimethyl-2-(2-oxo-2H-benzo[e][1,3]oxazin-4-ylamino)-pentanoic acid (4-cyano-1-methyl-piperidin-4-yl)-amide; MS: 412 (M+1)

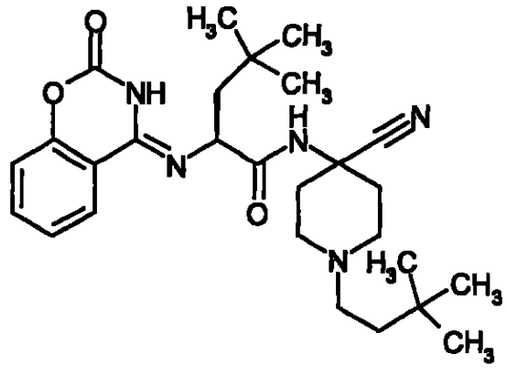


4,4-Dimethyl-2-(2-oxo-2H-benzo[e][1,3]oxazin-4-ylamino)-pentanoic acid (4-cyano-1-phenethyl-piperidin-4-yl)-amide; MS: 502 (M+1)

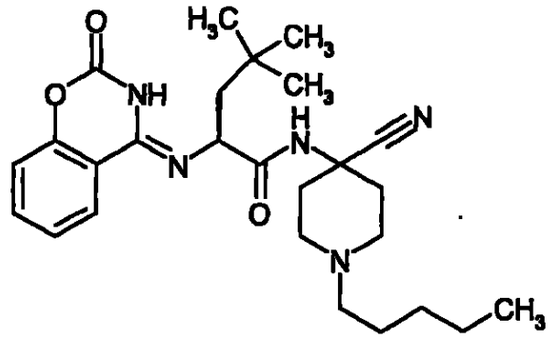
226



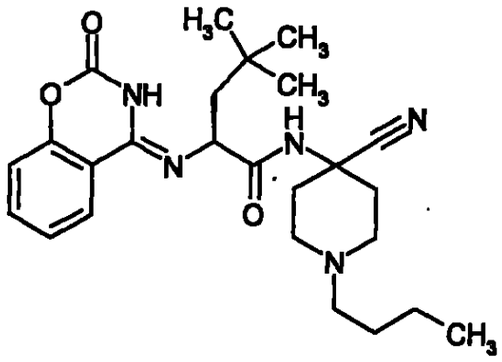
4,4-Dimethyl-2-(2-oxo-2H-benzo[e][1,3]oxazin-4-ylamino)-pentanoic acid [4-cyano-1-(2,2-dimethyl-propyl)-piperidin-4-yl]-amide; MS: 468 (M+1)



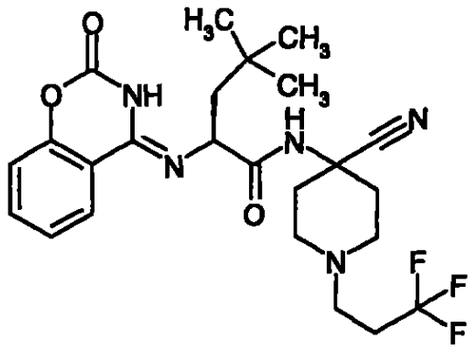
4,4-Dimethyl-2-(2-oxo-2H-benzo[e][1,3]oxazin-4-ylamino)-pentanoic acid [4-cyano-1-(3,3-dimethyl-butyl)-piperidin-4-yl]-amide; MS: 482 (M+1)



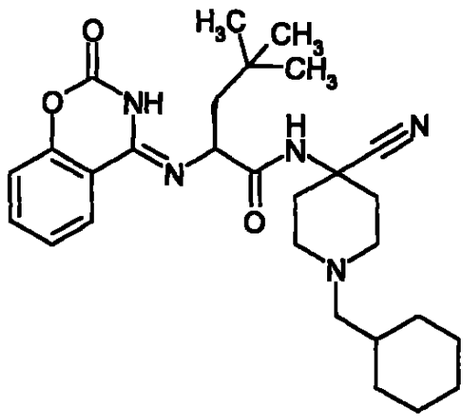
4,4-Dimethyl-2-(2-oxo-2H-benzo[e][1,3]oxazin-4-ylamino)-pentanoic acid (4-cyano-1-pentyl-piperidin-4-yl)-amide; MS: 468 (M+1)



4,4-Dimethyl-2-(2-oxo-2H-benzo[e][1,3]oxazin-4-ylamino)-pentanoic acid (1-butyl-4-cyano-piperidin-4-yl)-amide; MS: 454(M+1)

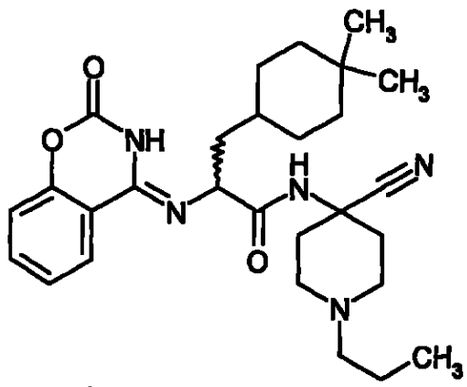


4,4-Dimethyl-2-(2-oxo-2H-benzo[e][1,3]oxazin-4-ylamino)-pentanoic acid [4-cyano-1-(3,3,3-trifluoro-propyl)-piperidin-4-yl]-amide; MS: 494 (M+1)

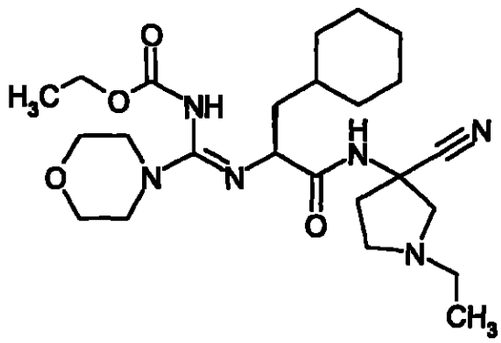


4,4-Dimethyl-2-(2-oxo-2H-benzo[e][1,3]oxazin-4-ylamino)-pentanoic acid (4-cyano-1-cyclohexylmethyl-piperidin-4-yl)-amide; MS: 494 (M+1)

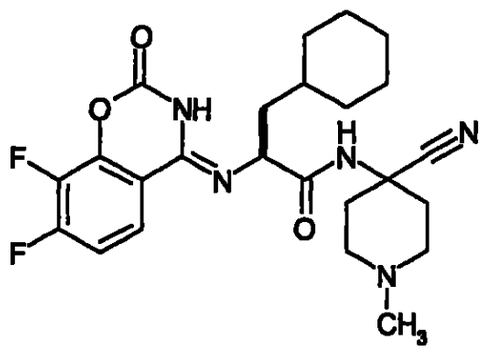
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N-(4-Cyano-1-propyl-piperidin-4-yl)-3-(4,4-dimethyl-cyclohexyl)-2-(2-oxo-2H-benzo[e][1,3]oxazin-4-ylamino)-propionamide; MS: 494 (M+1)



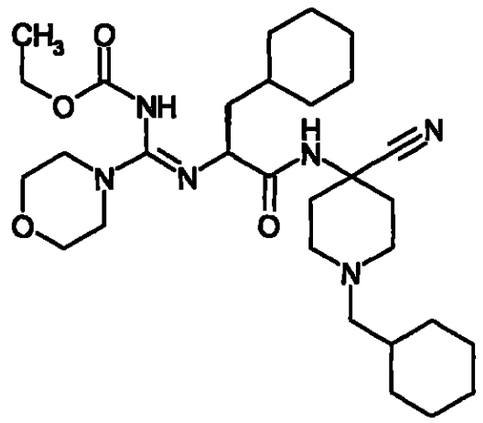
{[1-(3-Cyano-1-ethyl-pyrrolidin-3-ylcarbamoyl)-2-cyclohexyl-ethylamino]-morpholin-4-yl-methylene}-carbamic acid ethyl ester. MS: 477 (M+1).



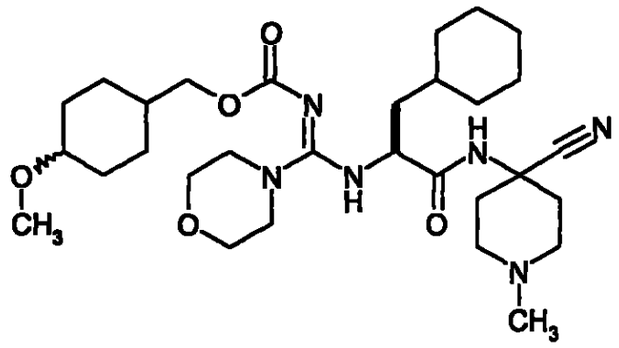
N-(4-Cyano-1-methyl-piperidin-4-yl)-3-cyclohexyl-2-(7,8-difluoro-2-oxo-2H-benzo[e][1,3]oxazin-4-ylamino)-propionamide; MS: 474 (M+1)

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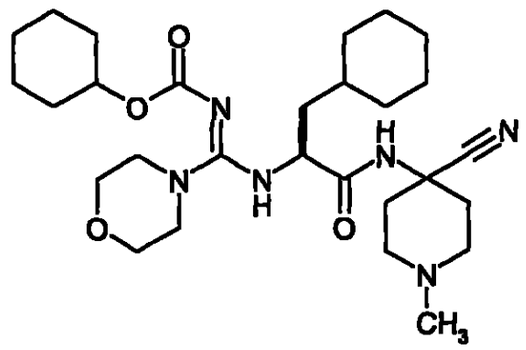
229



{[1-(4-Cyano-1-cyclohexylmethyl-piperidin-4-ylcarbamoyl)-2-cyclohexyl-ethylamino]-morpholin-4-yl-methylene}-carbamic acid ethyl ester; MS: 559 (M+1)



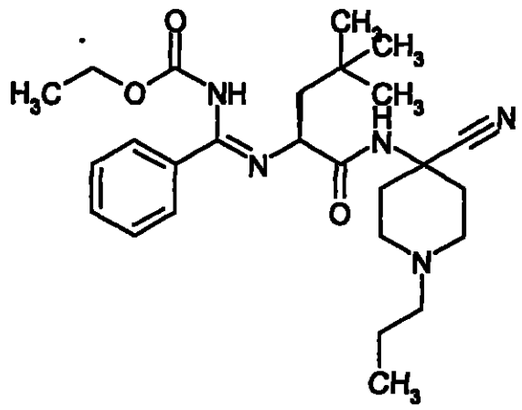
{[1-(4-Cyano-1-methyl-piperidin-4-ylcarbamoyl)-2-cyclohexyl-ethylamino]-morpholin-4-yl-methylene}-carbamic acid 4-methoxy-cyclohexylmethyl ester; MS: 575 (M+1)



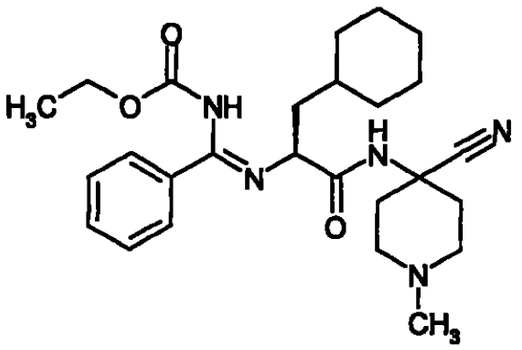
{[1-(4-Cyano-1-methyl-piperidin-4-ylcarbamoyl)-2-cyclohexyl-ethylamino]-morpholin-4-yl-methylene}-carbamic acid cyclohexyl ester; MS: 531 (M+1)

229

230



{[1-(4-Cyano-1-propyl-piperidin-4-ylcarbamoyl)-3,3-dimethyl-butylamino]-phenyl-methylene}-carbamic acid ethyl ester; MS: 470 (M+1)

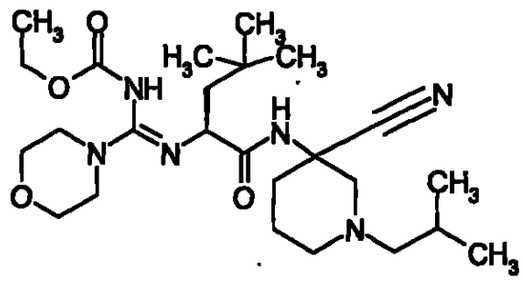


{[1-(4-Cyano-1-methyl-piperidin-4-ylcarbamoyl)-2-cyclohexyl-ethylamino]-phenyl-methylene}-carbamic acid ethyl ester; MS: 468 (M+1)

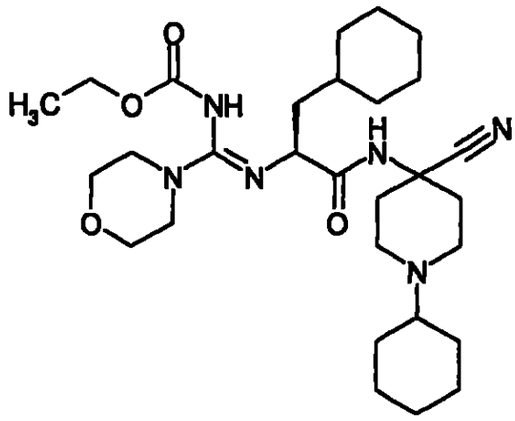
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231

Most preferred compounds of the formulas (Ia) and (Ib) are those chosen from the following:



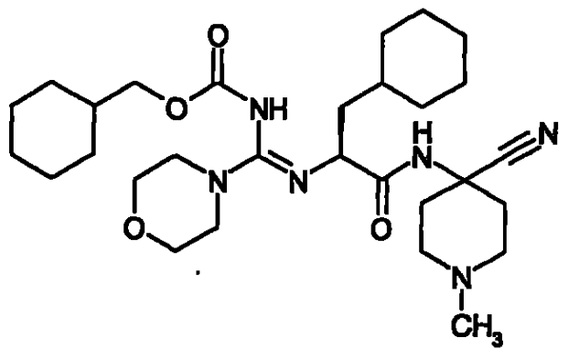
{[1-(3-cyano-1-isobutyl-piperdin-3-yl carbamoyl)-3,3-dimethyl-butylamino]-morpholin-4-yl-methylene}-carbamic acid ethyl ester; MS: 493 (M+1)



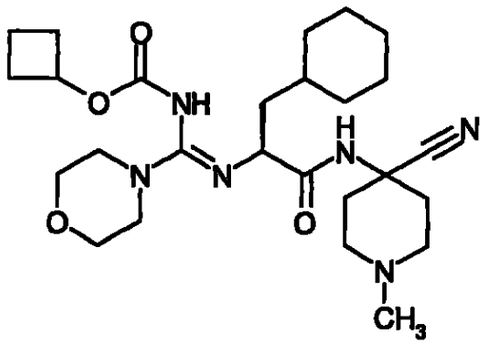
{[1-(4-cyano-1-cyclohexyl-piperidin-4-ylcarbamoyl)-2-cyclohexyl-ethylamino]-morpholin-4-yl-methylene}-carbamic acid ethyl ester; MS: 545 (M+1)

231

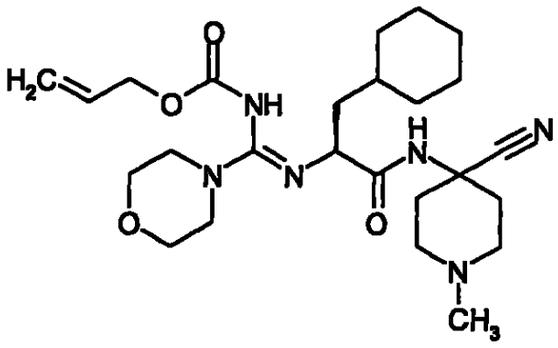
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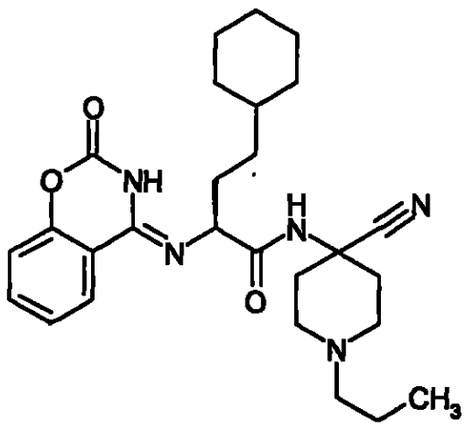
{[1-(4-cyano-1-methyl-piperidin-4-ylcarbamoyl)-2-cyclohexyl-ethylamino]-morpholin-4-yl-methylene}-carbamic acid cyclohexylmethyl ester; MS: 545 (M+1)



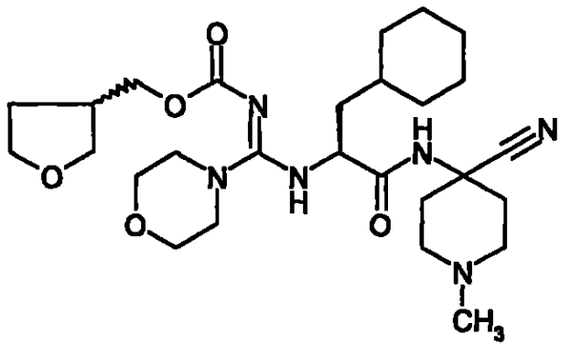
{[-1-(4-cyano-1-methyl-piperidin-4-ylcarbamoyl)-2-cyclohexyl-ethylamino]-morpholin-4-yl-methylene}-carbamic acid cyclobutyl ester; MS: 503 (M+1)



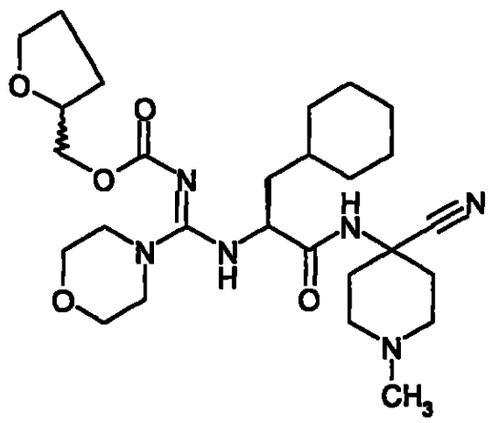
{[1-(4-cyano-1-methyl-piperidin-4-ylcarbamoyl)-2-cyclohexyl-ethylamino]-morpholin-4-yl-methylene}-carbamic acid allyl ester; MS: 489 (M+1)



N-(4-Cyano-1-propyl-piperidin-4-yl)-4-cyclohexyl-2-(2-oxo-2,3-dihydro-benzo[e][1,3]oxazin-4-ylideneamino)-butyramide; MS: 480 (M+1)



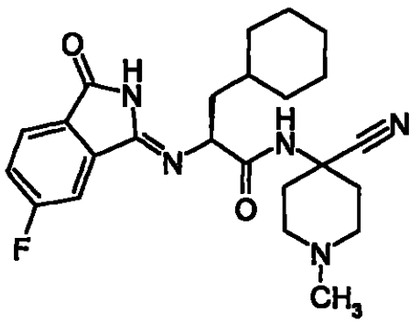
{[ 1-(4-cyano-1-methyl-piperidin-4-ylcarbamoyl)-2-cyclohexyl-ethylamino]-morpholin-4-yl-methylene}-carbamic acid tetrahydro-furan-3ylmethyl ester; MS: 533 (M+1)



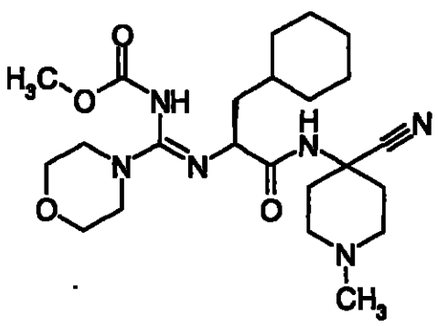
{[1-(4-cyano-1-methy-piperidin-4-ylcarbamoyl)-2-cyclohexyl-ethyl amino]-morpholin-4-yl-methylene}-carbamic acid tetrahydro-furan-2-ylmethyl ester; MS: 533 (M+1)

233

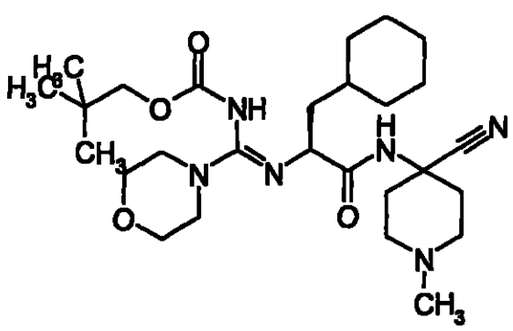
234



*N*-(4-Cyano-1-methyl-piperidin-4-yl)-3-cyclohexyl-2-(6-fluoro-3-oxo-2,3-dihydro-isoindol-1-ylideneamino)-propionamide; MS: 440 (M+1)

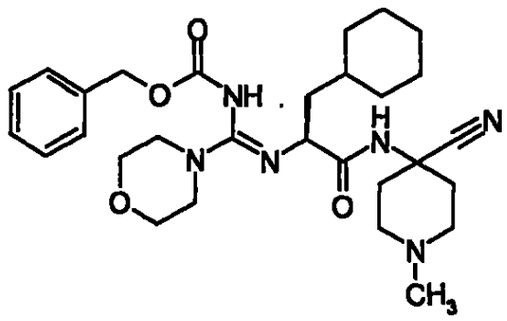


{[1-(4-Cyano-1-methyl-piperidin-4-ylcarbamoyl)-2-cyclohexyl-ethylimino]-morpholin-4-yl-methyl}-carbamic acid methyl ester; MS: 463 (M+1)

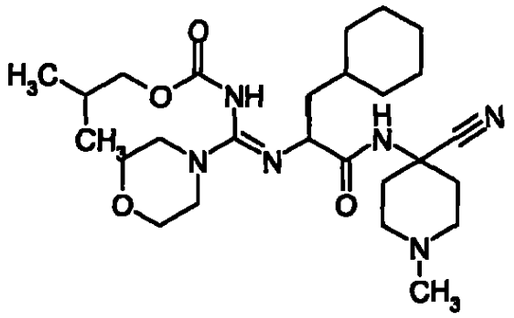


{[1-(4-Cyano-1-methyl-piperidin-4-ylcarbamoyl)-2-cyclohexyl-ethylimino]-morpholin-4-yl-methyl}-carbamic acid 2,2-dimethyl-propyl ester; MS: 519 (M+1)

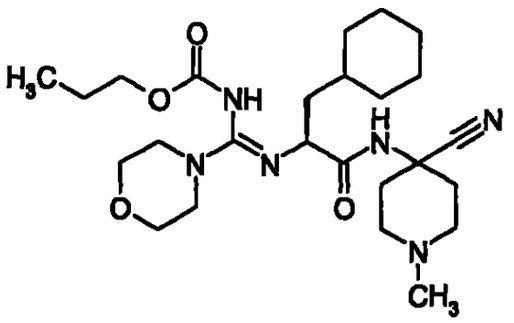
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235



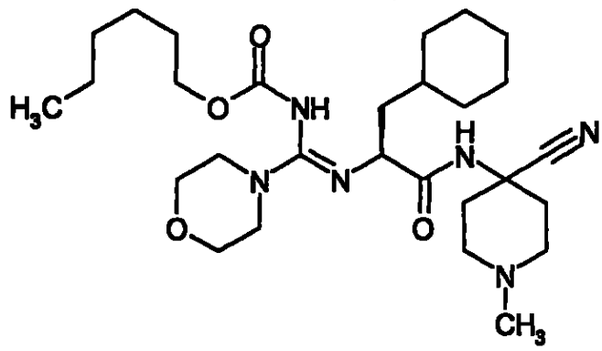
{[1-(4-Cyano-1-methyl-piperidin-4-ylcarbamoyl)-2-cyclohexyl-ethylimino]-morpholin-4-yl-methyl}-carbamic acid benzyl ester; MS: 539 (M+1)



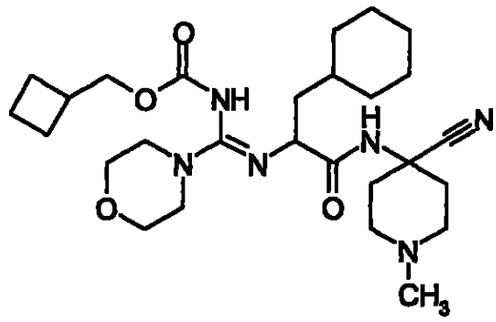
{[1-(4-Cyano-1-methyl-piperidin-4-ylcarbamoyl)-2-cyclohexyl-ethylimino]-morpholin-4-yl-methyl}-carbamic acid isobutyl ester; MS: 505 (M+1)



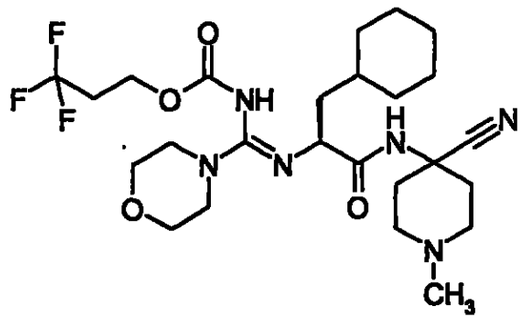
{[1-(4-Cyano-1-methyl-piperidin-4-ylcarbamoyl)-2-cyclohexyl-ethylimino]-morpholin-4-yl-methyl}-carbamic acid propyl ester; MS: 491 (M+1)



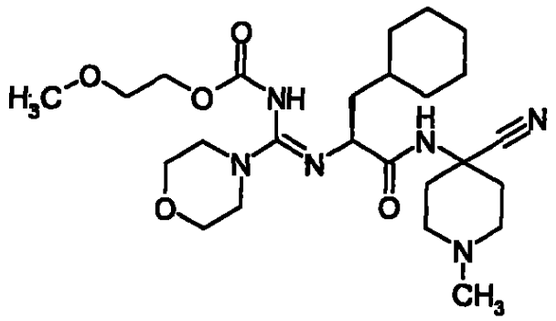
{[1-(4-Cyano-1-methyl-piperidin-4-ylcarbamoyl)-2-cyclohexyl-ethylimino]-morpholin-4-yl-methyl}-carbamic acid hexyl ester; MS: 533 (M+1)



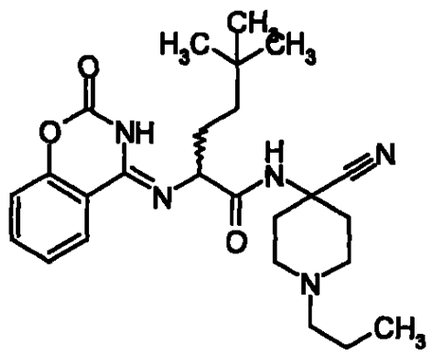
{[1-(4-Cyano-1-methyl-piperidin-4-ylcarbamoyl)-2-cyclohexyl-ethylimino]-morpholin-4-yl-methyl}-carbamic acid cyclobutylmethyl ester; MS: 517 (M+1)



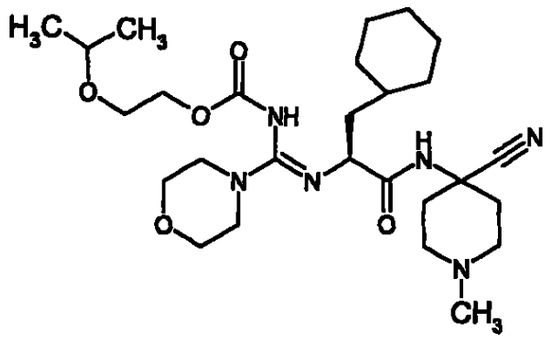
{[1-(4-Cyano-1-methyl-piperidin-4-ylcarbamoyl)-2-cyclohexyl-ethylimino]-morpholin-4-yl-methyl}-carbamic acid 3,3,3-trifluoro-propyl ester; MS: 545 (M+1)



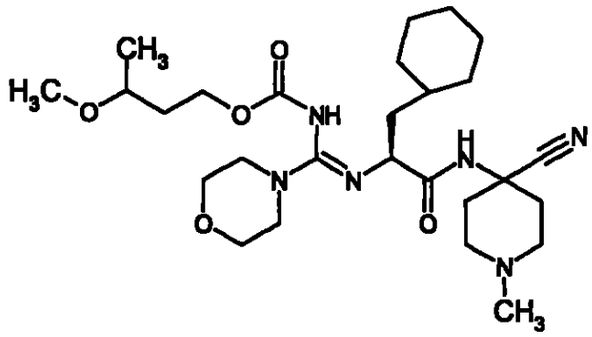
{[1-(4-Cyano-1-methyl-piperidin-4-ylcarbamoyl)-2-cyclohexyl-ethylimino]-morpholin-4-yl-methyl}-carbamic acid 2-methoxy-ethyl ester; MS: 507 (M+1)



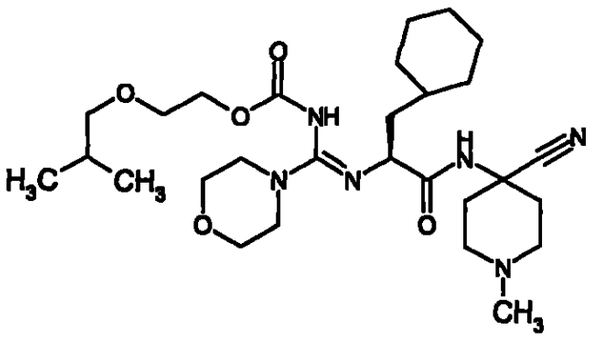
5,5-Dimethyl-2-(2-oxo-2,3-dihydro-benzo[*e*][1,3]oxazin-4-ylideneamino)-hexanoic acid (4-cyano-1-propyl-piperidin-4-yl)-amide; MS: 454 (M+1)



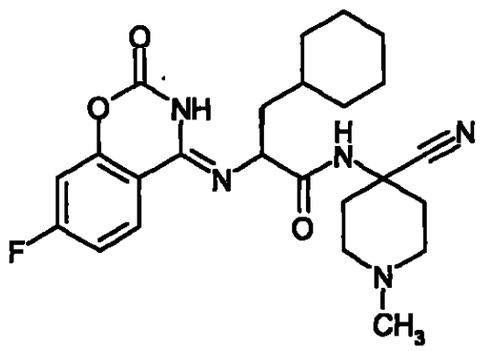
{[1-(4-Cyano-1-methyl-piperidin-4-ylcarbamoyl)-2-cyclohexyl-ethylimino]-morpholin-4-yl-methyl}-carbamic acid 2-isopropoxy-ethyl ester; MS: 534 (M+1)



{[1-(4-Cyano-1-methyl-piperidin-4-ylcarbamoyl)-2-cyclohexyl-ethylimino]-morpholin-4-yl-methyl}-carbamic acid 3-methoxy-butyl ester; MS: 534 (M+1)

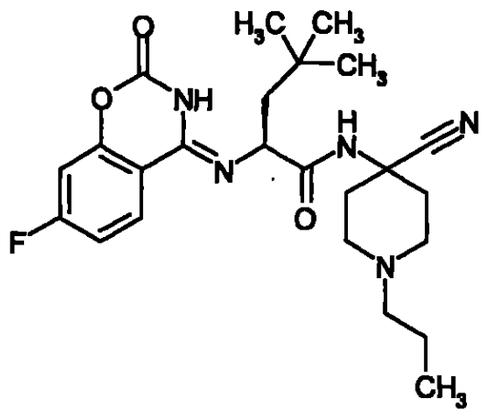


{[1-(4-Cyano-1-methyl-piperidin-4-ylcarbamoyl)-2-cyclohexyl-ethylimino]-morpholin-4-yl-methyl}-carbamic acid 2-isobutoxy-ethyl ester; MS: 549 (M+1)

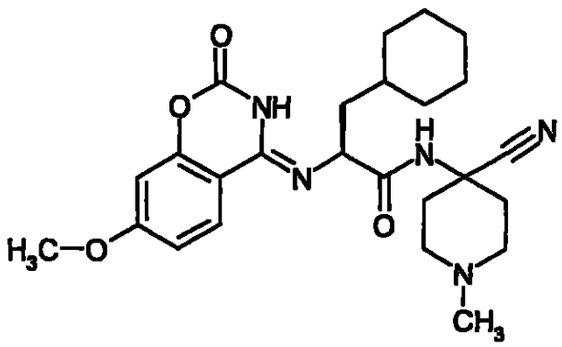


N-(4-Cyano-1-methyl-piperidin-4-yl)-4-cyclohexyl-2-(7-fluoro-2-oxo-2,3-dihydro-benzo[e][1,3]oxazin-4-ylideneamino)-butyramide; MS: 456 (M+1)

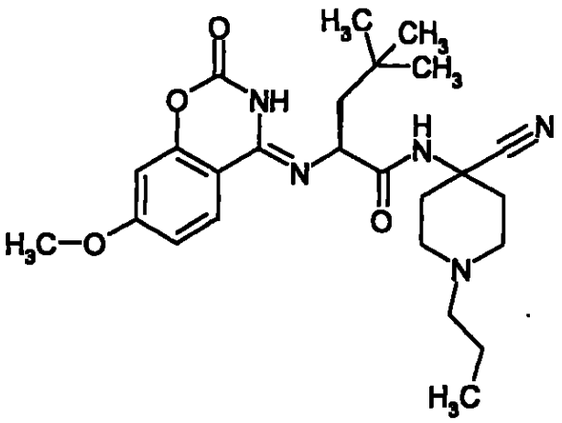
238
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2-(7-Fluoro-2-oxo-2,3-dihydro-benzo[e][1,3]oxazin-4-ylideneamino)-5,5-dimethyl-hexanoic acid(4-cyano-1-propyl-piperidin-4-yl)-amide; MS: 458 (M+1)



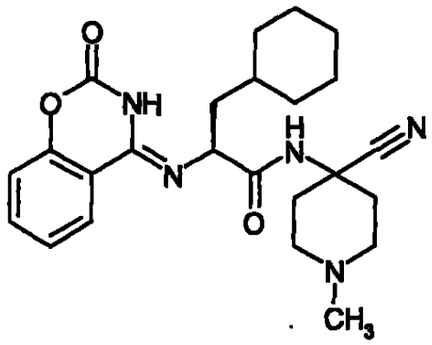
N-(4-Cyano-1-methyl-piperidin-4-yl)-4-cyclohexyl-2-(7-methoxy-2-oxo-2,3-dihydro-benzo[e][1,3]oxazin-4-ylideneamino)-butyramide; MS: 468 (M+1)



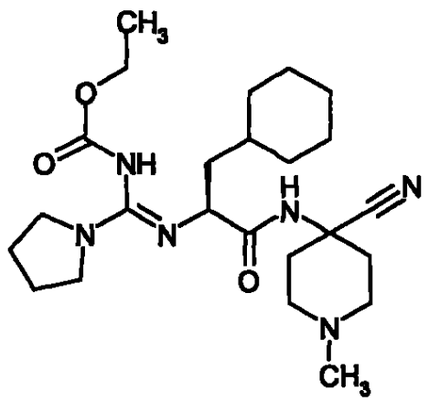
2-(7-Methoxy-2-oxo-2,3-dihydro-benzo[e][1,3]oxazin-4-ylideneamino)-5,5-dimethyl-hexanoic acid(4-cyano-1-propyl-piperidin-4-yl)-amide; MS: 470 (M+1)

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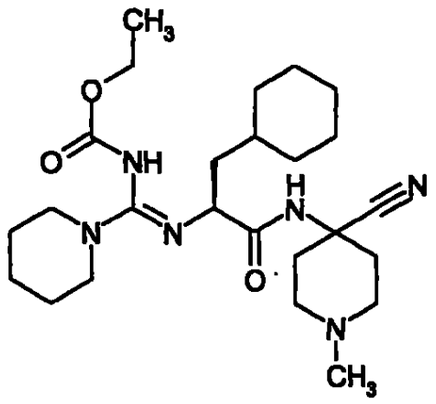
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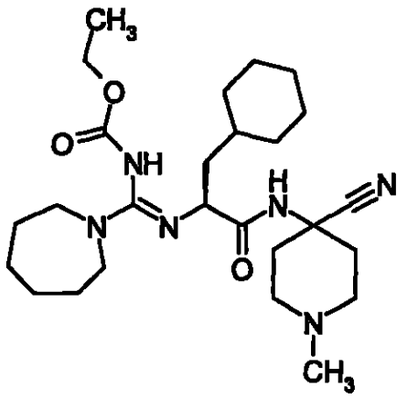
*N*-(4-Cyano-1-methyl-piperidin-4-yl)-3-cyclohexyl-2-(2-oxo-2,3-dihydro-benzo[*e*][1,3]oxazin-4-ylideneamino)-propionamide; MS: 438 (M+1).



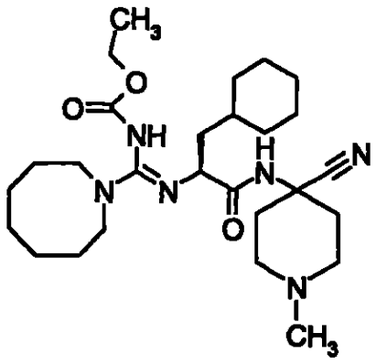
{[1-(4-Cyano-1-methyl-piperidin-4-ylcarbamoyl)-2-cyclohexyl-ethylimino]-pyrrolidin-1-yl-methyl}-carbamic acid ethyl ester; MS: 461 (M+1).



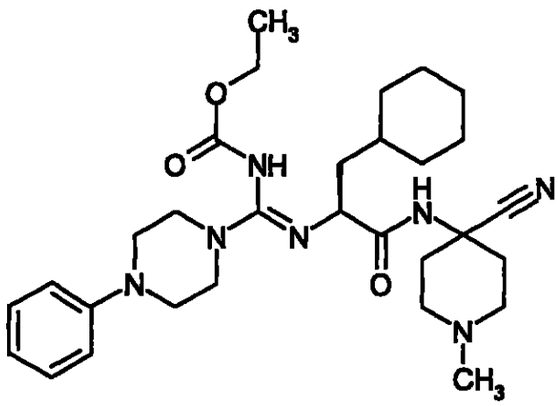
{[1-(4-Cyano-1-methyl-piperidin-4-ylcarbamoyl)-2-cyclohexyl-ethylimino]-piperidin-1-yl-methyl}-carbamic acid ethyl ester; MS: 475 (M+1).



{Azepan-1-yl-[1-(4-cyano-1-methyl-piperidin-4-ylcarbamoyl)-2-cyclohexyl-ethylimino]-methyl}-carbamic acid ethyl ester; MS: 489 (M+1).



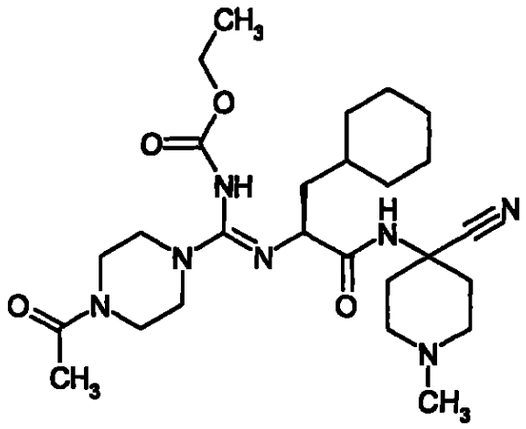
{Azocan-1-yl-[1-(4-cyano-1-methyl-piperidin-4-ylcarbamoyl)-2-cyclohexyl-ethylimino]-methyl}-carbamic acid ethyl ester; MS: 503 (M+1).



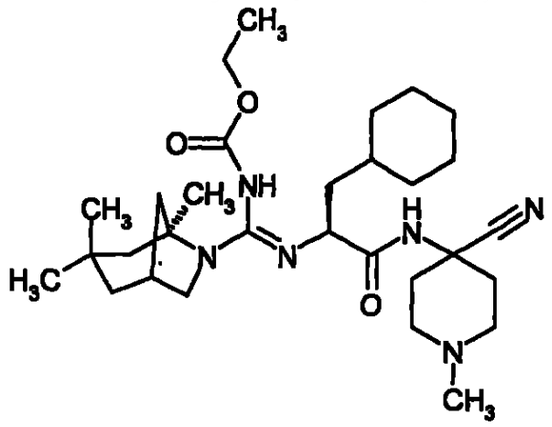
[[1-(4-Cyano-1-methyl-piperidin-4-ylcarbamoyl)-2-cyclohexyl-ethylimino]-(4-phenyl-piperazin-1-yl)-methyl]-carbamic acid ethyl ester; MS: 552 (M+1).

241

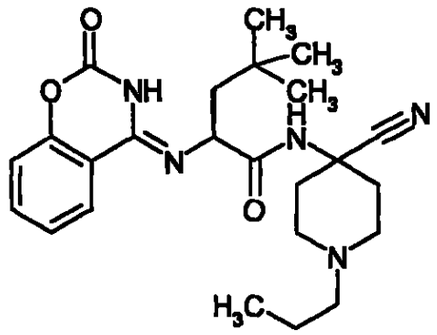
242



{(4-Acetyl-piperazin-1-yl)-[1-(4-cyano-1-methyl-piperidin-4-ylcarbamoyl)-2-cyclohexyl-ethylimino]-methyl}-carbamic acid ethyl ester; MS: 518 (M+1).



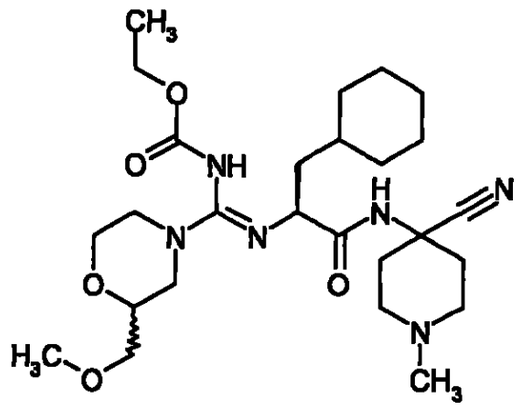
[[1-(4-Cyano-1-methyl-piperidin-4-ylcarbamoyl)-2-cyclohexyl-ethylimino]-(3,3,5-trimethyl-6-aza-bicyclo[3.2.1]oct-6-yl)-methyl]-carbamic acid ethyl ester; MS: 543 (M+1).



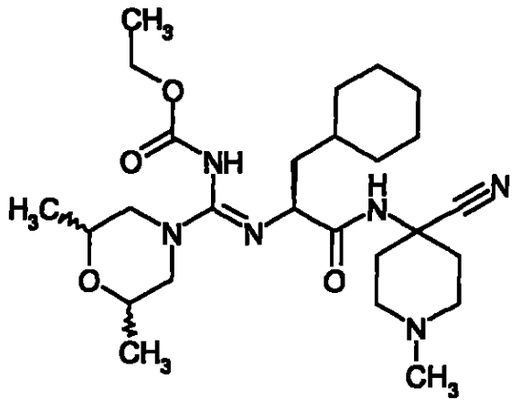
4,4-Dimethyl-2-(2-oxo-2,3-dihydro-benzo[e][1,3]oxazin-4-ylideneamino)-pentanoic acid (4-cyano-1-propyl-piperidin-4-yl)-amide; MS: 440 (M+1)

242

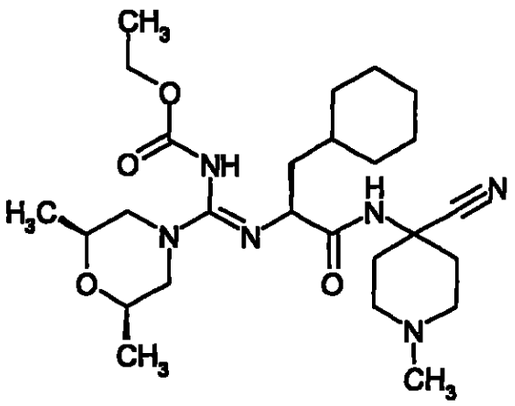
243



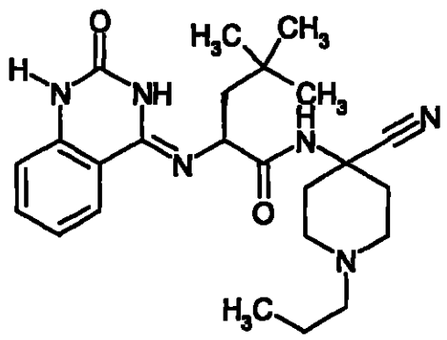
[[1-(4-Cyano-1-methyl-piperidin-4-ylcarbamoyl)-2-cyclohexyl-ethylimino]-(2-methoxymethyl-morpholin-4-yl)-methyl]-carbamic acid ethyl ester; MS: 521 (M+1)



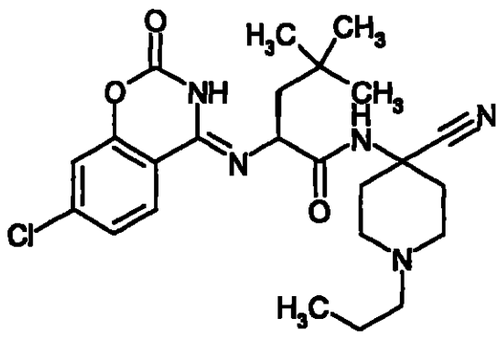
[[1-(4-Cyano-1-methyl-piperidin-4-ylcarbamoyl)-2-cyclohexyl-ethylimino]-(2,6-dimethyl-morpholin-4-yl)-methyl]-carbamic acid ethyl ester; MS: 505 (M+1)



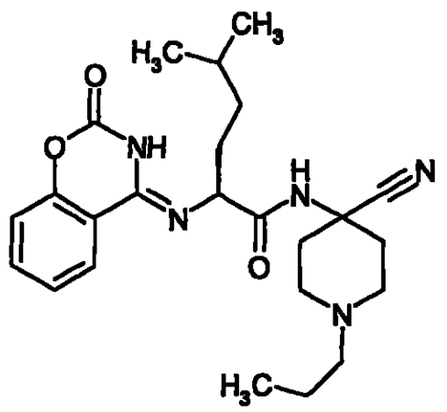
[[1-(4-Cyano-1-methyl-piperidin-4-ylcarbamoyl)-2-cyclohexyl-ethylimino]-(2,6-dimethyl-morpholin-4-yl)-methyl]-carbamic acid ethyl ester; MS: 505 (M+1)



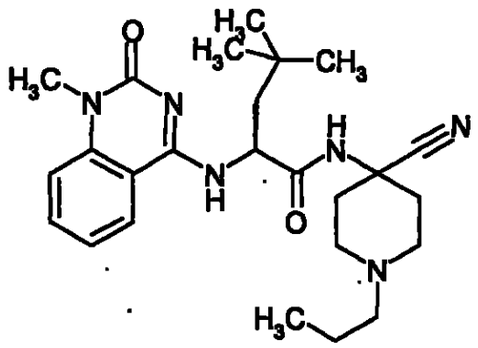
4,4-Dimethyl-2-(2-oxo-2,3-dihydro-1*H*-quinazolin-4-ylideneamino)-pentanoic acid (4-cyano-1-propyl-piperidin-4-yl)-amide; MS: 439 (M+1)



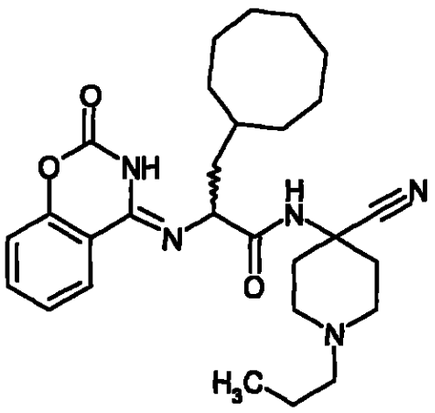
2-(7-Chloro-2-oxo-2,3-dihydro-benzo[*e*][1,3]oxazin-4-ylideneamino)-4,4-dimethyl-pentanoic acid (4-cyano-1-propyl-piperidin-4-yl)-amide; MS: 475 (M+1)



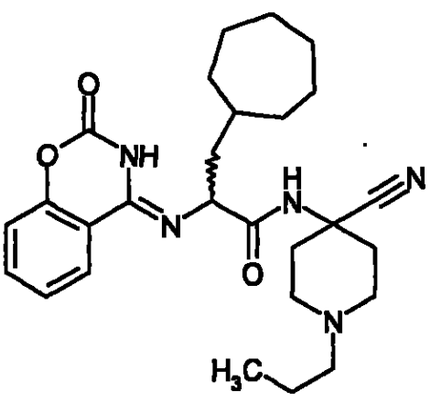
5-Methyl-2-(2-oxo-2,3-dihydro-benzo[*e*][1,3]oxazin-4-ylideneamino)-hexanoic acid (4-cyano-1-propyl-piperidin-4-yl)-amide; MS: 440 (M+1)



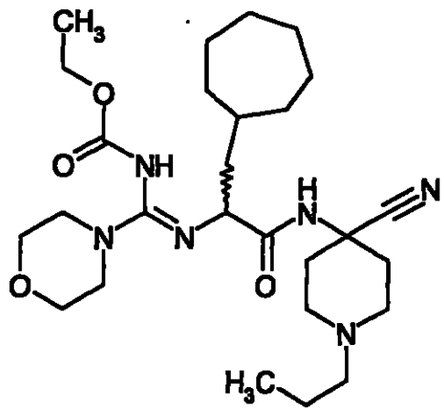
4,4-Dimethyl-2-(1-methyl-2-oxo-1,2-dihydro-quinazolin-4-ylamino)-pentanoic acid (4-cyano-1-propyl-piperidin-4-yl)-amide; MS: 453 (M+1)



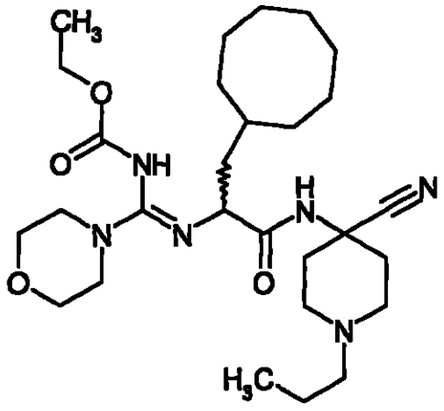
*N*-(4-Cyano-1-propyl-piperidin-4-yl)-3-cyclooctyl-2-(2-oxo-2,3-dihydro-benzo[*e*][1,3]oxazin-4-ylideneamino)-propionamide; MS: 494 (M+1)



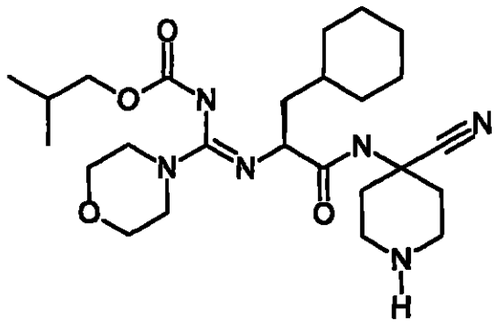
*N*-(4-Cyano-1-propyl-piperidin-4-yl)-3-cycloheptyl-2-(2-oxo-2,3-dihydro-benzo[*e*][1,3]oxazin-4-ylideneamino)-propionamide; MS: 480 (M+1)



{[1-(4-Cyano-1-propyl-piperidin-4-ylcarbamoyl)-2-cycloheptyl-ethylimino]-morpholin-4-yl-methyl}-carbamic acid ethyl ester; MS: 519 (M+1)



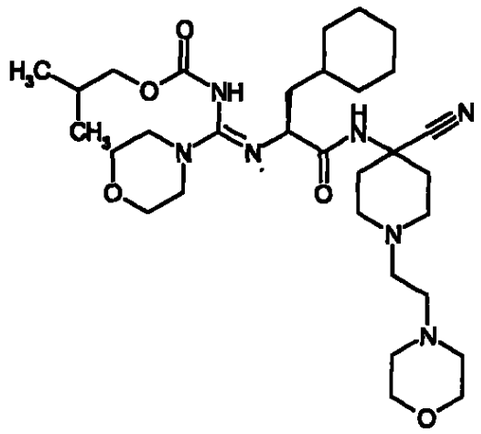
{[1-(4-Cyano-1-propyl-piperidin-4-ylcarbamoyl)-2-cyclooctyl-ethylimino]-morpholin-4-yl-methyl}-carbamic acid ethyl ester; MS: 533 (M+1)



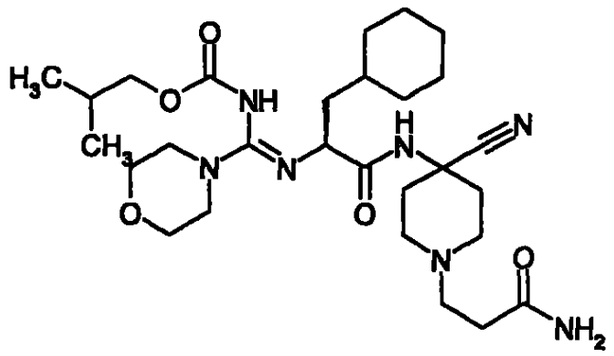
{[1-(4-Cyano-piperidin-4-ylcarbamoyl)-2-cyclohexyl-ethylamino]-morpholin-4-yl-methylene}-carbamic acid isobutyl ester; MS: 491 (M+1)

246

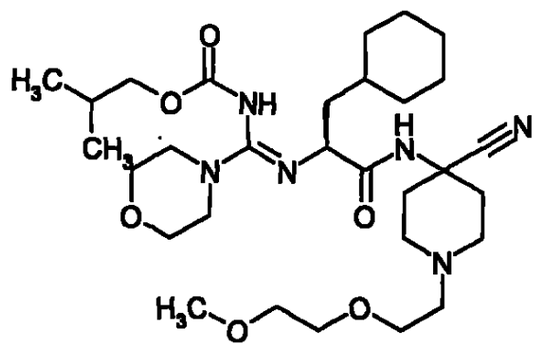
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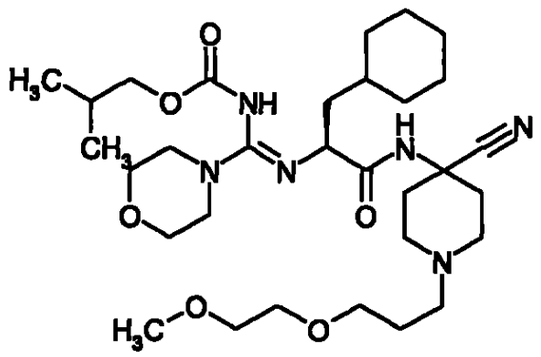
({1-[4-Cyano-1-(2-morpholin-4-yl-ethyl)-piperidin-4-ylcarbamoyl]-2-cyclohexyl-ethylamino}-morpholin-4-yl-methylene)-carbamic acid isobutyl ester; MS: 604 (M+1)



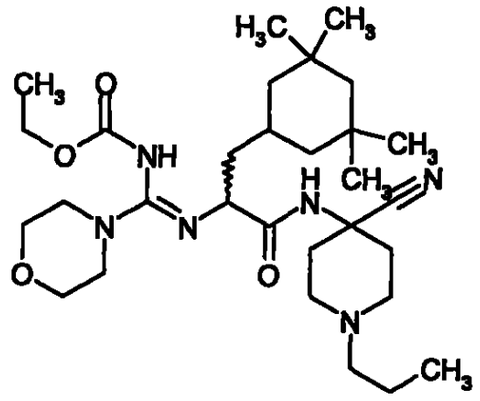
({1-[1-2-Carbamoyl-ethyl)-4-cyano-piperidin-4-ylcarbamoyl]-2-cyclohexyl-ethylamino}-morpholin-4-yl-methylene)-carbamic acid isobutyl ester; MS: 562 (M+1)



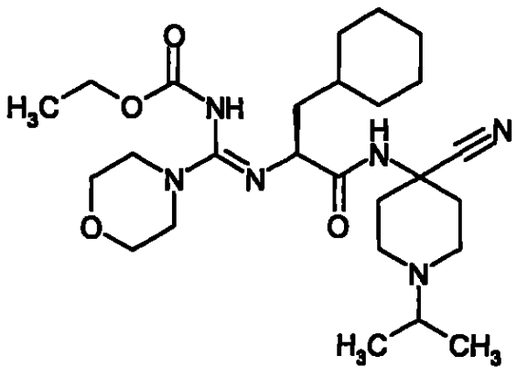
[(1-{4-Cyano-1-[2-(2-methoxyl-ethoxy)-ethyl]-piperidin-4-ylcarbamoyl}-2-cyclohexyl-ethylamino)-morpholin-4-yl-methylene]-carbamic acid isobutyl ester; MS: 593 (M+1)



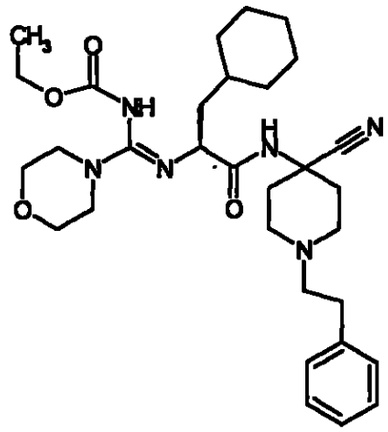
[(1-{4-Cyano-1-[3-(2-methoxyl-ethoxy)-propyl]-piperidin-4-ylcarbamoyl}-2-cyclohexyl-ethylamino)-morpholin-4-yl-methylene]-carbamic acid isobutyl ester; MS: 607 (M+1)



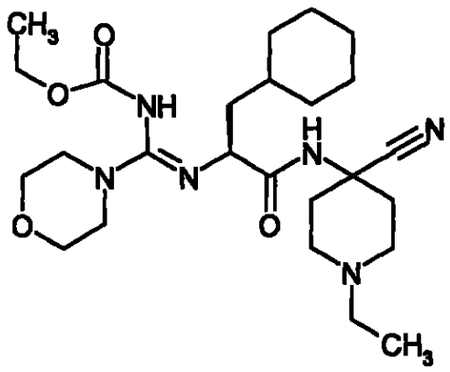
{[1-(4-Cyano-1-propyl-piperidin-4-ylcarbamoyl)-2-(3,3,5,5-tetramethyl-cyclohexyl)-ethylamino]-morpholin-4-yl-methylene}-carbamic acid ethyl ester; MS: 561 (M+1)



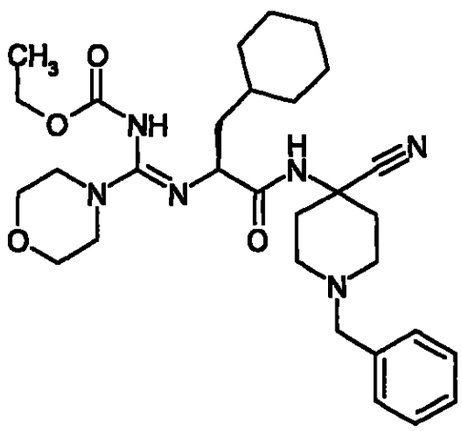
{[1-(4-Cyano-1-isopropyl-piperidin-4-ylcarbamoyl)-2-cyclohexyl-ethylamino]-morpholin-4-yl-methylene}-carbamic acid ethyl ester; MS: 505 (M+1)



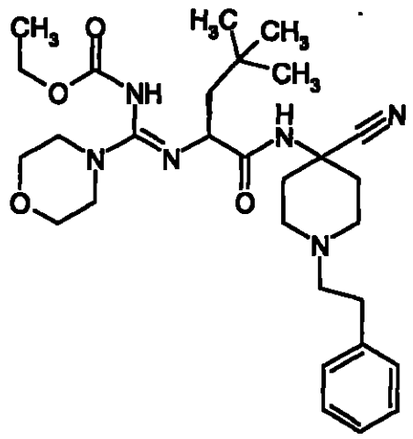
{[1-(4-Cyano-1-phenethyl-piperidin-4-ylcarbamoyl)-2-cyclohexyl-ethylamino]-morpholin-4-yl-methylene}-carbamic acid ethyl ester; MS: 567 (M+1)



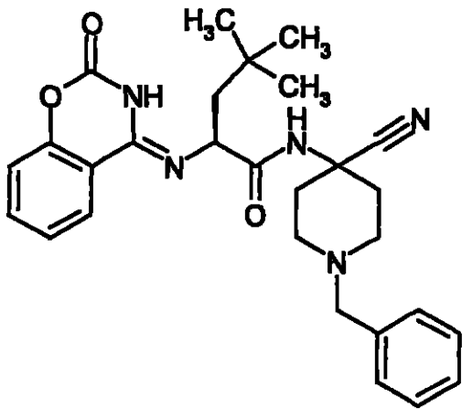
{[1-(4-Cyano-1-ethyl-piperidin-4-ylcarbamoyl)-2-cyclohexyl-ethylamino]-morpholin-4-yl-methylene}-carbamic acid ethyl ester; MS: 491 (M+1)



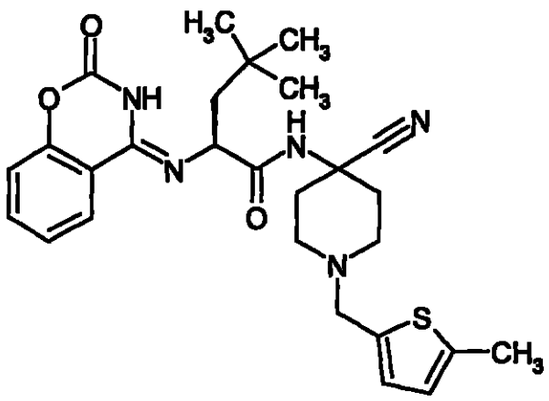
{[1-(1-Benzyl-4-cyano-piperidin-4-ylcarbamoyl)-2-cyclohexyl-ethylamino]-morpholin-4-yl-methylene}-carbamic acid ethyl ester; MS: 553 (M+1)



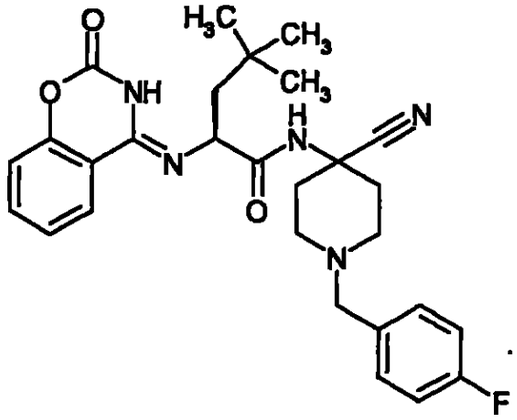
{[1-(4-cyano-1-phenethyl-piperidin-4-ylcarbamoyl)-3,3-dimethyl-butylamino]-morpholin-4-yl-methylene}-carbamic acid ethyl ester; MS: 541 (M+1)



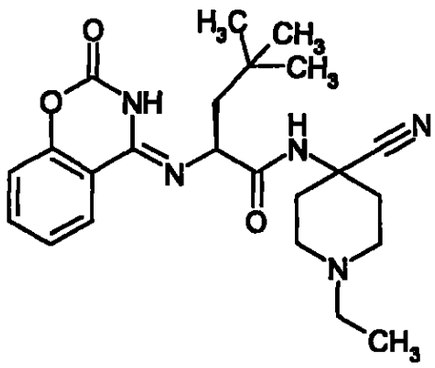
4,4-Dimethyl-2-(2-oxo-2H-benzo[e][1,3]oxazin-4-ylamino)-pentanoic acid (1-benzyl-4-cyano-piperidin-4-yl)-amide; MS: 488 (M+1)



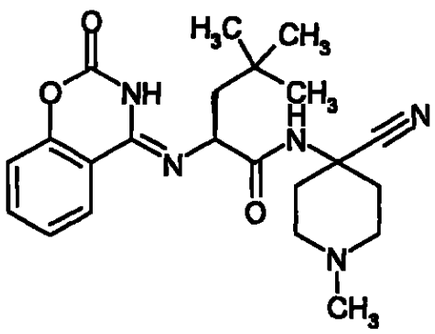
4,4-Dimethyl-2-(2-oxo-2H-benzo[e][1,3]oxazin-4-ylamino)-pentanoic acid [4-cyano-1-(5-methyl-thiophen-2-ylmethyl)-piperidin-4-yl]-amide; MS: 508 (M+1)



4,4-Dimethyl-2-(2-oxo-2H-benzo[e][1,3]oxazin-4-ylamino)-pentanoic acid [4-cyano-1-(4-fluoro-benzyl)-piperidin-4-yl]-amide; MS: 506 (M+1)



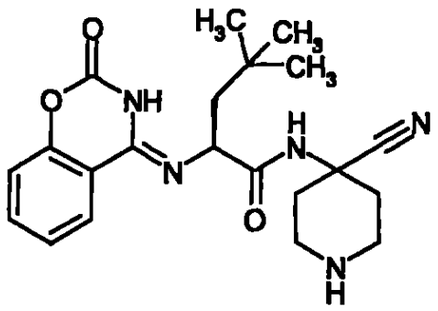
4,4-Dimethyl-2-(2-oxo-2H-benzo[e][1,3]oxazin-4-ylamino)-pentanoic acid (4-cyano-1-ethyl-piperidin-4-yl)-amide; MS: 426 (M+1)



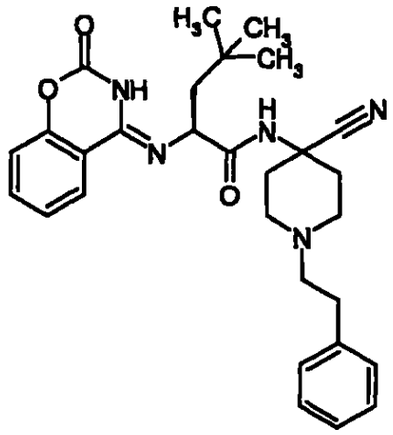
4,4-Dimethyl-2-(2-oxo-2H-benzo[e][1,3]oxazin-4-ylamino)-pentanoic acid (4-cyano-1-methyl-piperidin-4-yl)-amide; MS: 412 (M+1)

251

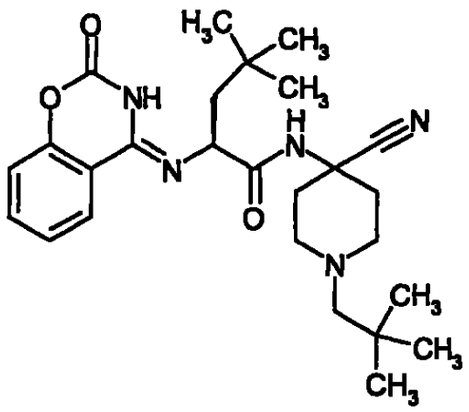
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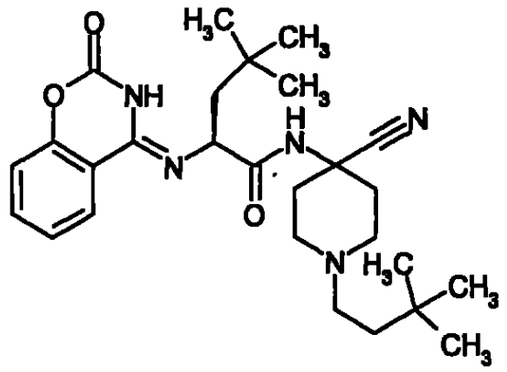
4,4-Dimethyl-2-(2-oxo-2H-benzo[e][1,3]oxazin-4-ylamino)-pentanoic acid (4-cyano-piperidin-4-yl)-amide; MS: 398 (M+1)



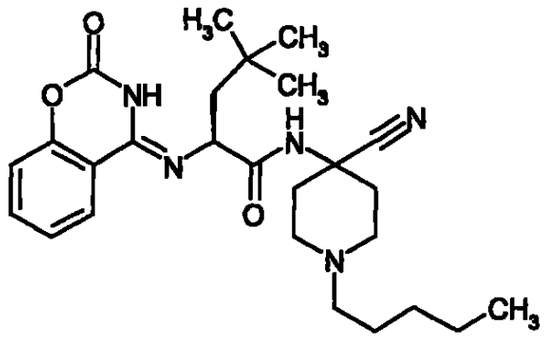
4,4-Dimethyl-2-(2-oxo-2H-benzo[e][1,3]oxazin-4-ylamino)-pentanoic acid (4-cyano-1-phenethyl-piperidin-4-yl)-amide; MS: 502 (M+1)



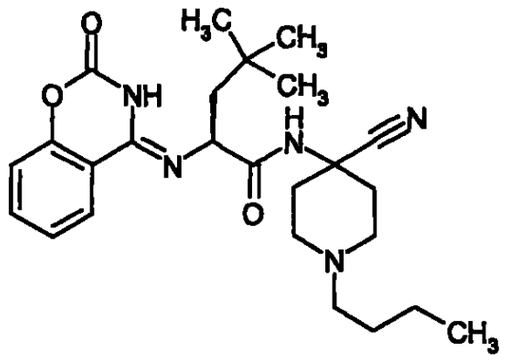
4,4-Dimethyl-2-(2-oxo-2H-benzo[e][1,3]oxazin-4-ylamino)-pentanoic acid [4-cyano-1-(2,2-dimethyl-propyl)-piperidin-4-yl]-amide; MS: 468 (M+1)



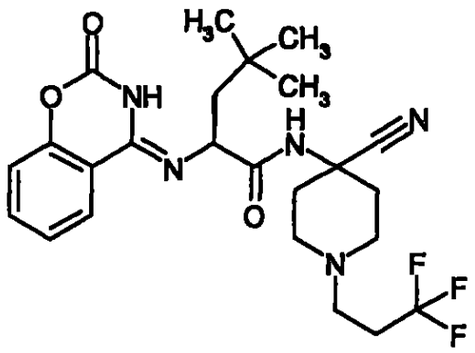
4,4-Dimethyl-2-(2-oxo-2H-benzo[e][1,3]oxazin-4-ylamino)-pentanoic acid [4-cyano-1-(3,3-dimethyl-butyl)-piperidin-4-yl]-amide; MS: 482 (M+1)



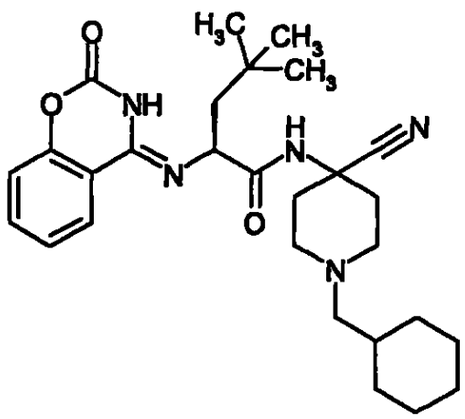
4,4-Dimethyl-2-(2-oxo-2H-benzo[e][1,3]oxazin-4-ylamino)-pentanoic acid (4-cyano-1-pentyl-piperidin-4-yl)-amide; MS: 468 (M+1)



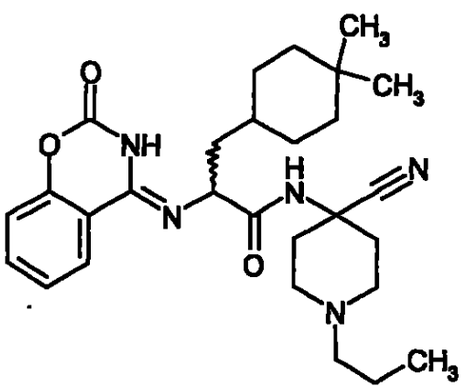
4,4-Dimethyl-2-(2-oxo-2H-benzo[e][1,3]oxazin-4-ylamino)-pentanoic acid (1-butyl-4-cyano-piperidin-4-yl)-amide; MS: 454(M+1)



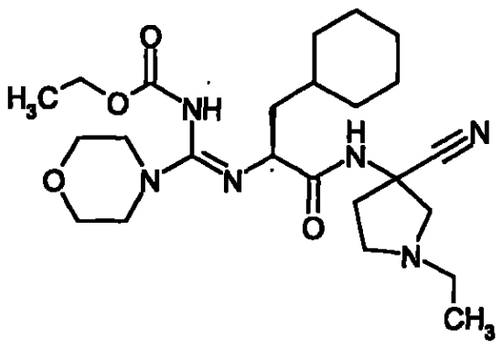
4,4-Dimethyl-2-(2-oxo-2H-benzo[e][1,3]oxazin-4-ylamino)-pentanoic acid [4-cyano-1-(3,3,3-trifluoro-propyl)-piperidin-4-yl]-amide; MS: 494 (M+1)



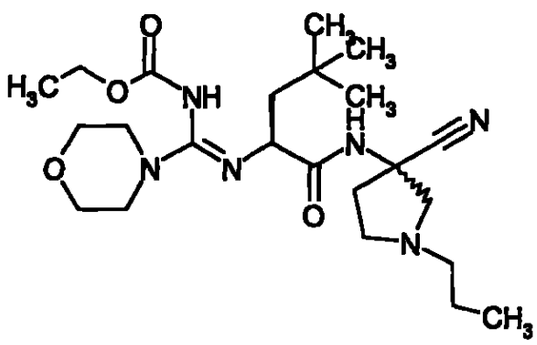
4,4-Dimethyl-2-(2-oxo-2H-benzo[e][1,3]oxazin-4-ylamino)-pentanoic acid (4-cyano-1-cyclohexylmethyl-piperidin-4-yl)-amide; MS: 494 (M+1)



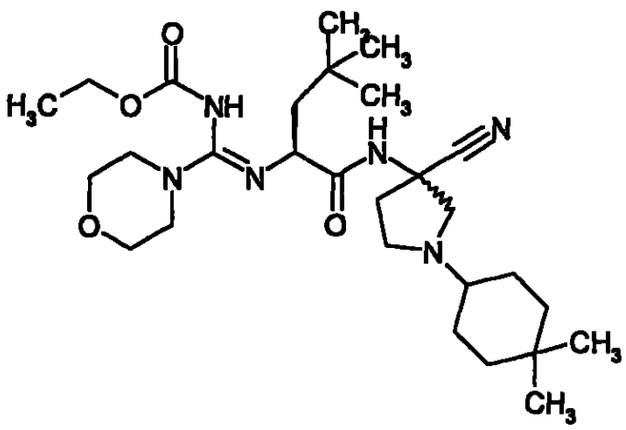
N-(4-Cyano-1-propyl-piperidin-4-yl)-3-(4,4-dimethyl-cyclohexyl)-2-(2-oxo-2H-benzo[e][1,3]oxazin-4-ylamino)-propionamide; MS: 494 (M+1)



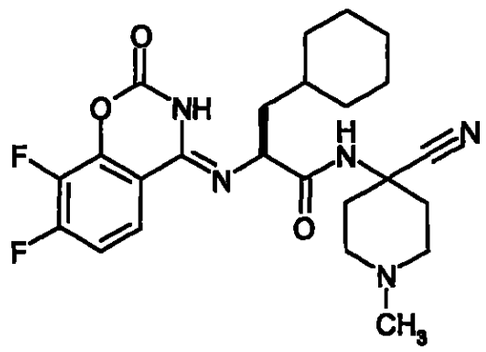
{[1-(3-Cyano-1-ethyl-pyrrolidin-3-ylcarbamoyl)-2-cyclohexyl-ethylamino]-morpholin-4-yl-methylene}-carbamic acid ethyl ester. MS: 477 (M+1).



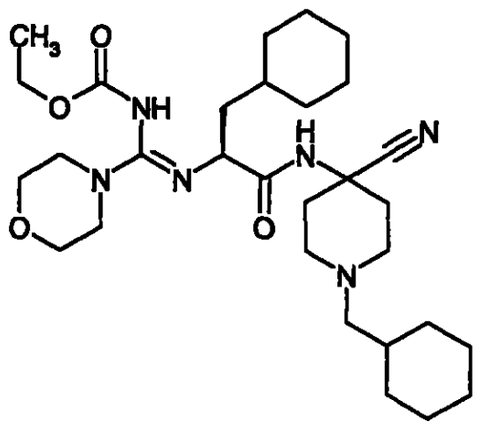
{[1-(3-Cyano-1-propyl-pyrrolidin-3-ylcarbamoyl)-3,3-dimethyl-butylamino]-morpholin-4-yl-methylene}-carbamic acid ethyl ester. MS: 465 (M+1).



({1-[3-Cyano-1-(4,4-dimethyl-cyclohexyl)-pyrrolidin-3-ylcarbamoyl]-3,3-dimethyl-butylamino}-morpholin-4-yl-methylene)-carbamic acid ethyl ester. MS: 533 (M+1).



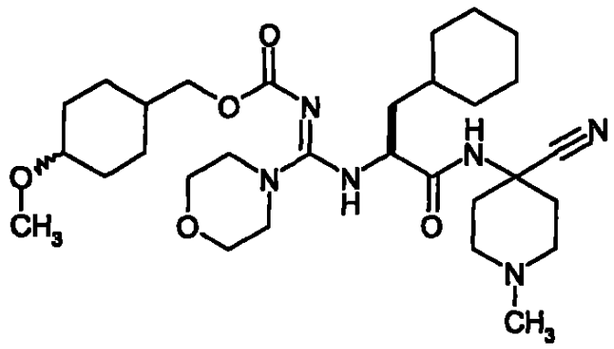
N-(4-Cyano-1-methyl-piperidin-4-yl)-3-cyclohexyl-2-(7,8-difluoro-2-oxo-2H-benzo[e][1,3]oxazin-4-ylamino)-propionamide; MS: 474 (M+1)



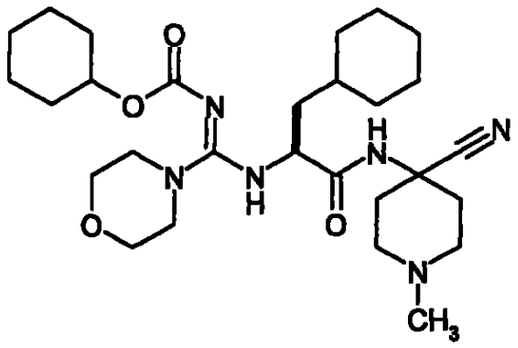
{[1-(4-Cyano-1-cyclohexylmethyl-piperidin-4-ylcarbamoyl)-2-cyclohexyl-ethylamino]-morpholin-4-yl-methylene}-carbamic acid ethyl ester; MS: 559 (M+1)

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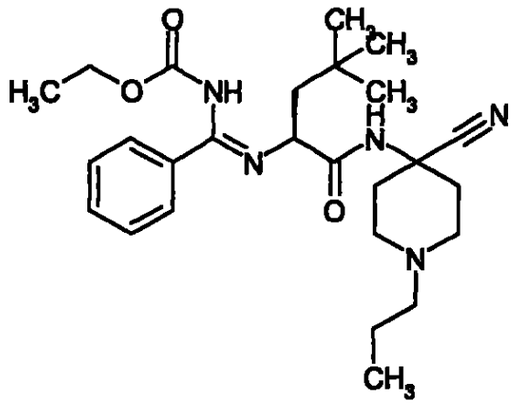
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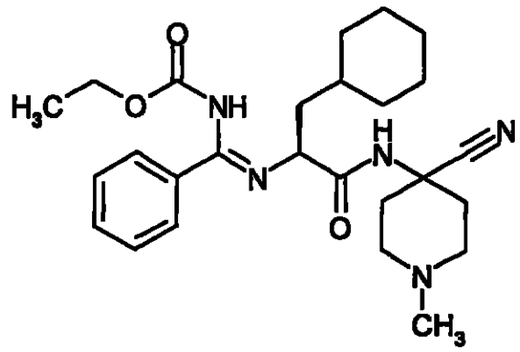
{[1-(4-Cyano-1-methyl-piperidin-4-ylcarbamoyl)-2-cyclohexyl-ethylamino]-morpholin-4-yl-methylene}-carbamic acid 4-methoxy-cyclohexylmethyl ester; MS: 575 (M+1)



{[1-(4-Cyano-1-methyl-piperidin-4-ylcarbamoyl)-2-cyclohexyl-ethylamino]-morpholin-4-yl-methylene}-carbamic acid cyclohexyl ester; MS: 531 (M+1)



{[1-(4-Cyano-1-propyl-piperidin-4-ylcarbamoyl)-3,3-dimethyl-butylamino]-phenyl-methylene}-carbamic acid ethyl ester; MS: 470 (M+1)



{[1-(4-Cyano-1-methyl-piperidin-4-ylcarbamoyl)-2-cyclohexyl-ethylamino]-phenyl-methylene}-carbamic acid ethyl ester; MS: 468 (M+1).

Any compounds of this invention containing one or more asymmetric carbon atoms may occur as racemates and racemic mixtures, single enantiomers, diastereomeric mixtures and individual diastereomers. All such isomeric forms of these compounds are expressly included in the present invention. Each stereogenic carbon may be in the R or S configuration unless otherwise specified, or a combination of configurations.

Some of the compounds of formulas (Ia) and (Ib) can exist in more than one tautomeric form. The invention includes all such tautomers.

It shall be understood by one of ordinary skill in the art that all compounds of the invention are those which are chemically stable.

The invention includes pharmaceutically acceptable derivatives of compounds of formula (Ia) and (Ib). A "pharmaceutically acceptable derivative" refers to any pharmaceutically acceptable acid, salt or ester of a compound of this invention, or any other compound which, upon administration to a patient, is capable of providing (directly or indirectly) a compound of this invention, a pharmacologically active metabolite or pharmacologically active residue thereof.

In addition, the compounds of this invention include prodrugs of compounds of the formulas (Ia) and (Ib). Prodrugs include those compounds that, upon simple transformation, are modified to produce the compounds of the invention. Simple chemical transformations include hydrolysis, oxidation and reduction which occur enzymatically, metabolically or otherwise. Specifically, when a prodrug of this invention is administered to a patient, the prodrug may be transformed into a compound of formula (Ia) and (Ib), thereby imparting the desired pharmacological effect.

In order that the invention herein described may be more fully understood, the following detailed description is set forth. As used herein, the following abbreviations are used:

BOC or t-BOC is tertiary-butoxycarbonyl;
t-Bu is tertiary-butyl;
DMF is dimethylformamide;
EtOAc is ethyl acetate;
THF is tetrahydrofuran;
Ar is argon;
EDC is 1-(3-dimethylaminopropyl)-3-ethylcarbodimide hydrochloride and
HOBT is 1-hydroxybenzotriazole.

Also, as used herein, each of the following terms, used alone or in conjunction with other terms, are defined as follows (except where noted to the contrary):

The term "alkyl" refers to a saturated aliphatic radical containing from one to ten carbon atoms or a mono- or polyunsaturated aliphatic hydrocarbon radical containing from two to twelve carbon atoms. The mono- or polyunsaturated aliphatic hydrocarbon radical containing at least one double or triple bond, respectively. "Alkyl" refers to both branched and unbranched alkyl groups. Examples of "alkyl" include alkyl groups which are straight chain alkyl groups containing from one to eight carbon atoms and branched alkyl groups containing from three to eight carbon atoms. Other examples include lower alkyl groups which are straight chain alkyl groups containing from one to six carbon

atoms and branched alkyl groups containing from three to six carbon atoms. It should be understood that any combination term using an "alk" or "alkyl" prefix refers to analogs according to the above definition of "alkyl". For example, terms such as "alkoxy", "alkythio" refer to alkyl groups linked to a second group via an oxygen or sulfur atom. "Alkanoyl" refers to an alkyl group linked to a carbonyl group (C=O). Each alkyl or alkyl analog described herein shall be understood to be optionally partially or fully halogenated.

The term "cycloalkyl" refers to the cyclic analog of an alkyl group, as defined above. Examples of cycloalkyl groups are saturated or unsaturated nonaromatic cycloalkyl groups containing from three to eight carbon atoms, and other examples include cycloalkyl groups having three to six carbon atoms. Each cycloalkyl described herein shall be understood to be optionally partially or fully halogenated.

The term "aryl" refers to phenyl and naphthyl.

The term "halo" refers to a halogen radical selected from fluoro, chloro, bromo or iodo. Representative halo groups of the invention are fluoro, chloro and bromo.

The term "heteroaryl" refers to a stable 5-8 membered (but preferably, 5 or 6 membered) monocyclic or 8-11 membered bicyclic aromatic heterocycle radical. Each heterocycle consists of carbon atoms and from 1 to 4 heteroatoms chosen from nitrogen, oxygen and sulfur. The heterocycle may be attached by any atom of the cycle, which results in the creation of a stable structure. Examples of "heteroaryl" include radicals such as furanyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, pyrazolyl, isoxazolyl, isothiazolyl, oxadiazolyl, triazolyl, tetrazolyl, thiadiazolyl, pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl, indolizinyl, indolyl, isoindolyl, benzofuranyl, benzothienyl, indazolyl, benzimidazolyl, benzthiazolyl, benzoxazolyl, purinyl, quinolizinyl, quinolinyl, isoquinolinyl, cinnolinyl, phthalazinyl, quinazolinyl, quinoxalinyl, naphthyridinyl, pteridinyl, carbazolyl, acridinyl, phenazinyl, phenothiazinyl and phenoxazinyl,

The term "heterocycle" refers to a stable 4-8 membered (but preferably, 5 or 6 membered) monocyclic or 8-11 membered bicyclic heterocycle radical which may be either saturated or unsaturated, and is non-aromatic. Each heterocycle consists of carbon atoms and from 1 to 4 heteroatoms chosen from nitrogen, oxygen and sulfur. The heterocycle may be attached by any atom of the cycle, which results in the creation of a stable structure. Examples of "heterocycle" include radicals such as pyrrolinyl, pyrrolidinyl, pyrazolinyl, pyrazolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, pyranyl, thiopyranyl, piperazinyl, indolinyl, azetidinyl, tetrahydropyranyl, tetrahydrothiopyranyl, tetrahydrofuranyl, hexahydropyrimidinyl, hexahydropyridazinyl, 1,4,5,6-tetrahydropyrimidin-2-ylamine, dihydro-oxazolyl, 1,2-thiazinanyl-1,1-dioxide, 1,2,6-thiadiazinanyl-1,1-dioxide, isothiazolidinyl-1,1-dioxide and imidazolidinyl-2,4-dione.

The terms "heterocycle", "heteroaryl" or "aryl", when associated with another moiety, unless otherwise specified shall have the same meaning as given above. For example, "aroyl" refers to phenyl or naphthyl linked to a carbonyl group (C=O).

Each aryl or heteroaryl unless otherwise specified includes it's partially or fully hydrogenated derivative. For example, quinolinyl may include decahydroquinolinyl and tetrahydroquinolinyl, naphthyl may include it's hydrogenated derivatives such as tetrahydranaphthyl. Other partially or fully hydrogenated derivatives of the aryl and heteroaryl compounds described herein will be apparent to one of ordinary skill in the art.

The term heterocycle as it pertains to "Het" shall to be understood to mean a stable non-aromatic spiroheterocycle, 4-8 membered (but preferably, 5 or 6 membered) monocyclic, 8-11 membered bicyclic heterocycle radical which may be either saturated or unsaturated or a C6-C10 bridged bicyclo wherein one or more carbon atoms are optionally replaced by a heteroatom. Each heterocycle consists of carbon atoms and from 1 to 4 heteroatoms chosen from nitrogen, oxygen and sulfur. The heterocycle may be attached by any atom of the cycle, which results in the creation of a stable structure. Examples of "Het" include the following heterocycles: azepanyl, piperidinyl, pyrrolidinyl, azetidinyl, oxepanyl,

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tetrahydropyranyl, tetrahydrothiopyranyl, tetrahydrofuranyl, oxetanyl, azocanyl, oxocanyl, 1,3-diazocanyl, 1,4-diazocanyl, 1,5-diazocanyl, 1,3-dioxocanyl, 1,4-dioxocanyl, 1,5-dioxocanyl, 1,3-oxazocanyl, 1,4-oxazocanyl, 1,5-oxazocanyl, 1,3-diazepanyl, 1,4-diazepanyl, 1,3-dioxepanyl, 1,4-dioxepanyl, 1,3-oxazepanyl, 1,4-oxazepanyl, 1,2-thiazocanyl-1,1-dioxide, 1,2,8-thiadiazocanyl-1,1-dioxide, 1,2-thiazepanyl-1,1-dioxide, 1,2,7-thiadiazepanyl-1,1-dioxide, tetrahydrothiophenyl, hexahydropyrimidinyl, hexahydropyridazinyl, piperazinyl, 1,4,5,6-tetrahydropyrimidinyl, pyrazolidinyl, dihydro-oxazolyl, dihydrothiazolyl, dihydroimidazolyl, isoxazolinyl, oxazolidinyl, 1,2-thiazinanyl-1,1-dioxide, 1,2,6-thiadiazinanyl-1,1-dioxide, isothiazolidinyl-1,1-dioxide, imidazolidinyl-2,4-dione, imidazolidinyl, morpholinyl, dioxanyl, tetrahydropyridinyl, thiomorpholinyl, thiazolidinyl, dihydropyranyl, dithianyl, decahydro-quinolinyl, decahydro-isoquinolinyl, 1,2,3,4-tetrahydro-quinolinyl, indolinyl, octahydro-quinolizinyl, dihydro-indolizinyl, octahydro-indolizinyl, octahydro-indolyl, decahydroquinazolinyl, decahydroquinoxalinyl, 1,2,3,4-tetrahydroquinazolinyl or 1,2,3,4-tetrahydroquinoxalinyl, aza-bicyclo[3.2.1]octane, aza-bicyclo[2.2.1]heptane, aza-bicyclo[2.2.2]octane, aza-bicyclo[3.2.2]nonane, aza-bicyclo[2.1.1]hexane, aza-bicyclo[3.1.1]heptane, aza-bicyclo[3.3.2]decane and 2-oxa or 2-thia-5-aza-bicyclo[2.2.1]heptaneeach; heterocyclic ring being substituted with one or more $R_5$. The substituent $R_5$ is defined above.

As used herein above and throughout this application, "nitrogen" and "sulfur" include any oxidized form of nitrogen and sulfur and the quaternized form of any basic nitrogen.

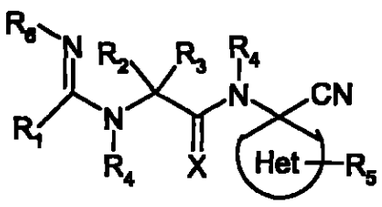
In order that this invention be more fully understood, the following examples are set forth. These examples are for the purpose of illustrating preferred embodiments of this invention, and are not to be construed as limiting the scope of the invention in any way.

The examples which follow are illustrative and, as recognized by one skilled in the art, particular reagents or conditions could be modified as needed for individual compounds. Starting materials used in the scheme below are either commercially available or easily prepared from commercially available materials by those skilled in the art.

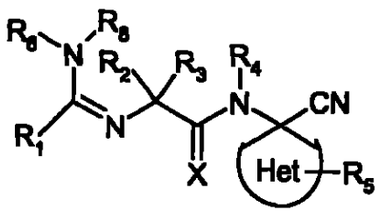
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## GENERAL SYNTHETIC METHODS

The invention also provides processes of making the present novel compounds of formula (Ia) and (Ib). Compounds of the invention may be prepared by methods described below, those found in US application serial no. 09/655,351, incorporated herein be reference in it's entirety, and by methods known to those of ordinary skill in the art.

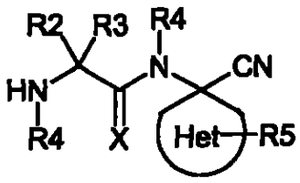


(Ia)



(Ib)

A key intermediate in the preparation of compounds of formula (Ia) and (Ib) is the dipeptide nitrile intermediate (III).



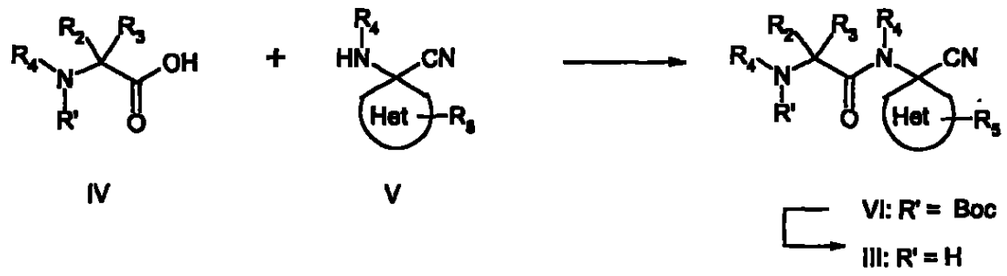
(III)

The synthesis of intermediates of formula (III) is described in US provisional patent application 60/222,900 and outlined below in Schemes I and II.

Scheme I

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IV V

As illustrated in Scheme I, an amino acid bearing a suitable protecting group R' (IV), is reacted with an amino nitrile (V) under suitable coupling conditions. An example of a suitable protecting group is the *t*-butoxycarbonyl (BOC) group. An example of standard coupling conditions would be combining the starting materials in the presence of a coupling reagent such as 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (EDC) with 1-hydroxybenzotriazole (HOBT), in a suitable solvent such as DMF or methylene chloride. A base such as N-methylmorpholine may be added. This is followed by deprotection to give amino acid nitrile III.

The intermediate aminonitrile (V) used in Scheme I above may be prepared as outlined in Scheme II.

Scheme II

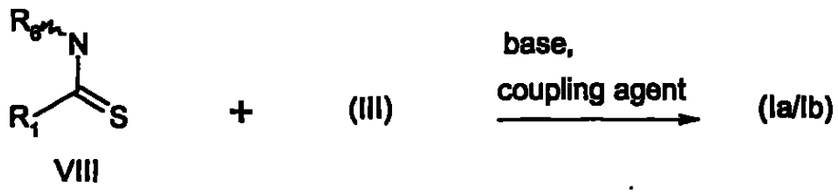



VII V

In this method, a ketone bearing "Het" (VII) is reacted with an a primary amine or an ammonium salt, such as ammonium chloride, and a cyanide salt, such as potassium cyanide or sodium cyanide, in a suitable solvent, such as water or a solution of ammonia in methanol, at about room temperature to reflux temperature.

Compounds having formula (Ia/Ib) may be prepared by Methods A-D, as illustrated in Schemes III-VI.

Scheme III (Method A)

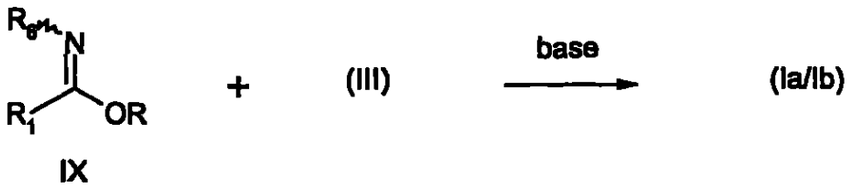



VIII

According to Method A, a dipeptide nitrile intermediate (III), or a basic salt thereof, is allowed to react with (VIII) in the presence of a suitable coupling agent to provide the desired product (Ia/Ib). Suitable reaction conditions are known to those skilled in the art and some examples of suitable coupling agents include 2-chloro-1-methylpyridinium iodide (Yong, Y.F. et al., J. Org. Chem. 1997, 62, 1540), phosgene or triphosgene (Barton, D.H. et al., J. Chem. Soc. Perkin Trans. I, 1982, 2085), alkyl halides (Brand, E. and Brand, F. C., Org. Synth., 1955, 3, 440) carbodiimides (Poss, M. A. et al., Tetrahedron Lett., 1992, 40, 5933) and mercury salts (Su, W., Synthetic Comm., 1996, 26, 407 and Wiggall, K. J. and Richardson, S. K. J., Heterocyclic Chem., 1995, 32, 867).

Compounds having formulas (Ia) and (Ib) may also be prepared by Method B as illustrated in Scheme IV, where R is an alkyl or aryl group.

Scheme IV (Method B)



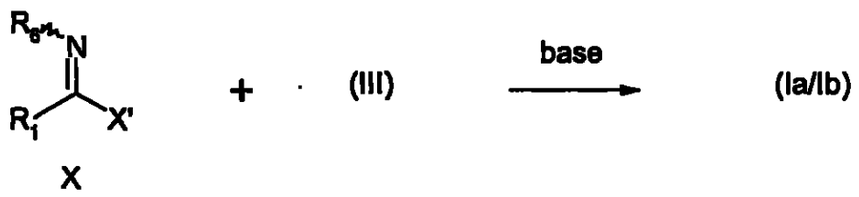

IX

According to Method B a dipeptide nitrile intermediate (III), or a basic salt thereof, is allowed to react with IX, with or without an added base such as triethylamine, to provide the desired product (Ia/Ib). Suitable reaction conditions are known to those skilled in the art and examples of such amine additions may be found in the chemical literature, for example Haake, M. and Schummelfeder, B., Synthesis, 1991, 9, 753; Dauwe, C. and Buddrus, J., Synthesis 1995, 2, 171; Ried, W. and Piechaczek, D., Justus Liebigs Ann. Chem. 1966, 97, 696 and Dean, W. D. and Papadopoulos, E. P., J. Heterocyclic Chem., 1982, 19, 1117.

The intermediate IX is either commercially available or can be synthesized by methods known to those skilled in the art and described in the literature, for example Francesconi, I. et. al., J. Med. Chem. 1999, 42, 2260; Kurzer, F., Lawson, A.,Org. Synth. 1963, 645, and Gutman, A. D. US 3984410, 1976.

In a similar reaction, intermediate X having a halogen or other suitable leaving group (X') may be used in place of intermediate IX, as illustrated in Method C, Scheme V.

Scheme V (Method C)

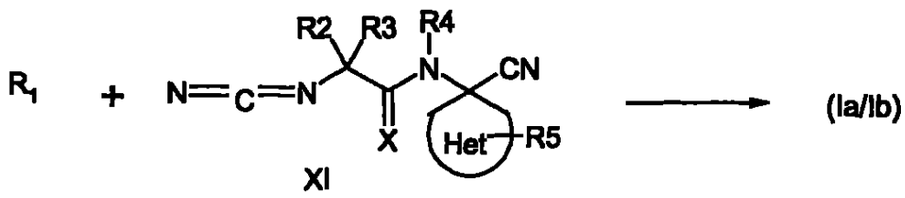



According to Method C, a dipeptide nitrile intermediate, or a basic salt thereof, is allowed to react with intermediate X, with or without an added base such as triethylamine, to provide the desired product (Ia/Ib). Procedures for accomplishing this reaction are known to those skilled in the art and described in the chemical literature (for example, Dunn, A. D. , Org. Prep. Proceed. Int., 1998, 30, 709; Lindstroem, S. et al., Heterocycles, 1994, 38, 529; Katritzky, A. R. and Saczewski, F., Synthesis, 1990, 561; Hontz, A. C.

and Wagner, E. C., Org Synth., 1963, IV, 383; Stephen, E. and Stephen, H., J. Chem. Soc., 1957, 490).

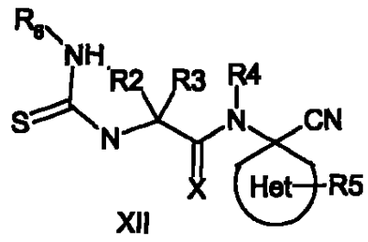
Compounds having formula (Ia/Ib) in which $R_1$ is an amine may also be prepared by Method D as illustrated in Scheme VI.

Scheme VI (Method D)




According to Method D, a carbodiimide (XI) derivative of (III) is allowed to react with an amine ($R_1$) to provide the desired guanidine (Ia/Ib) product. The conversion of amines to carbodiimides is known to those in the art and described in the literature (for example, Pri-Bar, I. and Schwartz, J., J. Chem. Soc. Chem. Commun., 1997, 347; Hirao, T. and Saegusa, T., J. Org. Chem., 1975, 40, 298). The reaction of carbodiimides with amine nucleophiles is also described in the literature (for example, Yoshiizumi, K. et al., Chem. Pharm. Bull., 1997, 45, 2005; Thomas, E. W. et al., J. Med. Chem., 1989, 32, 228; Lawson, A. and Tinkler, R. B., J. Chem. Soc. C, 1971, 1429.

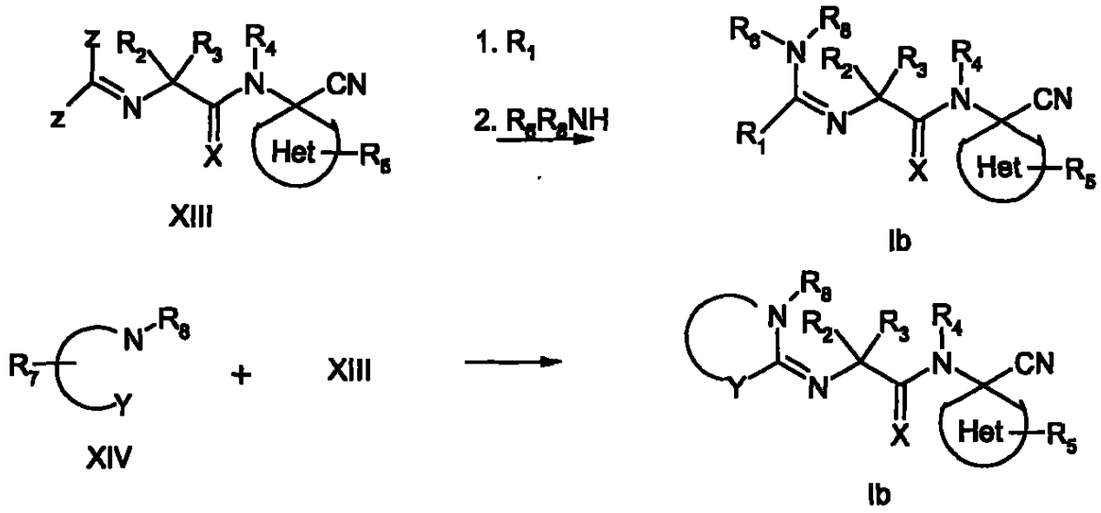
In a modification of Method D, one may start with the thiourea XII (formed by reaction of the corresponding amine with an isothiocyanate $R_6N=C=S$) and then form the corresponding carbodiimide (XI) *in situ* by reaction with a suitable desulfurizing agent, such as $HgCl_2$, in a suitable solvent such as DMF or acetonitrile.



XII

Compounds of formula (Ib), where $R_1$ is an amine may be prepared using a general procedure described by M. Haake and B. Schummfelder (Synthesis, 1991, 753). According to this procedure (Method E, Scheme VII), intermediate XIII bearing two suitable leaving groups Z, such as phenoxy groups, is reacted sequentially with amines $R_1$ and $R_6R_8NH$ in a suitable solvent such as methanol or isopropanol to provide the desired product. Reaction of the first amine may be carried out at about room temperature and reaction of the second amine is preferentially carried out with heating at the reflux temperature of the solvent. If XIII is allowed to react with a bifunctional nucleophile intermediate XIV, where Y is a nucleophilic heteroatom such as N, O or S, one may obtain the product of formula (Ib) where $R_1$ and $R_6$ form a heterocyclic ring. Intermediate XIII may be prepared by reaction of III ($R_4$ = H) with dichlorodiphenoxymethane, which in turn, may be prepared by heating diphenyl carbonate with $PCl_5$ (R.L. Webb and C.S. Labow, J. Het. Chem., 1982, 1205).

Scheme VII (Method E)

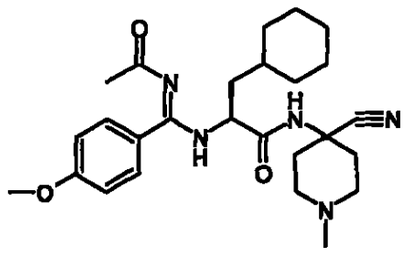



In order that this invention be more fully understood, the following examples are set forth. These examples are for the purpose of illustrating embodiments of this invention, and are not to be construed as limiting the scope of the invention in any way.

The examples which follow are illustrative and, as recognized by one skilled in the art, particular reagents or conditions could be modified as needed for individual compounds without undue experimentation. Starting materials used in the scheme below are either commercially available or easily prepared from commercially available materials by those skilled in the art.

## SYNTHETIC EXAMPLES

### EXAMPLE 1



2-{[Acetylimino-(4-methoxy-phenyl)-methyl]- amino}-N-(4-cyano-1-methyl-piperidin-4-yl)-3-cyclohexyl-propionamide (Method A).

(a) N-(4-methoxy-thiobenzoyl)acetamide.

A solution of acetyl chloride (4.69 g, 59.8 mmol) in acetone (20 mL) was added dropwise to a solution of 4-methoxythiobenzamide (5.00 g, 29.9 mmol) and pyridine (4.76 g, 60.1 mmol) in acetone (30 mL). The reaction mixture was heated to reflux for 30 min then poured onto ice water. The resulting precipitate was isolated via filtration and dried under vacuum overnight to provide a light yellow/orange solid (4.52 g, 72%). $^1$H NMR (400 MHz, $CDCl_3$) δ 2.56 (s, 3H), 3.87 (s, 3H), 6.89 (dd, $J$ = 6.9, 2.0 Hz, 2H), 7.77 (dd, J = 6.9, 2.0 Hz, 2H).

(b) 2-{[Acetylimino-(4-methoxy-phenyl)-methyl]-amino}-N-(4-cyano-1-methyl-piperidin-4-yl)-3-cyclohexyl-propionamide.

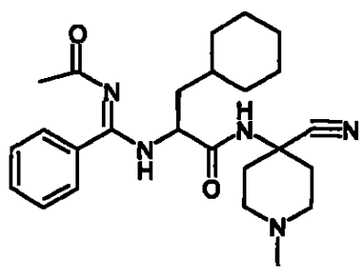
**2-Chloro-N-methylpyridinium iodide (660 mg, 2.58 mmol), was added to a solution of N-(4-methoxy-thiobenzoyl)acetamide (420 mg, 2.01 mmol), 2-amino-N-(4-cyano-**

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1-methyl-piperidin-4-yl)-3-cyclohexyl-propionamide bis hydrochloride salt (730 mg, 2.00 mmol), and N,N-diisopropylethylamine (1.05 mL, 6.02 mmol) in dichloromethane (8.0 mL). The reaction mixture was stirred at room temperature for 2 h, then diluted with dichloromethane (100 mL)and washed with 2x150 mL of saturated sodium bicarbonate. The organic phase was dried ($MgSO_4$) and concentrated. The resulting residue was chromatographed over 100 g of flash silica first using EtOAc, then dichloromethane/methanol 9:1 as the eluant to provide the desired product as an off white solid (377 mg, 40%). $^1H$ NMR (400 MHz, DMSO-d6) δ 0.70-0.90 (m, 2H), 1.00-1.30 (m, 4H), 1.35-1.65 (m, 8H), 1.72 (s, 3H), 1.85-2.20 (m, 6H), 2.48-2.60 (m, 1H), 3.78 (s, 3H), 4.20-4.35 (m, 1H), 6.95-6.99 (m, 2 H), 7.33 (d, $J$ = 8.4 Hz, 1H), 7.72 (d, $J$ = 8.4 Hz, 1H). MS, m/z 468 = M+1.

**EXAMPLE 2**



2-[(Acetylimino-phenyl-methyl)-amino]-N-(4-cyano-1-methyl-piperidin-4-yl)-3-cyclohexyl-propionamide.

(a) Thiobenzoyl acetamide was prepared according to the procedure from Example 1, step a, starting with thiobenzamide.

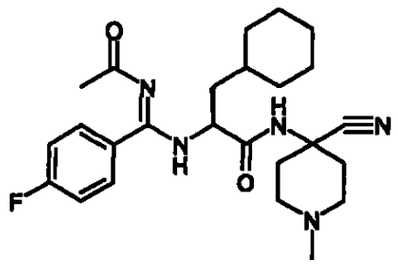
(b) The title compound was prepared starting from thiobenzoyl acetamide and 2-amino-N-(4-cyano-1-methyl-piperidin-4-yl)-3-cyclohexyl-propionamide bis

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hydrochloride salt according to the procedure from Example 1, step b. MS, m/z 438 = M+1.

EXAMPLE 3

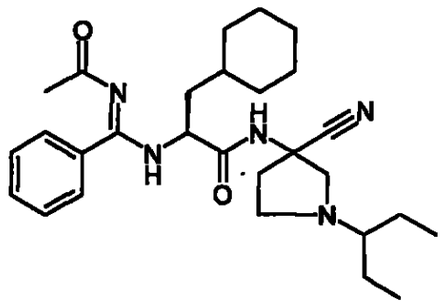


2-{[Acetylimino-(4-fluoro-phenyl)-methyl]-amino}-N-(4-cyano-1-methyl-piperidin-4-yl)-3-cyclohexyl-propionamide.

(a) N-(4-Fluoro-thiobenzoyl )acetamide was prepared according to the procedure from Example 1, step a, starting with 4-fluorothiobenzamide.

(b) The title compound was prepared starting from N-(4-fluoro-thiobenzoyl) acetamide and 2-amino-N-(4-cyano-1-methyl-piperidin-4-yl)-3-cyclohexyl-propionamide bis hydrochloride salt according to the procedure from Example 1, step b. MS, m/z 456 = M+1.

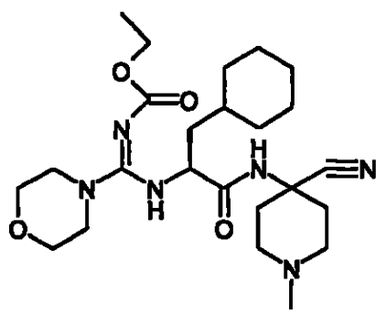
EXAMPLE 4



2-[(Acetylimino-phenyl-methyl)]-amino]-N-[3-cyano-1-(1-ethyl-propyl)-pyrrolidin-3-yl]-3-cyclohexyl-propionamide.

(a) The title compound was prepared starting from thiobenzoyl acetamide and 2-amino-N-[3-cyano-1-(1-ethyl-propyl)-pyrrolidin-3-yl]-3-cyclohexyl-propionamide bis hydrochloride salt according to the procedure from Example 1, step b, except that the compound was purified by HPLC using a 20 x 250 mm C18 reverse phase column with the method being 20% acetonitrile in water to 90% acetonitrile in water. MS, m/z 480 = M+1.

EXAMPLE 5



{[1-(4-Cyano-1-methyl-piperidin-4-ylcarbamoyl)-2-cyclohexyl-ethylamino]-morpholin-4-yl-methylen}-carbamic acid ethyl ester (Method A).

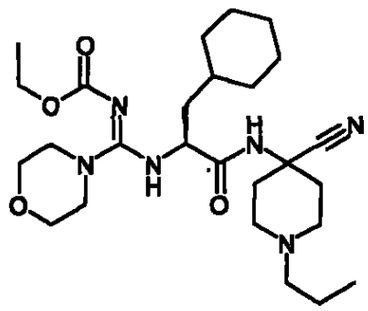
(a) (Morpholine-4-carbothioyl)-carbamic acid ethyl ester.

Morpholine (7.5 mL, 86.0 mmol) was added dropwise to a solution of ethyl isothiocyanato formate (10.0 mL, 84.8 mmol) in tetrahydrofuran (200 mL). The reaction mixture was stirred at room temperature for 2.5 h, then concentrated and dried under vacuum to provide the desired product as a white solid (16.5 g, 89%). This material was used without further purification. $^1$H NMR (400 MHz, $CDCl_3$) δ 1.28 (t, $J$ = 7.1 Hz, 3H), 3.61-3.97 (m, 8H), 4.16 (q, 7.1 Hz, 2H), 7.44 (br s, 1H).

(a) {[1-(4-Cyano-1-methyl-piperidin-4-ylcarbamoyl)-2-cyclohexyl-ethylamino]-morpholin-4-yl-methylen}-carbamic acid ethyl ester.

2-Chloro-N-methylpyridinium iodide (680 mg, 2.66 mmol), was added to a solution of (morpholine-4-carbothioyl)-carbamic acid ethyl ester (450 mg, 2.06 mmol), 2-amino-N-(4-cyano-1-methyl-piperidin-4-yl)-3-cyclohexyl-propionamide bis hydrochloride salt (745 mg, 2.04 mmol), and N,N-diisopropylethylamine (1.10 mL, 6.3 mmol) in dichloromethane (8.0 mL). The reaction was stirred at room temperature for 2.5 h then taken up in 10% citric acid solution and washed with EtOAc. The aqueous phase was then basified with saturated sodium carbonate and extracted with EtOAc. The organic extract was dried ($MgSO_4$) and concentrated to provide the desired product as a white solid (250 mg, 26%). This material was further purified by HPLC using a 20 x 250 mm $C_{18}$ reverse phase column with the method being 20% acetonitrile in water to 90% acetonitrile in water. MS, m/z 477 = M+1.

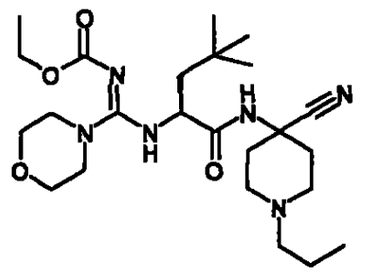
## EXAMPLE 6



{[1-(4-Cyano-1-propyl-piperidin-4-ylcarbamoyl)-2-cyclohexyl-ethylimino]-morpholin-4-yl-methyl}-carbamic acid ethyl ester.

The title compound was prepared starting from (morpholine-4-carbothioyl)-carbamic acid ethyl ester and 2-amino -N-(-4-cyano-1-propyl-piperidin-4-yl)-3-cyclohexylpropionamide bis hydrochloride salt according to the procedure from Example 5, step b, except that the compound was first purified by chromatography over silica gel using 9:1 methylene chloride : methanol as the eluant prior to reverse phase HPLC purification. MS, m/z 505 = M+1.

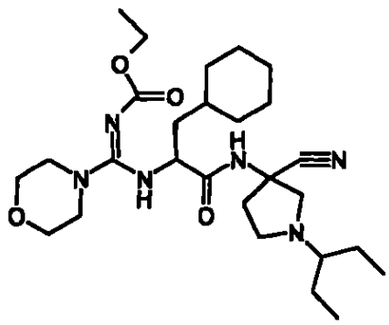
EXAMPLE 7



{[1-(4-Cyano-1-propyl-piperidin-4-ylcarbamoyl)-3,3-dimethyl-butylimino]-morpholin-4-yl-methyl}-carbamic acid ethyl ester.

The title compound was prepared starting from (morpholine-4-carbothioyl)-carbamic acid ethyl ester and 2-amino -4,4-dimethyl-pentanoic acid (4-cyano-1-propyl-piperidin-4-yl)amide bis hydrochloride salt according to the procedure from Example 5. MS, m/z 460 = M+1.

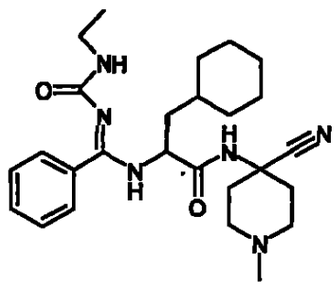
EXAMPLE 8



({1-[3-Cyano-1-(1-ethyl-propyl)-pyrrolidin-3-ylcarbamoyl]-2-cyclohexyl-ethylamino}-morpholin-4-yl-methylene)-carbamic acid ethyl ester.

The title compound was prepared starting from (morpholine-4-carbothioyl)-carbamic acid ethyl ester and 2-amino-N-[3-cyano-1-(1-ethyl-propyl)-pyrrolidin-3-yl]-3-cyclohexyl-propionamide bis hydrochloride salt according to the procedure from Example 5, step b, . MS, m/z 519 = M+1.

EXAMPLE 9



N-(4-Cyano-1-methyl-piperidin-4-yl)-3-cyclohexyl-2-[(ethylcarbamoylimino-phenyl-methyl)-amino]-propionamide (Method B).

(a) Benzimidic acid methyl ester.

Benzimidic acid methyl ester hydrochloride (5 g, 29.1 mmol) was partitioned between saturated sodium carbonate solution (200 mL) and diethyl ether (100 mL). The organic layer was dried ($MgSO_4$) and concentrated to provide the desired product as a colorless liquid (3.20 g, 81%). This material was used without further purification. $^1$H NMR (400 MHz, $CDCl_3$) δ 3.93 (s, 3H), 7.39-7.46 (m, 3H), 7.75 (d, J = 1.1 Hz, 2H).

(a) 1-Ethyl-3-(methoxy-phenyl-methylene)-urea.

A neat mixture of benzimidic acid methyl ester (750 mg, 5.56 mmol) and ethyl isocyanate (808 mg, 11.3 mmol) was stirred at 50 °C for 24 h. Excess isocyanate was removed under vacuum to provide the desired product as a colorless viscous oil (1.09 g, 95%). This material was used without further purification. $^1$H NMR (400 MHz, $CDCl_3$) δ 1.07 (t, $J$ = 7.3 Hz, 3 H), 3.25 (q, $J$ = 7.3 Hz, 2 H), 3.87 (s, 3H), 4.97 (br s, 1H), 7.26-7.40 (m, 2H), 7.45 (d, $J$ = 7.4 Hz, 1H), 7.69-7.71 (m, 2H). MS, m/z 207 = M+1.

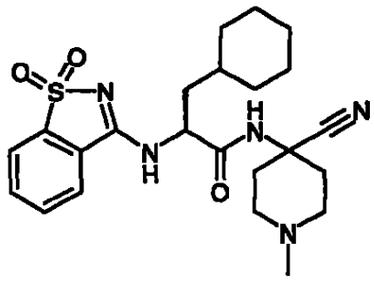
(a) N-(4-Cyano-1-methyl-piperidin-4-yl)-3-cyclohexyl-2-[(ethylcarbamoylimino-phenyl-methyl)-amino]-propionamide.

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A solution of 1-ethyl-3-(methoxy-phenyl-methylene)-urea (350 mg, 1.70 mmol), 2-amino-N-(4-cyano-1-methyl-piperidin-4-yl)-3-cyclohexyl-propionamide bis hydrochloride salt (512 mg, 1.40 mmol) and N,N-diisopropylethylamine (352 mg, 2.73 mmol) in dry methanol (5.0 mL) was stirred at room temperature for 60 h. The reaction mixture was concentrated and the resulting residue was chromatographed over 50 g of flash silica gel using dichloromethane to 5% methanol in dichloromethane as the eluant. This provided the desired product as a light yellow solid (280 mg, 43%) which was further purified by HPLC using a 20 x 250 mm $C_{18}$ reverse phase column with the method being 20% acetonitrile in water to 90% acetonitrile in water. MS, m/z 467 = M+1.

EXAMPLE 10

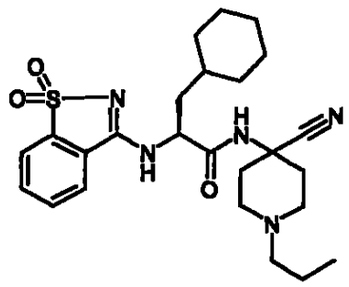


N-(4-Cyano-1-methyl-piperidin-4-yl)-3-cyclohexyl-2-(1,1-dioxo-1*H*-1$\lambda^6$-benzo[d]isothiazol-3-ylamino)-propionamide (Method C).

A suspension of 3-chloro-benzo[d]isothiazole 1,1-dioxide (300 mg, 1.49 mmol) and 2-amino -N-(-4-cyano-1-methyl-piperidin-4-yl)-3-cyclohexylpropionamide bis hydrochloride salt (500 mg, 1.37 mmol) was prepared in 5.5 mL of acetonitrile. Triethylamine (575 μL, 4.10 mmol) was added and the reaction mixture was stirred at room temperature for 1 day. The suspension was filtered to remove triethylamine hydrochloride and the filtrate was concentrated. The resulting residue was chromatographed over 50 g of flash silica using dichloromethane/ methanol 9:1 as the eluant to provide the desired product as a light yellow solid (310 mg, 49%). $^1$H NMR (400 MHz, $CDCl_3$) δ 0.25-0.45 (m, 1H), 0.65-0.85 (m, 2H), 0.95-1.10 (m, 2H), 1.30-1.60

(m, 7H), 1.75-1.85 (m, 2H), 1.85-2.2 (m, 2H), 2.31 (s, 3H), 2.35-2.50 (m, 3H), 2.65-2.80 (m, 2H), 4.60-4.70 (m, 1H), 7.35-7.50 (m, 2H), 7.58 (t, J = 7.3, 1H), 7.78 (d, J = 7.7 Hz, 1H), 7.81 (br s, 1H), 8.91 (br s, 1H). MS, m/z 458 = M+1.

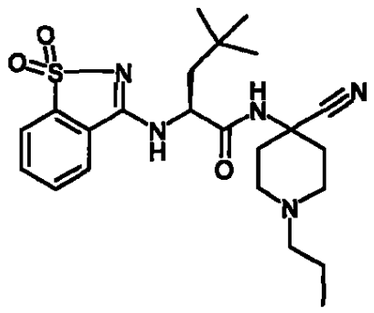
## EXAMPLE 11



N-(4-Cyano-1-propyl-piperidin-4-yl)-3-cyclohexyl-2-(1,1-dioxo-1*H*-1$\lambda^6$-benzo[d]isothiazol-3-ylamino)-propionamide.

The title compound was prepared starting from 3-chloro-benzo[d]isothiazole 1,1-dioxide and 2-amino -N-(-4-cyano-1-propyl-piperidin-4-yl)-3-cyclohexylpropionamide bis hydrochloride salt according to the procedure from Example 10, except that the compound was further purified by HPLC using a 20 x 250 mm $C_{18}$ reverse phase column with the method being 20% acetonitrile in water to acetonitrile. MS, m/z 486 = M+1.

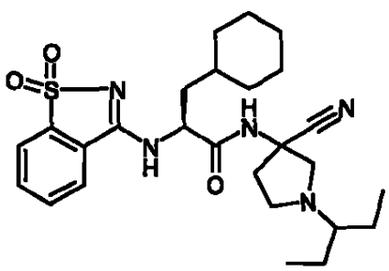
## EXAMPLE 12



2-(1,1-dioxo-1*H*-1λ$^6$-benzo[d]isothiazol-3-ylamino)-4,4-dimethyl-pentanoic acid(4-cyano-1-propylpiperidin-4-yl)-amide.

The title compound was prepared starting from 3-chloro-benzo[d]isothiazole 1,1-dioxide and 2-amino -4,4-dimethyl-pentanoic acid (4-cyano-1-propyl-piperidin-4-yl)amide bis hydrochloride salt according to the procedure from Example 10, except that the compound was further purified by HPLC using a 20 x 250 mm $C_{18}$ reverse phase column with the method being 20% acetonitrile in water to acetonitrile. MS, m/z 460 = M+1.

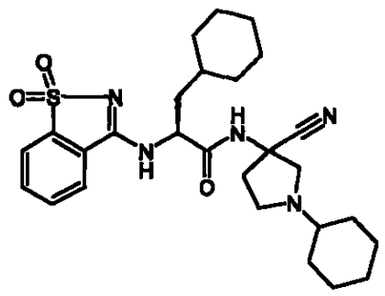
EXAMPLE 13



N-[3-Cyano-1-(1-ethyl-propyl)-pyrrolidin-3-yl]-3-cyclohexyl-2-(1,1-dioxo-1*H*-1λ$^6$-benzo[d]isothiazol-3-ylamino)-propionamide.

The title compound was prepared starting from 3-chloro benzo[d]isothiazole 1,1-dioxide and 2-amino-N-[3-cyano-1-(1-ethyl-propyl)-pyrrolidin-3-yl]-3-cyclohexyl-propionamide bis hydrochloride salt according to the procedure from Example10, except that the compound was further purified by HPLC using a 20 x 250 mm $C_{18}$ reverse phase column with the method being 40% acetonitrile in water to acetonitrile. MS, m/z 500 = M+1.

## EXAMPLE 14



N-(3-Cyano-1-cyclohexyl-pyrrolidin-3-yl)-3-cyclohexyl-2-(1,1-dioxo-1*H*-1$\lambda^6$-benzo[d]isothiazol-3-ylamino)-propionamide.

The title compound was prepared starting from 3-chloro benzo[d]isothiazole 1,1-dioxide and 2-amino-N-(3-cyano-1-cyclohexyl-pyrrolidin-3-yl)-3-cyclohexyl-propionamide bis hydrochloride salt according to the procedure from Example 10, except that the compound was further purified by HPLC using a 20 x 250 mm $C_{18}$ reverse phase column with the method being 40% acetonitrile in water to acetonitrile. MS, m/z 512 = M+1.

## EXAMPLE 15

N-(4-Cyano-methyl-piperidin-4-yl)-3-cyclohexyl-2-(3-oxo-3H-isoindol-1-ylamino)-propionamide.

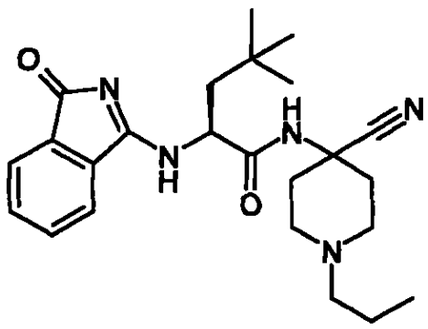
The title compound was prepared starting from 3-imino-2, 3-dihydro-isoindol-1-one and 2-amino-N-(4-cyano-1-methyl-piperidin-4-yl)-3-cyclohexyl-propionamide bis

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hydrochloride salt according to the procedure from Example 10, except that refluxing THF was used as the solvent. The compound was further purified by HPLC using a 20 x 250 mm $C_{18}$ reverse phase column with the method being 20% acetonitrile in water to acetonitrile. MS, m/z 422.5 = M+1.

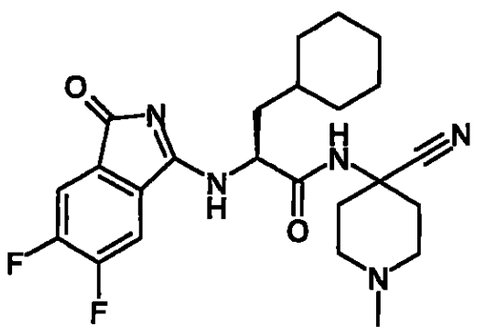
EXAMPLE 16



4,4-Dimethyl-2-(3-oxo-3H-isoindol-1-ylamino)-pentanoicacid-(4-cyano-1-propyl-piperidin-4-yl)-amide.

The title compound was prepared from 3-imino-2, 3-dihydro-isoindol-1-one and 2-amino -4,4-dimethyl-pentanoic acid (4-cyano-1-propyl-piperidin-4-yl)amide bis hydrochloride salt according to the procedure from Example 15. MS, m/z 424.5 = M+1.

EXAMPLE 17



N-(4-cyano-1-methyl-piperidin-4-yl)-3-cyclohexyl-2-(5,6-difluoro-3-oxo-3H-isoindol-1-ylamino) propionamide.

(a) 2-Chloro-4,5-difluorobenzoic acid methyl ester.

2-Chloro-4,5-difluorobenzoic acid (1.93 g, 10 mmol) was dissolved in 20 mL of acetone. Cesium carbonate (5.29 g, 15 mmol) was added followed by iodomethane (1.0 mL, 15 mmol). This reaction mixture was heated under reflux for 1 h and then cooled to room temperature. This suspension was then diluted with 40 mL of ethyl ether. The solid was removed by filtration and washed with ethyl ether. The filtrate was evaporated *in vacuo* to give the title compound in quantitative yield as a clear oil.

(b) 2-Cyano-4,5-difluorobenzoic acid methyl ester.

The above oil (2.06 g, 10 mmol) was dissolved in 10 mL of *N*-methyl pyrrolidinone. Copper (I) cyanide (1.79 g, 20 mmol) was added. This mixture was heated at 195 °C under nitrogen for 1 h. After cooling to room temperature, this solution was diluted with 100 mL of water. The resulting solid was collected by filtration. This solid was then suspended in a rapidly stirred solution of potassium cyanide (0.5 g) in 30 mL of water for 1 h. EtOAc (30 mL) was added. The mixture was filtered through diatomaceous earth. The organic phase was separated and the aqueous phase was extracted with EtOAc (20 mL x 2). The combined organic phase was washed with brine and dried over magnesium sulfate. The solvent was removed in vacuo. The residue was crystallized from ethyl ether and petroleum ether to give the title compound as a yellow solid (1.26 g, 64 %).

(c) 5,6-Difluoro-2,3-dihydro-3-imino-1*H*-isoindol-1-one.

The above solid (0.493 g, 2.5 mmol) was dissolved in 20 mL of MeOH. This solution was saturated with ammonia at 0 °C and then stirred in a pressure tube at room

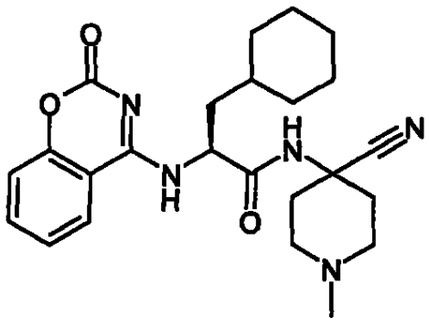
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temperature for 3 days. The solid was collected by filtration and washed with ethyl ether to give the title compound as a yellow solid ( 0.363 g, 80 %).

The title compound was prepared from 5,6-difluoro-2,3-dihydro-3-imino-1*H*-isoindol-1-one and 2-amino-N-(4-cyano-1-methyl-piperidin-4-yl)-3-cyclohexyl-propionamide bis hydrochloride salt according to the procedure from Example 15. MS, m/z 458.3 = M+1.

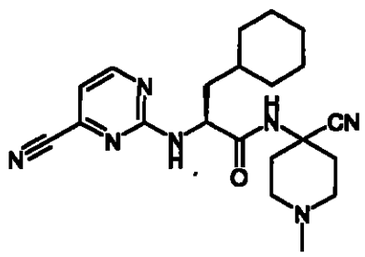
EXAMPLE 18



N-(4-cyano-1-methyl-piperidin-4-yl)-3-cyclohexyl-2-(2-oxo-2H-benzo[e][1,3] oxazin-4-ylamino)-propionamide.

The title compound was prepared starting from 4-chloro-benzo[e][1,3] oxazin-2-one (prepared from benzo [e][1,3] oxazin-2,4-dione and $PCl_5$ in refluxing toluene) and 2-amino-N-(4-cyano-1-methyl-piperidin-4-yl)-3-cyclohexyl-propionamide bis hydrochloride salt according to the procedure from Example 10. MS, m/z 438 = M+1.

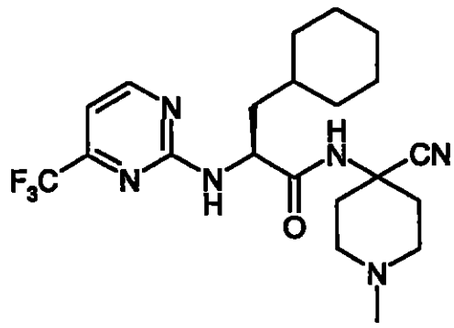
EXAMPLE 19



N-(4-cyano-1-methyl-piperidin-4-yl)-2-(4-cyano-pyrimidin-2-ylamino)-3-cyclohexyl-propionamide (Method C).

2-Chloro-4-pyrimidinecarbonitrile (0.3 mmol, Daves, G. D. Jr., O'Brien, D. E., Cheng, C. C. *J. Het. Chem*, **1964**, *1*, 130) and 2-amino-*N*-(4-cyano-1-methyl-piperidin-4-yl)-3-cyclohexyl-propionamide (0.7 mmol) were dissolved in acetonitrile (10 mL) containing *N,N*-diisopropylethylamine (0.6 mmol). The solution was heated to a gentle reflux for 17 h. The volatiles were evaporated and the residue was subjected to chromatography (silica gel, eluant = EtOAc then MeOH). The methanolic fraction was concentrated to a colorless solid which was rechromatographed (10% MeOH/EtOAc) to afford the title compound as a colorless solid (52%). The material was recrystallized from dichloromethane/petroleum ether.

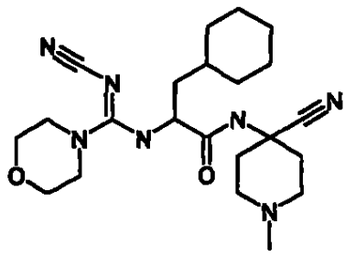
EXAMPLE 20



N-(4-cyano-1-methyl-piperidin-4-yl)-2-(4-trifluoromethyl-pyrimidin-2-ylamino)-3-cyclohexyl-propionamide.

The title compound was prepared from 2-chloro-4-trifluoromethyl pyrimidine and 2-amino-*N*-(4-cyano-1-methyl-piperidin-4-yl)-3-cyclohexyl-propionamide according to the procedure from Example 19. MS, m/z 439.5 = M+1.

EXAMPLE 21



N-(4-cyano-1-methyl-piperidine-4-yl)-3-cyclohexyl-2[N-cyano-morpholine-4-carboximidoyl)-amino]-propionamide (Method D).

(a) 2-(N-Cyano-iminomethylene-amino)-N-(4-cyano-1-methyl-piperidine-4-yl)-3-cyclohexyl-propionamide.

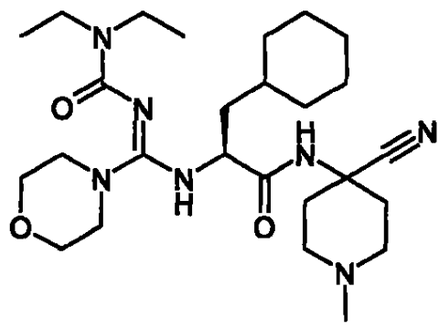
A solution of diphenylcyanocarbonimidate (455 mg, 1.91 mmol), 2-amino-N-(4-cyano-1-methyl-piperidin-4-yl)-3-cyclohexyl-propionamide bis hydrochloride salt (680 mg, 1.86 mmol) and N,N-diisopropylethylamine (482 mg, 3.73 mmol) in isopropanol (5.0 mL) was stirred overnight at room temperature. The reaction mixture was then filtered to provide the desired carbodiimide as a white powder (140 mg, 22%). This material was used without further purification. $^1$H NMR (400 MHz, $CDCl_3$) δ 0.80-1.00 (m, 2H), 1.05-1.20 (m, 1H), 1.20-1.40 (2H), 1.50-1.85 (m, 8H), 2.32 (s, 3H), 2.40-2.50 (m, 2H), 2.55-2.70 (m, 4H), 2.85-2.95 (m, 2H), 4.10-4.20 (m, 1H), 8.77 (br s, 1H). MS, m/z 343 = M+1.

(b) 2-(N-Cyano-benzimidoyl-amino)-N-(4-cyano-1-methyl-piperidine-4-yl)-3-cyclohexyl-propionamide.

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A suspension of 2-(N-cyano-iminomethylene-amino)-N-(4-cyano-1-methyl-piperidine-4-yl)-3-cyclohexyl-propionamide (120 mg, 0.35 mmol) in tetrahydrofuran (1 mL) was treated with morpholine (4 mL, 45.9 mmol). The reaction mixture was stirred at room temperature for 3 days then concentrated to dryness. The residue was purified by HPLC using a 20 x 250 mm $C_{18}$ reverse phase column with the method being 20% acetonitrile in water to 90% acetonitrile in water. MS, m/z 430 = M+1.

EXAMPLE 22



N-(4-Cyano-1-methyl-piperidin-4-yl)-3-cyclohexyl-2-{[(diethyl-carbamoylimino)-morpholin-4-yl-methyl]-amino}-propionamide (Method D).

(a) N,N-Diethyl carbamoyl thiocyanate.

A suspension of sodium thiocyanate (3.30 g, 40.7 mmol) in dry acetonitrile (25 mL) at 80°C was treated dropwise with a solution of N,N-diethyl carbamoyl chloride (5.0 g, 36.9 mmol) in dry acetonitrile (15 mL). The reaction mixture was stirred at 80°C for 50 min, cooled to room temperature, then filtered through a fine glass frit. The resulting filtrate was used as a 0.9 M solution of N,N-diethyl carbamoyl thiocyanate in acetonitrile.

(b) N-(4-Cyano-1-methyl-piperidin-4-yl)-3-cyclohexyl-2-(3-diethylamino-carbonyl-thioureido)-propionamide

A solution of 2-amino -N-(-4-cyano-1-propyl-piperidin-4-yl)-3-cyclohexylpropionamide bis hydrochloride salt (560 mg, 1.53 mmol) and triethylamine (500 μL, 3.59 mmol) in acetonitrile (4 mL) was treated with a solution of N,N-diethyl carbamoyl thiocyanate in acetonitrile (3.0 mL, 2.7 mmol). The reaction mixture was stirred overnight at room temperature and concentrated on a rotary evaporator. The resulting residue was chromatographed (ethyl acetate: hexanes 1:1 then ethyl acetate and finally methanol: methylene chloride 1:9 as the eluant) to provide the desired product as a light yellow solid (340 mg, 49%). MS, m/z 451.3 = M+1.

The title compound was prepared by treating a solution of the resulting thiourea (340 mg, 0.75 mmol) and triethylamine (230 μL, 1.65 mmol) in dry acetonitrile (4 mL) with mercury (II) chloride (225 mg, 0.83 mmol) and morpholine (200 μL, 2.23 mmol). The reaction mixture was stirred at room temperature for 4 h then filtered through a 0.45 μm filter disc. The resulting filtrate was filtered through a column of silica (5% methanol/methylene chloride as the eluant) and the resulting crude product was further purified by HPLC using a 20 x 250 mm $C_{18}$ reverse phase column with the method being 20% acetonitrile in water to acetonitrile. MS, m/z 504.6 = M+1.

The following examples were prepared by Method D in a parallel fashion:

## EXAMPLE 23

{[1-(4-Cyano-1-methyl-piperidin-4-ylcarbamoyl)-2-cyclohexyl-ethylamino]-pyrrolidin-1-yl-methyl}-carbamic acid ethyl ester. MS, m/z 461 = M+1.

## EXAMPLE 24

{[1-(4-Cyano-1-methyl-piperidin-4-ylcarbamoyl)-2-cyclohexyl-ethylamino]-piperidin-1-yl-methyl}-carbamic acid ethyl ester. MS, m/z 477 = M+1.

## EXAMPLE 25

{Azepan-1-yl-[1-(4-cyano-1-methyl-piperidin-4-ylcarbamoyl)-2-cyclohexyl-ethylamino]-methylene}-carbamic acid ethyl ester. MS, m/z 490 = M+1.

EXAMPLE 26

{Azocan-1-yl-[1-(4-cyano-1-methyl-piperidin-4-ylcarbamoyl)-2-cyclohexyl-ethylamino]-methylene}-carbamic acid ethyl ester. MS, m/z 504 = M+1.

EXAMPLE 27

1-{[1-(4-Cyano-1-methyl-piperidin-4-ylcarbamoyl)-2-cyclohexyl-ethylamino]-ethoxycarbonylimino-methyl}-piperidine-4-carboxylic acid ethyl ester. MS, m/z 548 = M+1.

EXAMPLE 28

1-{[1-(4-Cyano-1-methyl-piperidin-4-ylcarbamoyl)-2-cyclohexyl-ethylamino]-ethoxycarbonylimino-methyl}-piperidine-3-carboxylic acid ethyl ester. MS, m/z 548 = M+1.

EXAMPLE 29

[[1-(4-Cyano-1-methyl-piperidin-4-ylcarbamoyl)-2-cyclohexyl-ethylamino]-(4-pyrrolidin-1-yl-piperidin-1-yl)-methylene]-carbamic acid ethyl ester. MS, m/z 545 = M+1.

EXAMPLE 30

{[1,4']Bipiperidinyl-1'-yl-[1-(4-cyano-1-methyl-piperidin-4-ylcarbamoyl)-2-cyclohexyl-ethylamino]-methylene}-carbamic acid ethyl ester. MS, m/z 559 = M+1.

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EXAMPLE 31

[[1-(4-Cyano-1-methyl-piperidin-4-ylcarbamoyl)-2-cyclohexyl-ethylamino]-(4-phenyl-piperazin-1-yl)-methylene]-carbamic acid ethyl ester. MS, m/z 553 = M+1.

EXAMPLE 32

[[1-(4-Cyano-1-methyl-piperidin-4-ylcarbamoyl)-2-cyclohexyl-ethylamino]-(4-ethyl-piperazin-1-yl)-methylene]-carbamic acid ethyl ester. MS, m/z 505 = M+1.

EXAMPLE 33

{(4-Acetyl-piperazin-1-yl)-[1-(4-cyano-1-methyl-piperidin-4-ylcarbamoyl)-2-cyclohexyl-ethylamino]-methylene}-carbamic acid ethyl ester. MS, m/z 519 = M+1.

EXAMPLE 34

4-{[1-(4-Cyano-1-methyl-piperidin-4-ylcarbamoyl)-2-cyclohexyl-ethylamino]-ethoxycarbonylimino-methyl}-piperazine-1-carboxylic acid ethyl ester. MS, m/z 549 = M+1.

EXAMPLE 35

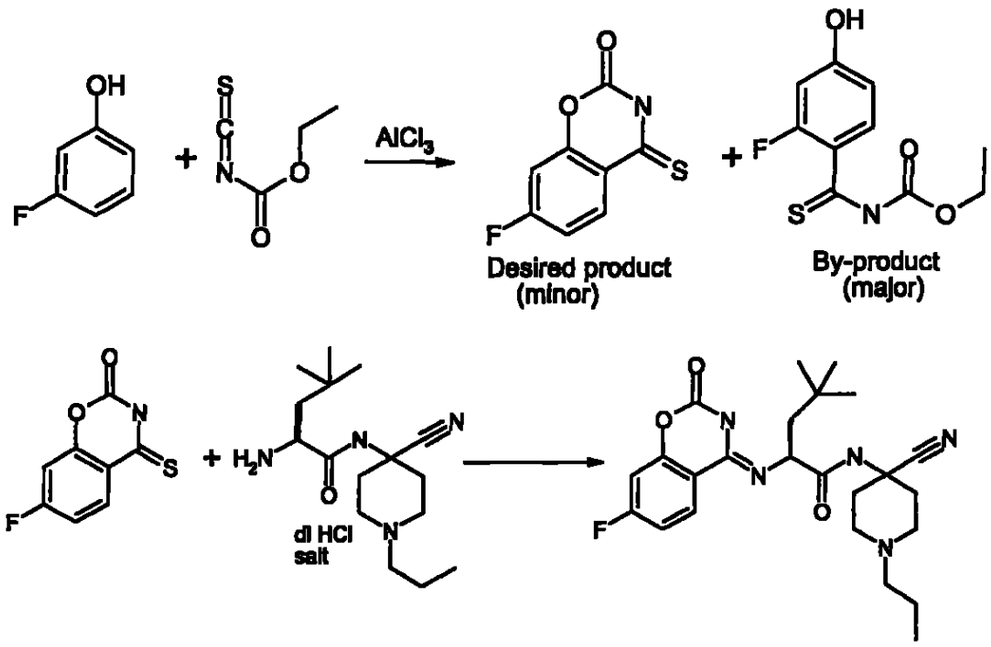
[[1-(4-Cyano-1-methyl-piperidin-4-ylcarbamoyl)-2-cyclohexyl-ethylamino]-(3,3,5-trimethyl-6-aza-bicyclo[3.2.1]oct-6-yl)-methylene]-carbamic acid ethyl ester. MS, m/z 544 = M+1.

EXAMPLE 36

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2-(7-Fluoro-2-oxo-2,3-dihydro-benzo[e][1,3]oxazin-4-yldeneamino)-5,5-dimethyl-hexanoic acid(4-cyano-1-propyl-piperidin-4-yl)-amide.



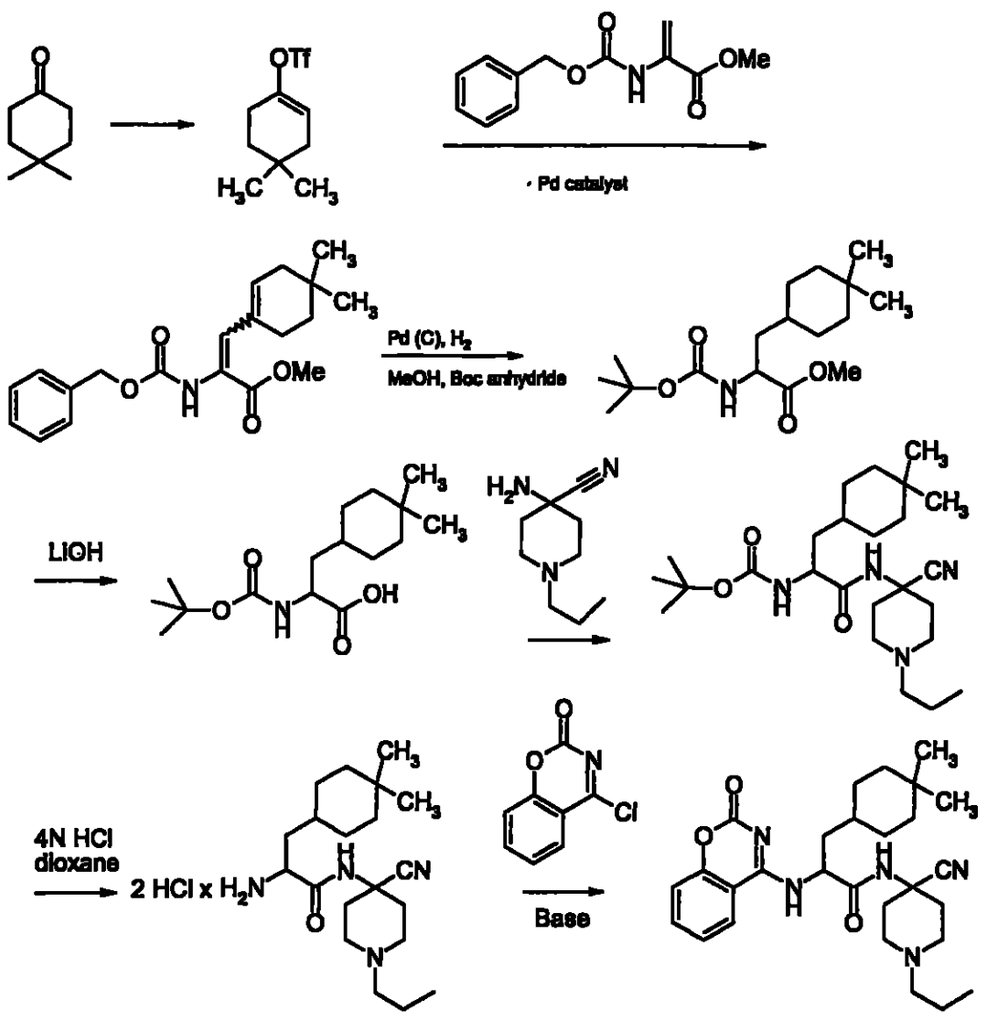

To a stirred solution of aluminum chloride (7.13 g, 53.5mmol) in nitromethane (40 mL) at 0°C was added ethyl isothiocyanato formate (3.5 g, 26.8 mmol). The reaction was stirred at 0 °C for 1h and then at room temperature for 48 h. The reaction mixture was then poured over crushed ice and filtered to give 2.0 g of an orange solid.
The solid was dissolved in pyridine (20 mL) and heated at reflux for 4 h. The reaction was diluted with methylene chloride and washed with water. The organic fraction was dried over anhydrous sodium sulfate and evaporated on a rotary evaporator. The crude product was purified by flash column chromatography over silica gel using 25% EtOAc and hexane to give 0.27 g of 7-fluoro-4-thioxo-3,4-dihydro-benzo[e][1,3]oxazin-2-one (5.1%).

To the above intermediate (0.135 g, 0.685 mmol) and 2-amino-5,5-dimethyl-hexanoic acid (4-cyano-1-propyl-piperidin-4-yl)-amide (0.251 g, 0.685 mmol) in dry THF(10 mL)

was added diisopropylethyl amine (0.36 mL, 2.06 mmol) and 2-chloro-1-methylpyridinium iodide(0.288g, 0.89 mmol). The reaction was stirred at room temperature for 48 h. Solvent was evaporated and the residue dissolved in methylene chloride, washed with water, dried over anhydrous sodium sulfate and evaporated. The crude product was purified initially by flash column chromatography over silica gel using 10% MeOH/methylene chloride (0.25 g, 79.8%). Final purification by HPLC afforded the title compound, 1HNMR and MS were consistent with the desired product; MS: 458 (M+1).

## EXAMPLE 37

N-(4-Cyano-1-propyl-piperidin-4-yl)-3-(4,4-dimethyl-cyclohexyl)-2-(2-oxo-2H-benzo[e][1,3]oxazin-4-ylamino)-propionamide.




To a solution of 4,4-dimethyl cyclohexanone (4.60 g, 36.5 mmol) in dry THF (82 mL) cooled in a dry ice/acetone bath, was added sodium bis (trimethylsilyl)amide (38 mL of a 1.0 M solution in THF, 38 mmol). The reaction mixture was stirred under an argon atmosphere at –78 °C for 30 min. A solution of 2-(N,N-bis trifluoromethanesulfonyl)amino-5-chloropyridine (15g, 37.7 mmol) in dry THF (20 mL) was introduced via syringe and the resulting solution was warmed to room temperature and stirred overnight. The reaction mixture was washed with half saturated brine (60 mL) and the aqueous phase was extracted with diethyl ether. The combined organic extracts were dried ($MgSO_4$) and concentrated to provide a dark brown oil (23 g). Chromatography over silica gel using petroleum ether as the eluant provided trifluoro-methane sulfonic acid 4,4-dimethyl-cyclohexyl-1-enyl ester as a colorless liquid (5.2 g,

56%). $^1$H NMR (400 MHz, $CDCl_3$) δ 0.98 (s, 6H), 1.53 (t, J = 6.5 Hz, 2H), 1.95-1.99 (m, 2H), 2.30-2.40 (m, 2H), 5.65-5.70 (m, 1H).

A mixture of the above triflate ester (2.26 g, 8.75 mmol), Cbz dehydroalanine methyl ester (2.10 g, 8.93 mmol), Pd $(OAc)_2$ (160 mg, 0.71 mmol), and KOAc (3.42 g, 34.8 mmol) in dry DMF was stirred at room temperature for 24 h. The reaction mixture was diluted with water (400 mL) and extracted with EtOAc (2 x 150 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated. Chromatography of the resulting residue over silica gel using 1:20 EtOAc/ hexanes then 3:17 EtOAc/ hexanes provided 2-benzyloxycarbonylamino-3-(4,4-dimethyl-cyclohex-1-enyl)-acrylic acid methyl ester as a yellow oil (1.38 g, 46%). $^1$H NMR (400 MHz, $CDCl_3$) δ 0.88 (s, 6H), 1.34 (t, J = 6.4 Hz, 2H), 1.95-2.00 (m, 2H), 2.23-2.30 (m, 2H), 3.74 (s, 3H), 5.15 (s, 2H), 5.90-6.10 (m, 1H), 6.10-6.15 (m, 1H), 7.0 (s, 1H), 7.25-7.36 (m, 5H). m/z 382.4 ($MK^+$).

A suspension of the above acrylic acid ester (2.18 g, 6.35 mmol), Boc anhydride (1.52 g, 6.96 mmol), and 10% Pd/ C (300 mg) in MeOH was shaken on a Parr apparatus under 40 psi of hydrogen gas for 17 h. The reaction mixture was filtered through a pad of diatomaceous earth and concentrated to provide 2-tert-butoxycarbonylamino-3-(4,4-dimethyl-cyclohexyl)-propionic acid methyl ester as a yellow oil (1.87 g, 94%). $^1$H NMR (400 MHz, $CDCl_3$) δ 0.85 (s, 3H), 0.88 (s, 3H), 1.05-1.20 (m, 5H), 1.21-1.40 (m, 2H), 1.44 (s, 9H), 1.45-1.59 (m, m, 2H), 1.60-1.78 (m, 2H), 3.72 (broad s, 3H), 4.27-4.40 (m, 1H), 4.82-4.96 (m, 1H).

A suspension of the above methyl ester (1.87 g, 5.97 mmol) and lithium hydroxide monohydrate (1.76 g, 41.9 mmol) in THF (18 mL), MeOH (6 mL), and water (6 mL) was stirred at room temperature for 4 h. The reaction mixture was acidified with 10% citric acid (aqueous) and extracted with diethyl ether (3 x 100 mL). The combined organic layers were dried ($MgSO_4$) and concentrated to provide a the corresponding carboxylic acid as a white foam (1.21 g, 68%). $^1$H NMR (400 MHz, DMSO $d_6$) δ 0.83 (s, 3H), 0.85 (s, 3H), 0.87-1.10 (m, 4H), 1.10-1.46 (m, 3H), 1.35 (s, 9H), 1.46-1.60 (m, 4H), 3.88-3.94 (m, 1H), 7.0 (d, 8.2 Hz, 1H), 11.7-12.9 (broad s, 1H).

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Isobutyl chloroformate (0.55 mL, 4.24 mmol) was added dropwise to a solution of the above carboxylic acid (1.21 g, 4.04 mmol) and N-methyl morpholine (0.89 mL, 8.10 mmol) in dry THF cooled to 0 °C. The reaction mixture was stirred at 0 °C for 1h. A solution of 4-amino-1-propyl-piperidine-4-carbonitrile (780 mg, 4.65 mmol) in dry THF (5 mL) was added and the reaction mixture was allowed to warm to room temperature and stirred overnight. Volatiles were removed on a rotary evaporator and the resulting residue was dissolved in EtOAc (50 mL) and washed with saturated $Na_2CO_3$ (50 mL). The organic phase was dried ($MgSO_4$) and concentrated. Chromatography of this crude material over silica gel using a gradient of dichloromethane to 5% MeOH in dichloromethane provided [1-(4-cyano-1-propyl-piperidin-4-ylcarbamoyl)-2-(4,4-dimethyl-cyclohexyl)-ethyl]-carbamic acid *tert*-butyl ester as a white foam (1.17 g, 65%). $^1$H NMR (400 MHz, $CDCl_3$) δ 0.85 (s, 3H), 0.88 (s, 3H), 0.89 (t, J = 7.3 Hz, 3H), 1.05-1.30 (m, 6H), 1.30-1.40 (m, 2H), 1.45 (s, 9H), 1.40-1.60 (m, 5H), 1.70-1.83 (m, 1H), 1.87-2.02 (m, 2H), 2.32-2.54 (m, 6H), 2.68-2.90 (m, 2H), 4.00-4.10 (m, 1H), 4.80-5.00 (m, 1H), 6.70-6.90 (m, 1H); m/z 449.5 $(M+H)^+$, 447.4 $(M-H)^-$.

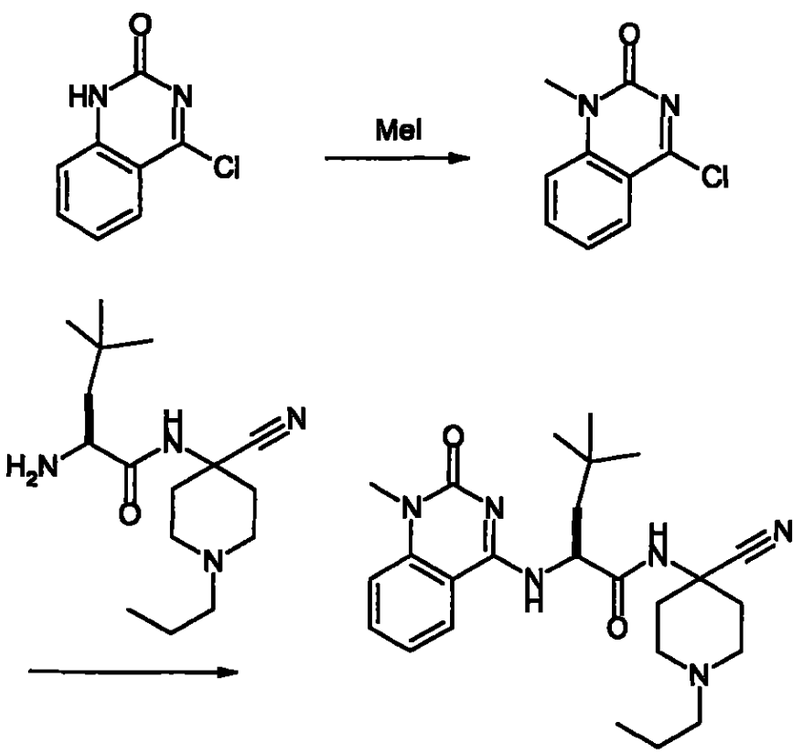
The above *tert*-butyl ester (1.17 g, 2.6 mmol) was dissolved in a solution of HCl in 1,4-dioxane (10.0 mL of a 4.0 M solution, 40 mmol) and stirred under an active sweep of argon gas for 10 min. The solution was concentrated on a rotary evaporator then taken up in $CHCl_3$ (50 mL) and concentrated again to provide the amine dihydrochloride as a white powder (1.05 g, 95%). m/z = 349.5 $(M+H)^+$.

A suspension of 4-chloro benzoxazin-2-one (500 mg, 2.69 mmol), the above amine salt (400 mg, 0.95 mmol), and polystyrene supported diisopropylamine (2.40 g, 8.40 mmol) in dry acetonitrile was heated at 50 °C for 5 h. The reaction mixture was filtered through a pad of diatomaceous earth and the filtrate was concentrated. The resulting residue was chromatographed over silica gel using methylene chloride then 2.5% MeOH in methylene chloride and finally 10% MeOH in methylene chloride as the eluant to provide the title compound as a white solid (45 mg, 10%). $^1$H NMR (400 MHz, DMSO $d_6$) δ 0.82 (t, J = 7.5 Hz, 3H), 0.83 (s, 3H), 0.84 (s, 3H), 1.00-1.20 (m, 5H), 1.25-1.42 (m, 5H), 1.48-1.58

(m, 2H), 1.60-1.70 (m, 1H), 1.80-1.92 (m, 2H), 2.10-2.30 (m, 6H), 2.55-2.68 (m, 2H), 4.83-4.92 (m, 1H), 7.29 (d, J = 8.3 Hz, 1H), 7.36 (t, J = 7.7 Hz, 1H), 7.73 (t, J = 7.3 Hz, 1H), 8.36 (d, J = 8.1 Hz, 1H), 8.73 (s, 1H), 8.98-9.10 (m, 1H); m/z = 494.5 $(M+H)^+$, 492.4 $(M-H)^-$.

## EXAMPLE 38

4,4-Dimethyl-2-(1-methyl-2-oxo-1,2-dihydro-quinazolin-4-ylamino)-pentanoic acid (4-cyano-1-propyl-piperidin-4-yl)-amide.



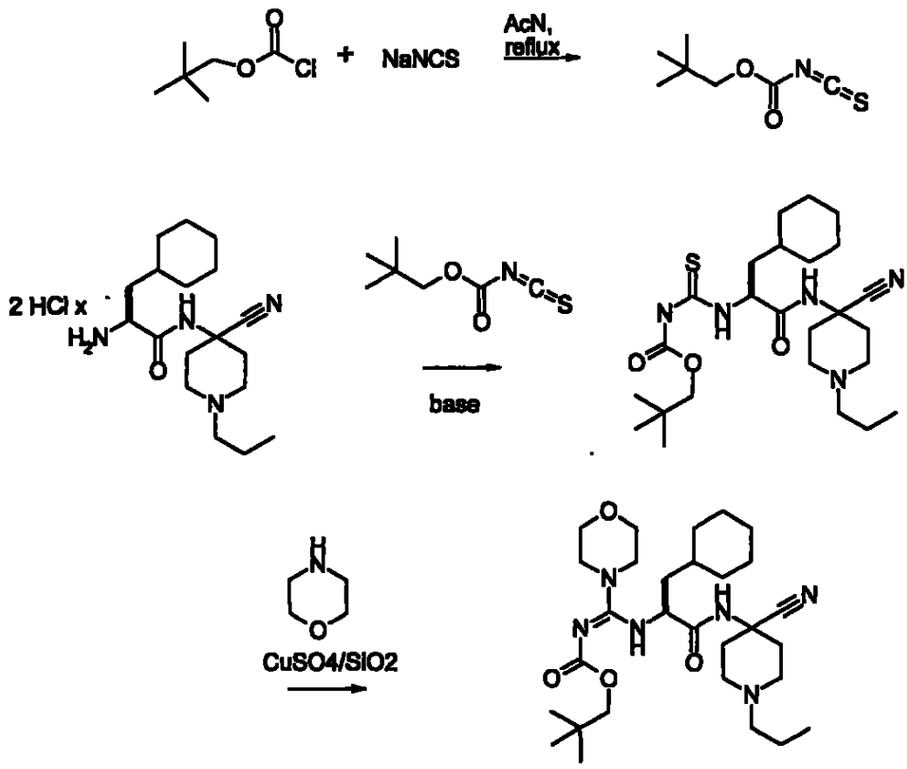

A mixture of 4-chloro-1,2-dihydro-2-oxo-quinazoline (1.0 g, 5.5 mmol), iodomethane (0.86 mL, 2.5 equiv.) and potassium carbonate (1.91 g, 2.5 equiv.) in DMF (15 mL) was heated at 80 °C for 90 min before the solvent was removed at reduced pressure at 80 °C. The residue was taken up in dichloromethane and filtered. The filtrate was concentrated

and column chromatography on silica gel (eluent: EtOAc) gave the N-methyl analog (0.21 g, 19.5%).

A mixture of the above intermediate (100 mg, 0.5 mmol), 2-amino-4,4-dimethylpentanoic acid (4-cyano-1-propyl-piperidin-4-yl)amide (151 mg, 0.5 mmol), Cu (powder, 66 mg, 1 mmol) and potassium carbonate (285 mg, 2 mmol) in NMP (3 mL) was heated at 150 °C for 16 h. After it was cooled to room temperature, it was filtered. The filtrate was diluted with water and extracted with dichloromethane. The organic phase was washed with brine, dried (sodium sulfate), concentrated and chromatographed on silica gel affording the title compound (101 mg, 44.6%); MS: 453 (M+1).

## EXAMPLE 39

{[1-(4-Cyano-1-methyl-piperidin-4-ylcarbamoyl)-2-cyclohexyl-ethylimino]-morpholin-4-yl-methyl}-carbamic acid 2,2-dimethyl-propyl ester.



To a solution of sodium thiocyanate (4.46 g, 55 mmol) in 50 mL of acetonitrile was added neopentyl chloroformate (6.15 mL, 50 mmol). This mixture was heated at 80 °C for 2 h. After cooling to room temperature, the solid was removed by filtration and the filtrate was used as a 1 M stock solution of neopentyl isothiocyanatoformate.

2-Amino-*N*-(4-cyano-1-methyl-piperidin-4-yl)-3-cyclohexyl-propionamide dihydrochloride salt (6.33 g, 17.32 mmol) was suspended in 50 mL of methylene chloride. Triethylamine (5.00 mL, 35.9 mL) was added. To this solution at 0 °C was added the above solution (20 mL, 20 mmol). This mixture was stirred at 0 °C for 1 h. The solvent was removed in vacuo. The residue was purified by flash chromatography on silica gel eluting with 5% MeOH in ethyl ether (Rf = 0.2) to give the thiourea (4.76 g, 59%) as a yellow oil; MS: M+1 = 466.

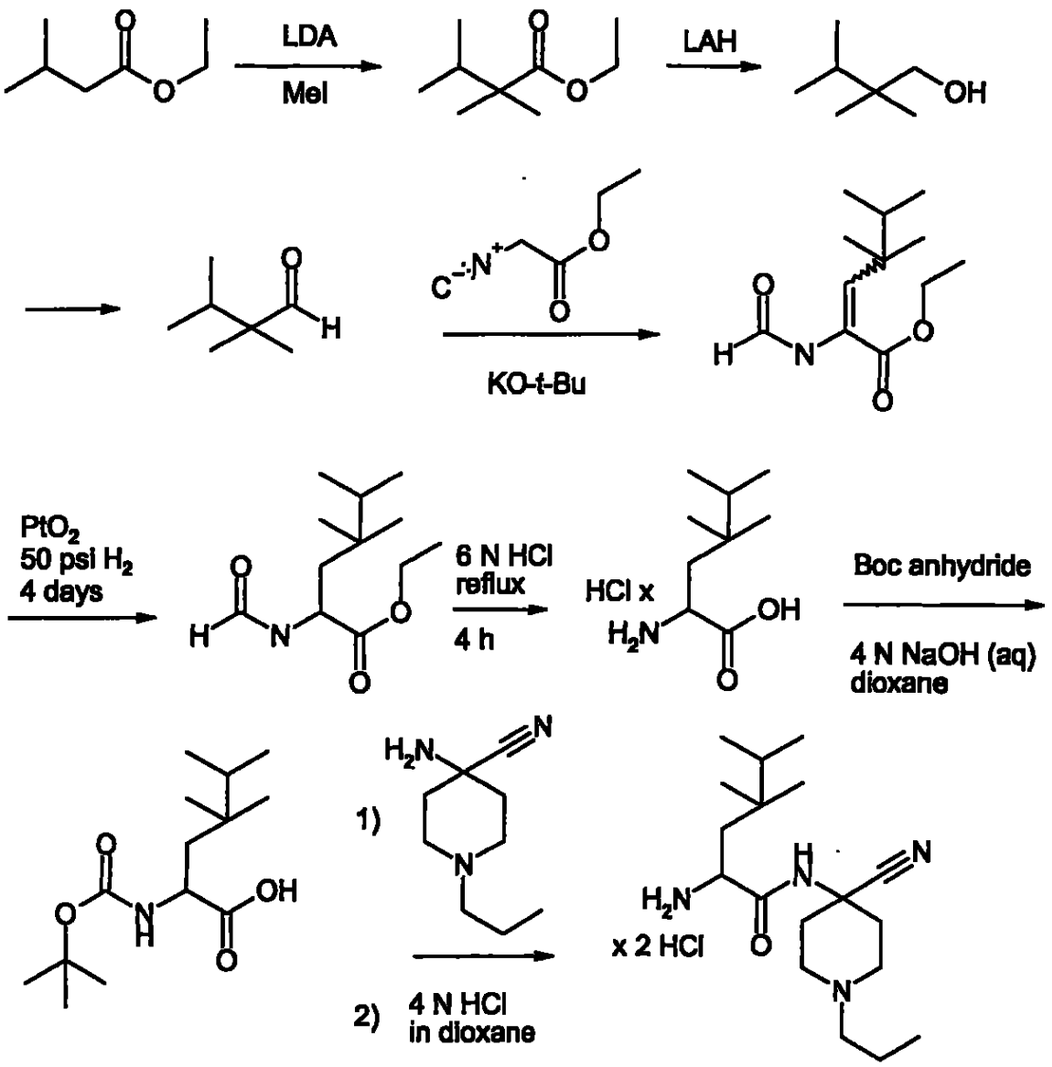
The thiourea (4.67 g, 10.0 mmol) was dissolved in 30 mL of THF. Copper sulfate on silica gel (4.00 g, 10.0 mmol) was added followed by 1 mL of triethylamine. This mixture was stirred at room temperature for 30 min. Morpholine (1.25 mL, 20 mmol) was added. The reaction mixture was heated under reflux for 2 h.. Another 4 g of copper sulfate on silica gel and 1.25 mL of morpholine were added. The reaction mixture was heated for an additional 2 h.. After cooling to room temperature, solids were removed by filtration and washed with acetonitrile. The filtrate was concentrated under reduced pressure and then purified by flash chromatography on silica gel, eluting with a mixture of ethyl ether, methylene chloride and MeOH (2:1:0.1) to give a yellow oil. This oil was crystalized from ethyl ether and hexane to give the title compound (1.81 g, 35%) as a white solid; M+1 = 519.

## EXAMPLE 40

2-Amino-4,4,5-trimethyl-hexanoic acid (4-cyano-1-propyl-piperidin-4-yl)-amide bis-hydrochloride.

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Lithium diisopropylamide (1.5 M solution in cyclohexane/THF/ethylbenzene) (113 mL, 169 mmol, 1.1 equiv) was syringed into a 1000 mL round-bottom flask under a blanket of Ar. Dry THF (150 mL) was added and the mixture was cooled to -78 °C with a dry-ice/acetone bath. 3-Methyl-butanoic acid ethyl ester (20 g, 23 mL, 154 mmol, 1.0 equiv) was added dropwise from a syringe over a 10 min period followed by stirring at -78 °C for 1 h. Methyl iodide (10.5 mL, 169 mmol, 1.1 equiv) was added dropwise from a syringe over a 10 min period and the creamy mixture was stirred for 1 h at -78 °C, resulting in a very thick mixture. The dry-ice bath was removed and replaced with an ice

bath at 0 °C. Another 150 mL of dry THF was added followed by another addition of LDA (113 mL, 169 mmol, 1.1 equiv). The resulting mixture was stirred for 10 min and then the flask was re-immersed in a dry-ice/acetone bath. Stirring was continued for another 50 min and then methyl iodide was added dropwise (10.5 mL, 169 mmol, 1.1 equiv) and the dry-ice/acetone bath was removed and the resulting mixture was stirred at ambient temperature for 14 h. The reaction mixture was quenched with 3 mL of conc. HCl and 2 N HCl was added until the pH was adjusted to <1. The mixture was further diluted with 150 mL water and 500 mL $Et_2O$. The layers were separated and the organic layer was washed with 1 x 100 mL 2 N HCl, 1 x 100 mL saturated $NaHCO_3$, and 1 x 200 mL brine. The organic layer was dried over $Na_2SO_4$ and then concentrated in vacuo to provide 2,2,3-trimethylbutanoic acid ethyl ester as an orange oil mixed with ethyl benzene (36.4 g of which 22.1 g was product by NMR). The mixture was used without further purification.

A 500 mL round-bottom-flask equipped with a stir bar was flushed with Ar and charged with 50 mL dry THF and a 1 M solution of LAH in $Et_2O$ (87.5 mL, 87.5 mmol, 0.625 equiv). The solution was cooled to 0 °C with an ice bath and the above ethyl ester (22.1 g, 140 mmol, 1.0 equiv) (approximately a 50% solution in ethylbenzene) was added dropwise at such a rate that the solution did not reflux (required 50 min). After addition of the ester, the reaction was stirred at 0 °C for 2 h and then at ambient temperature for 14 h. The reaction solution was re-cooled to 0 °C and carefully quenched by addition of EtOAc. 1 N NaOH was added until a granular precipitate formed (7.5 mL). The mixture was filtered on a pad of diatomaceous earth which was then washed 3 x 100 mL $Et_2O$. The organics were combined and dried over $Na_2SO_4$. The solution was decanted and concentrated in vacuo to yield 2,2,3-trimethyl-butanol 2,2,3-trimethyl-butanol as a nearly colorless oil (11.7 g of alcohol in 15.4 g of a mix with ethylbenzene). The crude product was used without further purification.

A 1000 mL round-bottom-flask was equipped with a stir bar, flushed with Ar and charged with 300 mL dry $CH_2Cl_2$ and oxalyl chloride (13.2 mL, 151 mmol, 1.5 equiv). The solution was cooled to -78 °C with a dry-ice/acetone bath. Dry DMSO (21.5 mL,

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302 mmol, 3.0 equiv) was added dropwise over a 30 min period (vigorous gas evolution). The above alcohol (11.7 g, 100 mmol, 1.0 equiv) was added (with residual ethylbenzene) over a 10 min period. The resulting solution was stirred for 90 min. Triethylamine (56 mL, 403 mmol, 4.0 equiv) was added over 5 min and the cold-bath was removed. The resulting creamy white mixture was stirred at room temperature over 1.5 h. The reaction mixture was carefully diluted with 200 mL water (more gas evolution). Layers were separated and the organic phase was washed with 1 x 100 mL 2 N HCl and 1 x 100 mL brine. The organic layer was dried over $Na_2SO_4$, decanted and concentrated *in vacuo*. The crude aldehyde was distilled fractionally through a 4 inch Vigoreux column at 57-67 °C at 15 mm Hg to provide the 2,2,3-trimethyl-butanal (9.1 g) as a colorless oil.

A clean and dry 250 mL round-bottom flask was equipped with a stir bar and flushed with Ar. Dry THF was added (40 mL) followed by addition of a 1.0 M solution of KO-*t*-Bu (32.2 mL, 32.2 mmol, 1.05 equiv). The solution was cooled to -78 °C in a dry-ice/acetone bath. Ethyl isocyanoacetate (3.35 mL, 30.7 mmol, 1.0 equiv) was added dropwise over a 10 min period. The resulting mixture was stirred an additional 5 min followed by addition, via syringe, of 2,2,3-trimethyl-butanal (3.5 g, 30.7 mmol, 1.0 equiv). The cold-bath was removed and resulting mixture was stirred at room temperature for 1 h. The reaction mixture was diluted by addition of a mix of 125 mL $Et_2O$, 20 g ice, 2 mL AcOH. After the ice melted, 50 mL of water was added and the layers were mixed and separated. The organic layer was washed with 1 x 50 mL sat. $NaHCO_3$ and dried over $Na_2SO_4$. The organic layer was decanted and concentrated. The crude enamide was purified by flash chromatography on silica gel using $CH_2Cl_2$ to 4% MeOH in $CH_2Cl_2$ to provide 2-formylamino-4,4,5-trimethyl-hex-2-enoic acid ethyl ester as a thick oil (4.54 g); MS: 228 (M+1).

The above ethyl ester (4.54 g, 20 mmol, 1.0 equiv) was dissolved in 35 mL of MeOH in a Parr bottle followed by addition of $PtO_2$ (1 g, 4.4 mmol, 0.22 equiv). The mixture was shaken on a Parr hydrogenation apparatus for 4 days at which time MS showed consumption of the starting material; MS: 230 (M+1), 216 (M+1 of methyl ester). The

liquid was carefully decanted and the Pt was washed 3 x 20 mL MeOH followed each time by decantation, being careful not to allow the Pt to dry (if allowed to dry, the Pt may ignite). The MeOH solutions were combined and concentrated to a thick oil that was suspended in 25 mL of 6 N HCl and the mixture was refluxed for 4 h during which time 5 mL of conc. HCl was added at the end of each of the first 3 h.. The mixture was cooled and the water and excess HCl were removed on a rotovap at a bath temperature of 70 °C. After about 50% concentration, a flaky crystalline solid formed. The mixture was cooled to 0 °C and the precipitate was collected by filtration. The filtrate was again concentrated by about 50% and cooled again to 0 °C to provide a second crop of crystals. The crystals were combined and dried under high vacuum to provide 2-amino-4,4,5-trimethyl-hexanoic acid hydrochloride as an off-white crystalline solid (2.32 g); MS: 174 (M-Cl+1).

The above amino acid salt (2.32 g, 11.1 mmol, 1.0 equiv) was dissolved in 100 mL of 50/50 dioxane/4 N NaOH. The solution was cooled to 0 °C and Boc anhydride (3.6 g, 16.6 mmol, 1.5 equiv) was added. The cold-bath was removed and the reaction stirred at ambient temperature for 16 h. The pH was carefully adjusted to 2 with conc. HCl, and the product was extracted with 3 x 100 mL $CH_2Cl_2$. The organic layers were combined and dried over $Na_2SO_4$. The solution was decanted and concentrated using 100 mL of hexane as a chaser to provide a thick glass, which was triturated with 100 mL of hexane. After vigorous stirring for 4 h, a waxy solid resulted which was filtered and dried in air to provide 2-*tert*-butoxycarbonylamino-4,4,5-trimethyl-hexanoic acid (1.42 g).

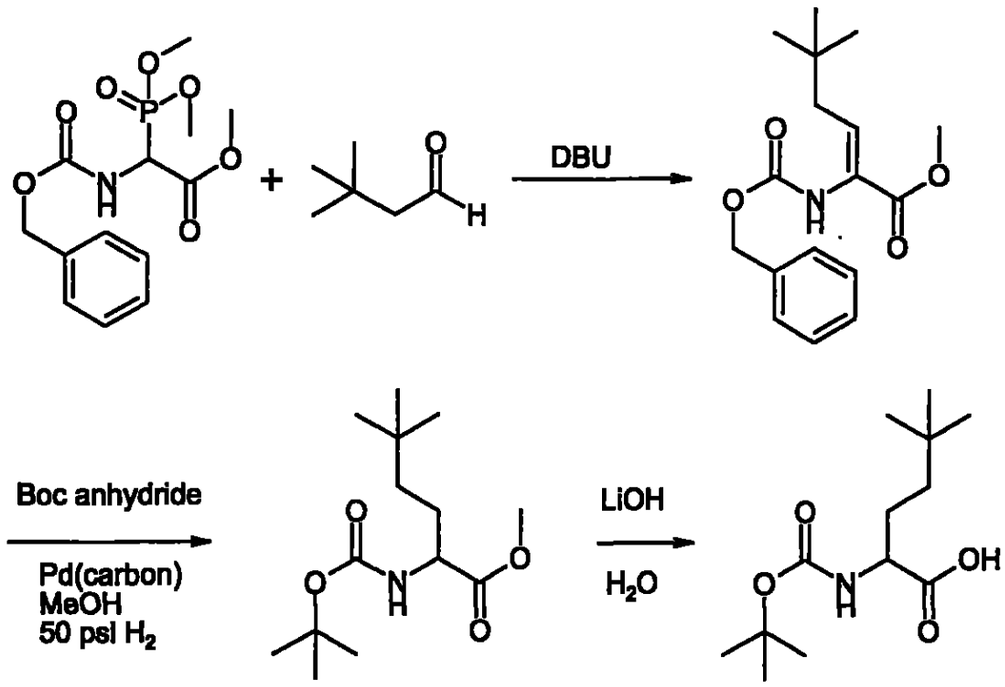
The above carboxylic acid (0.400 g, 1.46 mmol, 1.0 equiv) was dissolved in 15 mL of THF and cooled to 0 °C. *N*-Methylmorpholine (0.338 mL, 3.07 mmol, 2.1 equiv) was added followed by dropwise addition, over 1 min, of isobutylchloroformate (0.19 mL, 1.0 equiv). A white precipitate immediately formed. The mixture was stirred for 30 min at which time a solution of 4-amino-4-cyano-1-propyl-piperidine (0.257 g, 1.54 mmol, 1.05 equiv) in 5 mL of THF was added. The resulting mixture was stirred for 16 h at room temperature. The volatiles were removed on a rotovap and the resulting paste was triturated with 100 mL water with vigorous stirring to give a fluffy white solid which was

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collected by filtration. The solid was washed with 100 mL of water and dried under vacuum to yield the desired product as an off-white powder (0.521 g); MS: 423 (M+1). The Boc protecting group was removed by treatment of the solid under Ar with 20 mL of 4N HCl in dioxane for 1 h. The resulting paste was diluted with 40 mL of $Et_2O$ and the solid was filtered under Ar. The resulting paste was washed 1 x 25 mL $Et_2O$ and dried *in vacuo* to yield the title compound as the dihydrochloride salt; MS: 323 (M+1).

EXAMPLE 41

2-*tert*-Butoxycarbonylamino-5,5-dimethyl-hexanoic acid




*N*-(Benzyloxycarbonyl)-α-phosphonoglycine trimethyl ester (2 g, 6.0 mmol, 1.0 equiv) was dissolved in dry THF (20 mL). *tert*-Butylacetaldehyde (0.758 mL, 6.0 mmol, 1.0 equiv) and DBU (0.903 mL, 6.0 mmol, 1.0 equiv) were added and the reaction mixture was stirred for 16 h. The solution was diluted with 100 mL of $CH_2Cl_2$ and washed with 1 x 50 mL water, and 1 x 50 mL brine. The organic layer was dried over $Na_2SO_4$, decanted and concentrated *in vacuo* to provide 2-benzyloxycarbonylamino-5,5-dimethyl-hex-2-

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enoic acid methyl ester as a thick oil (1.73 g, 94%) which was used without further purification; MS: 306 (M+1).

The above ester (1.73 g, 5.67 mmol, 1.0 equiv) was dissolved in a Parr bottle with Boc anhydride (1.36 g, 6.23 mmol, 1.0 equiv) and MeOH (35 mL). Pd on carbon (Degussa type) (0.5g) was added. The mixture was shaken under 50 psi $H_2$ for16 h. The mixture was filtered on diatomaceous earth followed by washing of the diatomaceous earth with 3 x 50 mL MeOH. The organics were combined and concentrated to provide 2-*tert*-butoxycarbonylamino-5,5-dimethyl-hexanoic acid methyl ester as a very thick oil which was used without further purification.

The above ester (1.31 g, 4.79 mmol, 1.0 equiv) was dissolved in 50 mL of MeOH. 1 N LiOH (50 mL) was added and the mixture was stirred 16 h. Concentrated HCl was added carefully until the pH approached 2 at which time a bright white solid precipitated. The solid was collected by filtration and washed 2 x 20 mL water and dried under vacuum to provide the title compound (1.05 g, 85%); MS: 258 (M-1).

## METHODS OF THERAPEUTIC USE

The compounds of the invention are useful in inhibiting the activity of cathepsin S, K, F, L and B. In doing so, these compounds are useful in blocking disease processes mediated by these cysteine proteases.

Compounds of this invention effectively block degradation of the invariant chain to CLIP by cathepsin S, and thus inhibit antigen presentation and antigen-specific immune responses. Control of antigen specific immune responses is an attractive means for treating autoimmune diseases and other undesirable T-cell mediated immune responses. Thus, there is provided methods of treatment using the compounds of this invention for such conditions. These encompass autoimmune diseases and other diseases involving

inappropriate antigen specific immune responses including, but not limited to, rheumatoid arthritis, systemic lupus erythematosus, Crohn's disease, ulcerative colitis, multiple sclerosis, Guillain-Barre syndrome, psoriasis, Grave's disease, myasthenia gravis, scleroderma, glomerulonephritis, dermatitis including contact and atopic dermatitis, insulin-dependent diabetes mellitus and asthma including allergic asthma. The compounds of the invention can also be used to treat other disorders associated with extracellular proteolysis such as Alzheimer's disease and atherosclerosis. The compounds of the invention can also be used to treat other disorders associated with inappropriate autoimmune responses, T-cell mediated immune responses, or extracellular proteolysis mediated by cathepsin S, unrelated to those listed above or discussed in the Background of the Invention. Therefore, the invention also provides methods of modulating an autoimmune disease comprising administering to a patient in need of such treatment a pharmaceutically effect amount of a compound according to the invention.

Compounds of the invention also inhibit cathepsin K. In doing so, they may block inappropriate degradation of bone collagen and other bone matrix proteases. Thus, there is provided a method for treating diseases where these processes play a role such as osteoporosis. Inhibition of cathepsins F, L, and B are also within the scope of the invention due to similarity of the active sites in cysteine proteases as described above.

For therapeutic use, the compounds of the invention may be administered in any conventional dosage form in any conventional manner. Routes of administration include, but are not limited to, intravenously, intramuscularly, subcutaneously, intrasynovially, by infusion, sublingually, transdermally, orally, topically or by inhalation. The preferred modes of administration are oral and intravenous.

The compounds of this invention may be administered alone or in combination with adjuvants that enhance stability of the inhibitors, facilitate administration of pharmaceutical compositions containing them in certain embodiments, provide increased dissolution or dispersion, increase inhibitory activity, provide adjunct therapy, and the like, including other active ingredients. Advantageously, such combination therapies

utilize lower dosages of the conventional therapeutics, thus avoiding possible toxicity and adverse side effects incurred when those agents are used as monotherapies. Compounds of the invention may be physically combined with the conventional therapeutics or other adjuvants into a single pharmaceutical composition. Advantageously, the compounds may then be administered together in a single dosage form. In some embodiments, the pharmaceutical compositions comprising such combinations of compounds contain at least about 15%, but more preferably at least about 20%, of a compound of the invention (w/w) or a combination thereof. Alternatively, the compounds may be administered separately (either serially or in parallel). Separate dosing allows for greater flexibility in the dosing regime.

As mentioned above, dosage forms of the compounds of this invention include pharmaceutically acceptable carriers and adjuvants known to those of ordinary skill in the art. These carriers and adjuvants include, for example, ion exchangers, alumina, aluminum stearate, lecithin, serum proteins, buffer substances, water, salts or electrolytes and cellulose-based substances. Preferred dosage forms include, tablet, capsule, caplet, liquid, solution, suspension, emulsion, lozenges, syrup, reconstitutable powder, granule, suppository and transdermal patch. Methods for preparing such dosage forms are known (see, for example, H.C. Ansel and N.G. Popovish, *Pharmaceutical Dosage Forms and Drug Delivery Systems*, 5th ed., Lea and Febiger (1990)). Dosage levels and requirements are well-recognized in the art and may be selected by those of ordinary skill in the art from available methods and techniques suitable for a particular patient. In some embodiments, dosage levels range from about 10-1000 mg/dose for a 70 kg patient. Although one dose per day may be sufficient, up to 5 doses per day may be given. For oral doses, up to 2000 mg/day may be required. As the skilled artisan will appreciate, lower or higher doses may be required depending on particular factors. For instance, specific dosage and treatment regimens will depend on factors such as the patient's general health profile, the severity and course of the patient's disorder or disposition thereto, and the judgment of the treating physician.

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## ASSESSMENT OF BIOLOGICAL PROPERTIES

Expression and Purification of recombinant human Cathepsin S

Cloning of human cathepsin S:
U937 RNA was subjected to reverse transcriptase / polymerase chain reaction with primer A (5'cacaatgaaacggctggtttg 3') and primer B (5'ctagatttctgggtaagaggg 3') designed to specifically amplify the cathepsin S cDNA. The resulting 900 bp DNA fragment was subcloned into pGEM-T (Promega) and sequenced to confirm its identity. This construct was used for all subsequent manipulations. This procedure is typical for cloning of known genes and is established in its field.

Human Pre-Pro-Cat S was removed from pGem-T vector (Promega, 2800 Woods Hollow Rd, Madison, WI 53711) by digestion with restriction enzyme SacII, followed by treatment with T4 DNA polymerase to generate a blunt end, and a second restriction enzyme digest with SalI. It was subcloned into pFastBac1 donor plasmid (GibcoBRL, 8717 Grovemont Cr., Gaithersburg, MD 20884) which had been cut with restriction enzyme BamH1 and blunt-ended and then cut with restriction enzyme SalI. The ligation mixture was used to transform DH5a competent cells (GibcoBRL) and plated on LB plates containing 100ug/ml ampicillin. Colonies were grown in overnight cultures of LB media containing 50ug/ml Ampicillin, plasmid DNA isolated and correct insert confirmed by restriction enzyme digestion. Recombinant pFastBac donor plasmid was transformed into DH10Bac competent cells (GibcoBRL). Large white colonies were picked from LB plates containing 50ug/ml kanamycin, 7ug/ml gentamicin, 10ug/ml tetracycline, 100ug/ml Bluo-gal, and 40ug/ml IPTG. DNA was isolated and used to transfect Sf9 insect cells using CellFECTIN reagent (GibcoBRL). Cells and supernatant were harvested after 72 hours. Viral supernatant was passaged twice and presence of Cat S confirmed by PCR of the supernatant.

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SF9 cells were infected with recombinant baculovirus at a MOI of 5 for 48-72 hrs. Cell pellet was lysed and incubated in buffer at pH 4.5 at 37 for 2 hours to activate Cat S from pro-form to active mature form (Bromme, D & McGrath, M., Protein Science, 1996, 5:789-791.) Presence of Cat S was confirmed by SDS-PAGE and Western blot using rabbit anti-human proCat S.

Inhibition of Cathepsin S

Human recombinant cathepsin S expressed in Baculovirus is used at a final concentration of 10 nM in buffer. Buffer is 50 mM Na acetate, pH 6.5, 2.5 mM EDTA, 2.5 mM TCEP. Enzyme is incubated with either compound or DMSO for 10 min at 37 $^{0}$C. Substrate 7-amino-4-methylcoumarin, CBZ-L-valyl-L-valyl-L-arginineamide (custom synthesis by Molecular Probes) is diluted to 20 uM in water (final concentration of 5 M), added to assay and incubated for additional 10 minutes at 37 $^{0}$C. Compound activity is measured by diminished fluorescence compared to DMSO control when read at 360 nm excitation and 460 nm emission.

Examples listed above were evaluated for inhibition of cathepsin S in the above assay. All had $IC_{50}$ values of 100 micromolar or below.

Inhibition of Cathepsin K, F, L and B:

Inhibition of these enzymes by particular compounds of the invention may be determined without undue experimentation by using art recognized methods as provided hereinbelow each of which is incorporated herein by reference:

Cathepsin B, and L assays are to be found in the following references:

1. Methods in Enzymology, Vol.244, Proteolytic Enzymes: Serine and Cysteine Peptidases, Alan J. Barrett, ed.

Cathepsin K assay is to be found in the following reference:

2. Bromme, D., Okamoto, K., Wang, B. B., and Biroc, S. (1996) *J. Biol. Chem.* 271, 2126-2132.

Cathepsin F assays are to be found in the following references:

3. Wang, B., Shi, G.P., Yao, P.M., Li, Z., Chapman, H.A., and Bromme, D. (1998) *J. Biol. Chem.* 273, 32000-32008.

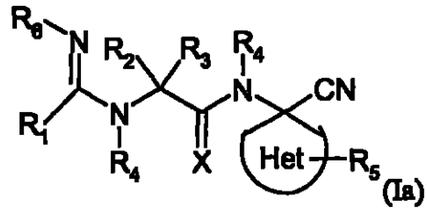
4. Santamaria, I., Velasco, G., Pendas, A.M., Paz, A., and Lopez-Otin, C (1999) J. *Biol. Chem.* 274, 13800-13809.

Preferred compounds to be evaluated for inhibition of Cathepsin K, F, L and B in the above assays desirably have $IC_{50}$ values of 100 micromolar or below.

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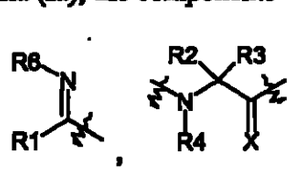
**What is claimed is:**

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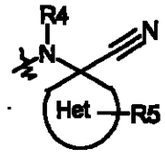


(Ia)

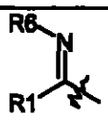
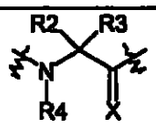
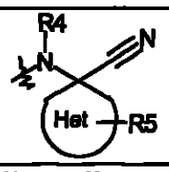
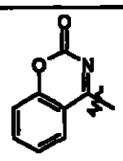
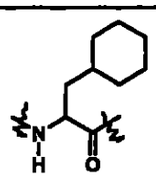
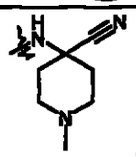
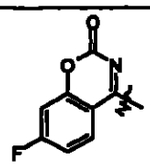
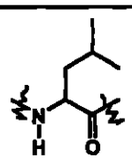
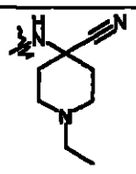
wherein for the Formula (Ia), the components

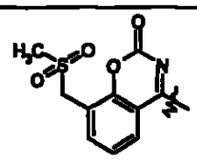
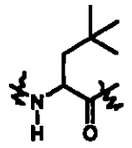
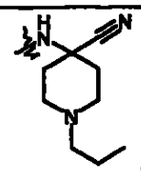
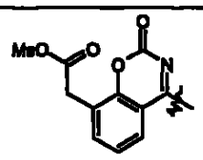
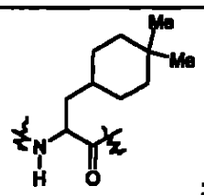
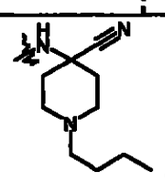
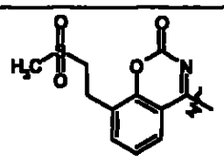
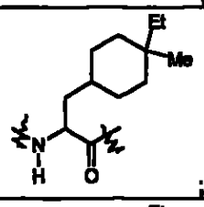
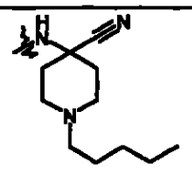
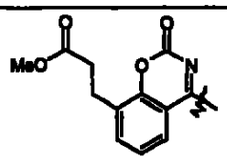
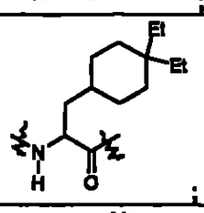
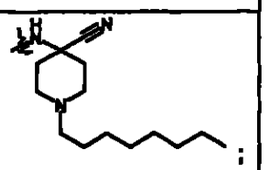
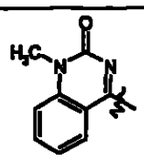
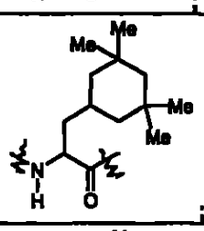
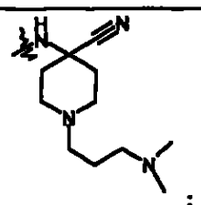
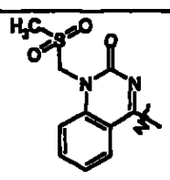
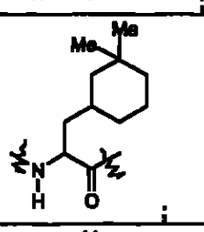
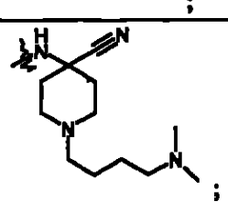
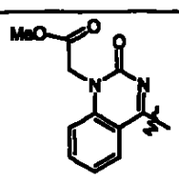
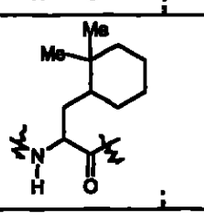
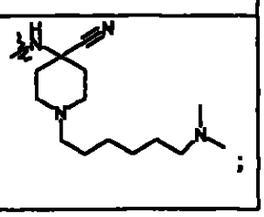


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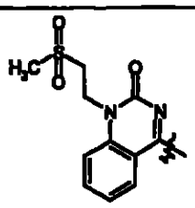
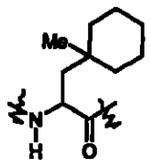
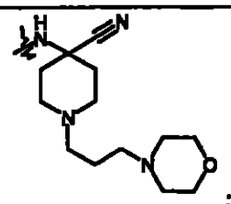
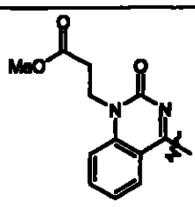
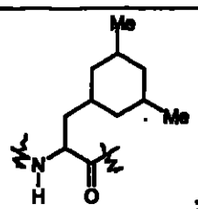
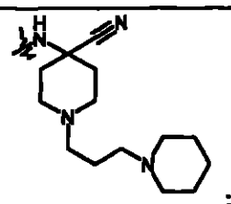
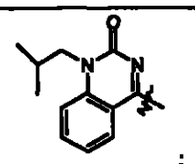
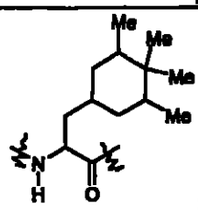
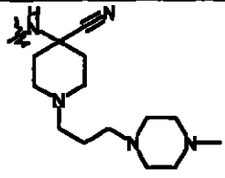
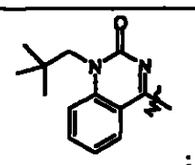
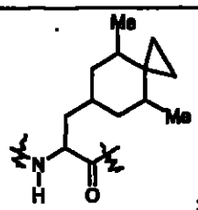
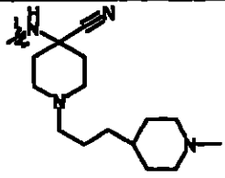
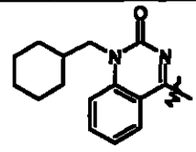
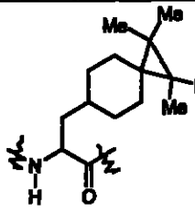
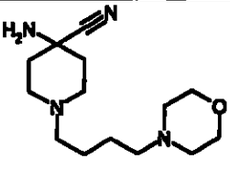
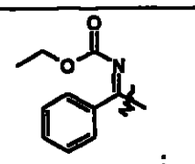
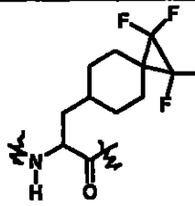
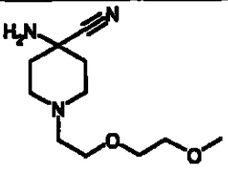
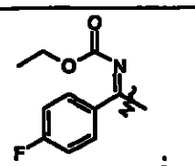
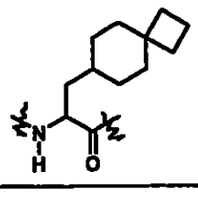
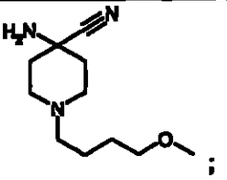


are chosen from any combination of A, B and C as follows:

| | | | | | |
|---|---|---|---|---|---|
| A |  | B |  | C |  |
| A1 |  ; | B1 |  ; | C1 |  ; |
| A2 |  ; | B2 |  ; | C2 |  ; |

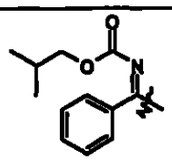
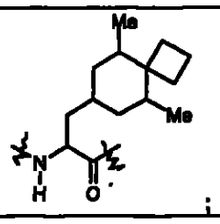
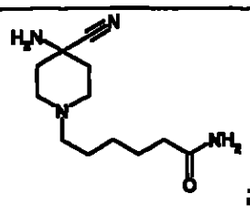
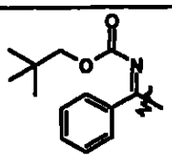
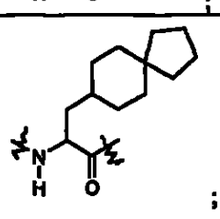
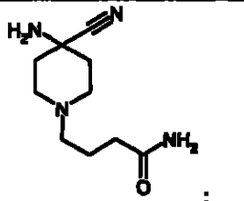
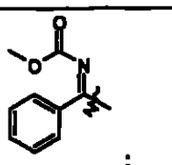
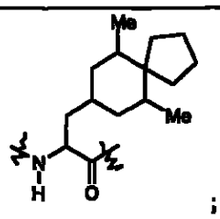
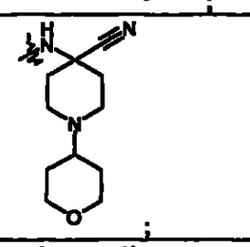
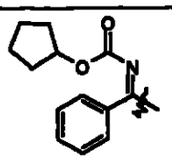
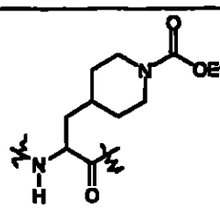
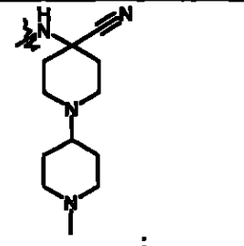
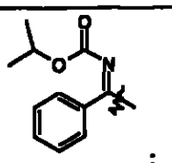
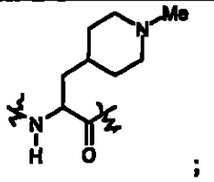
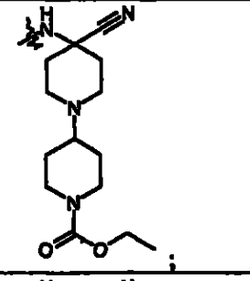
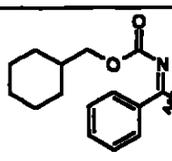
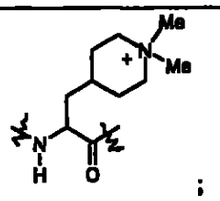
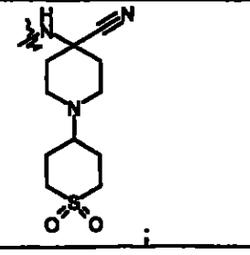
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|---|---|---|---|---|---|
| A3 |  ; | B3 |  ; | C3 |  ; |
| A4 |  ; | B4 |  ; | C4 |  ; |
| A5 |  ; | B5 |  ; | C5 |  ; |
| A6 |  ; | B6 |  ; | C6 |  ; |
| A7 |  ; | B7 |  ; | C7 |  ; |
| A8 |  ; | B8 |  ; | C8 |  ; |
| A9 |  ; | B9 |  ; | C9 |  ; |

311
312

| | | | | | |
|---|---|---|---|---|---|
| A10 |  ; | B10 |  ; | C10 |  ; |
| A11 |  ; | B11 |  ; | C11 |  ; |
| A12 |  ; | B12 |  ; | C12 |  ; |
| A13 |  ; | B13 |  ; | C13 |  ; |
| A14 |  ; | B14 |  ; | C14 |  ; |
| A15 |  ; | B15 |  ; | C15 |  ; |
| A16 |  ; | B16 |  ; | C16 |  ; |

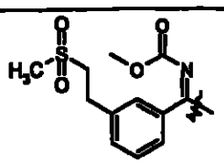
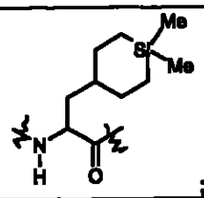
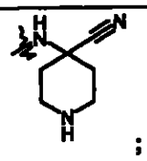
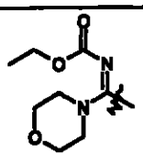
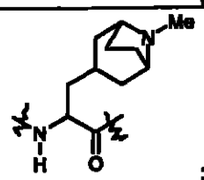
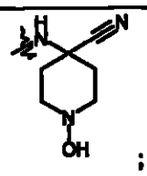
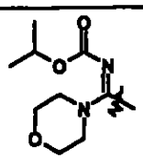
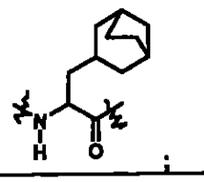
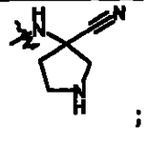
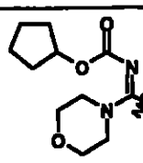
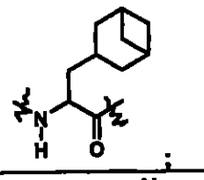
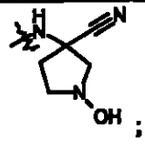
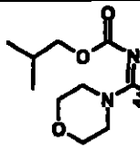
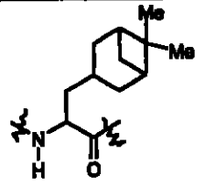
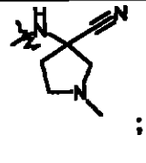
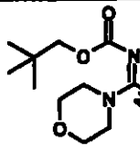
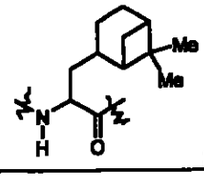
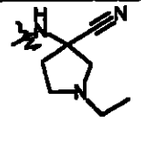
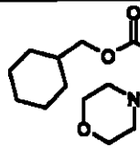
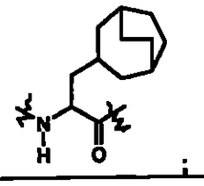
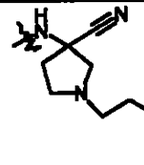
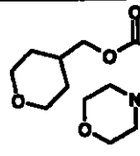
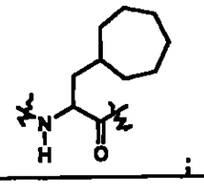
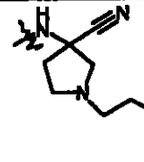
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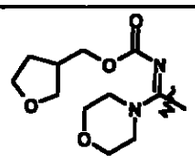
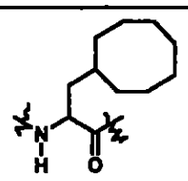
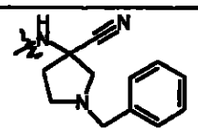
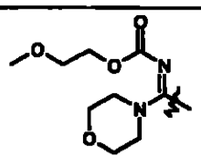
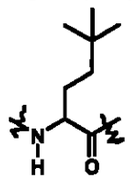
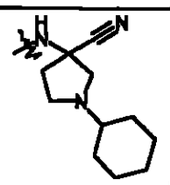
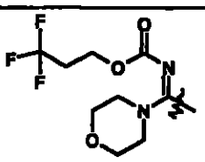
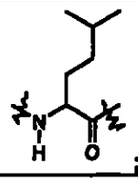
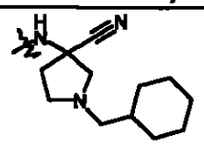
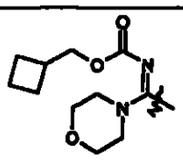
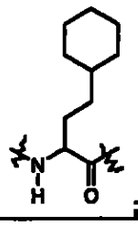
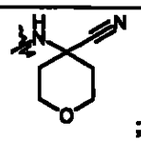
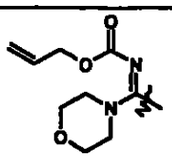
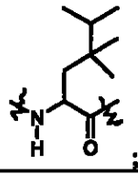
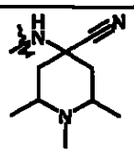
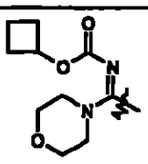
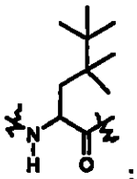
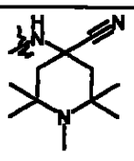
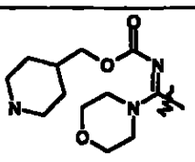
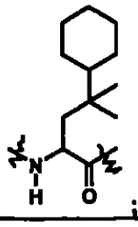
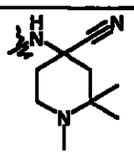
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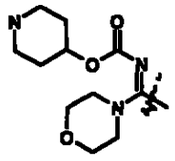
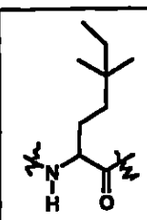
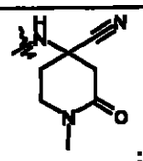
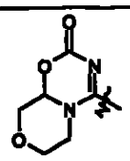
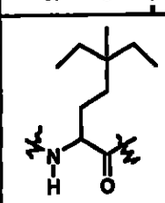
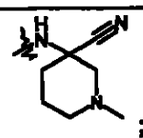
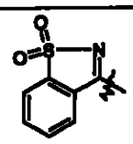
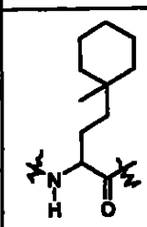
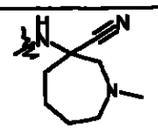
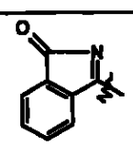
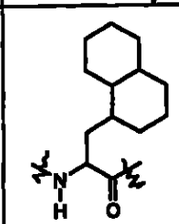
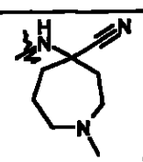
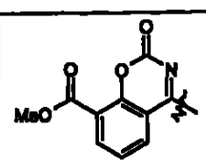
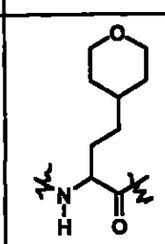
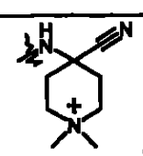
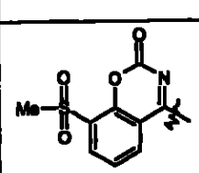
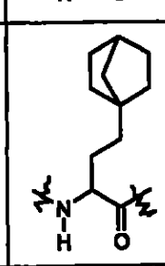
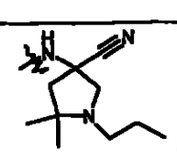
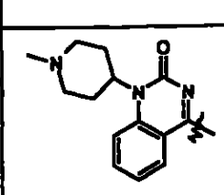
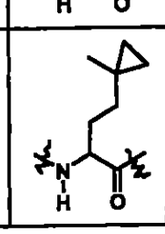
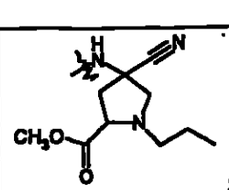
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| A26 |  ; | B26 |  ; | C26 |  ; |
| A27 |  ; | B27 |  ; | C27 |  ; |
| A28 |  ; | B28 |  ; | C28 |  ; |
| A29 |  ; | B29 |  ; | C29 |  ; |
| A30 |  ; | B30 |  ; | C30 |  ; |

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| A33 |  ; | B33 |  ; | C33 |  ; |
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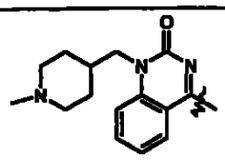
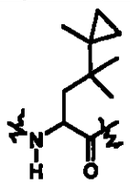
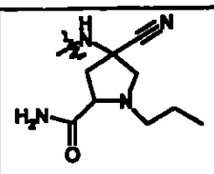
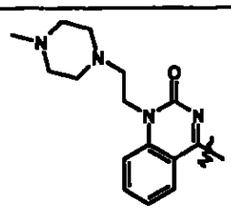
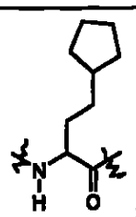
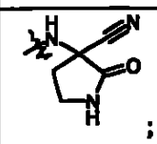
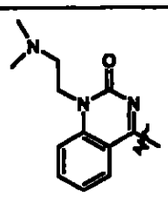
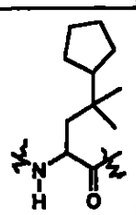
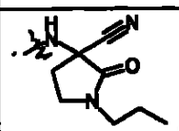
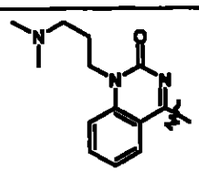
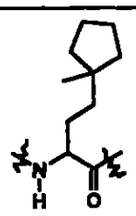
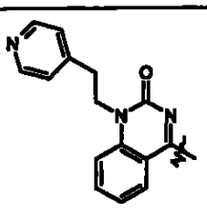
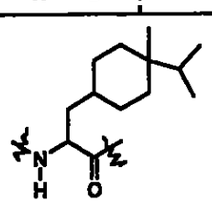
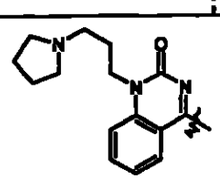
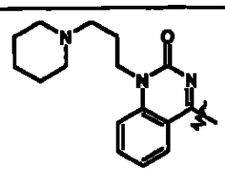
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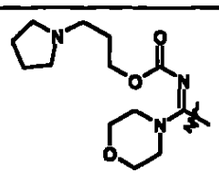
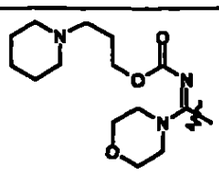
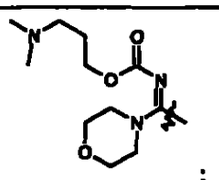
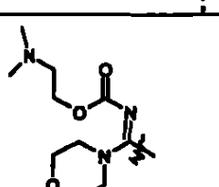
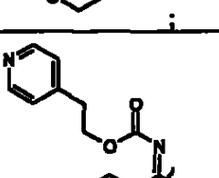
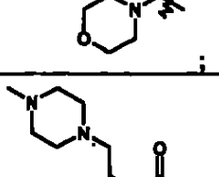
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| | | | | | |
|---|---|---|---|---|---|
| A38 |  ; | B38 |  ; | C38 |  ; |
| A39 |  ; | B39 |  ; | C39 |  ; |
| A40 |  ; | B40 |  ; | C40 |  ; |
| A41 |  ; | B41 |  ; | C41 |  ; |
| A42 |  ; | B42 |  ; | C42 |  ; |
| A43 |  ; | B43 |  ; | C43 |  ; |
| A44 |  ; | B44 |  ; | C44 |  ; |

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| | | | | | |
|---|---|---|---|---|---|
| A45 |  ; | B45 |  ; | C45 |  ; |
| A46 |  ; | B46 |  ; | C46 |  ; |
| A47 |  ; | B47 |  ; | C47 |  ; |
| A48 |  ; | B48 |  ; | C48 |  ; |
| A49 |  ; | B49 |  ; | | |
| A50 |  ; | | | | |
| A51 |  ; | | | | |

| | | | | | |
|---|---|---|---|---|---|
| A52 |  | | | | |
| A53 |  | | | | |
| A54 |  | | | | |
| A55 |  | | | | |
| A56 |  | | | | |
| A57 |  | | | | |

and the pharmaceutically acceptable derivatives thereof.

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2. A compound chosen from:

{[1-(3-Cyano-1-isobutyl-piperdin-3-yl carbamoyl)-3,3-dimethyl-butylamino]-morpholin-4-yl-methylene}-carbamic acid ethyl ester;

N-(2-Cyano-octahydro-quinolizin-2-yl)-3-cyclohexyl-2-(1,1-dioxo-1H-1λ-benzo-3-ylamino)-propionamide;

{[1-3-Cyano-1-methyl-piperidin-3-ylcarbamoyl)-3,3-dimethyl-butylamino]-morpholin-4-yl-methylene}-carbamic acid ethyl ester;

{[1-(2-Cyano-octahydro-quinolizin-2-ylcarbamoyl)-3,3-dimethyl-butylamino]-morpholin-4-yl-methylene}-carbamic acid ethyl ester;

{[1-(4-Cyano-1-propyl-piperidin-4-ylcarbamoyl)-3-methyl-butylamino]-morpholin-4-yl-methylene}-carbamic acid ethyl ester;

{[1-(4-Cyano-1-cyclohexyl-piperidin-4-ylcarbamoyl)-2-cyclohexyl-ethylamino]-morpholin-4-yl-methylene}-carbamic acid ethyl ester;

{[1-(4-Cyano-1-methyl-piperidin-4-ylcarbamoyl)-2-cyclohexyl-ethylamino]-morpholin-4-yl-methylene}-carbamic acid cyclohexylmethyl ester;

{[-1-(4-Cyano-1-methyl-piperidin-4-ylcarbamoyl)-2-cyclohexyl-ethylamino]-morpholin-4-yl-methylene}-carbamic acid cyclobutyl ester;

{[1-(4-Cyano-1-methyl-piperidin-4-ylcarbamoyl)-2-cyclohexyl-ethylamino]-morpholin-4-yl-methylene}-carbamic acid allyl ester;

N-(4-Cyano-1-propyl-piperidin-4-yl)-4-cyclohexyl-2-(2-oxo-2,3-dihydro-benzo[e][1,3]oxazin-4-ylideneamino)-butyramide;

{[1-(4-Cyano-1-propyl-piperidin-4-ylcarbamoyl)-3-cyclohexyl-propylamino]-morpholin-4-yl-methylene}-carbamic acid ester;

{[ 1-(4-Cyano-1-methyl-piperidin-4-ylcarbamoyl)-2-cyclohexyl-ethylamino]-morpholin-4-yl-methylene}-carbamic acid tetrahydro-furan-3ylmethyl ester;

{[1-(4-Cyano-1-methy-piperidin-4-ylcarbamoyl)-2-cyclohexyl-ethyl amino]-morpholin-4-yl-methylene}-carbamic acid tetrahydro-furan-2-ylmethyl ester;

*N*-(4-Cyano-1-methyl-piperidin-4-yl)-3-cyclohexyl-2-(5,6-difluoro-3-oxo-2,3-dihydro-isoindol-1-ylideneamino)-propionamide;

2-(5,6-Difluoro-3-oxo-2,3-dihydro-isoindol-1-ylideneamino)-4,4-dimethyl-pentanoic acid (4-cyano-1-propyl-piperidin-4-yl)-amide;

2-(6-Fluoro-3-oxo-2,3-dihydro-isoindol-1-ylideneamino)-4,4-dimethyl-pentanoic acid (4-cyano-1-propyl-piperidin-4-yl)-amide;

*N*-(4-Cyano-1-methyl-piperidin-4-yl)-3-cyclohexyl-2-(6-fluoro-3-oxo-2,3-dihydro-isoindol-1-ylideneamino)-propionamide;

{[1-(4-Cyano-1-propyl-piperidin-4-ylcarbamoyl)-3,3-dimethyl-butylimino]-morpholin-4-yl-methyl}-carbamic acid methyl ester;

{[1-(4-Cyano-1-methyl-piperidin-4-ylcarbamoyl)-2-cyclohexyl-ethylimino]-morpholin-4-yl-methyl}-carbamic acid methyl ester;

{[1-(4-Cyano-1-methyl-piperidin-4-ylcarbamoyl)-2-cyclohexyl-ethylimino]-morpholin-4-yl-methyl}-carbamic acid 2,2-dimethyl-propyl ester;

{[1-(4-Cyano-1-methyl-piperidin-4-ylcarbamoyl)-3,3-dimethyl-butylimino]-morpholin-4-yl-methyl}-carbamic acid methyl ester;

{[1-(4-Cyano-1-methyl-piperidin-4-ylcarbamoyl)-2-cyclohexyl-ethylimino]-morpholin-4-yl-methyl}-carbamic acid benzyl ester;

{[1-(4-Cyano-1-methyl-piperidin-4-ylcarbamoyl)-2-cyclohexyl-ethylimino]-morpholin-4-yl-methyl}-carbamic acid isobutyl ester;

{[1-(4-Cyano-1-methyl-piperidin-4-ylcarbamoyl)-2-cyclohexyl-ethylimino]-morpholin-4-yl-methyl}-carbamic acid propyl ester;

{[1-(4-Cyano-1-methyl-piperidin-4-ylcarbamoyl)-2-cyclohexyl-ethylimino]-morpholin-4-yl-methyl}-carbamic acid hexyl ester;

{[1-(4-Cyano-1-methyl-piperidin-4-ylcarbamoyl)-2-cyclohexyl-ethylimino]-morpholin-4-yl-methyl}-carbamic acid cyclobutylmethyl ester;

{[1-(4-Cyano-1-methyl-piperidin-4-ylcarbamoyl)-2-cyclohexyl-ethylimino]-morpholin-4-yl-methyl}-carbamic acid 3,3,3-trifluoro-propyl ester;

{[1-(4-Cyano-1-methyl-piperidin-4-ylcarbamoyl)-2-cyclohexyl-ethylimino]-morpholin-4-yl-methyl}-carbamic acid 2-methoxy-ethyl ester;

5,5-Dimethyl-2-(2-oxo-2,3-dihydro-benzo[*e*][1,3]oxazin-4-ylideneamino)-hexanoic acid (4-cyano-1-propyl-piperidin-4-yl)-amide;

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{[1-(4-Cyano-1-propyl-piperidin-4-ylcarbamoyl)-4,4-dimethyl-pentylimino]-morpholin-4-yl-methyl}-carbamic acid ethyl ester;

{[1-(4-Cyano-1-methyl-piperidin-4-ylcarbamoyl)-2-cyclohexyl-ethylimino]-morpholin-4-yl-methyl}-carbamic acid 2-isopropoxy-ethyl ester;

{[1-(4-Cyano-1-methyl-piperidin-4-ylcarbamoyl)-2-cyclohexyl-ethylimino]-morpholin-4-yl-methyl}-carbamic acid 3-methoxy-butyl ester;

{[1-(4-Cyano-1-methyl-piperidin-4-ylcarbamoyl)-2-cyclohexyl-ethylimino]-morpholin-4-yl-methyl}-carbamic acid 2-isobutoxy-ethyl ester;

{[1-(4-Cyano-1-propyl-piperidin-4-ylcarbamoyl)-3,3-dimethyl-butylimino]-morpholin-4-yl-methyl}-carbamic acid 2-methoxy-ethyl ester;

N-(4-Cyano-1-methyl-piperidin-4-yl)-4-cyclohexyl-2-(6-methoxy-2-oxo-2,3-dihydro-benzo[e][1,3]oxazin-4-ylideneamino)-butyramide;

N-(4-Cyano-1-methyl-piperidin-4-yl)-4-cyclohexyl-2-(6-fluoro-2-oxo-2,3-dihydro-benzo[e][1,3]oxazin-4-ylideneamino)-butyramide;

N-(4-Cyano-1-methyl-piperidin-4-yl)-4-cyclohexyl-2-(7-fluoro-2-oxo-2,3-dihydro-benzo[e][1,3]oxazin-4-ylideneamino)-butyramide;

2-(7-Fluoro-2-oxo-2,3-dihydro-benzo[e][1,3]oxazin-4-yldeneamino)-5,5-dimethyl-hexanoic acid(4-cyano-1-propyl-piperidin-4-yl)-amide;

N-(4-Cyano-1-methyl-piperidin-4-yl)-4-cyclohexyl-2-(7-methoxy-2-oxo-2,3-dihydro-benzo[e][1,3]oxazin-4-ylideneamino)-butyramide;

2-(7-Methoxy-2-oxo-2,3-dihydro-benzo[e][1,3]oxazin-4-yldeneamino)-5,5-dimethyl-hexanoic acid(4-cyano-1-propyl-piperidin-4-yl)-amide;

{[1-(4-Cyano-1-propyl-piperidin-4-ylcarbamoyl)-5-methyl-hexylimino]-morpholin-4-yl-methyl}-carbamic acid ethyl ester;

2-[(*N*-Benzyl-morpholine-4-carboximidoyl)-amino]-*N*-(4-cyano-1-methyl-piperidin-4-yl)-3-cyclohexyl-propionamide;

*N*-(4-Cyano-1-methyl-piperidin-4-yl)-3-cyclohexyl-2-(2-oxo-2,3-dihydro-benzo[*e*][1,3]oxazin-4-ylideneamino)-propionamide;

{[1-(4-Cyano-1-methyl-piperidin-4-ylcarbamoyl)-2-cyclohexyl-ethylimino]-pyrrolidin-1-yl-methyl}-carbamic acid ethyl ester;

{[1-(4-Cyano-1-methyl-piperidin-4-ylcarbamoyl)-2-cyclohexyl-ethylimino]-piperidin-1-yl-methyl}-carbamic acid ethyl ester;

{Azepan-1-yl-[1-(4-cyano-1-methyl-piperidin-4-ylcarbamoyl)-2-cyclohexyl-ethylimino]-methyl}-carbamic acid ethyl ester;

{Azocan-1-yl-[1-(4-cyano-1-methyl-piperidin-4-ylcarbamoyl)-2-cyclohexyl-ethylimino]-methyl}-carbamic acid ethyl ester;

1-{[1-(4-Cyano-1-methyl-piperidin-4-ylcarbamoyl)-2-cyclohexyl-ethylimino]-ethoxycarbonylamino-methyl}-piperidine-4-carboxylic acid ethyl ester;

1-{[1-(4-Cyano-1-methyl-piperidin-4-ylcarbamoyl)-2-cyclohexyl-ethylimino]-ethoxycarbonylamino-methyl}-piperidine-3-carboxylic acid ethyl ester;

[[1-(4-Cyano-1-methyl-piperidin-4-ylcarbamoyl)-2-cyclohexyl-ethylimino]-(4-pyrrolidin-1-yl-piperidin-1-yl)-methyl]-carbamic acid ethyl ester;

{[1,4']Bipiperidinyl-1'-yl-[1-(4-cyano-1-methyl-piperidin-4-ylcarbamoyl)-2-cyclohexyl-ethylimino]-methyl}-carbamic acid ethyl ester;

[[1-(4-Cyano-1-methyl-piperidin-4-ylcarbamoyl)-2-cyclohexyl-ethylimino]-(4-phenyl-piperazin-1-yl)-methyl]-carbamic acid ethyl ester;

[[1-(4-Cyano-1-methyl-piperidin-4-ylcarbamoyl)-2-cyclohexyl-ethylimino]-(4-ethyl-piperazin-1-yl)-methyl]-carbamic acid ethyl ester;

{(4-Acetyl-piperazin-1-yl)-[1-(4-cyano-1-methyl-piperidin-4-ylcarbamoyl)-2-cyclohexyl-ethylimino]-methyl}-carbamic acid ethyl ester;

4-{[1-(4-Cyano-1-methyl-piperidin-4-ylcarbamoyl)-2-cyclohexyl-ethylimino]-ethoxycarbonylamino-methyl}-piperazine-1-carboxylic acid ethyl ester;

[[1-(4-Cyano-1-methyl-piperidin-4-ylcarbamoyl)-2-cyclohexyl-ethylimino]-(3,3,5-trimethyl-6-aza-bicyclo[3.2.1]oct-6-yl)-methyl]-carbamic acid ethyl ester;

{(3-Acetylamino-pyrrolidin-1-yl)-[1-(4-cyano-1-methyl-piperidin-4-ylcarbamoyl)-2-cyclohexyl-ethylimino]-methyl}-carbamic acid ethyl ester;

{(3-Acetylamino-pyrrolidin-1-yl)-[1-(4-cyano-1-methyl-piperidin-4-ylcarbamoyl)-2-cyclohexyl-ethylimino]-methyl}-carbamic acid ethyl ester;

{(3-Azapent-3-yl)-[1-(4-cyano-1-methyl-piperidin-4-ylcarbamoyl)-2-cyclohexyl-ethylimino]-methyl}-carbamic acid ethyl ester;

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{(1-Methoxy-3-azapent-3-yl)-[1-(4-cyano-1-methyl-piperidin-4-ylcarbamoyl)-2-cyclohexyl-ethylimino]-methyl}-carbamic acid ethyl ester;

[[1-(4-Cyano-1-methyl-piperidin-4-ylcarbamoyl)-2-cyclohexyl-ethylimino]-(3-oxo-piperazin-1-yl)-methyl]-carbamic acid ethyl ester;

{(1,5-Dimethoxy-3-azapent-3-yl)-[1-(4-cyano-1-methyl-piperidin-4-ylcarbamoyl)-2-cyclohexyl-ethylimino]-methyl}-carbamic acid ethyl ester;

4,4-Dimethyl-2-(2-oxo-2,3-dihydro-benzo[e][1,3]oxazin-4-ylideneamino)-pentanoic acid (4-cyano-1-propyl-piperidin-4-yl)-amide;

{(4-Carbamoyl-piperidin-1-yl)-[1-(4-cyano-1-methyl-piperidin-4-ylcarbamoyl)-2-cyclohexyl-ethylimino]-methyl}-carbamic acid ethyl ester;

[[1-(4-Cyano-1-methyl-piperidin-4-ylcarbamoyl)-2-cyclohexyl-ethylimino]-(2-methoxymethyl-morpholin-4-yl)-methyl]-carbamic acid ethyl ester;

(4-{[1-(4-Cyano-1-methyl-piperidin-4-ylcarbamoyl)-2-cyclohexyl-ethylimino]-ethoxycarbonylamino-methyl}-piperazin-1-yl)-acetic acid ethyl ester;

[[1-(4-Cyano-1-methyl-piperidin-4-ylcarbamoyl)-2-cyclohexyl-ethylimino]-(2,6-dimethyl-morpholin-4-yl)-methyl]-carbamic acid ethyl ester;

[[1-(4-Cyano-1-methyl-piperidin-4-ylcarbamoyl)-2-cyclohexyl-ethylimino]-(2,6-dimethyl-morpholin-4-yl)-methyl]-carbamic acid ethyl ester;

{[1-(4-Cyano-1-methyl-piperidin-4-ylcarbamoyl)-2-cyclohexyl-ethylimino]-thiomorpholin-4-yl-methyl}-carbamic acid ethyl ester;

4,4-Dimethyl-2-(6-methyl-2-oxo-2,3-dihydro-benzo[*e*][1,3]oxazin-4-ylideneamino)-pentanoic acid (4-cyano-1-propyl-piperidin-4-yl)-amide;

2-(6-Chloro-2-oxo-2,3-dihydro-benzo[*e*][1,3]oxazin-4-ylideneamino)-4,4-dimethyl-pentanoic acid (4-cyano-1-propyl-piperidin-4-yl)-amide;

4,4-Dimethyl-2-(2-oxo-2,3-dihydro-1*H*-quinazolin-4-ylideneamino)-pentanoic acid (4-cyano-1-propyl-piperidin-4-yl)-amide;

2-(7-Chloro-2-oxo-2,3-dihydro-benzo[*e*][1,3]oxazin-4-ylideneamino)-4,4-dimethyl-pentanoic acid (4-cyano-1-propyl-piperidin-4-yl)-amide;

5-Methyl-2-(2-oxo-2,3-dihydro-benzo[*e*][1,3]oxazin-4-ylideneamino)-hexanoic acid (4-cyano-1-propyl-piperidin-4-yl)-amide;

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4,4-Dimethyl-2-(1-methyl-2-oxo-1,2-dihydro-quinazolin-4-ylamino)-pentanoic acid (4-cyano-1-propyl-piperidin-4-yl)-amide;

3-*tert*-Butylsulfanyl-*N*-(4-cyano-1-propyl-piperidin-4-yl)-2-(2-oxo-2,3-dihydro-benzo[*e*][1,3]oxazin-4-ylideneamino)-propionamide;

{[2-*tert*-Butylsulfanyl-1-(4-cyano-1-propyl-piperidin-4-ylcarbamoyl)-ethylimino]-morpholin-4-yl-methyl}-carbamic acid ethyl ester;

3-Benzylsulfanyl-*N*-(4-cyano-1-propyl-piperidin-4-yl)-2-(2-oxo-2,3-dihydro-benzo[*e*][1,3]oxazin-4-ylideneamino)-propionamide;

{[2-Benzylsulfanyl-1-(4-cyano-1-propyl-piperidin-4-ylcarbamoyl)-ethylimino]-morpholin-4-yl-methyl}-carbamic acid ethyl ester;

*N*-(4-Cyano-1-propyl-piperidin-4-yl)-3-cyclooctyl-2-(2-oxo-2,3-dihydro-benzo[*e*][1,3]oxazin-4-ylideneamino)-propionamide;

*N*-(4-Cyano-1-propyl-piperidin-4-yl)-3-cycloheptyl-2-(2-oxo-2,3-dihydro-benzo[*e*][1,3]oxazin-4-ylideneamino)-propionamide;

{[1-(4-Cyano-1-propyl-piperidin-4-ylcarbamoyl)-2-cycloheptyl-ethylimino]-morpholin-4-yl-methyl}-carbamic acid ethyl ester;

{[1-(4-Cyano-1-propyl-piperidin-4-ylcarbamoyl)-2-cyclooctyl-ethylimino]-morpholin-4-yl-methyl}-carbamic acid ethyl ester;

{[1-(4-Cyano-piperidin-4-ylcarbamoyl)-2-cyclohexyl-ethylamino]-morpholin-4-yl-methylene}-carbamic acid isobutyl ester;

({1-[4-Cyano-1-(2-morpholin-4-yl-ethyl)-piperidin-4-ylcarbamoyl]-2-cyclohexyl-ethylamino}-morpholin-4-yl-methylene)-carbamic acid isobutyl ester;

({1-[1-2-Carbamoyl-ethyl)-4-cyano-piperidin-4-ylcarbamoyl]-2-cyclohexyl-ethylamino}-morpholin-4-yl-methylene)-carbamic acid isobutyl ester;

[(1-{4-Cyano-1-[2-(2-methoxyl-ethoxy)-ethyl]-piperidin-4-ylcarbamoyl}-2-cyclohexyl-ethylamino)-morpholin-4-yl-methylene]-carbamic acid isobutyl ester;

[(1-{4-Cyano-1-[3-(2-methoxyl-ethoxy)-propyl]-piperidin-4-ylcarbamoyl}-2-cyclohexyl-ethylamino)-morpholin-4-yl-methylene]-carbamic acid isobutyl ester;

{[2-tert-Butoxy-1-(4-cyano-1-propyl-piperidin-4-ylcarbamoly)-ethylamino]-morpholin-4-yl-methylene}-carbamic acid ethyl ester;

N-(4-Cyano-1-methyl-piperidin-4-yl)-3-cyclohexyl-2-{[diethyl-carbamoylimino)-morpholin-4-yl-methyl]-amino}-propionamide;

{[1-(4-Cyano-1-propyl-piperidin-4-ylcarbamoyl)-2-(3,3,5,5-tetramethyl-cyclohexyl)-ethylamino]-morpholin-4-yl-methylene}-carbamic acid ethyl ester;

{[1-(4-Cyano-1-propyl-piperidin-4-ylcarbamoyl)-2-(4,4-dipropyl-cyclohexyl)-ethylamino]-morpholin-4-yl-methylene}-carbamic acid ethyl ester;

{[1-(4-Cyano-1-isopropyl-piperidin-4-ylcarbamoyl)-2-cyclohexyl-ethylamino]-morpholin-4-yl-methylene}-carbamic acid ethyl ester;

{[1-(4-Cyano-1-phenethyl-piperidin-4-ylcarbamoyl)-2-cyclohexyl-ethylamino]-morpholin-4-yl-methylene}-carbamic acid ethyl ester;

{[1-(4-Cyano-1-ethyl-piperidin-4-ylcarbamoyl)-2-cyclohexyl-ethylamino]-morpholin-4-yl-methylene}-carbamic acid ethyl ester;

{[1-(1-Benzyl-4-cyano-piperidin-4-ylcarbamoyl)-2-cyclohexyl-ethylamino]-morpholin-4-yl-methylene}-carbamic acid ethyl ester;

4-Cyano-4-{3-cyclohexyl-2-[(ethoxycarbonylimino-morpholin-4-yl-methyl)-amino]-propionylamino}-piperidine-1-carboxylic acid benzyl ester;

{[1-(1-Benzyl-4-cyano-piperidin-4-ylcarbamoyl)-3,3-dimethyl-butylamino]-morpholin-4-yl-methylene}-carbamic acid ethyl ester;

{[1-(4-Cyano-1-phenethyl-piperidin-4-ylcarbamoyl)-3,3-dimethyl-butylamino]-morpholin-4-yl-methylene}-carbamic acid ethyl ester;

4,4-Dimethyl-2-(2-oxo-2H-benzo[e][1,3]oxazin-4-ylamino)-pentanoic acid (1-benzyl-4-cyano-piperidin-4-yl)-amide;

4,4-Dimethyl-2-(2-oxo-2H-benzo[e][1,3]oxazin-4-ylamino)-pentanoic acid [4-cyano-1-(5-methyl-thiophen-2-ylmethyl)-piperidin-4-yl]-amide;

4,4-Dimethyl-2-(2-oxo-2H-benzo[e][1,3]oxazin-4-ylamino)-pentanoic acid [4-cyano-1-(4-fluoro-benzyl)-piperidin-4-yl]-amide;

4,4-Dimethyl-2-(2-oxo-2H-benzo[e][1,3]oxazin-4-ylamino)-pentanoic acid (4-cyano-1-ethyl-piperidin-4-yl)-amide;

4,4-Dimethyl-2-(2-oxo-2H-benzo[e][1,3]oxazin-4-ylamino)-pentanoic acid (4-cyano-1-methyl-piperidin-4-yl)-amide;

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4,4-Dimethyl-2-(2-oxo-2H-benzo[e][1,3]oxazin-4-ylamino)-pentanoic acid (4-cyano-piperidin-4-yl)-amide;

4,4-Dimethyl-2-(2-oxo-2H-benzo[e][1,3]oxazin-4-ylamino)-pentanoic acid (4-cyano-1-phenethyl-piperidin-4-yl)-amide;

4,4-Dimethyl-2-(2-oxo-2H-benzo[e][1,3]oxazin-4-ylamino)-pentanoic acid [4-cyano-1-(2,2-dimethyl-propyl)-piperidin-4-yl]-amide;

4,4-Dimethyl-2-(2-oxo-2H-benzo[e][1,3]oxazin-4-ylamino)-pentanoic acid [4-cyano-1-(3,3-dimethyl-butyl)-piperidin-4-yl]-amide;

4,4-Dimethyl-2-(2-oxo-2H-benzo[e][1,3]oxazin-4-ylamino)-pentanoic acid (4-cyano-1-pentyl-piperidin-4-yl)-amide;

4,4-Dimethyl-2-(2-oxo-2H-benzo[e][1,3]oxazin-4-ylamino)-pentanoic acid (1-butyl-4-cyano-piperidin-4-yl)-amide;

4,4-Dimethyl-2-(2-oxo-2H-benzo[e][1,3]oxazin-4-ylamino)-pentanoic acid [4-cyano-1-(3,3,3-trifluoro-propyl)-piperidin-4-yl]-amide;

4,4-Dimethyl-2-(2-oxo-2H-benzo[e][1,3]oxazin-4-ylamino)-pentanoic acid (4-cyano-1-cyclohexylmethyl-piperidin-4-yl)-amide;

N-(4-Cyano-1-propyl-piperidin-4-yl)-3-(4,4-dimethyl-cyclohexyl)-2-(2-oxo-2H-benzo[e][1,3]oxazin-4-ylamino)-propionamide;

N-(4-Cyano-1-propyl-piperidin-4-yl)-3-(4,4-dipropyl-cyclohexyl)-2-(2-oxo-2H-benzo[e][1,3]oxazin-4-ylamino)-propionamide;

N-(4-Cyano-1-propyl-piperidin-4-yl)-3-(4-tert-butyl-cyclohexyl)-2-(2-oxo-2H-benzo[e][1,3]oxazin-4-ylamino)-propionamide;

N-(4-Cyano-1-propyl-piperidin-4-yl)-3-(3,3,5,5-tetramethyl-cyclohexyl)-2-(2-oxo-2H-benzo[e][1,3]oxazin-4-ylamino)-propionamide;

{[1-(3-Cyano-1-ethyl-pyrrolidin-3-ylcarbamoyl)-2-cyclohexyl-ethylamino]-morpholin-4-yl-methylene}-carbamic acid ethyl ester;

2-[(Methanesulfonylimino-morpholin-4-yl-methyl)-amino]-4,4-dimethyl-pentanoic acid (4-cyano-1-propyl-piperidin-4-yl)-amide;

{[1-(3-Cyano-1-propyl-pyrrolidin-3-ylcarbamoyl)-3,3-dimethyl-butylamino]-morpholin-4-yl-methylene}-carbamic acid ethyl ester;

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({1-[3-Cyano-1-(4,4-dimethyl-cyclohexyl)-pyrrolidin-3-ylcarbamoyl]-3,3-dimethyl-butylamino}-morpholin-4-yl-methylene)-carbamic acid ethyl ester;

{[1-(3-Cyano-1-ethyl-5,5-dimethyl-pyrrolidin-3-ylcarbamoyl)-3,3-dimethyl-butylamino]-morpholin-4-yl-methylene}-carbamic acid ethyl ester;

N-(4-Cyano-1-methyl-piperidin-4-yl)-3-cyclohexyl-2-(7,8-difluoro-2-oxo-2H-benzo[e][1,3]oxazin-4-ylamino)-propionamide;

{[1-(4-Cyano-1-cyclohexylmethyl-piperidin-4-ylcarbamoyl)-2-cyclohexyl-ethylamino]-morpholin-4-yl-methylene}-carbamic acid ethyl ester;

3-Cyano-3-[4,4-dimethyl-2-(2-oxo-2*H*-benzo[*e*][1,3]oxazin-4-ylamino)-pentanoylamino]-azepane-1-carboxylic acid benzyl ester;

4,4-Dimethyl-2-(2-oxo-2*H*-benzo[*e*][1,3]oxazin-4-ylamino)-pentanoic acid (3-cyano-1-propyl-azepan-3-yl)-amide;

4,4-Dimethyl-2-(2-oxo-2*H*-benzo[*e*][1,3]oxazin-4-ylamino)-pentanoic acid (4-cyano-1-propyl-azepan-4-yl)-amide;

{[1-(4-Cyano-1-methyl-piperidin-4-ylcarbamoyl)-2-cyclohexyl-ethylamino]-morpholin-4-yl-methylene}-carbamic acid 4-methoxy-cyclohexylmethyl ester;

{[1-(4-Cyano-1-methyl-piperidin-4-ylcarbamoyl)-2-cyclohexyl-ethylamino]-morpholin-4-yl-methylene}-carbamic acid cyclohexyl ester;

{[1-(4-Cyano-1-propyl-piperidin-4-ylcarbamoyl)-3,3-dimethyl-butylamino]-phenyl-methylene}-carbamic acid ethyl ester;

{[1-(4-Cyano-1-methyl-piperidin-4-ylcarbamoyl)-2-cyclohexyl-ethylamino]-phenyl-methylene}-carbamic acid ethyl ester;

2-{[N-(4-Cyano-phenyl)-morpholine-4-carboximidoyl]-amino}-4,4-dimethyl-pentanoic acid (4-cyano-1-propyl-piperidin-4-yl)-amide;

4,4-Dimethyl-2-{[N-(4-trifluoromethyl-phenyl)-morpholine-4-carboximidoyl]-amino}-pentanoic acid (4-cyano-1-propyl-piperidin-4-yl)-amide

and the pharmaceutically acceptable derivatives thereof.

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3. The compound according to claim 2 wherein the compound is chosen from

{[1-(3-Cyano-1-isobutyl-piperdin-3-yl carbamoyl)-3,3-dimethyl-butylamino]-morpholin-4-yl-methylene}-carbamic acid ethyl ester;

{[1-(4-Cyano-1-cyclohexyl-piperidin-4-ylcarbamoyl)-2-cyclohexyl-ethylamino]-morpholin-4-yl-methylene}-carbamic acid ethyl ester;

{[1-(4-Cyano-1-methyl-piperidin-4-ylcarbamoyl)-2-cyclohexyl-ethylamino]-morpholin-4yl-methylene}-carbamic acid cyclohexylmethyl ester;

{[-1-(4-Cyano-1-methyl-piperidin-4-ylcarbamoyl)-2-cyclohexyl-ethylamino]-morpholin-4-yl-methylene}-carbamic acid cyclobutyl ester;

{[1-(4-Cyano-1-methyl-piperidin-4-ylcarbamoyl)-2-cyclohexyl-ethylamino]-morpholin-4-yl-methylene}-carbamic acid allyl ester;

N-(4-Cyano-1-propyl-piperidin-4-yl)-4-cyclohexyl-2-(2-oxo-2,3-dihydro-benzo[e][1,3]oxazin-4-ylideneamino)-butyramide;

{[ 1-(4-Cyano-1-methyl-piperidin-4-ylcarbamoyl)-2-cyclohexyl-ethylamino]-morpholin-4-yl-methylene}-carbamic acid tetrahydro-furan-3ylmethyl ester;

{[1-(4-Cyano-1-methy-piperidin-4-ylcarbamoyl)-2-cyclohexyl-ethyl amino]-morpholin-4-yl-methylene}-carbamic acid tetrahydro-furan-2-ylmethyl ester;

*N*-(4-Cyano-1-methyl-piperidin-4-yl)-3-cyclohexyl-2-(5,6-difluoro-3-oxo-2,3-dihydro-isoindol-1-ylideneamino)-propionamide;

2-(5,6-Difluoro-3-oxo-2,3-dihydro-isoindol-1-ylideneamino)-4,4-dimethyl-pentanoic acid (4-cyano-1-propyl-piperidin-4-yl)-amide;

2-(6-Fluoro-3-oxo-2,3-dihydro-isoindol-1-ylideneamino)-4,4-dimethyl-pentanoic acid (4-cyano-1-propyl-piperidin-4-yl)-amide;

*N*-(4-Cyano-1-methyl-piperidin-4-yl)-3-cyclohexyl-2-(6-fluoro-3-oxo-2,3-dihydro-isoindol-1-ylideneamino)-propionamide;

{[1-(4-Cyano-1-propyl-piperidin-4-ylcarbamoyl)-3,3-dimethyl-butylimino]-morpholin-4-yl-methyl}-carbamic acid methyl ester;

{[1-(4-Cyano-1-methyl-piperidin-4-ylcarbamoyl)-2-cyclohexyl-ethylimino]-morpholin-4-yl-methyl}-carbamic acid methyl ester;

{[1-(4-Cyano-1-methyl-piperidin-4-ylcarbamoyl)-2-cyclohexyl-ethylimino]-morpholin-4-yl-methyl}-carbamic acid 2,2-dimethyl-propyl ester;

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{[1-(4-Cyano-1-methyl-piperidin-4-ylcarbamoyl)-3,3-dimethyl-butylimino]-morpholin-4-yl-methyl}-carbamic acid methyl ester;

{[1-(4-Cyano-1-methyl-piperidin-4-ylcarbamoyl)-2-cyclohexyl-ethylimino]-morpholin-4-yl-methyl}-carbamic acid benzyl ester;

{[1-(4-Cyano-1-methyl-piperidin-4-ylcarbamoyl)-2-cyclohexyl-ethylimino]-morpholin-4-yl-methyl}-carbamic acid isobutyl ester;

{[1-(4-Cyano-1-methyl-piperidin-4-ylcarbamoyl)-2-cyclohexyl-ethylimino]-morpholin-4-yl-methyl}-carbamic acid propyl ester;

{[1-(4-Cyano-1-methyl-piperidin-4-ylcarbamoyl)-2-cyclohexyl-ethylimino]-morpholin-4-yl-methyl}-carbamic acid hexyl ester;

{[1-(4-Cyano-1-methyl-piperidin-4-ylcarbamoyl)-2-cyclohexyl-ethylimino]-morpholin-4-yl-methyl}-carbamic acid cyclobutylmethyl ester;

{[1-(4-Cyano-1-methyl-piperidin-4-ylcarbamoyl)-2-cyclohexyl-ethylimino]-morpholin-4-yl-methyl}-carbamic acid 3,3,3-trifluoro-propyl ester;

{[1-(4-Cyano-1-methyl-piperidin-4-ylcarbamoyl)-2-cyclohexyl-ethylimino]-morpholin-4-yl-methyl}-carbamic acid 2-methoxy-ethyl ester;

5,5-Dimethyl-2-(2-oxo-2,3-dihydro-benzo[*e*][1,3]oxazin-4-ylideneamino)-hexanoic acid (4-cyano-1-propyl-piperidin-4-yl)-amide;

{[1-(4-Cyano-1-methyl-piperidin-4-ylcarbamoyl)-2-cyclohexyl-ethylimino]-morpholin-4-yl-methyl}-carbamic acid 2-isopropoxy-ethyl ester;

{[1-(4-Cyano-1-methyl-piperidin-4-ylcarbamoyl)-2-cyclohexyl-ethylimino]-morpholin-4-yl-methyl}-carbamic acid 3-methoxy-butyl ester;

{[1-(4-Cyano-1-methyl-piperidin-4-ylcarbamoyl)-2-cyclohexyl-ethylimino]-morpholin-4-yl-methyl}-carbamic acid 2-isobutoxy-ethyl ester;

{[1-(4-Cyano-1-propyl-piperidin-4-ylcarbamoyl)-3,3-dimethyl-butylimino]-morpholin-4-yl-methyl}-carbamic acid 2-methoxy-ethyl ester;

N-(4-Cyano-1-methyl-piperidin-4-yl)-4-cyclohexyl-2-(6-methoxy-2-oxo-2,3-dihydro-benzo[e][1,3]oxazin-4-ylideneamino)-butyramide;

N-(4-Cyano-1-methyl-piperidin-4-yl)-4-cyclohexyl-2-(6-fluoro-2-oxo-2,3-dihydro-benzo[e][1,3]oxazin-4-ylideneamino)-butyramide;

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N-(4-Cyano-1-methyl-piperidin-4-yl)-4-cyclohexyl-2-(7-fluoro-2-oxo-2,3-dihydro-benzo[e][1,3]oxazin-4-ylideneamino)-butyramide;

2-(7-Fluoro-2-oxo-2,3-dihydro-benzo[e][1,3]oxazin-4-yldeneamino)-5,5-dimethyl-hexanoic acid(4-cyano-1-propyl-piperidin-4-yl)-amide;

N-(4-Cyano-1-methyl-piperidin-4-yl)-4-cyclohexyl-2-(7-methoxy-2-oxo-2,3-dihydro-benzo[e][1,3]oxazin-4-ylideneamino)-butyramide;

2-(7-Methoxy-2-oxo-2,3-dihydro-benzo[e][1,3]oxazin-4-yldeneamino)-5,5-dimethyl-hexanoic acid(4-cyano-1-propyl-piperidin-4-yl)-amide;

*N*-(4-Cyano-1-methyl-piperidin-4-yl)-3-cyclohexyl-2-(2-oxo-2,3-dihydro-benzo[*e*][1,3]oxazin-4-ylideneamino)-propionamide;

{[1-(4-Cyano-1-methyl-piperidin-4-ylcarbamoyl)-2-cyclohexyl-ethylimino]-pyrrolidin-1-yl-methyl}-carbamic acid ethyl ester;

{[1-(4-Cyano-1-methyl-piperidin-4-ylcarbamoyl)-2-cyclohexyl-ethylimino]-piperidin-1-yl-methyl}-carbamic acid ethyl ester;

{Azepan-1-yl-[1-(4-cyano-1-methyl-piperidin-4-ylcarbamoyl)-2-cyclohexyl-ethylimino]-methyl}-carbamic acid ethyl ester;

{Azocan-1-yl-[1-(4-cyano-1-methyl-piperidin-4-ylcarbamoyl)-2-cyclohexyl-ethylimino]-methyl}-carbamic acid ethyl ester;

1-{[1-(4-Cyano-1-methyl-piperidin-4-ylcarbamoyl)-2-cyclohexyl-ethylimino]-ethoxycarbonylamino-methyl}-piperidine-4-carboxylic acid ethyl ester;

1-{[1-(4-Cyano-1-methyl-piperidin-4-ylcarbamoyl)-2-cyclohexyl-ethylimino]-ethoxycarbonylamino-methyl}-piperidine-3-carboxylic acid ethyl ester;

[[1-(4-Cyano-1-methyl-piperidin-4-ylcarbamoyl)-2-cyclohexyl-ethylimino]-(4-phenyl-piperazin-1-yl)-methyl]-carbamic acid ethyl ester;

[[1-(4-Cyano-1-methyl-piperidin-4-ylcarbamoyl)-2-cyclohexyl-ethylimino]-(4-ethyl-piperazin-1-yl)-methyl]-carbamic acid ethyl ester;

{(4-Acetyl-piperazin-1-yl)-[1-(4-cyano-1-methyl-piperidin-4-ylcarbamoyl)-2-cyclohexyl-ethylimino]-methyl}-carbamic acid ethyl ester;

4-{[1-(4-Cyano-1-methyl-piperidin-4-ylcarbamoyl)-2-cyclohexyl-ethylimino]-ethoxycarbonylamino-methyl}-piperazine-1-carboxylic acid ethyl ester;

[[1-(4-Cyano-1-methyl-piperidin-4-ylcarbamoyl)-2-cyclohexyl-ethylimino]-(3,3,5-trimethyl-6-aza-bicyclo[3.2.1]oct-6-yl)-methyl]-carbamic acid ethyl ester;

{(3-Acetylamino-pyrrolidin-1-yl)-[1-(4-cyano-1-methyl-piperidin-4-ylcarbamoyl)-2-cyclohexyl-ethylimino]-methyl}-carbamic acid ethyl ester;

{(3-Acetylamino-pyrrolidin-1-yl)-[1-(4-cyano-1-methyl-piperidin-4-ylcarbamoyl)-2-cyclohexyl-ethylimino]-methyl}-carbamic acid ethyl ester;

{(3-Azapent-3-yl)-[1-(4-cyano-1-methyl-piperidin-4-ylcarbamoyl)-2-cyclohexyl-ethylimino]-methyl}-carbamic acid ethyl ester;

{(1-Methoxy-3-azapent-3-yl)-[1-(4-cyano-1-methyl-piperidin-4-ylcarbamoyl)-2-cyclohexyl-ethylimino]-methyl}-carbamic acid ethyl ester;

[[1-(4-Cyano-1-methyl-piperidin-4-ylcarbamoyl)-2-cyclohexyl-ethylimino]-(3-oxo-piperazin-1-yl)-methyl]-carbamic acid ethyl ester;

{(1,5-Dimethoxy-3-azapent-3-yl)-[1-(4-cyano-1-methyl-piperidin-4-ylcarbamoyl)-2-cyclohexyl-ethylimino]-methyl}-carbamic acid ethyl ester;

4,4-Dimethyl-2-(2-oxo-2,3-dihydro-benzo[e][1,3]oxazin-4-ylideneamino)-pentanoic acid (4-cyano-1-propyl-piperidin-4-yl)-amide;

{(4-Carbamoyl-piperidin-1-yl)-[1-(4-cyano-1-methyl-piperidin-4-ylcarbamoyl)-2-cyclohexyl-ethylimino]-methyl}-carbamic acid ethyl ester;

[[1-(4-Cyano-1-methyl-piperidin-4-ylcarbamoyl)-2-cyclohexyl-ethylimino]-(2-methoxymethyl-morpholin-4-yl)-methyl]-carbamic acid ethyl ester;

(4-{[1-(4-Cyano-1-methyl-piperidin-4-ylcarbamoyl)-2-cyclohexyl-ethylimino]-ethoxycarbonylamino-methyl}-piperazin-1-yl)-acetic acid ethyl ester;

[[1-(4-Cyano-1-methyl-piperidin-4-ylcarbamoyl)-2-cyclohexyl-ethylimino]-(2,6-dimethyl-morpholin-4-yl)-methyl]-carbamic acid ethyl ester;

[[1-(4-Cyano-1-methyl-piperidin-4-ylcarbamoyl)-2-cyclohexyl-ethylimino]-(2,6-dimethyl-morpholin-4-yl)-methyl]-carbamic acid ethyl ester;

{[1-(4-Cyano-1-methyl-piperidin-4-ylcarbamoyl)-2-cyclohexyl-ethylimino]-thiomorpholin-4-yl-methyl}-carbamic acid ethyl ester;

4,4-Dimethyl-2-(6-methyl-2-oxo-2,3-dihydro-benzo[e][1,3]oxazin-4-ylideneamino)-pentanoic acid (4-cyano-1-propyl-piperidin-4-yl)-amide;

2-(6-Chloro-2-oxo-2,3-dihydro-benzo[e][1,3]oxazin-4-ylideneamino)-4,4-dimethyl-pentanoic acid (4-cyano-1-propyl-piperidin-4-yl)-amide;

4,4-Dimethyl-2-(2-oxo-2,3-dihydro-1*H*-quinazolin-4-ylideneamino)-pentanoic acid (4-cyano-1-propyl-piperidin-4-yl)-amide;

2-(7-Chloro-2-oxo-2,3-dihydro-benzo[*e*][1,3]oxazin-4-ylideneamino)-4,4-dimethyl-pentanoic acid (4-cyano-1-propyl-piperidin-4-yl)-amide;

5-Methyl-2-(2-oxo-2,3-dihydro-benzo[*e*][1,3]oxazin-4-ylideneamino)-hexanoic acid (4-cyano-1-propyl-piperidin-4-yl)-amide;

4,4-Dimethyl-2-(1-methyl-2-oxo-1,2-dihydro-quinazolin-4-ylamino)-pentanoic acid (4-cyano-1-propyl-piperidin-4-yl)-amide;

3-*tert*-Butylsulfanyl-*N*-(4-cyano-1-propyl-piperidin-4-yl)-2-(2-oxo-2,3-dihydro-benzo[*e*][1,3]oxazin-4-ylideneamino)-propionamide;

3-Benzylsulfanyl-*N*-(4-cyano-1-propyl-piperidin-4-yl)-2-(2-oxo-2,3-dihydro-benzo[*e*][1,3]oxazin-4-ylideneamino)-propionamide;

{[2-Benzylsulfanyl-1-(4-cyano-1-propyl-piperidin-4-ylcarbamoyl)-ethylimino]-morpholin-4-yl-methyl}-carbamic acid ethyl ester;

*N*-(4-Cyano-1-propyl-piperidin-4-yl)-3-cyclooctyl-2-(2-oxo-2,3-dihydro-benzo[*e*][1,3]oxazin-4-ylideneamino)-propionamide;

*N*-(4-Cyano-1-propyl-piperidin-4-yl)-3-cycloheptyl-2-(2-oxo-2,3-dihydro-benzo[*e*][1,3]oxazin-4-ylideneamino)-propionamide;

{[1-(4-Cyano-1-propyl-piperidin-4-ylcarbamoyl)-2-cycloheptyl-ethylimino]-morpholin-4-yl-methyl}-carbamic acid ethyl ester;

{[1-(4-Cyano-1-propyl-piperidin-4-ylcarbamoyl)-2-cyclooctyl-ethylimino]-morpholin-4-yl-methyl}-carbamic acid ethyl ester;

{[1-(4-Cyano-piperidin-4-ylcarbamoyl)-2-cyclohexyl-ethylamino]-morpholin-4-yl-methylene}-carbamic acid isobutyl ester;

({1-[4-Cyano-1-(2-morpholin-4-yl-ethyl)-piperidin-4-ylcarbamoyl]-2-cyclohexyl-ethylamino}-morpholin-4-yl-methylene)-carbamic acid isobutyl ester;

({1-[1-2-Carbamoyl-ethyl)-4-cyano-piperidin-4-ylcarbamoyl]-2-cyclohexyl-ethylamino}-morpholin-4-yl-methylene)-carbamic acid isobutyl ester;

[(1-{4-Cyano-1-[2-(2-methoxyl-ethoxy)-ethyl]-piperidin-4-ylcarbamoyl}-2-cyclohexyl-ethylamino)-morpholin-4-yl-methylene]-carbamic acid isobutyl ester;

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[(1-{4-Cyano-1-[3-(2-methoxyl-ethoxy)-propyl]-piperidin-4-ylcarbamoyl}-2-cyclohexyl-ethylamino)-morpholin-4-yl-methylene]-carbamic acid isobutyl ester;

{[2-tert-Butoxy-1-(4-cyano-1-propyl-piperidin-4-ylcarbamoly)-ethylamino]-morpholin-4-yl-methylene}-carbamic acid ethyl ester;

N-(4-Cyano-1-methyl-piperidin-4-yl)-3-cyclohexyl-2-{[diethyl-carbamoylimino)-morpholin-4-yl-methyl]-amino}-propionamide;

{[1-(4-Cyano-1-propyl-piperidin-4-ylcarbamoyl)-2-(3,3,5,5-tetramethyl-cyclohexyl)-ethylamino]-morpholin-4-yl-methylene}-carbamic acid ethyl ester;

{[1-(4-Cyano-1-propyl-piperidin-4-ylcarbamoyl)-2-(4,4-dipropyl-cyclohexyl)-ethylamino]-morpholin-4-yl-methylene}-carbamic acid ethyl ester;

{[1-(4-Cyano-1-isopropyl-piperidin-4-ylcarbamoyl)-2-cyclohexyl-ethylamino]-morpholin-4-yl-methylene}-carbamic acid ethyl ester;

{[1-(4-Cyano-1-phenethyl-piperidin-4-ylcarbamoyl)-2-cyclohexyl-ethylamino]-morpholin-4-yl-methylene}-carbamic acid ethyl ester;

{[1-(4-Cyano-1-ethyl-piperidin-4-ylcarbamoyl)-2-cyclohexyl-ethylamino]-morpholin-4-yl-methylene}-carbamic acid ethyl ester;

{[1-(1-Benzyl-4-cyano-piperidin-4-ylcarbamoyl)-2-cyclohexyl-ethylamino]-morpholin-4-yl-methylene}-carbamic acid ethyl ester;

4-Cyano-4-{3-cyclohexyl-2-[(ethoxycarbonylimino-morpholin-4-yl-methyl)-amino]-propionylamino}-piperidine-1-carboxylic acid benzyl ester;

{[1-(1-Benzyl-4-cyano-piperidin-4-ylcarbamoyl)-3,3-dimethyl-butylamino]-morpholin-4-yl-methylene}-carbamic acid ethyl ester;

{[1-(4-Cyano-1-phenethyl-piperidin-4-ylcarbamoyl)-3,3-dimethyl-butylamino]-morpholin-4-yl-methylene}-carbamic acid ethyl ester;

4,4-Dimethyl-2-(2-oxo-2H-benzo[e][1,3]oxazin-4-ylamino)-pentanoic acid (1-benzyl-4-cyano-piperidin-4-yl)-amide;

4,4-Dimethyl-2-(2-oxo-2H-benzo[e][1,3]oxazin-4-ylamino)-pentanoic acid [4-cyano-1-(5-methyl-thiophen-2-ylmethyl)-piperidin-4-yl]-amide;

4,4-Dimethyl-2-(2-oxo-2H-benzo[e][1,3]oxazin-4-ylamino)-pentanoic acid [4-cyano-1-(4-fluoro-benzyl)-piperidin-4-yl]-amide;

4,4-Dimethyl-2-(2-oxo-2H-benzo[e][1,3]oxazin-4-ylamino)-pentanoic acid (4-cyano-1-ethyl-piperidin-4-yl)-amide;

4,4-Dimethyl-2-(2-oxo-2H-benzo[e][1,3]oxazin-4-ylamino)-pentanoic acid (4-cyano-1-methyl-piperidin-4-yl)-amide;

4,4-Dimethyl-2-(2-oxo-2H-benzo[e][1,3]oxazin-4-ylamino)-pentanoic acid (4-cyano-piperidin-4-yl)-amide;

4,4-Dimethyl-2-(2-oxo-2H-benzo[e][1,3]oxazin-4-ylamino)-pentanoic acid (4-cyano-1-phenethyl-piperidin-4-yl)-amide;

4,4-Dimethyl-2-(2-oxo-2H-benzo[e][1,3]oxazin-4-ylamino)-pentanoic acid [4-cyano-1-(2,2-dimethyl-propyl)-piperidin-4-yl]-amide;

4,4-Dimethyl-2-(2-oxo-2H-benzo[e][1,3]oxazin-4-ylamino)-pentanoic acid [4-cyano-1-(3,3-dimethyl-butyl)-piperidin-4-yl]-amide;

4,4-Dimethyl-2-(2-oxo-2H-benzo[e][1,3]oxazin-4-ylamino)-pentanoic acid (4-cyano-1-pentyl-piperidin-4-yl)-amide;

4,4-Dimethyl-2-(2-oxo-2H-benzo[e][1,3]oxazin-4-ylamino)-pentanoic acid (1-butyl-4-cyano-piperidin-4-yl)-amide;

4,4-Dimethyl-2-(2-oxo-2H-benzo[e][1,3]oxazin-4-ylamino)-pentanoic acid [4-cyano-1-(3,3,3-trifluoro-propyl)-piperidin-4-yl]-amide;

4,4-Dimethyl-2-(2-oxo-2H-benzo[e][1,3]oxazin-4-ylamino)-pentanoic acid (4-cyano-1-cyclohexylmethyl-piperidin-4-yl)-amide;

N-(4-Cyano-1-propyl-piperidin-4-yl)-3-(4,4-dimethyl-cyclohexyl)-2-(2-oxo-2H-benzo[e][1,3]oxazin-4-ylamino)-propionamide;

N-(4-Cyano-1-propyl-piperidin-4-yl)-3-(4,4-dipropyl-cyclohexyl)-2-(2-oxo-2H-benzo[e][1,3]oxazin-4-ylamino)-propionamide;

N-(4-Cyano-1-propyl-piperidin-4-yl)-3-(4-tert-butyl-cyclohexyl)-2-(2-oxo-2H-benzo[e][1,3]oxazin-4-ylamino)-propionamide;

N-(4-Cyano-1-propyl-piperidin-4-yl)-3-(3,3,5,5-tetramethyl-cyclohexyl)-2-(2-oxo-2H-benzo[e][1,3]oxazin-4-ylamino)-propionamide;

{[1-(3-Cyano-1-ethyl-pyrrolidin-3-ylcarbamoyl)-2-cyclohexyl-ethylamino]-morpholin-4-yl-methylene}-carbamic acid ethyl ester;

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{[1-(3-Cyano-1-propyl-pyrrolidin-3-ylcarbamoyl)-3,3-dimethyl-butylamino]-morpholin-4-yl-methylene}-carbamic acid ethyl ester;

({1-[3-Cyano-1-(4,4-dimethyl-cyclohexyl)-pyrrolidin-3-ylcarbamoyl]-3,3-dimethyl-butylamino}-morpholin-4-yl-methylene)-carbamic acid ethyl ester;

N-(4-Cyano-1-methyl-piperidin-4-yl)-3-cyclohexyl-2-(7,8-difluoro-2-oxo-2H-benzo[e][1,3]oxazin-4-ylamino)-propionamide;

{[1-(4-Cyano-1-cyclohexylmethyl-piperidin-4-ylcarbamoyl)-2-cyclohexyl-ethylamino]-morpholin-4-yl-methylene}-carbamic acid ethyl ester;

3-Cyano-3-[4,4-dimethyl-2-(2-oxo-2*H*-benzo[*e*][1,3]oxazin-4-ylamino)-pentanoylamino]-azepane-1-carboxylic acid benzyl ester;

4,4-Dimethyl-2-(2-oxo-2*H*-benzo[*e*][1,3]oxazin-4-ylamino)-pentanoic acid (3-cyano-1-propyl-azepan-3-yl)-amide;

4,4-Dimethyl-2-(2-oxo-2*H*-benzo[*e*][1,3]oxazin-4-ylamino)-pentanoic acid (4-cyano-1-propyl-azepan-4-yl)-amide;

{[1-(4-Cyano-1-methyl-piperidin-4-ylcarbamoyl)-2-cyclohexyl-ethylamino]-morpholin-4-yl-methylene}-carbamic acid 4-methoxy-cyclohexylmethyl ester;

{[1-(4-Cyano-1-methyl-piperidin-4-ylcarbamoyl)-2-cyclohexyl-ethylamino]-morpholin-4-yl-methylene}-carbamic acid cyclohexyl ester;

{[1-(4-Cyano-1-propyl-piperidin-4-ylcarbamoyl)-3,3-dimethyl-butylamino]-phenyl-methylene}-carbamic acid ethyl ester;

and

{[1-(4-Cyano-1-methyl-piperidin-4-ylcarbamoyl)-2-cyclohexyl-ethylamino]-phenyl-methylene}-carbamic acid ethyl ester.

4. The compound according to claim 3 wherein the compound is chosen from:

{[1-(4-Cyano-1-cyclohexyl-piperidin-4-ylcarbamoyl)-2-cyclohexyl-ethylamino]-morpholin-4-yl-methylene}-carbamic acid ethyl ester;

{[1-(4-cyano-1-methyl-piperidin-4-ylcarbamoyl)-2-cyclohexyl-ethylamino]-morpholin-4-yl-methylene}-carbamic acid cyclohexylmethyl ester;

{[-1-(4-Cyano-1-methyl-piperidin-4-ylcarbamoyl)-2-cyclohexyl-ethylamino]-morpholin-4-yl-methylene}-carbamic acid cyclobutyl ester;

{[1-(4-Cyano-1-methyl-piperidin-4-ylcarbamoyl)-2-cyclohexyl-ethylamino]-morpholin-4-yl-methylene}-carbamic acid allyl ester;

{[ 1-(4-Cyano-1-methyl-piperidin-4-ylcarbamoyl)-2-cyclohexyl-ethylamino]-morpholin-4-yl-methylene}-carbamic acid tetrahydro-furan-3ylmethyl ester;

{[1-(4-Cyano-1-methy-piperidin-4-ylcarbamoyl)-2-cyclohexyl-ethyl amino]-morpholin-4-yl-methylene}-carbamic acid tetrahydro-furan-2-ylmethyl ester;

{[1-(4-Cyano-1-methyl-piperidin-4-ylcarbamoyl)-2-cyclohexyl-ethylimino]-morpholin-4-yl-methyl}-carbamic acid methyl ester;

{[1-(4-Cyano-1-methyl-piperidin-4-ylcarbamoyl)-2-cyclohexyl-ethylimino]-morpholin-4-yl-methyl}-carbamic acid 2,2-dimethyl-propyl ester;

{[1-(4-Cyano-1-methyl-piperidin-4-ylcarbamoyl)-2-cyclohexyl-ethylimino]-morpholin-4-yl-methyl}-carbamic acid benzyl ester;

{[1-(4-Cyano-1-methyl-piperidin-4-ylcarbamoyl)-2-cyclohexyl-ethylimino]-morpholin-4-yl-methyl}-carbamic acid isobutyl ester;

{[1-(4-Cyano-1-methyl-piperidin-4-ylcarbamoyl)-2-cyclohexyl-ethylimino]-morpholin-4-yl-methyl}-carbamic acid propyl ester;

{[1-(4-Cyano-1-methyl-piperidin-4-ylcarbamoyl)-2-cyclohexyl-ethylimino]-morpholin-4-yl-methyl}-carbamic acid hexyl ester;

{[1-(4-Cyano-1-methyl-piperidin-4-ylcarbamoyl)-2-cyclohexyl-ethylimino]-morpholin-4-yl-methyl}-carbamic acid cyclobutylmethyl ester;

{[1-(4-Cyano-1-methyl-piperidin-4-ylcarbamoyl)-2-cyclohexyl-ethylimino]-morpholin-4-yl-methyl}-carbamic acid 3,3,3-trifluoro-propyl ester;

{[1-(4-Cyano-1-methyl-piperidin-4-ylcarbamoyl)-2-cyclohexyl-ethylimino]-morpholin-4-yl-methyl}-carbamic acid 2-methoxy-ethyl ester;

5,5-Dimethyl-2-(2-oxo-2,3-dihydro-benzo[*e*][1,3]oxazin-4-ylideneamino)-hexanoic acid (4-cyano-1-propyl-piperidin-4-yl)-amide;

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{[1-(4-Cyano-1-methyl-piperidin-4-ylcarbamoyl)-2-cyclohexyl-ethylimino]-morpholin-4-yl-methyl}-carbamic acid 2-isopropoxy-ethyl ester;

{[1-(4-Cyano-1-methyl-piperidin-4-ylcarbamoyl)-2-cyclohexyl-ethylimino]-morpholin-4-yl-methyl}-carbamic acid 3-methoxy-butyl ester;

{[1-(4-Cyano-1-methyl-piperidin-4-ylcarbamoyl)-2-cyclohexyl-ethylimino]-morpholin-4-yl-methyl}-carbamic acid 2-isobutoxy-ethyl ester;

N-(4-Cyano-1-methyl-piperidin-4-yl)-4-cyclohexyl-2-(7-fluoro-2-oxo-2,3-dihydro-benzo[e][1,3]oxazin-4-ylideneamino)-butyramide;

2-(7-Fluoro-2-oxo-2,3-dihydro-benzo[e][1,3]oxazin-4-yldeneamino)-5,5-dimethyl-hexanoic acid(4-cyano-1-propyl-piperidin-4-yl)-amide;

N-(4-Cyano-1-methyl-piperidin-4-yl)-4-cyclohexyl-2-(7-methoxy-2-oxo-2,3-dihydro-benzo[e][1,3]oxazin-4-ylideneamino)-butyramide;

2-(7-Methoxy-2-oxo-2,3-dihydro-benzo[e][1,3]oxazin-4-yldeneamino)-5,5-dimethyl-hexanoic acid(4-cyano-1-propyl-piperidin-4-yl)-amide;

*N*-(4-Cyano-1-methyl-piperidin-4-yl)-3-cyclohexyl-2-(2-oxo-2,3-dihydro-benzo[*e*][1,3]oxazin-4-ylideneamino)-propionamide;

4,4-Dimethyl-2-(2-oxo-2,3-dihydro-benzo[e][1,3]oxazin-4-ylideneamino)-pentanoic acid (4-cyano-1-propyl-piperidin-4-yl)-amide;

4,4-Dimethyl-2-(2-oxo-2,3-dihydro-1*H*-quinazolin-4-ylideneamino)-pentanoic acid (4-cyano-1-propyl-piperidin-4-yl)-amide;

2-(7-Chloro-2-oxo-2,3-dihydro-benzo[*e*][1,3]oxazin-4-ylideneamino)-4,4-dimethyl-pentanoic acid (4-cyano-1-propyl-piperidin-4-yl)-amide;

4,4-Dimethyl-2-(1-methyl-2-oxo-1,2-dihydro-quinazolin-4-ylamino)-pentanoic acid (4-cyano-1-propyl-piperidin-4-yl)-amide;

*N*-(4-Cyano-1-propyl-piperidin-4-yl)-3-cyclooctyl-2-(2-oxo-2,3-dihydro-benzo[*e*][1,3]oxazin-4-ylideneamino)-propionamide;

*N*-(4-Cyano-1-propyl-piperidin-4-yl)-3-cycloheptyl-2-(2-oxo-2,3-dihydro-benzo[*e*][1,3]oxazin-4-ylideneamino)-propionamide;

{[1-(4-Cyano-1-propyl-piperidin-4-ylcarbamoyl)-2-cycloheptyl-ethylimino]-morpholin-4-yl-methyl}-carbamic acid ethyl ester;

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{[1-(4-Cyano-1-propyl-piperidin-4-ylcarbamoyl)-2-cyclooctyl-ethylimino]-morpholin-4-yl-methyl}-carbamic acid ethyl ester;

({1-[1-2-Carbamoyl-ethyl)-4-cyano-piperidin-4-ylcarbamoyl]-2-cyclohexyl-ethylamino}-morpholin-4-yl-methylene)-carbamic acid isobutyl ester;

[(1-{4-Cyano-1-[2-(2-methoxyl-ethoxy)-ethyl]-piperidin-4-ylcarbamoyl}-2-cyclohexyl-ethylamino)-morpholin-4-yl-methylene]-carbamic acid isobutyl ester;

[(1-{4-Cyano-1-[3-(2-methoxyl-ethoxy)-propyl]-piperidin-4-ylcarbamoyl}-2-cyclohexyl-ethylamino)-morpholin-4-yl-methylene]-carbamic acid isobutyl ester;

{[1-(4-Cyano-1-isopropyl-piperidin-4-ylcarbamoyl)-2-cyclohexyl-ethylamino]-morpholin-4-yl-methylene}-carbamic acid ethyl ester;

{[1-(4-Cyano-1-phenethyl-piperidin-4-ylcarbamoyl)-2-cyclohexyl-ethylamino]-morpholin-4-yl-methylene}-carbamic acid ethyl ester;

{[1-(4-Cyano-1-ethyl-piperidin-4-ylcarbamoyl)-2-cyclohexyl-ethylamino]-morpholin-4-yl-methylene}-carbamic acid ethyl ester;

{[1-(1-Benzyl-4-cyano-piperidin-4-ylcarbamoyl)-2-cyclohexyl-ethylamino]-morpholin-4-yl-methylene}-carbamic acid ethyl ester;

4,4-Dimethyl-2-(2-oxo-2H-benzo[e][1,3]oxazin-4-ylamino)-pentanoic acid (1-benzyl-4-cyano-piperidin-4-yl)-amide;

4,4-Dimethyl-2-(2-oxo-2H-benzo[e][1,3]oxazin-4-ylamino)-pentanoic acid [4-cyano-1-(5-methyl-thiophen-2-ylmethyl)-piperidin-4-yl]-amide;

4,4-Dimethyl-2-(2-oxo-2H-benzo[e][1,3]oxazin-4-ylamino)-pentanoic acid [4-cyano-1-(4-fluoro-benzyl)-piperidin-4-yl]-amide;

4,4-Dimethyl-2-(2-oxo-2H-benzo[e][1,3]oxazin-4-ylamino)-pentanoic acid (4-cyano-1-ethyl-piperidin-4-yl)-amide;

4,4-Dimethyl-2-(2-oxo-2H-benzo[e][1,3]oxazin-4-ylamino)-pentanoic acid (4-cyano-1-methyl-piperidin-4-yl)-amide;

4,4-Dimethyl-2-(2-oxo-2H-benzo[e][1,3]oxazin-4-ylamino)-pentanoic acid (4-cyano-1-phenethyl-piperidin-4-yl)-amide;

4,4-Dimethyl-2-(2-oxo-2H-benzo[e][1,3]oxazin-4-ylamino)-pentanoic acid [4-cyano-1-(2,2-dimethyl-propyl)-piperidin-4-yl]-amide;

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4,4-Dimethyl-2-(2-oxo-2H-benzo[e][1,3]oxazin-4-ylamino)-pentanoic acid [4-cyano-1-(3,3-dimethyl-butyl)-piperidin-4-yl]-amide;

4,4-Dimethyl-2-(2-oxo-2H-benzo[e][1,3]oxazin-4-ylamino)-pentanoic acid (4-cyano-1-pentyl-piperidin-4-yl)-amide;

4,4-Dimethyl-2-(2-oxo-2H-benzo[e][1,3]oxazin-4-ylamino)-pentanoic acid (1-butyl-4-cyano-piperidin-4-yl)-amide;

4,4-Dimethyl-2-(2-oxo-2H-benzo[e][1,3]oxazin-4-ylamino)-pentanoic acid [4-cyano-1-(3,3,3-trifluoro-propyl)-piperidin-4-yl]-amide;

4,4-Dimethyl-2-(2-oxo-2H-benzo[e][1,3]oxazin-4-ylamino)-pentanoic acid (4-cyano-1-cyclohexylmethyl-piperidin-4-yl)-amide;

N-(4-Cyano-1-propyl-piperidin-4-yl)-3-(4,4-dimethyl-cyclohexyl)-2-(2-oxo-2H-benzo[e][1,3]oxazin-4-ylamino)-propionamide;

{[1-(3-Cyano-1-ethyl-pyrrolidin-3-ylcarbamoyl)-2-cyclohexyl-ethylamino]-morpholin-4-yl-methylene}-carbamic acid ethyl ester;

N-(4-Cyano-1-methyl-piperidin-4-yl)-3-cyclohexyl-2-(7,8-difluoro-2-oxo-2H-benzo[e][1,3]oxazin-4-ylamino)-propionamide;

{[1-(4-Cyano-1-cyclohexylmethyl-piperidin-4-ylcarbamoyl)-2-cyclohexyl-ethylamino]-morpholin-4-yl-methylene}-carbamic acid ethyl ester;

{[1-(4-Cyano-1-methyl-piperidin-4-ylcarbamoyl)-2-cyclohexyl-ethylamino]-morpholin-4-yl-methylene}-carbamic acid 4-methoxy-cyclohexylmethyl ester;

{[1-(4-Cyano-1-methyl-piperidin-4-ylcarbamoyl)-2-cyclohexyl-ethylamino]-morpholin-4-yl-methylene}-carbamic acid cyclohexyl ester;

{[1-(4-Cyano-1-propyl-piperidin-4-ylcarbamoyl)-3,3-dimethyl-butylamino]-phenyl-methylene}-carbamic acid ethyl ester;

and

{[1-(4-Cyano-1-methyl-piperidin-4-ylcarbamoyl)-2-cyclohexyl-ethylamino]-phenyl-methylene}-carbamic acid ethyl ester.

5. A pharmaceutical composition comprising a pharmaceutically effective amount of a compound according to claims 1 or 2.

6. A method of modulating an autoimmune disease, said method comprising administering to a patient in need of such treatment a pharmaceutically effective amount of a compound according to claims 1 or 2.

7. The method according to claim 6 wherein the autoimmune disease is rheumatoid arthritis, systemic lupus erythematosus, Crohn's disease, ulcerative colitis, multiple sclerosis, Guillain-Barre syndrome, psoriasis, Grave's disease, myasthenia gravis, scleroderma, glomerulonephritis, dermatitis, endometriosis or insulin-dependent diabetes mellitus.

8. A method of treating Alzheimer's disease comprising administering to a patient in need of such treatment a pharmaceutically effective amount of a compound according to claims 1 or 2.

9. A method of treating atherosclerosis comprising administering to a patient in need of such treatment a pharmaceutically effective amount of a compound according to claims 1 or 2.

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10. A method of treating osteoporosis comprising administering to a patient in need of such treatment a pharmaceutically effective amount of a compound according to claims 1 or 2.

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11. A method of treating asthma comprising administering to a patient in need of such treatment a pharmaceutically effective amount of a compound according to claims 1 or 2.

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# INTERNATIONAL SEARCH REPORT

Int ·nal Application No
PCT/US 01/08084

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D211/60 C07D211/66 C07D413/12 C07D405/12 C07D401/12
C07D487/08 C07D455/02 C07D207/16 C07D413/14 A61K31/5377
A61P25/28 A61P9/10 A61P19/10 A61P11/06

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 7 C07D A61K A61P

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

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, 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. |
|---|---|---|
| E | WO 01 19816 A (BOEHRINGER INGELHEIM PHARMA ;EMMANUEL MICHEL J (US); FRYE LEAH L ()<br>22 March 2001 (2001-03-22)<br>examples 72-89 | 1-11 |
| A | US 5 776 718 A (KLAUS JEFFREY LEE ET AL)<br>7 July 1998 (1998-07-07)<br>the whole document | 1,5,6,<br>8-11 |

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in 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 document 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 |
|---|---|
| 2 October 2001 | 12/10/2001 |

| Name and mailing address of the ISA | Authorized officer |
|---|---|
| European Patent Office, P.B. 5818 Patentlaan 2<br>NL – 2280 HV Rijswijk<br>Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,<br>Fax: (+31-70) 340-3016 | Diederen, J |

Form PCT/ISA/210 (second sheet) (July 1992)

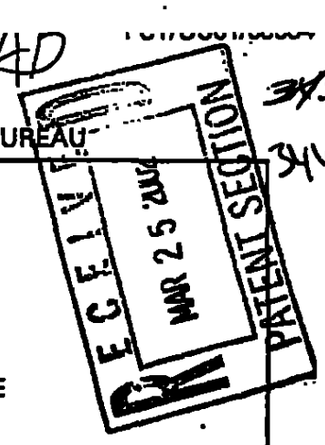
## INTERNATIONAL SEARCH REPORT

Int al Application No
PCT/US 01/08084

| Patent document cited in search report | Publication date | Patent family member(s) | Publication date |
|---|---|---|---|
| WO 0119816 A | 22-03-2001 | AU 7081800 A | 17-04-2001 |
| | | WO 0119816 A1 | 22-03-2001 |
| US 5776718 A | 07-07-1998 | AU 713492 B2 | 02-12-1999 |
| | | AU 5367496 A | 16-10-1996 |
| | | CA 2216151 A1 | 03-10-1996 |
| | | CN 1184472 A ,B | 10-06-1998 |
| | | CZ 9702981 A3 | 18-03-1998 |
| | | EP 0817778 A1 | 14-01-1998 |
| | | JP 11503417 T | 26-03-1999 |
| | | NO 974403 A | 17-11-1997 |
| | | PL 322409 A1 | 19-01-1998 |
| | | WO 9630353 A1 | 03-10-1996 |
| | | ZA 9602336 A | 31-07-1996 |

# PATENT COOPERATION TREATY

AD




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From the INTERNATIONAL BUREAU

## PCT

NOTICE INFORMING THE APPLICANT OF THE COMMUNICATION OF THE INTERNATIONAL APPLICATION TO THE DESIGNATED OFFICES

(PCT Rule 47.1(c), first sentence)

To:
RAYMOND, Robert, P.
Boehringer Ingelheim
Pharmaceuticals, Inc.
900 Ridgebury Road
P.O. Box 368
Ridgefield, CT 06877
ETATS-UNIS D'AMERIQUE

| Date of mailing (day/month/year) |
|---|
| 14 March 2002 (14.03.02) |

| Applicant's or agent's file reference | IMPORTANT NOTICE |
|---|---|
| 9/193PCT CLP | |

| International application No. | International filing date (day/month/year) | Priority date (day/month/year) |
|---|---|---|
| PCT/US01/08084 | 14 March 2001 (14.03.01) | 08 September 2000 (08.09.00) |

Applicant
BOEHRINGER INGELHEIM PHARMACEUTICALS, INC. et al

1. Notice is hereby given that the International Bureau has communicated, as provided in Article 20, the international application to the following designated Offices on the date indicated above as the date of mailing of this notice:

   KR,US

   In accordance with Rule 47.1(c), third sentence, those Offices will accept the present notice as conclusive evidence that the communication of the international application has duly taken place on the date of mailing indicated above and no copy of the international application is required to be furnished by the applicant to the designated Office(s).

2. The following designated Offices have waived the requirement for such a communication at this time:

   AE,AU,BG,BR,CA,CN,CO,CZ,EA,EE,EP,HR,HU,ID,IL,IN,JP,LT,LV,MX,NO,NZ,PL,RO,SG,SI,SK, TR,UA,UZ,VN,YU,ZA

   The communication will be made to those Offices only upon their request. Furthermore, those Offices do not require the applicant to furnish a copy of the international application (Rule 49.1(a-bis)).

3. Enclosed with this notice is a copy of the international application as published by the International Bureau on

   14 March 2002 (14.03.02) under No. WO 02/20485

### REMINDER REGARDING CHAPTER II (Article 31(2)(a) and Rule 54.2)

If the applicant wishes to postpone entry into the national phase until 30 months (or later in some Offices) from the priority date, a demand for international preliminary examination must be filed with the competent International Preliminary Examining Authority before the expiration of 19 months from the priority date.

It is the applicant's sole responsibility to monitor the 19-month time limit.

Note that only an applicant who is a national or resident of a PCT Contracting State which is bound by Chapter II has the right to file a demand for international preliminary examination (at present, all PCT Contracting States are bound by Chapter II).

### REMINDER REGARDING ENTRY INTO THE NATIONAL PHASE (Article 22 or 39(1))

If the applicant wishes to proceed with the international application in the national phase, he must, within 20 months or 30 months, or later in some Offices, perform the acts referred to therein before each designated or elected Office.

For further important information on the time limits and acts to be performed for entering the national phase, see the Annex to Form PCT/IB/301 (Notification of Receipt of Record Copy) and the PCT Applicant's Guide, Volume II.

NAT'L PHASE LD = 3.8.03

| The International Bureau of WIPO<br>34, chemin des Colombettes<br>1211 Geneva 20, Switzerland | Authorized officer<br>J. Zahra |
|---|---|
| Facsimile No. (41-22) 740.14.35 | Telephone No. (41-22) 338.91.11 |

Form PCT/IB/308 (April 2001) 4706843

Notional Phase 3-8-03 LAST DAY

# PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

## PCT

**INFORMATION CONCERNING ELECTED OFFICES NOTIFIED OF THEIR ELECTION**

(PCT Rule 61.3)

To:

RAYMOND, Robert, P.
Boehringer Ingelheim
Pharmaceuticals, Inc.
900 Ridgebury Road
P.O. Box 368
Ridgefield, CT 06877
ETATS-UNIS D'AMERIQUE

| Date of mailing (day/month/year) | |
|---|---|
| 27 July 2002 (27.07.02) | |
| **Applicant's or agent's file reference** | **IMPORTANT INFORMATION** |
| 9/193PCT | |

| International application No. | International filing date (day/month/year) | Priority date (day/month/year) |
|---|---|---|
| PCT/US01/08084 | 14 March 2001 (14.03.01) | 08 September 2000 (08.09.00) |

**Applicant**
BOEHRINGER INGELHEIM PHARMACEUTICALS, INC. et al

1. The applicant is hereby informed that the International Bureau has, according to Article 31(7), notified each of the following Offices of its election:

   EP :AT,BE,CH,CY,DE,DK,ES,FI,FR,GB,GR,IE,IT,LU,MC,NL,PT,SE,TR
   National :AU,BG,CA,CN,IL,JP,KR,NO,NZ,PL,RO,SK,US

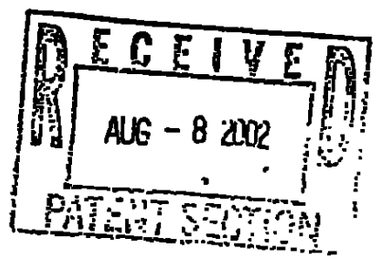
2. The following Offices have waived the requirement for the notification of their election; the notification will be sent to them by the International Bureau only upon their request:

   EA :AM,AZ,BY,KG,KZ,MD,RU,TJ,TM
   National :AE,BR,CO,CZ,EE,HR,HU,ID,IN,LT,LV,MX,SG,SI,TR,UA,UZ,VN,YU,ZA

3. The applicant is reminded that he must enter the "national phase" before the expiration of 30 months from the priority date before each of the Offices listed above. This must be done by paying the national fee(s) and furnishing , if prescribed, a translation of the international application (Article 39(1)(a)), as well as, where applicable, by furnishing a translation of any annexes of the international preliminary examination report (Article 36(3)(b) and Rule 74.1).

   Some offices have fixed time limits expiring later than the above-mentioned time limit. For detailed information about the applicable time limits and the acts to be performed upon entry into the national phase before a particular Office, see Volume II of the PCT Applicant's Guide.

   The entry into the European regional phase is postponed until 31 months from the priority date for all States designated for the purposes of obtaining a European patent.




The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No. (41-22) 740.14.35

Authorized officer:
Farid ABBOU

Telephone No. (41-22) 338.83.38



received

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# PATENT COOPERATION TREATY

1 AB

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To: ROBERT P. RAYMOND
BOEHRINGER INGELHEIM PHARMACEUTICALS, INC
900 RIDGEBURY ROAD
P. O. BOX 368
RIDGEFIELD CT 06877

National Phase 3-8-03
Last Day

# PCT

**NOTIFICATION OF TRANSMITTAL OF INTERNATIONAL PRELIMINARY EXAMINATION REPORT**

(PCT Rule 71.1)

| | |
|---|---|
| Applicant's or agent's file reference 0/193PCT CIP | Date of Mailing (day/month/year) |
| | IMPORTANT NOTIFICATION |

| International application No. | International filing date (day/month/year) | Priority Date (day/month/year) |
|---|---|---|
| PCT/US01/08084 | 14 MARCH 2001 | 08 SEPTEMBER 2000 |

Applicant
BOEHRINGER INGELHE I PHARMACEUTICALS, INC

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. REMINDER

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices)(Article 39(1))(see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

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NOV 26 2002
PATENT SECTION

| | |
|---|---|
| Name and mailing address of the IPEA/US<br>Commissioner of Patents and Trademarks<br>Box PCT<br>Washington, D.C. 20231 | Authorized officer<br>EBENEZER SACKEY |
| Facsimile No. (703) 305-3230 | Telephone No. (703)-308-1235 |

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# PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To: ROBERT P. RAYMOND
BOEHRINGER INGELHEIM PHARMACEUTICALS, INC
900 RIDGEBURY ROAD
P. O. BOX 900
RIDGEFIELD CT 06877

# PCT

## NOTIFICATION OF TRANSMITTAL OF INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Rule 71.1)

| | |
|---|---|
| Date of Mailing (day/month/year) | 22 NOV 2002 |
| Applicant's or agent's file reference: 9/188PCT | IMPORTANT NOTIFICATION |

| International application No. | International filing date (day/month/year) | Priority Date (day/month/year) |
|---|---|---|
| PCT/US01/08084 | 14 MARCH 2001 | 08 SEPTEMBER 2000 |

Applicant
BOEHRINGER INGELHEIM PHARMACEUTICALS, INC

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

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The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices)(Article 39(1))(see also the reminder sent by the International Bureau with Form PCT/IB/301).

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For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

| Name and mailing address of the IPEA/US | Authorized officer |
|---|---|
| Commissioner of Patents and Trademarks<br>Box PCT<br>Washington, D.C. 20231 | EBENEZER SACKEY |
| Facsimile No. (703) 305-3230 | Telephone No. (703)-308-1245 |

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# PATENT COOPERATION TREATY

# PCT

## INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

| Applicant's or agent's file reference 9/199PCT | FOR FURTHER ACTION | See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416) |
|---|---|---|
| International application No. PCT/US01/08084 | International filing date (day/month/year) 14 MARCH 2001 | Priority date (day/month/year) 08 SEPTEMBER 2000 |
| International Patent Classification (IPC) or national classification and IPC Please See Supplemental Sheet. | | |
| Applicant BOEHRINGER INGELHEIM PHARMACEUTICALS, INC | | |

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 4 sheets.

☐ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority. (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of 0 sheets.

3. This report contains indications relating to the following items:

- I ☒ Basis of the report
- II ☐ Priority
- III ☐ Non-establishment of report with regard to novelty, inventive step or industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☐ Certain documents cited
- VII ☐ Certain defects in the international application
- VIII ☐ Certain observations on the international application

| Date of submission of the demand | Date of completion of this report |
|---|---|
| 11 JANUARY 2002 | 28 OCTOBER 2002 |
| Name and mailing address of the IPEA/US<br>Commissioner of Patents and Trademarks<br>Box PCT<br>Washington, D.C. 20231 | Authorized officer<br>EBENEZER SACKEY |
| Facsimile No. (703) 305-3230 | Telephone No. (703)-308-1235 |

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INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/US01/06084

## I. Basis of the report

1. With regard to the elements of the international application:*

[X] the international application as originally filed

[X] the description:
pages 1-251 , as originally filed
pages NONE , filed with the demand
pages NONE , filed with the letter of

[X] the claims:
pages 252-283 , as originally filed
pages NONE , as amended (together with any statement) under Article 19
pages NONE , filed with the demand
pages NONE , filed with the letter of

[X] the drawings:
pages NONE , as originally filed
pages NONE , filed with the demand
pages NONE , filed with the letter of

[X] the sequence listing part of the description:
pages NONE , as originally filed
pages NONE , filed with the demand
pages NONE , filed with the letter of

2. With regard to the language, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.
These elements were available or furnished to this Authority in the following language which is:

[ ] the language of a translation furnished for the purposes of international search (under Rule 23.1(b)).

[ ] the language of publication of the international application (under Rule 48.3(b)).

[ ] the language of the translation furnished for the purposes of international preliminary examination (under Rules 55.2 and/or 55.3).

3. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

[ ] contained in the international application in printed form.

[ ] filed together with the international application in computer readable form.

[ ] furnished subsequently to this Authority in written form.

[ ] furnished subsequently to this Authority in computer readable form.

[ ] The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

[ ] The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. [X] The amendments have resulted in the cancellation of:

[X] the description, pages NONE

[X] the claims, Nos. NONE

[X] the drawings, sheets/fig NONE

5. [ ] This report has been drawn as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).**

** Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17).*

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INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/US01/08084

**V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

**1. statement**

| | | | |
|---|---|---|---|
| Novelty (N) | Claims | 1-11 | YES |
| | Claims | NONE | NO |
| Inventive Step (IS) | Claims | 1-11 | YES |
| | Claims | NONE | NO |
| Industrial Applicability (IA) | Claims | 1-11 | YES |
| | Claims | NONE | NO |

**2. citations and explanations (Rule 70.7)**

Claims 1-11 meet the criteria set out in PCT Article 35(2)-(4), because the prior art does not teach or fairly suggest my amidino and guanidino peptidyl compounds of formula (Ia), or any method of use of such compounds.

NEW CITATIONS

NONE

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/US01/08084

Supplemental Box
(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of: Boxes I - VIII

Sheet 10

CLASSIFICATION:

The International Patent Classification (IPC) and/or the National classification are as listed below:

IPC(7): A61K 31/335, 31/495, 31/537; C07D 417/00, 207/06, 207/16, 211/60, 211/66, 413/12, 413/14, 405/12, 401/12, 487/08, 455/02, and US CL: 514/231.500

## IN THE UNITED STATES RECEIVING OFFICE (RO/US)

| | | |
|---|---|---|
| International Appln. No. | : | PCT/US01/08084 |
| Filed | : | 14 March 2001 |
| Application of: | | Boehringer Ingelheim Pharmaceuticals, Inc. |
| Authorized Officer | : | Sellers, Dian |
| For | : | NOVEL COMPOUNDS USEFUL AS REVERSIBLE INHIBITORS OF CYSTEINE PROTEASES |

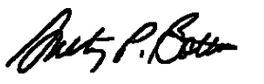
Assistant Commissioner For Patents
Box PCT
Washington, D.C. 20231
Attn: RO/US

## RESPONSE TO INVITATION TO CORRECT DEFECTS IN THE INTERNATIONAL APPLICATION

Sir:

This communication is response to the invitation to correct defects dated 09 April 2001, a copy of which is attached herewith. Specifically, addressing Annex A. In A, part 1, Applicant has withdrawn the designation of the US, therefore all inventor/applicants are now listed only as inventors, this is reflected in the changes to sheets 1-4 in the Request, replacement sheets 1-4 are attached herewith. In part 2 thereof, nationality and residence is now indicated, sheets 1-3 of the Request. This change to the Request is respectfully requested.

Respectfully submitted,



Anthony P. Bottino
Attorney for Applicant(s)
Reg. No. 41,629

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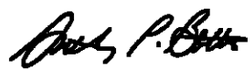
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Patent Department
Boehringer Ingelheim Corp.
900 Ridgebury Road
P.O. Box 368
Ridgefield, CT. 06877
Tel.: (203) 791-6764

I hereby certify that this correspondence is being deposited with the U.S. Postal Service as first class mail in an envelope addressed to:

Assistant Commissioner for Patents
Washington, DC 20231

on April 23, 2001



By: Anthony P. Bottino
Reg. No. 41,629

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# PCT

## REQUEST

The undersigned requests that the present international application be processed according to the Patent Cooperation Treaty.

For receiving Office use only

International Application No.

International Filing Date

Name of receiving Office and "PCT International Application"

Applicant's or agent's file reference *(if desired) (12 characters maximum)* 9/193PCT

**Box No. I TITLE OF INVENTION**

NOVEL COMPOUNDS USEFUL AS REVERSIBLE INHIBITORS OF CYSTEINE PROTEASES

**Box No. II APPLICANT**

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

BOEHRINGER INGELHEIM PHARMACEUTICALS, INC.
900 Ridgebury Road
P.O. Box 368
Ridgefield, CT 06877-0368
United States of America

☐ This person is also inventor.

Telephone No.
203-798-9988

Facsimile No.
203-798-4408

Teleprinter No.

State *(that is, country)* of nationality: US

State *(that is, country)* of residence: US

This person is applicant for the purposes of: ☒ all designated States ☐ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box

**Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)**

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

BEKKALI, Younes
60 Padanaram Road, Unit 34
Danbury, Connecticut 06811
United States of America

This person is:

☐ applicant only

☐ applicant and inventor

☒ inventor only *(If this check-box is marked, do not fill in below.)*

State *(that is, country)* of nationality: CA

State *(that is, country)* of residence: US

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box

☒ Further applicants and/or (further) inventors are indicated on a continuation sheet.

**Box No. IV AGENT OR COMMON REPRESENTATIVE; OR ADDRESS FOR CORRESPONDENCE**

The person identified below is hereby/has been appointed to act on behalf of the applicant(s) before the competent International Authorities as: ☒ agent ☐ common representative

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

RAYMOND, Robert P.; STEMPEL, Alan R.; DEVLIN, Mary Ellen;
BOTTINO, Anthony P.; POCCHIARI, Susan K.; DATLOW, Philip I.;
WITKOWSKI, Timothy X.,
BOEHRINGER INGELHEIM PHARMACEUTICALS, INC.
900 Ridgebury Road, P.O. Box 368
Ridgefield, CT 06877
United States

Telephone No.
203-798-9988

Facsimile No.
203-798-4408

Teleprinter No.

☐ Address for correspondence: Mark this check-box where no agent or common representative is/has been appointed and the space above is used instead to indicate a special address to which correspondence should be sent.

3:74

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**Continuation of Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)**

*If none of the following sub-boxes is used, this sheet should not be included in the request.*

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*
HICKEY, Eugene R.
5 Woodbury Drive
Danbury, Connecticut 06811
United States of America

This person is:
☐ applicant only
☐ applicant and inventor
☒ inventor only *(If this check-box is marked, do not fill in below.)*

State *(that is, country)* of nationality: US
State *(that is, country)* of residence: US

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*
LIU, Wiemen
56 Wakelee Avenue, Ext. #12
Shelton, Connecticut 06484
United States of America

This person is:
☐ applicant only
☐ applicant and inventor
☒ inventor only *(If this check-box is marked, do not fill in below.)*

State *(that is, country)* of nationality: CN
State *(that is, country)* of residence: US

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*
PATEL, Usha R.
20 Dairy Farm Drive
Brookfield, Connecticut 06804
United States of America

This person is:
☐ applicant only
☐ applicant and inventor
☒ inventor only *(If this check-box is marked, do not fill in below.)*

State *(that is, country)* of nationality: US
State *(that is, country)* of residence: US

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*
SPERO, Denise M.
18 Limekiln Road
West Redding, Connecticut 06896
United States of America

This person is:
☐ applicant only
☐ applicant and inventor
☒ inventor only *(If this check-box is marked, do not fill in below.)*

State *(that is, country)* of nationality: US
State *(that is, country)* of residence: US

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box

☒ Further applicants and/or (further) inventors are indicated on another continuation sheet.

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356

**Continuation of Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)**

*If none of the following sub-boxes is used, this sheet should not be included in the request.*

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

SUN, Sanxing

38 Padanaram Avenue, 21B

Danbury, Connecticut 06811

United States of America

This person is:

☐ applicant only

☐ applicant and inventor

☑ inventor only *(If this check-box is marked, do not fill in below.)*

State *(that is, country)* of nationality: CN

State *(that is, country)* of residence: US

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

THOMSON, David S.

166 Minuteman Road

Ridgefield, CT 06877

United States of America

This person is:

☐ applicant only

☐ applicant and inventor

☑ inventor only *(If this check-box is marked, do not fill in below.)*

State *(that is, country)* of nationality: GB

State *(that is, country)* of residence: US

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

WARD, Yancey D.

11 Narraganset Trail

Sandy Hook, Connecticut 06482

United States of America

This person is:

☐ applicant only

☐ applicant and inventor

☑ inventor only *(If this check-box is marked, do not fill in below.)*

State *(that is, country)* of nationality: US

State *(that is, country)* of residence: US

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

YOUNG, Erick R.R.

10292 Avalon Valley Drive

Danbury, Connecticut 06811

United States of America

This person is:

☐ applicant only

☐ applicant and inventor

☑ inventor only *(If this check-box is marked, do not fill in below.)*

State *(that is, country)* of nationality: US

State *(that is, country)* of residence: US

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box

☐ Further applicants and/or (further) inventors are indicated on another continuation sheet.

3/8

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**Box No.V DESIGNATION OF STATES**

The following designations are hereby made under Rule 4.9(a) *(mark the applicable check-boxes; at least one must be marked)*:

Regional Patent

☐ AP ARIPO Patent: GH Ghana, GM Gambia, KE Kenya, LS Lesotho, MW Malawi, MZ Mozambique, SD Sudan, SL Sierra Leone, SZ Swaziland, TZ United Republic of Tanzania, UG Uganda, ZW Zimbabwe, and any other State which is a Contracting State of the Harare Protocol and of the PCT

☑ EA Eurasian Patent: AM Armenia, AZ Azerbaijan, BY Belarus, KG Kyrgyzstan, KZ Kazakhstan, MD Republic of Moldova, RU Russian Federation, TJ Tajikistan, TM Turkmenistan, and any other State which is a Contracting State of the Eurasian Patent Convention and of the PCT

☑ EP European Patent: AT Austria, BE Belgium, CH and LI Switzerland and Liechtenstein, CY Cyprus, DE Germany, DK Denmark, ES Spain, FI Finland, FR France, GB United Kingdom, GR Greece, IE Ireland, IT Italy, LU Luxembourg, MC Monaco, NL Netherlands, PT Portugal, SE Sweden, and any other State which is a Contracting State of the European Patent Convention and of the PCT

☐ OA OAPI Patent: BF Burkina Faso, BJ Benin, CF Central African Republic, CG Congo, CI Côte d'Ivoire, CM Cameroon, GA Gabon, GN Guinea, GW Guinea-Bissau, ML Mali, MR Mauritania, NE Niger, SN Senegal, TD Chad, TG Togo, and any other State which is a member State of OAPI and a Contracting State of the PCT *(if other kind of protection or treatment desired, specify on dotted line)* .....

National Patent *(if other kind of protection or treatment desired, specify on dotted line)*:

| | | | |
|---|---|---|---|
| ☑ AE | United Arab Emirates | ☐ LC | Saint Lucia |
| ☐ AG | Antigua and Barbuda | ☐ LK | Sri Lanka |
| ☐ AL | Albania | ☐ LR | Liberia |
| ☐ AM | Armenia | ☐ LS | Lesotho |
| ☐ AT | Austria | ☑ LT | Lithuania |
| ☑ AU | Australia | ☐ LU | Luxembourg |
| ☐ AZ | Azerbaijan | ☑ LV | Latvia |
| ☐ BA | Bosnia and Herzegovina | ☐ MA | Morocco |
| ☐ BB | Barbados | ☐ MD | Republic of Moldova |
| ☑ BG | Bulgaria | ☐ MG | Madagascar |
| ☑ BR | Brazil | ☐ MK | The former Yugoslav Republic of Macedonia |
| ☐ BY | Belarus | ☐ MN | Mongolia |
| ☐ BZ | Belize | ☐ MW | Malawi |
| ☑ CA | Canada | ☑ MX | Mexico |
| ☐ CH | and LI Switzerland and Liechtenstein | ☐ MZ | Mozambique |
| ☑ CN | China | ☑ NO | Norway |
| ☐ CR | Costa Rica | ☑ NZ | New Zealand |
| ☐ CU | Cuba | ☑ PL | Poland |
| ☑ CZ | Czech Republic | ☐ PT | Portugal |
| ☐ DE | Germany | ☑ RO | Romania |
| ☐ DK | Denmark | ☐ RU | Russian Federation |
| ☐ DM | Dominica | ☐ SD | Sudan |
| ☐ DZ | Algeria | ☐ SE | Sweden |
| ☑ EE | Estonia | ☑ SG | Singapore |
| ☐ ES | Spain | ☑ SI | Slovenia |
| ☐ FI | Finland | ☑ SK | Slovakia |
| ☐ GB | United Kingdom | ☐ SL | Sierra Leone |
| ☐ GD | Grenada | ☐ TJ | Tajikistan |
| ☐ GE | Georgia | ☐ TM | Turkmenistan |
| ☐ GH | Ghana | ☑ TR | Turkey |
| ☐ GM | Gambia | ☐ TT | Trinidad and Tobago |
| ☑ HR | Croatia | ☐ TZ | United Republic of Tanzania |
| ☑ HU | Hungary | ☑ UA | Ukraine |
| ☑ ID | Indonesia | ☐ UG | Uganda |
| ☑ IL | Israel | ☐ US | United States of America |
| ☑ IN | India | ☑ UZ | Uzbekistan |
| ☐ IS | Iceland | ☑ VN | Viet Nam |
| ☑ JP | Japan | ☑ YU | Yugoslavia |
| ☐ KE | Kenya | ☑ ZA | South Africa |
| ☐ KG | Kyrgyzstan | ☐ ZW | Zimbabwe |
| ☐ KP | Democratic People's Republic of Korea | | |
| ☑ KR | Republic of Korea | | |
| ☐ KZ | Kazakhstan | | |

Check-box reserved for designating States which have become party to the PCT after issuance of this sheet:

☑ Colombia .....

**Precautionary Designation Statement:** In addition to the designations made above, the applicant also makes under Rule 4.9(b) all other designations which would be permitted under the PCT except any designation(s) indicated in the Supplemental Box as being excluded from the scope of this statement. The applicant declares that those additional designations are subject to confirmation and that any designation which is not confirmed before the expiration of 15 months from the priority date is to be regarded as withdrawn by the applicant at the expiration of that time limit. *(Confirmation (including fees) must reach the receiving Office within the 15-month time limit.)*

5-9-01 357
LAST DAY 358

# PATENT COOPERATION TREATY

From the RECEIVING OFFICE

To:
ROBERT P. RAYMOND
BOEHRINGER INGELHEIM PHARMACEUTICALS, INC.
900 RIDGEBURY ROAD, P.O. BOX 368
RIDGEFIELD, CT 06877

# PCT

## INVITATION TO CORRECT DEFECTS IN THE INTERNATIONAL APPLICATION

(PCT Articles 3(4)(i) and 14(1) and Rule 26)

| | |
|---|---|
| Applicant's or agent's file reference: 9/193PCT | Date of mailing (day/month/year): 09 APR 2001 |
| International application No.: PCT/US01/08084 | REPLY DUE within 1 month / days from the above date of mailing |
| Applicant: BOEHRINGER INGELHEIM PHARMACEUTICALS, INC. | International filing date (day/month/year): 14 MAR 01 |

1. The applicant is hereby invited, within the time limit indicated above, to correct the defects in the international application as filed, the defects specified on the attached
   - [X] Annex A
   - [ ] Annex B1 *(text matter of the international application as filed)*
   - [ ] Annex C1 *(drawings of the international application as filed)*

2. The applicant is hereby invited, within the time limit indicated above, to correct the defects in the translation of the international application furnished under Rule 12.3, the defects specified on the attached
   - [ ] Annex A
   - [ ] Annex B2 *(text matter of the translation of the international application)*
   - [ ] Annex C2 *(drawings of the translation of the international application)*

**Additional observations (if necessary):**

**HOW TO CORRECT THE DEFECTS?**

Correction must be submitted by filing a replacement sheet embodying the correction and a letter accompanying the replacement sheet, which shall draw attention to the difference between the replaced sheet and the replacement sheet. A correction may be stated in a letter only if it is of such a nature that it can be transferred from the letter to the record copy without adversely affecting the clarity and direct reproducibility of the sheet onto which the correction is to be transferred (Rule 26.4(a)).

**ATTENTION**

Failure to correct the defects will result in the international application being considered withdrawn by this receiving Office (see Rule 26.5 for further details).

A copy of this invitation and any attachments has been sent to the International Bureau and the International Searching Authority. [X]

| | |
|---|---|
| Name and mailing address of the receiving Office<br>Assistant Commissioner for Patent<br>Box PCT<br>Washington, D.C. 20231 Attn:RO/US<br>Facsimile No. 703-305-3230 | Authorized officer<br>Dian Sellers<br>Telephone No. 703-308-3742 |

Form PCT/RO/106 (July 1998)

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# ANNEX A TO FORM PCT/RO/106

International application No.
PCT/US01/08084

**The receiving Office has found the following defects in the international application as filed:**

1. As to signature* of the international application (Rules 4.15 and 90.4), the request:
   - a. ☐ is not signed.
   - b. ☐ is not signed by all applicants.
   - c. ☐ is not accompanied by the statement referred to in the check list in Box No. VIII of the request explaining the lack of the signature of an applicant for the designation of the United States of America.
   - d. ☒ is signed by what appears to be an agent/common representative but
     - ☐ the international application is not accompanied by a power of attorney appointing him.
     - ☒ the power of attorney accompanying the international application was not signed by all the applicants.
   - e. ☐ other (*specify*):
     RE: BEKKALI, Y., HICKEY, E.R., LIU, W., PATEL, U.R., SPERO, D.M., SUN, S., THOMSON, D.S., WARD, Y.D., YOUNG, E.R.R.

* All applicants must sign, including inventors if they are also applicants (e.g. where the United States of America is designated).

2. As to indications concerning the applicant, the request (Rules 4.4 and 4.5):
   - a. ☐ does not properly indicate the applicant's name (*specify*):
   - b. ☐ does not indicate the applicant's address.
   - c. ☐ does not properly indicate the applicant's address (*specify*):
   - d. ☒ does not indicate the applicant's nationality.
   - e. ☒ does not indicate the applicant's residence.
   - f. ☐ other (*specify*):
     RE: BEKKALI, Y., HICKEY, E.R., LIU, W., PATEL, U.R., SPERO, D.M., SUN, S., THOMSON, D.S., WARD, Y.D., YOUNG, E.R.R.

3. As to the language of certain elements of the international application, other than the description and claims (Rules 12.1(c) and 26.3*ter(a) and (c)*):
   - a. ☐ the request is not in a language which is both a language accepted by this receiving Office and a language of publication, which is (are):
   - b. ☐ the text matter of the drawings is not in the language in which the international application is to be published, which is:
   - c. ☐ the abstract is not in the language in which the international application is to be published, which is:

4. The title of the invention:
   - a. ☐ is not indicated in Box No. I of the request (Rule 4.1(a)).
   - b. ☐ is not indicated at the top of the first sheet of the description (Rule 5.1(a)).
   - c. ☐ as appearing in Box No. I of the request is not identical with the title heading the description (Rule 5.1(a)).

5. As to the abstract (Rule 8):
   - ☐ the international application does not contain an abstract.

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# PCT

## REQUEST

The undersigned requests that the present international application be processed according to the Patent Cooperation Treaty.

For receiving Office use only

International Application No. PCT/US 01/08084

International Filing Date RO/US 14MAR2001 (14.03.01)

Name of receiving Office and "PCT International Application"

PCT INTERNATIONAL APPLICATION FOR

Applicant's or agent's file reference *(if desired) (12 characters maximum)* 9/193PCT

**Box No. I TITLE OF INVENTION**

NOVEL COMPOUNDS USEFUL AS REVERSIBLE INHIBITORS OF CYSTEINE PROTEASES

**Box No. II APPLICANT**

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

BOEHRINGER INGELHEIM PHARMACEUTICALS, INC.
900 Ridgebury Road
P.O. Box 368
Ridgefield, CT 06877-0368
United States of America

☐ This person is also inventor.

Telephone No. 203-798-9988

Facsimile No. 203-798-4408

Teleprinter No.

State *(that is, country)* of nationality: US

State *(that is, country)* of residence: US

This person is applicant for this purpose of: ☒ all designated States ☐ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box

**Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)**

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

BEKKALI, Younes

60 Padanaram Road, Unit 34

Danbury, Connecticut 06811
United States of America

This person is:

☐ applicant only

☒ applicant and inventor

☒ inventor only *(If this check-box is marked, do not fill in below.)*

State *(that is, country)* of nationality: CA

State *(that is, country)* of residence:

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box

☒ Further applicants and/or (further) inventors are indicated on a continuation sheet.

**Box No. IV AGENT OR COMMON REPRESENTATIVE; OR ADDRESS FOR CORRESPONDENCE**

The person identified below is hereby/has been appointed to act on behalf of the applicant(s) before the competent International Authorities as: ☐ agent ☐ common representative

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

RAYMOND, Robert P.; STEMPEL, Alan R.; DEVLIN, Mary Ellen; BOTTINO, Anthony P.; POCCHIARI, Susan K.; DATLOW, Philip I.; WITKOWSKI, Timothy X.,
BOEHRINGER INGELHEIM PHARMACEUTICALS, INC.
900 Ridgebury Road, P.O. Box 368
Ridgefield, CT 06877
United States of America

Telephone No. 203-798-9988

Facsimile No. 203-798-4408

Teleprinter No.

☐ Address for correspondence: Mark this check-box where no agent or common representative is/has been appointed and the space above is used instead to indicate a special address to which correspondence should be sent.



deleted by RO/US

A RO/US

Sheet No. 2

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| Continuation of Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S) | |
|---|---|
| *If none of the following sub-boxes is used, this sheet should not be included in the request.* | |
| Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*<br>HICKEY, Eugene R.<br>5 Woodbury Drive<br>Danbury, Connecticut 06811<br>United States of America | This person is:<br>☐ applicant only<br>☒ applicant and inventor<br>☒ inventor only *(If this check-box is marked, do not fill in below.)* |
| State *(that is, country)* of nationality: | State *(that is, country)* of residence: |
| This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box | |

deleted by RO/US

| Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*<br>LIU, Wiemen<br>56 Wakelee Avenue, Ext. #12<br>Shelton, Connecticut 06484<br>United States of America | This person is:<br>☐ applicant only<br>☒ applicant and inventor<br>☒ inventor only *(If this check-box is marked, do not fill in below.)* |
|---|---|
| State *(that is, country)* of nationality:<br>CN | State *(that is, country)* of residence: |
| This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box | |

RO/US

| Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*<br>PATEL, Usha R.<br>20 Dairy Farm Drive<br>Brookfield, Connecticut 06804<br>United States of America | This person is:<br>☐ applicant only<br>☒ applicant and inventor<br>☒ inventor only *(If this check-box is marked, do not fill in below.)* |
|---|---|
| State *(that is, country)* of nationality: | State *(that is, country)* of residence: |
| This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box | |

| Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*<br>SPERO, Denise M.<br>18 Limekiln Road<br>West Redding, Connecticut 06896<br>United States of America | This person is:<br>☐ applicant only<br>☒ applicant and inventor<br>☒ inventor only *(If this check-box is marked, do not fill in below.)* |
|---|---|
| State *(that is, country)* of nationality: | State *(that is, country)* of residence: |
| This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box | |

☒ Further applicants and/or (further) inventors are indicated on another continuation sheet.

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**Continuation of Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)**

*If none of the following sub-boxes is used, this sheet should not be included in the request.*

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

SUN, Sanxing

38 Padanaram Avenue, 21B

Danbury, Connecticut 06811

United States of America

This person is:

☐ applicant only

☒ ▲ applicant and inventor

☑ ▲▲ inventor only *(If this check-box is marked, do not fill in below.)*

State *(that is, country)* of nationality: CN

State *(that is, country)* of residence:

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box

---

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

THOMSON, David S.

166 Minuteman Road

Ridgefield, CT 06877

United States of America

This person is:

☐ applicant only

☒ ▲ applicant and inventor

☑ ▲▲ inventor only *(If this check-box is marked, do not fill in below.)*

State *(that is, country)* of nationality: GB

State *(that is, country)* of residence:

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box

---

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

WARD, Yancey D.

11 Narragansett Trail

Sandy Hook, Connecticut 06482

United States of America

This person is:

☐ applicant only

☒ ▲ applicant and inventor

☑ ▲▲ inventor only *(If this check-box is marked, do not fill in below.)*

State *(that is, country)* of nationality:

State *(that is, country)* of residence:

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box

---

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

YOUNG, Erick R.R.

10292 Avalon Valley Drive

Danbury, Connecticut 06811

United States of America

This person is:

☐ applicant only

☒ ▲ applicant and inventor

☑ ▲▲ inventor only *(If this check-box is marked, do not fill in below.)*

State *(that is, country)* of nationality:

State *(that is, country)* of residence:

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box

---

☐ Further applicants and/or (further) inventors are indicated on another continuation sheet.



▲ delete by RO/US

▲ RO/US

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# PATENT COOPERATION TREATY

From the RECEIVING OFFICE

To:
ROBERT P. RAYMOND
BOEHRINGER INGELHEIM PHARMACEUTICALS, INC.
900 RIDGEBURY ROAD, P.O. BOX 368
RIDGEFIELD, CT 06877

# PCT

NOTIFICATION REGARDING CERTAIN CORRECTIONS MADE *EX OFFICIO*

(PCT Administrative Instructions, Section 327)

| | |
|---|---|
| Date of mailing *(day/month/year)* | 09 APR 2001 |
| Applicant's or agent's file reference: 9/193PCT | REPLY DUE: NONE. However, see paragraph 3 below |
| International application No.: PCT/US01/08084 | International filing date *(day/month/year)*: 14 MAR 01 |
| Applicant: BOEHRINGER INGELHEIM PHARMACEUTICALS, INC. | |

1. The applicant is hereby notified that this receiving Office has corrected formal defects in the international application *ex officio*, as shown on the attached copy of:

- [x] the request, sheet No.: 1, 2, 3
- [ ] the description, sheet No.: _____
- [ ] the claims, sheet No.: _____
- [ ] the drawings, sheet No.: _____
- [ ] other *(specify)*: _____

2. If the applicant agrees with these corrections, no further action is required in this regard.

3. In case of disagreement with these corrections, the applicant should promply inform this receiving Office accordingly.

| | |
|---|---|
| Name and mailing address of the receiving Office<br>Assistant Commissioner for Patent<br>Box PCT<br>Washington, D.C. 20231 Attn:RO/US<br>Facsimile No. 703-305-3230 | Authorized officer<br>Dian Sellers<br><br>Telephone No. 703-308-3742 |

Form PCT/RO/146 (July 1992)

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| TO: | UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) |
|---|---|
| ROBERT P. RAYMOND<br>BOEHRINGER INGELHEIM PHARMACEUTICALS, INC.<br>900 RIDGEBURY ROAD, P.O. BOX 368<br>RIDGEFIELD, CT 06877 | NOTIFICATION FSTATUS OF REQUIREMENTS UNDER 35 U.S.C. 371 |
| | DATE OF MAILING (day/month/year) 09 APR 2001 |
| | FILE REFERENCE 9/193PCT |

**IDENTIFICATION OF INTERNATIONAL APPLICATION**

| International application No. | International filing date (day/month/year) | Priority Date Claimed |
|---|---|---|
| PCT/US01/08084 | 14 MAR 01 | 08 SEP 00 |

Applicant for DO/EO/US

EMMANUEL, MICHEL JOSE

**NOTIFICATION**

The applicant is hereby advised that the U.S. Patent and Trademark Office in its capacity as [X] Designated Office [ ] Elected Office has received following items as of the date of mailing indicated above.

1. [ ] U.S. Nation fee [35 U.S.C 371 (c) (1)]
2. [ ] Oath of declaration [35 U.S.C 371 (c) (4)]
3. [X] Copy of International application as [35 U.S.C 371 (c) (2)]
4. [ ] Translation of Application [35 U.S.C 371 (c) (2)]
5. [ ] Amendments under PCT Article 19 [35 U.S.C 371 (c) (3)]
6. [ ] Translation of PCT Article 19 Amendments [35 U.S.C 371 (c) (3)]
7. [ ] Search Report or Declaration under PCT Article 17(2) [35 U.S.C 371 (a)]
8. [ ] International Preliminary Examination Report and its Annexes, if any, under PCT Article 36(3)(b) [35 U.S.C 371 (a)]
9. [ ] Translation of Annexs to the International Preliminary Examination Report under PCT Article 36(3)(b) [35 U.S.C 371 (c) (5)]
10. [ ] Other items received:
    - [ ] Assignment Document
    - [ ] Prior Art Statement
    - [ ] Preliminary Amendment

A. [ ] Requirements for U.S. National processing have been met. Processing will commence
   - [ ] at the expiration of the applicable time limit under either
     - [ ] PCT Article 22 [35 U.S.C 371 (b)] or
     - [ ] PCT Article 39 [35 U.S.C 371 (b)]
   - [ ] on the date indicated below under the provisions of 35 U.S.C 371 (f)

| U.S. NATIONAL SERIAL# | DATE UNDER 35 U.S.C. 102(e) | DATE OF COMMENCEMENT OF NATIONAL PROCESSING |
|---|---|---|
| | | |

*All correspondence submitted after the date of commencement of U.S. National processing indicated above should refer to the U.S. National Serial Number and the appropriate U.S. National processing organization of Officer.*

B. [ ] As the above identified application has been accepted for U.S. National processing under the provision of 35 U.S.C.371 (f) before expiration of the applicable time limit under [ ] PCT Article 22 [ ] PCT Article 39, applicant is reminded that
   - [ ] Amendments under PCT Article 19 and/or
   - [ ] the International Preliminary Examination Report and its Annexes, if any, under PCT Article 36(3) (a), and (b) and any translation thereof, if applicable, must be submitted to the Patent and Trademark Office as soon as they are available.

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| International application No. | International filing date | Priority Date Claimed |
|---|---|---|
| PCT/US01/08084 | 14 MAR 01 | 08 SEP 00 |

C. [X] In order that U.S. National processing may begin, certain items must be received by the DO/EO/US by the expiration of applicable time limit under

- [X] PCT Article 22 or
- [X] PCT Article 39.

Specifically:

- [X] 1. U.S. National Fee
- [X] 2. Oath or Declaration
- [ ] 3. Copy of Application
- [ ] 4. Translation of application
- [X] 5. Amendments under PCT Article 19, if any
- [ ] 6. Translation of PCT Article 19 Amendments, if applicable
- [ ] 7. Search Report or PCT Article 17(2) declaration
- [ ] 8. International Preliminary Examination Report and its Annexes, if any, under PCT Article 36(3)(a), if applicable
- [ ] 9. Translation of Annexes to the International Preliminary Examination Report under PCT Article 36(3)(b), if appliable

***THE ABOVE CHECK ITEMS MUST BE TIMELY RECEIVED TO AVOID ABANDONMENT OF THE APPLICATION. [35. U.S.C. 371(d)]***

D. Further information for the applicant:

This is only a reminder.

**UNITED STATES DESIGNATED/ELECTED OFFICE**

| Address Only: | Authorized Officer |
|---|---|
| Assistant Commissioner for Patent<br>Box PCT<br>Washington, D.C. 20231 Attn:RO/US | Dian Sellers Dian Sellers<br>703-305-3742 |

Form PCT/DO/EO/901(b)(U.S VERSION)(4-97) U.S. DEPARTMENT of COMMERCE-Patent and Trademark

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*This sheet is not part of and does not count as a sheet of the international application.*

# PCT

## FEE CALCULATION SHEET

**Annex to the Request**

For receiving Office use only

International application No. PCT/US 01/08084

Date stamp of the receiving Office RO/US 14 MAR 2001 (14.03.01)

Applicant's or agent's file reference 9/193PCT

Applicant: BOEHRINGER INGELHEIM PHARMACEUTICALS, INC.

**CALCULATION OF PRESCRIBED FEES**

1. TRANSMITTAL FEE . . . . . 240.00 T — 240

2. SEARCH FEE . . . . . 450.00 S — 450

International search to be carried out by EPO

*(If two or more International Searching Authorities are competent in relation to the international application, indicate the name of the Authority which is chosen to carry out the international search.)*

3. INTERNATIONAL FEE . 289

Basic Fee

The international application contains 254 sheets.

first 30 sheets . . . . . 382.00 b1 — 382

254 − 259 remaining sheets × 9.00 additional amount = 2286.00 2331 b2 — 2331

Add amounts entered at b1 and b2 and enter total at B . . . . 2668.00 2713 B — 2713

Designation Fees

The international application contains 38 designations.

8 − 6 number of designation fees payable *(maximum 8)* × 82.00 amount of designation fee = 656.00 492 D — 492

Add amounts entered at B and D and enter total at I . . . . . 3324.00 I — 3205

*(Applicants from certain States are entitled to a reduction of 75% of the international fee. Where the applicant is (or all applicants are) so entitled, the total to be entered at I is 25% of the sum of the amounts entered at B and D.)*

4. FEE FOR PRIORITY DOCUMENT *(if applicable)* . . . . . 15.00 P — 15

5. TOTAL FEES PAYABLE . . . . . 4028.00 TOTAL — 3910

Add amounts entered at T, S, I and P, and enter total in the TOTAL box

☐ The designation fees are not paid at this time.

**MODE OF PAYMENT**

☒ authorization to charge deposit account (see below) ☐ bank draft ☐ coupons

☐ cheque ☐ cash ☐ other *(specify)*:

☐ postal money order ☐ revenue stamps

**DEPOSIT ACCOUNT AUTHORIZATION** *(this mode of payment may not be available at all receiving Offices)*

The RO/ US ☒ is hereby authorized to charge the total fees indicated above to my deposit account.

☒ *(this check-box may be marked only if the conditions for deposit accounts of the receiving Office so permit)* is hereby authorized to charge any deficiency or credit any overpayment in the total fees indicated above to my deposit account.

☐ is hereby authorized to charge the fee for preparation and transmittal of the priority document to the International Bureau of WIPO to my deposit account.

02-2955 — Deposit Account No.

13 March 2001 — Date *(day/month/year)*

Signature

Form PCT/RO/101 (Annex) (January 2000; reprint July 2000)

*See Notes to the fee calculation sheet*

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# PCT

## REQUEST

The undersigned requests that the present international application be processed according to the Patent Cooperation Treaty.

For receiving Office use only

International Application No.

International Filing Date

Name of receiving Office and "PCT International Application"

Applicant's or agent's file reference *(if desired) (12 characters maximum)* 9/193PCT

**Box No. I TITLE OF INVENTION**

NOVEL COMPOUNDS USEFUL AS REVERSIBLE INHIBITORS OF CYSTEINE PROTEASES

**Box No. II APPLICANT**

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BOEHRINGER INGELHEIM PHARMACEUTICALS, INC.
900 Ridgebury Road
P.O. Box 368
Ridgefield, CT 06877-0368
United States

☐ This person is also inventor.

Telephone No. 203-798-9988

Facsimile No. 203-798-4408

Teleprinter No.

State *(that is, country)* of nationality: US

State *(that is, country)* of residence: US

This person is applicant for the purposes of: ☒ all designated States ☐ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box

**Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)**

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BEKKALI, Younes

60 Padanaram Road, Unit 34

Danbury, Connecticut 06811
United States

This person is:

☐ applicant only

☐ applicant and inventor

☒ inventor only *(If this check-box is marked, do not fill in below.)*

State *(that is, country)* of nationality: CA

State *(that is, country)* of residence:

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box

☒ Further applicants and/or (further) inventors are indicated on a continuation sheet.

**Box No. IV AGENT OR COMMON REPRESENTATIVE; OR ADDRESS FOR CORRESPONDENCE**

The person identified below is hereby/has been appointed to act on behalf of the applicant(s) before the competent International Authorities as: ☐ agent ☐ common representative

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

RAYMOND, Robert P.; STEMPEL, Alan R.; DEVLIN, Mary Ellen;
BOTTINO, Anthony P.; POCCHIARI, Susan K.; DATLOW, Philip I.;
WITKOWSKI, Timothy X.,
BOEHRINGER INGELHEIM PHARMACEUTICALS, INC.
900 Ridgebury Road, P.O. Box 368
Ridgefield, CT 06877
United States

Telephone No. 203-798-9988

Facsimile No. 203-798-4408

Teleprinter No.

☐ Address for correspondence: Mark this check-box where no agent or common representative is/has been appointed and the space above is used instead to indicate a special address to which correspondence should be sent.

367

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**Continuation of Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)**

*If none of the following sub-boxes is used, this sheet should not be included in the request.*

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*
HICKEY, Eugene R.

5 Woodbury Drive

Danbury, Connecticut 06811

United States of America

This person is:
- ☐ applicant only
- ☐ applicant and inventor
- ☒ inventor only *(If this check-box is marked, do not fill in below.)*

State *(that is, country)* of nationality:

State *(that is, country)* of residence:

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*
LIU, Wiemen

56 Wakelee Avenue, Ext. #12

Shelton, Connecticut 06484

United States of America

This person is:
- ☐ applicant only
- ☐ applicant and inventor
- ☒ inventor only *(If this check-box is marked, do not fill in below.)*

State *(that is, country)* of nationality:
CN

State *(that is, country)* of residence:

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*
PATEL, Usha R.

20 Dairy Farm Drive

Brookfield, Connecticut 06804

United States of America

This person is:
- ☐ applicant only
- ☐ applicant and inventor
- ☒ inventor only *(If this check-box is marked, do not fill in below.)*

State *(that is, country)* of nationality:

State *(that is, country)* of residence:

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*
SPERO, Denise M.

18 Limekiln Road

West Redding, Connecticut 06896

United States of America

This person is:
- ☐ applicant only
- ☐ applicant and inventor
- ☒ inventor only *(If this check-box is marked, do not fill in below.)*

State *(that is, country)* of nationality:

State *(that is, country)* of residence:

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box

☒ Further applicants and/or (further) inventors are indicated on another continuation sheet.

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**Continuation of Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)**

*If none of the following sub-boxes is used, this sheet should not be included in the request.*

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

SUN, Sanxing

38 Padanaram Avenue, 21B

Danbury, Connecticut 06811

United States of America

This person is:

- ☐ applicant only
- ☐ applicant and inventor
- ☑ inventor only *(If this check-box is marked, do not fill in below.)*

State *(that is, country)* of nationality: CN

State *(that is, country)* of residence:

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

THOMSON, David S.

166 Minuteman Road

Ridgefield, CT 06877

United States of America

This person is:

- ☐ applicant only
- ☐ applicant and inventor
- ☑ inventor only *(If this check-box is marked, do not fill in below.)*

State *(that is, country)* of nationality: GB

State *(that is, country)* of residence:

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

WARD, Yancey D.

11 Narragansett Trail

Sandy Hook, Connecticut 06482

United States of America

This person is:

- ☐ applicant only
- ☐ applicant and inventor
- ☑ inventor only *(If this check-box is marked, do not fill in below.)*

State *(that is, country)* of nationality:

State *(that is, country)* of residence:

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

YOUNG, Erick R.R.

10292 Avalon Valley Drive

Danbury, Connecticut 06811

United States of America

This person is:

- ☐ applicant only
- ☐ applicant and inventor
- ☑ inventor only *(If this check-box is marked, do not fill in below.)*

State *(that is, country)* of nationality:

State *(that is, country)* of residence:

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box

☐ Further applicants and/or (further) inventors are indicated on another continuation sheet.

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**Box No.V DESIGNATION OF STATES**

The following designations are hereby made under Rule 4.9(a) *(mark the applicable check-boxes; at least one must be marked)*:

**Regional Patent**

- ☐ AP ARIPO Patent: GH Ghana, GM Gambia, KE Kenya, LS Lesotho, MW Malawi, MZ Mozambique, SD Sudan, SL Sierra Leone, SZ Swaziland, TZ United Republic of Tanzania, UG Uganda, ZW Zimbabwe, and any other State which is a Contracting State of the Harare Protocol and of the PCT
- ☑ EA Eurasian Patent: AM Armenia, AZ Azerbaijan, BY Belarus, KG Kyrgyzstan, KZ Kazakhstan, MD Republic of Moldova, RU Russian Federation, TJ Tajikistan, TM Turkmenistan, and any other State which is a Contracting State of the Eurasian Patent Convention and of the PCT
- ☑ EP European Patent: AT Austria, BE Belgium, CH and LI Switzerland and Liechtenstein, CY Cyprus, DE Germany, DK Denmark, ES Spain, FI Finland, FR France, GB United Kingdom, GR Greece, IE Ireland, IT Italy, LU Luxembourg, MC Monaco, NL Netherlands, PT Portugal, SE Sweden, and any other State which is a Contracting State of the European Patent Convention and of the PCT
- ☐ OA OAPI Patent: BF Burkina Faso, BJ Benin, CF Central African Republic, CG Congo, CI Côte d'Ivoire, CM Cameroon, GA Gabon, GN Guinea, GW Guinea-Bissau, ML Mali, MR Mauritania, NE Niger, SN Senegal, TD Chad, TG Togo, and any other State which is a member State of OAPI and a Contracting State of the PCT *(if other kind of protection or treatment desired, specify on dotted line)* .....

**National Patent** *(if other kind of protection or treatment desired, specify on dotted line)*:

| | | | |
|---|---|---|---|
| ☑ AE | United Arab Emirates | ☐ LC | Saint Lucia |
| ☐ AG | Antigua and Barbuda | ☐ LK | Sri Lanka |
| ☐ AL | Albania | ☐ LR | Liberia |
| ☐ AM | Armenia | ☐ LS | Lesotho |
| ☐ AT | Austria | ☑ LT | Lithuania |
| ☑ AU | Australia | ☐ LU | Luxembourg |
| ☐ AZ | Azerbaijan | ☑ LV | Latvia |
| ☐ BA | Bosnia and Herzegovina | ☐ MA | Morocco |
| ☐ BB | Barbados | ☐ MD | Republic of Moldova |
| ☑ BG | Bulgaria | ☐ MG | Madagascar |
| ☑ BR | Brazil | ☐ MK | The former Yugoslav Republic of Macedonia |
| ☐ BY | Belarus | ☐ MN | Mongolia |
| ☐ BZ | Belize | ☐ MW | Malawi |
| ☑ CA | Canada | ☑ MX | Mexico |
| ☐ CH | and LI Switzerland and Liechtenstein | ☐ MZ | Mozambique |
| ☑ CN | China | ☑ NO | Norway |
| ☐ CR | Costa Rica | ☑ NZ | New Zealand |
| ☐ CU | Cuba | ☑ PL | Poland |
| ☑ CZ | Czech Republic | ☐ PT | Portugal |
| ☐ DE | Germany | ☑ RO | Romania |
| ☐ DK | Denmark | ☐ RU | Russian Federation |
| ☐ DM | Dominica | ☐ SD | Sudan |
| ☐ DZ | Algeria | ☐ SE | Sweden |
| ☑ EE | Estonia | ☑ SG | Singapore |
| ☐ ES | Spain | ☑ SI | Slovenia |
| ☐ FI | Finland | ☑ SK | Slovakia |
| ☐ GB | United Kingdom | ☐ SL | Sierra Leone |
| ☐ GD | Grenada | ☐ TJ | Tajikistan |
| ☐ GE | Georgia | ☐ TM | Turkmenistan |
| ☐ GH | Ghana | ☑ TR | Turkey |
| ☐ GM | Gambia | ☐ TT | Trinidad and Tobago |
| ☑ HR | Croatia | ☐ TZ | United Republic of Tanzania |
| ☑ HU | Hungary | ☑ UA | Ukraine |
| ☑ ID | Indonesia | ☐ UG | Uganda |
| ☑ IL | Israel | ☑ US | United States of America |
| ☑ IN | India | ☑ UZ | Uzbekistan |
| ☐ IS | Iceland | ☑ VN | Viet Nam |
| ☑ JP | Japan | ☑ YU | Yugoslavia |
| ☐ KE | Kenya | ☑ ZA | South Africa |
| ☐ KG | Kyrgyzstan | ☐ ZW | Zimbabwe |
| ☐ KP | Democratic People's Republic of Korea | | Check-box reserved for designating States which have become party to the PCT after issuance of this sheet: |
| ☑ KR | Republic of Korea | ☑ | Colombia |
| ☐ KZ | Kazakhstan | | |

**Precautionary Designation Statement:** In addition to the designations made above, the applicant also makes under Rule 4.9(b) all other designations which would be permitted under the PCT except any designation(s) indicated in the Supplemental Box as being excluded from the scope of this statement. The applicant declares that those additional designations are subject to confirmation and that any designation which is not confirmed before the expiration of 15 months from the priority date is to be regarded as withdrawn by the applicant at the expiration of that time limit. *(Confirmation (including fee) must reach the receiving Office within the 15-month time limit.)*

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**Box No. VI PRIORITY CLAIM** ☐ Further priority claims are indicated in the Supplemental Box.

| Filing date of earlier application (day/month/year) | Number of earlier application | Where earlier application is: | | |
|---|---|---|---|---|
| | | national application: country | regional application:* regional Office | international application: receiving Office |
| item (1) 08 September 2000 | 09/655,351 | US | | |
| item (2) | | | | |
| item (3) | | | | |

☒ The receiving Office is requested to prepare and transmit to the International Bureau a certified copy of the earlier application(s) *(only if the earlier application was filed with the Office which for the purposes of the present international application is the receiving Office)* identified above as item(s): #1

* *Where the earlier application is an ARIPO application, it is mandatory to indicate in the Supplemental Box at least one country party to the Paris Convention for the Protection of Industrial Property for which that earlier application was filed (Rule 4.10(b)(ii)). See Supplemental Box.*

**Box No. VII INTERNATIONAL SEARCHING AUTHORITY**

**Choice of International Searching Authority (ISA)** *(if two or more International Searching Authorities are competent to carry out the international search, indicate the Authority chosen; the two-letter code may be used)*:

ISA/ EPO

**Request to use results of earlier search; reference to that search** *(if an earlier search has been carried out by or requested from the International Searching Authority)*:

Date *(day/month/year)* Number Country *(or regional Office)*

**Box No. VIII CHECK LIST; LANGUAGE OF FILING**

This international application contains the following number of sheets:

| | |
|---|---|
| request | : 6 |
| description (excluding sequence listing part) | : 251 |
| claims | : 32 |
| abstract | : 1 |
| drawings | : |
| sequence listing part of description | : |
| Total number of sheets | : 289 |

This international application is accompanied by the item(s) marked below:

1. ☒ fee calculation sheet
2. ☐ separate signed power of attorney
3. ☒ copy of general power of attorney; reference number, if any:
4. ☐ statement explaining lack of signature
5. ☐ priority document(s) identified in Box No. VI as item(s):
6. ☐ translation of international application into (language):
7. ☐ separate indications concerning deposited microorganism or other biological material
8. ☐ nucleotide and/or amino acid sequence listing in computer readable form
9. ☐ other *(specify)*:

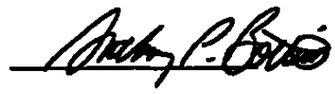
Figure of the drawings which should accompany the abstract:

Language of filing of the international application: English

**Box No. IX SIGNATURE OF APPLICANT OR AGENT**

*Next to each signature, indicate the name of the person signing and the capacity in which the person signs (if such capacity is not obvious from reading the request).*

Anthony P. Bottino, Agent



**For receiving Office use only**

| | |
|---|---|
| 1. Date of actual receipt of the purported international application: | 2. Drawings: |
| 3. Corrected date of actual receipt due to later but timely received papers or drawings completing the purported international application: | ☐ received: |
| 4. Date of timely receipt of the required corrections under PCT Article 11(2): | ☐ not received: |
| 5. International Searching Authority (if two or more are competent): ISA/ EPO | 6. ☐ Transmittal of search copy delayed until search fee is paid. |

**For International Bureau use only**

Date of receipt of the record copy by the International Bureau:

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*This sheet is not part of and does not count as a sheet of the international application.*

# PCT

## FEE CALCULATION SHEET
**Annex to the Request**

For receiving Office use only

International application No.

Date stamp of the receiving Office

Applicant's or agent's file reference 9193PCT

Applicant
BOEHRINGER INGELHEIM PHARMACEUTICALS, INC.

**CALCULATION OF PRESCRIBED FEES**

1. TRANSMITTAL FEE . . . . . 240.00 T

2. SEARCH FEE . . . . . 450.00 S

International search to be carried out by EPO

*(If two or more International Searching Authorities are competent in relation to the international application, indicate the name of the Authority which is chosen to carry out the international search.)*

3. INTERNATIONAL FEE

**Basic Fee**

The international application contains 284 sheets.

first 30 sheets . . . . . 382.00 b1

254 remaining sheets x 9.00 additional amount = 2286.00 b2

Add amounts entered at b1 and b2 and enter total at B . . . . 2668.00 B

**Designation Fees**

The international application contains 38 designations.

8 number of designation fees payable *(maximum 8)* x 82.00 amount of designation fee = 656.00 D

Add amounts entered at B and D and enter total at I . . . . . 3324.00 I

*(Applicants from certain States are entitled to a reduction of 75% of the international fee. Where the applicant is (or all applicants are) so entitled, the total to be entered at I is 25% of the sum of the amounts entered at B and D.)*

4. FEE FOR PRIORITY DOCUMENT *(if applicable)* . . . . . 15.00 P

5. TOTAL FEES PAYABLE . . . . . 4029.00

Add amounts entered at T, S, I and P, and enter total in the TOTAL box TOTAL

☐ The designation fees are not paid at this time.

**MODE OF PAYMENT**

☒ authorization to charge deposit account (see below)
☐ bank draft
☐ coupons
☐ cheque
☐ cash
☐ other *(specify):*
☐ postal money order
☐ revenue stamps

**DEPOSIT ACCOUNT AUTHORIZATION** *(this mode of payment may not be available at all receiving Offices)*

The RO/ US ☒ is hereby authorized to charge the total fees indicated above to my deposit account.

☒ *(this check-box may be marked only if the conditions for deposit accounts of the receiving Office so permit)* is hereby authorized to charge any deficiency or credit any overpayment in the total fees indicated above to my deposit account.

☐ is hereby authorized to charge the fee for preparation and transmittal of the priority document to the International Bureau of WIPO to my deposit account.

02-2955 Deposit Account No.

13 March 2001 Date *(day/month/year)*

Signature



*See Notes to the fee calculation sheet*

*This sheet is not part of and does not count as a sheet of the international application.*

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# PCT

## FEE CALCULATION SHEET
### Annex to the Request

For receiving Office use only

International application No.

Date stamp of the receiving Office

Applicant's or agent's file reference 8/183PCT

Applicant
BOEHRINGER INGELHEIM PHARMACEUTICALS, INC.

**CALCULATION OF PRESCRIBED FEES**

1. TRANSMITTAL FEE . . . . . 240.00 T

2. SEARCH FEE . . . . . 450.00 S

International search to be carried out by EPO

*(If two or more International Searching Authorities are competent in relation to the international application, indicate the name of the Authority which is chosen to carry out the international search.)*

3. INTERNATIONAL FEE

Basic Fee

The international application contains 284 sheets.

first 30 sheets . . . . . 382.00 b1

254 remaining sheets x 9.00 additional amount = 2286.00 b2

Add amounts entered at b1 and b2 and enter total at B . . . . 2668.00 B

Designation Fees

The international application contains 38 designations.

8 number of designation fees payable *(maximum 8)* x 82.00 amount of designation fee = 656.00 D

Add amounts entered at B and D and enter total at I . . . . . 3324.00 I

*(Applicants from certain States are entitled to a reduction of 75% of the international fee. Where the applicant is (or all applicants are) so entitled, the total to be entered at I is 25% of the sum of the amounts entered at B and D.)*

4. FEE FOR PRIORITY DOCUMENT *(if applicable)* . . . . . 15.00 P

5. TOTAL FEES PAYABLE . . . . . 4029.00

Add amounts entered at T, S, I and P, and enter total in the TOTAL box TOTAL

☐ The designation fees are not paid at this time.

**MODE OF PAYMENT**

☒ authorization to charge deposit account (see below)
☐ bank draft
☐ coupons
☐ cheque
☐ cash
☐ other *(specify)*:
☐ postal money order
☐ revenue stamps

**DEPOSIT ACCOUNT AUTHORIZATION** *(this mode of payment may not be available at all receiving Offices)*

The RO/ US ☒ is hereby authorized to charge the total fees indicated above to my deposit account.

☒ *(this check-box may be marked only if the conditions for deposit accounts of the receiving Office so permit)* is hereby authorized to charge any deficiency or credit any overpayment in the total fees indicated above to my deposit account.

☐ is hereby authorized to charge the fee for preparation and transmittal of the priority document to the International Bureau of WIPO to my deposit account.

02-2855 (Deposit Account No.)

13 March 2001 (Date *(day/month/year)*)

Signature

Form PCT/RO/101 (Annex) (January 2000; reprint July 2000)

*See Notes to the fee calculation sheet*

DUPLICATE

# PCT

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## GENERAL POWER OF ATTORNEY

*(for several international applications filed under the Patent Cooperation Treaty)*

(PCT Rule 90.5)

The undersigned person(s):
*(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

BOEHRINGER INGELHEIM PHARMACEUTICALS, INC.
900 Ridgebury Road, P.O. Box 368
Ridgefield, Connecticut 06877
United States of America

hereby appoint(s) the following person as: ☒ agent ☐ common representative

Name and address
*(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

RAYMOND, Robert P.
STEMPEL, Alan R.
DEVLIN, Mary-Ellen M.
BOTTINO, Anthony P.
POCCHIARI, Susan K.
DATLOW, Philip I.
WITKOWSKI, Timothy X.

to represent the undersigned before

☒ all the competent International Authorities
☐ the International Searching Authority only
☐ the International Preliminary Examining Authority only

in connection with any and all international applications filed by the undersigned with the following Office

THE UNITED STATES PATENT AND TRADEMARK OFFICE as receiving Office

and to make or receive payments on behalf of the undersigned.

Signature(s) *(where there are several persons, each of them must sign; next to each signature, indicate the name of the person signing and the capacity in which the person signs, if such capacity is not obvious from reading this power)*

BOEHRINGER INGELHEIM PHARMACEUTICALS, INC.

By: Ursula B. Bartels
Secretary

Date: 2/15/00

Form PCT/Model of general power of attorney (for several international applications) (July 1992)

File Demand 4-8-02 Last Day PCT/US01/08084

PATENT COOPERATION TREATY

National Phase 03-08-03 Last Day 375

From the INTERNATIONAL BUREAU

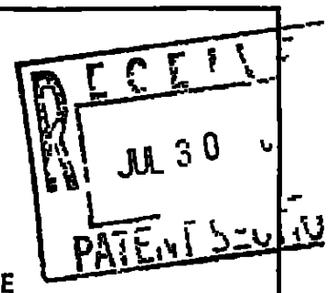
# PCT

## NOTIFICATION CONCERNING SUBMISSION OR TRANSMITTAL OF PRIORITY DOCUMENT

(PCT Administrative Instructions Section 411)

To

RAYMOND Robert P
Boehringer Ingelheim
Pharmaceuticals Inc
900 Ridgebury Road
P O Box 368
Ridgefield CT 06877
ETATS UNIS D AMERIQUE




| | |
|---|---|
| Date of mailing (day/month/year)<br>19 July 2001 (19 07 01) | |
| Applicant's or agent's file reference<br>9/193PCT | IMPORTANT NOTIFICATION |
| International application No.<br>PCT/US01/08084 | International filing date (day/month/year)<br>14 March 2001 (14 03 01) |
| International publication date (day/month/year)<br>Not yet published | Priority date (day/month/year)<br>08 September 2000 (08 09 00) |
| Applicant<br>BOEHRINGER INGELHEIM PHARMACEUTICALS INC et al | |

1 The applicant is hereby notified of the date of receipt (except where the letters NR appear in the right hand column) by the International Bureau of the priority document(s) relating to the earlier application(s) indicated below Unless otherwise indicated by an asterisk appearing next to a date of receipt, or by the letters NR in the right hand column the priority document concerned was submitted or transmitted to the International Bureau in compliance with Rule 17 1(a) or (b)

2 This updates and replaces any previously issued notification concerning submission or transmittal of priority documents

3. An asterisk, ) appearing next to a date of receipt, in the right hand column denotes a priority document submitted or transmitted to the International Bureau but not in compliance with Rule 17 1(a) or (b) In such a case the attention of the applicant is directed to Rule 17 1(c) which provides that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity upon entry into the national phase to furnish the priority document within a time limit which is reasonable under the circumstances.

4. The letters NR" appearing in the right hand column denote a priority document which was not received by the International Bureau or which the applicant did not request the receiving Office to prepare and transmit to the International Bureau as provided by Rule 17 1(a) or (b) respectively In such a case the attention of the applicant is directed to Rule 17 1(c) which provides that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity upon entry into the national phase to furnish the priority document within a time limit which is reasonable under the circumstances

| Priority date | Priority application No. | Country or regional Office or PCT receiving Office | Date of receipt of priority document |
|---|---|---|---|
| 08 Sept 2000 (08 09 00) | 09/655 351 | US | 29 May 2001 (29 05 01) |


The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20 Switzerland

Facsimile No (41 22) 740.14.35

Authorized officer
Khemais BRAHMI

Telephone No (41 22) 338 83.38

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*The demand must be filed directly with the competent International Preliminary Examining Authority or, if two or more Authorities are competent, with the one chosen by the applicant. The full name or two-letter code of that Authority may be indicated by the applicant on the line below:*

IPEA/ US

# PCT

**CHAPTER II**

## DEMAND

under Article 31 of the Patent Cooperation Treaty:
The undersigned requests that the international application specified below be the subject of international preliminary examination according to the Patent Cooperation Treaty and hereby elects all eligible States (except where otherwise indicated).

For International Preliminary Examining Authority use only

| Identification of IPEA | Date of receipt of DEMAND |
|---|---|
| | |

**Box No. I IDENTIFICATION OF THE INTERNATIONAL APPLICATION**

Applicant's or agent's file reference: 9/193PCT

| International application No. | International filing date *(day/month/year)* | (Earliest) Priority date *(day/month/year)* |
|---|---|---|
| PCT/US01/08084 | 14/03/2001 | 08/09/2000 |

Title of invention: NOVEL COMPOUNDS USEFUL AS REVERSIBLE INHIBITORS OF CYSTEIN PROTEASES

**Box No. II APPLICANT(S)**

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

BOEHRINGER INGELHEIM PHARMACEUTICALS, INC.
900 Ridgebury Road
P.O. Box 368
Ridgefield, Connecticut 06877-0368

Telephone No.: 203-798-9988
Facsimile No.: 203-798-4408
Teleprinter No.:
Applicant's registration No. with the Office:

| State *(that is, country)* of nationality: | State *(that is, country)* of residence: |
|---|---|
| US | US |

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

| State *(that is, country)* of nationality: | State *(that is, country)* of residence: |
|---|---|
| | |

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

| State *(that is, country)* of nationality: | State *(that is, country)* of residence: |
|---|---|
| | |

☐ Further applicants are indicated on a continuation sheet.

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Sheet No. 2

International application No. PCT/US01/08084

**Box No. III AGENT OR COMMON REPRESENTATIVE; OR ADDRESS FOR CORRESPONDENCE**

The following person is ☑ agent ☐ common representative

and ☑ has been appointed earlier and represents the applicant(s) also for international preliminary examination.

☐ is hereby appointed and any earlier appointment of (an) agent(s)/common representative is hereby revoked.

☐ is hereby appointed, specifically for the procedure before the International Preliminary Examining Authority, in addition to the agent(s)/common representative appointed earlier.

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

RAYMOND, Robert P.; STEMPEL, Alan R.; DEVLIN, Mary-Ellen M.; BOTTINO, Anthony P.; POCCHIARI, Susan K.; DATLOW, Phillip I.; WITKOWSKI, Timothy X.
BOEHRINGER INGELHEIM CORPORATION
900 Ridgebury Road, P. O. Box 368
Ridgefield, CT 06877-0368
United States of America

Telephone No. 203-798-9988

Facsimile No. 203-798-4408

Teleprinter No.

Agent's registration No. with the Office

☐ Address for correspondence: Mark this check-box where no agent or common representative is/has been appointed and the space above is used instead to indicate a special address to which correspondence should be sent.

**Box No. IV BASIS FOR INTERNATIONAL PRELIMINARY EXAMINATION**

Statement concerning amendments:*

1. The applicant wishes the international preliminary examination to start on the basis of:

☑ the international application as originally filed

the description ☐ as originally filed
☐ as amended under Article 34

the claims ☐ as originally filed
☐ as amended under Article 19 (together with any accompanying statement)
☐ as amended under Article 34

the drawings ☐ as originally filed
☐ as amended under Article 34

2. ☐ The applicant wishes any amendment to the claims under Article 19 to be considered as reversed.

3. ☐ The applicant wishes the start of the international preliminary examination to be postponed until the expiration of 20 months from the priority date unless the International Preliminary Examining Authority receives a copy of any amendments made under Article 19 or a notice from the applicant that he does not wish to make such amendments (Rule 69.1(d)). *(This check-box may be marked only where the time limit under Article 19 has not yet expired.)*

* Where no check-box is marked, international preliminary examination will start on the basis of the international application as originally filed or, where a copy of amendments to the claims under Article 19 and/or amendments of the international application under Article 34 are received by the International Preliminary Examining Authority before it has begun to draw up a written opinion or the international preliminary examination report, as so amended.

Language for the purposes of international preliminary examination: English

☑ which is the language in which the international application was filed.
☐ which is the language of a translation furnished for the purposes of international search.
☐ which is the language of publication of the international application.
☐ which is the language of the translation (to be) furnished for the purposes of international preliminary examination.

**Box No. V ELECTION OF STATES**

The applicant hereby elects all eligible States *(that is, all States which have been designated and which are bound by Chapter II of the PCT)*

excluding the following States which the applicant wishes not to elect:

International application No. PCT/US01/08084

**Box No. VI CHECK LIST**

| The demand is accompanied by the following elements, in the language referred to in Box No. IV, for the purposes of international preliminary examination: | | | For International Preliminary Examining Authority use only: received | not received |
|---|---|---|---|---|
| 1. translation of international application | : | sheets | ☐ | ☐ |
| 2. amendments under Article 34 | : | sheets | ☐ | ☐ |
| 3. copy (or, where required, translation) of amendments under Article 19 | : | sheets | ☐ | ☐ |
| 4. copy (or, where required, translation) of statement under Article 19 | : | sheets | ☐ | ☐ |
| 5. letter | : | sheets | ☐ | ☐ |
| 6. other *(specify)* | : | sheets | ☐ | ☐ |

The demand is also accompanied by the item(s) marked below:

1. ☑ fee calculation sheet
2. ☐ original separate power of attorney
3. ☐ original general power of attorney
4. ☐ copy of general power of attorney; reference number, if any:
5. ☐ statement explaining lack of signature
6. ☐ sequence listing in computer readable form
7. ☐ other *(specify)*:

**Box No. VII SIGNATURE OF APPLICANT, AGENT OR COMMON REPRESENTATIVE**

*Next to each signature, indicate the name of the person signing and the capacity in which the person signs (if such capacity is not obvious from reading the demand).*

Anthony P. Bottino, Agent

**For International Preliminary Examining Authority use only**

1. Date of actual receipt of DEMAND:
2. Adjusted date of receipt of demand due to CORRECTIONS under Rule 60.1(b):
3. ☐ The date of receipt of the demand is AFTER the expiration of 19 months from the priority date and item 4 or 5, below, does not apply. ☐ The applicant has been informed accordingly.
4. ☐ The date of receipt of the demand is WITHIN the period of 19 months from the priority date as extended by virtue of Rule 80.5.
5. ☐ Although the date of receipt of the demand is after the expiration of 19 months from the priority date, the delay in arrival is EXCUSED pursuant to Rule 82.

**For International Bureau use only**

Demand received from IPEA on:

~~355~~ 379

**CHAPTER II**

# PCT

## FEE CALCULATION SHEET

**Annex to the Demand**

| | |
|---|---|
| International application No. PCT/US01/08084 | For International Preliminary Examining Authority use only |
| Applicant's or agent's file reference 9/193PCT | Date stamp of the IPEA |

Applicant

BOEHRINGER INGELHEIM PHARMACEUTICALS, INC.

### CALCULATION OF PRESCRIBED FEES

| | | | |
|---|---|---|---|
| 1. Preliminary examination fee ..... | 750.00 | P | |
| 2. Handling fee *(Applicants from certain States are entitled to a reduction of 75% of the handling fee. Where the applicant is (or all applicants are) so entitled, the amount to be entered at H is 25% of the handling fee.)* ..... | 137.00 | H | |
| 3. Total of prescribed fees Add the amounts entered at P and H and enter total in the TOTAL box ..... | 887.00 TOTAL | | |

### MODE OF PAYMENT

- [x] authorization to charge deposit account with the IPEA (see below)
- [ ] cash
- [ ] cheque
- [ ] revenue stamps
- [ ] postal money order
- [ ] coupons
- [ ] bank draft
- [ ] other *(specify)*:

### AUTHORIZATION TO CHARGE (OR CREDIT) DEPOSIT ACCOUNT

*(This mode of payment may not be available at all IPEAs)*

IPEA/ US

- [x] Authorization to charge the total fees indicated above.
- [x] *(This check-box may be marked only if the conditions for deposit accounts of the IPEA so permit)* Authorization to charge any deficiency or credit any overpayment in the total fees indicated above.

Deposit Account No.: 02-2955

Date: January 11, 2002

Name: Anthony P. Bottino

Signature: Anthony P. Bottino

Form PCT/IPEA/401 (Annex) (March 2001; reprint July 2001) *See Notes to the fee calculation sheet*

# PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

AB 379 380

# PCT

To:

ROBERT P. RAYMOND
BOEHRINGER INGELHEIM PHARMACEUTICALS, INC.
900 RIDGEBURY ROAD, P.O. BOX 368
RIDGEFIELD CT 06877

## NOTIFICATION OF RECEIPT OF DEMAND BY COMPETENT INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

(PCT Rule 59.3(e) and 61.1(b), first sentence and Administrative Instructions, Section 601(a))

| | |
|---|---|
| Date of mailing *(day/month/year)* | 25 APR 2002 |
| Applicant's or agent's file reference | IMPORTANT NOTIFICATION |
| 9/193PCT | |

| International application No. | International filing date *(day/month/year)* | Priority date *(day/month/year)* |
|---|---|---|
| PCT/US01/08084 | 14 MAR 01 | 08 SEP 00 |

Applicant: BOEHRINGER INGELHEIM PHARMACEUTICALS, INC.

1. The applicant is hereby notified that this International Preliminary Examining Authority considers the following date as the date of receipt of the demand for international preliminary examination of the international application:

IPEA/US 11 JAN 2002

2. That date of receipt is:

☒ the actual date of receipt of the demand by this Authority (Rule 61.1(b)).

☐ the actual date of receipt of the demand on behalf of this Authority (Rule 59.3(e)).

☐ the date on which this Authority has, in response to the invitation to correct defects in the demand (Form PCT/IPEA/404), received the required corrections.

3. ☐ ATTENTION: That date of receipt is AFTER the expiration of 19 months from the priority date. Consequently, the election(s) made in the demand does (do) not have the effect of postponing the entry into the national phase until 30 months from the priority date (or later in some Offices) (Article 39(1)). Therefore, the acts for entry into the national phase must be performed within 20 months from the priority date (or later in some Offices) (Article 22). For details, see the *PCT Applicant's Guide*, Volume II.

☐ *(If applicable)* This notification confirms the information given by telephone; facsimile transmission or in person on: _____

4. Only where paragraph 3 applies, a copy of this notification has been sent to the International Bureau.

RECEIVED
APR 30 2002
PATENT SECTION

| Name and mailing address of the IPEA/US | Authorized officer |
|---|---|
| Assistant Commissioner for Patents<br>Box PCT<br>Washington, D.C. 20231 Attn: IPEA/US<br>Facsimile No. | Telephone No. |

Form PCT/IPEA/402 (July 1998)

# PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

AB 381

To:

ROBERT P. RAYMOND
BOEHRINGER INGELHEIM PHARMACEUTICALS, INC.
900 RIDGEBURY ROAD, P.O. BOX 368
RIDGEFIELD CT 06877

# PCT

## NOTIFICATION OF RECEIPT OF DEMAND BY COMPETENT INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

(PCT Rule 59.3(e) and 61.1(b), first sentence and Administrative Instructions, Section 601(a))

| | |
|---|---|
| Date of mailing *(day/month/year)* | 25 APR 2002 |
| Applicant's or agent's file reference: 9/193PCT | IMPORTANT NOTIFICATION |

| International application No. | International filing date *(day/month/year)* | Priority date *(day/month/year)* |
|---|---|---|
| PCT/US01/08084 | 14 MAR 01 | 08 SEP 00 |

Applicant: BOEHRINGER INGELHEIM PHARMACEUTICALS, INC.

1. The applicant is hereby notified that this International Preliminary Examining Authority considers the following date as the date of receipt of the demand for international preliminary examination of the international application:

IPEA/US 11 JAN 2002

2. That date of receipt is:

☒ the actual date of receipt of the demand by this Authority (Rule 61.1(b)).

☐ the actual date of receipt of the demand on behalf of this Authority (Rule 59.3(e)).

☐ the date on which this Authority has, in response to the invitation to correct defects in the demand (Form PCT/IPEA/404), received the required corrections.

3. ☐ ATTENTION: That date of receipt is AFTER the expiration of 19 months from the priority date. Consequently, the election(s) made in the demand does (do) not have the effect of postponing the entry into the national phase until 30 months from the priority date (or later in some Offices) (Article 39(1)). Therefore, the acts for entry into the national phase must be performed within 20 months from the priority date (or later in some Offices) (Article 22). For details, see the *PCT Applicant's Guide*, Volume II.

☐ *(If applicable)* This notification confirms the information given by telephone; facsimile transmission or in person on: _____

4. Only where paragraph 3 applies, a copy of this notification has been sent to the International Bureau.

RECEIVED
APR 30 2002
PATENT SECTION

| | |
|---|---|
| Name and mailing address of the IPEA/US<br>Assistant Commissioner for Patents<br>Box PCT<br>Washington, D.C. 20231 Attn: IPEA/US<br>Facsimile No. | Authorized officer<br>Valerie Fogle<br>Telephone No. |

Form PCT/IPEA/402 (July 1998)

387

382

## IN THE INTERNATIONAL BUREAU WIPO

| | | |
|---|---|---|
| International Appln. No. | : | PCT/US01/08084 |
| Filed | : | 14 March 2001 |
| Application of: | | Boehringer Ingelheim Pharmaceuticals, Inc. |
| Authorized Officer | : | To be assigned |
| For | : | NOVEL COMPOUNDS USEFUL AS REVERSIBLE INHIBITORS OF CYSTEINE PROTEASES |

March 19,2002

International Bureau WIPO
P.O. Box 18,
CH-1211 Geneva 20

## RECORDING OF CHANGE IN THE REQUEST UNDER PCT RULE 92$^{bis}$.1(a)(ii) IN THE INTERNATIONAL APPLICATION

Sir:

This communication is to correct a spelling error for Denice M. Spero in the inventor list made in the Request of the above-identified International Application. This change to the Request is respectfully requested.

Name as filed:

SPERO, Denise, M.

Correct spelling:

SPERO, Denice, M.

Respectfully submitted,

Anthony P. Bottino
Attorney for Applicant(s)
Reg. No. 41,629

National Phase 3-8-03 LAST DAY

PCT/US01/08084

APR 29 2002

PATENT SECTION

# PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

## PCT

**NOTIFICATION OF THE RECORDING OF A CHANGE**

(PCT Rule 92bis.1 and Administrative Instructions, Section 422)

To:

RAYMOND, Robert, P.
Boehringer Ingelheim
Pharmaceuticals, Inc.
900 Ridgebury Road
P.O. Box 368
Ridgefield, CT 06877
ETATS-UNIS D'AMERIQUE

| | |
|---|---|
| Date of mailing (day/month/year)<br>11 April 2002 (11.04.02) | |
| Applicant's or agent's file reference<br>9/193PCT | IMPORTANT NOTIFICATION |
| International application No.<br>PCT/US01/08084 | International filing date (day/month/year)<br>14 March 2001 (14.03.01) |

1. The following indications appeared on record concerning:

[X] the applicant [X] the inventor [ ] the agent [ ] the common representative

| Name and Address | State of Nationality | State of Residence |
|---|---|---|
| SPERO, Denise, M.<br>18 Limekiln Road<br>West Redding, CT 06896<br>United States of America | | US |
| | Telephone No. | |
| | Facsimile No. | |
| | Teleprinter No. | |

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

[ ] the person [X] the name [ ] the address [ ] the nationality [ ] the residence

| Name and Address | State of Nationality | State of Residence |
|---|---|---|
| SPERO, Denice, M.<br>18 Limekiln Road<br>West Redding, CT 06896<br>United States of America | | US |
| | Telephone No. | |
| | Facsimile No. | |
| | Teleprinter No. | |

3. Further observations, if necessary:
**Please note spelling of name of applicant/inventor.**

4. A copy of this notification has been sent to:

[X] the receiving Office
[ ] the International Searching Authority
[ ] the International Preliminary Examining Authority
[X] 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>Alison OSBORNE |
| Facsimile No.: (41-22) 740.14.35 | Telephone No.: (41-22) 338.83.38 |

Form PCT/IB/306 (March 1994)

004783889

# NITRILOS ESPIROHETEROCÍCLICOS, ÚTILES COMO INHIBIDORES REVERSIBLES DE CISTEÍNA-PROTEASAS

## DATOS DE SOLICITUD RELACIONADA

Esta solicitud es una continuación en parte de la solicitud de EE.UU. nº de serie 09/655.351, presentada el 8 de septiembre de 2000.

## CAMPO TÉCNICO DE LA INVENCIÓN

Esta invención se refiere a compuestos de amidino- y guanidino-peptidilo, activos como inhibidores de cisteína--proteasa. Los compuestos son inhibidores reversibles de la cisteína-proteasa catepsina S, K, F, L y B y, por lo tanto, son útiles en el tratamiento de enfermedades autoinmunes y otras enfermedades. La invención se refiere también a procedimientos para preparar compuestos de este tipo y a composiciones farmacéuticas que los comprenden.

## ANTECEDENTES DE LA INVENCIÓN

Catepsina S y catepsina K son miembros de la familia papaína, dentro de la superfamilia papaína de cisteína-proteasas. La familia papaína es el mayor grupo de cisteína-proteasas, e incluye proteasas tales como catepsinas B, H, K, L, O y S (A.J. Barrett et al., 1996, Perspectives in Drug Discovery and Design,6,1). Las cisteínas-proteasas juegan importantes papeles en la biología humana y en enfermedades que incluyen aterosclerosis, enfisema, osteoporosis, inflamación crónica y trastornos inmunológicos (H.A. Chapman et al., 1997, Ann. Rev. Physiol., 59, 63). Catepsina S juega un papel clave en la regulación de la presentación de antígenos y de la inmunidad (H.A. Chapman, 1998, Current Opinion in Immuno-

logy, 10, 93; R.J. Riese et al., 1998, J. Clin. Invest., 101, 2351; R.J. Riese et al., 1996, Immunity, 4, 357). Ratones deficientes en catepsina S tienen una degradación de la cadena invariante perjudicada, que resulta en una presentación de antígenos y formación del centro germinal reducidas y una susceptibilidad disminuida a la artritis inducida por colágeno indicando el potencial terapéutico para un inhibidor de catepsina S (G. Shi et al., 1999, Immunity, 10, 197; T.Y. Nakagawa et al, 1999, Immunity, 10, 207).

La especificidad de la respuesta inmunitaria se basa en el tratamiento de proteínas extrañas y en la presentación de péptido antigénico en la superficie de la célula. El péptido antigénico se presenta unido a MHC de Clase II, una glicoproteína heterodímera que se expresa en determinadas células de la línea hematopoyética presentadoras de antígenos, tales como células B, macrófagos y células dendríticas. La presentación de antígeno a células efectoras, tales como células T, es una etapa fundamental en el reconocimiento no propio y, así, en el inicio de la respuesta inmunitaria.

Recientemente, heterodímeros MHC de Clase II demostraron asociarse intracelularmente con una tercera molécula designada cadena invariante. La cadena invariante facilita el transporte de Clase II al compartimiento endosomal y estabiliza la proteína de Clase II antes de la carga con antígeno. La cadena invariante interactúa directamente con dímeros de Clase II en la muesca de unión al antígeno y, por lo tanto, debe ser proteolizada y separada, o el antígeno no puede ser cargado ni presentado. La actual investigación sugiere que la cadena invariante se proteoliza selectivamente por parte de catepsina S, que está compartimentalizada con complejos MHC de Clase II dentro de la célula. Catepsina S degrada la cadena invariante a un pequeño péptido, denominado CLIP, que ocupa la muesca de unión al antígeno. CLIP se libera de MHC de Clase II mediante la interacción de MHC de Clase II con HLA-DM, una molécula

similar a MHC, liberando de esta forma a MHC de Clase II para que se asocie con péptidos antigénicos. A continuación, complejos de MHC de Clase II-antígeno son transportados a la superficie de la célula para la presentación a células T, y la iniciación de la respuesta inmunitaria.

La catepsina S, a través de la degradación proteolítica de la cadena invariante a CLIP, proporciona una etapa fundamental en la generación de una respuesta inmunitaria. Se deduce que la inhibición de la presentación de antígenos a través de la prevención de la degradación de la cadena invariante por parte de catepsina S podría proporcionar un mecanismo para la inmunorregulación. El control de las respuestas inmunitarias específicas para antígenos ha sido largamente deseado como una terapia útil y segura de enfermedades autoinmunes. Enfermedades de este tipo incluyen la enfermedad de Crohn y artritis, así como otras respuestas inmunológicas mediadas por células T (C. Janeway y P. Travers, 1996, Immunobiology, The Immune System in Health and Disease, capítulo 12). Además de ello, catepsina S, que tiene una amplia especificidad del pH, ha estado implicada en una diversidad de otras enfermedades que implican la proteolisis extracelular, tal como la enfermedad de Alzheimer (U. Muller--Ladner et al., 1996, Perspectives in Drug Discovery and Design, 6, 87), aterosclerosis (G.K. Sukhova et al., 1998, J. Clin. Invest., 102, 576) y endometriosis (documento WO 9963115, 1999).

Se ha encontrado que un inhibidor de catepsina S bloquea el aumento en títulos de IgE y la infiltración de eosinófilos en el pulmón en un modelo de ratón de hipersensibilidad pulmonar, sugiriendo que la catepsina S pueda estar implicada en el asma (R. J. Riese et al., J. Clin. Investigation, 1998, 101, 2351).

Otra cisteína-proteasa, la catepsina F, ha sido encontrada en macrófagos y también está implicada en el tratamiento de antígenos. Se ha postulado que catepsina F en macrófa-

gos de pulmón estimulados y, posiblemente, otras células presentadoras de antígenos, podría jugar un papel en la inflamación de las vías respiratorias (G.-P. Shi et al., J. Exp. Med., 2000, 191, 1177).

Se ha encontrado que catepsina K, otra cistetína-proteasa, está muy expresada en osteoclastos y que degrada el colágeno de los huesos y otras proteínas de la matriz ósea. Inhibidores de catepsina K han demostrado inhibir la resorción de huesos en ratones. Por lo tanto, catepsina K puede jugar un papel en la resorción ósea osteoclástica, e inhibidores de catepsina K pueden ser útiles en el tratamiento de enfermedades que implican la resorción de los huesos tales como osteoporosis (F. Lazner et al., Human Molecular Genetics, 1999, 8, 1839).

Cisteína-proteasas se caracterizan por tener un residuo cisteína en el sitio activo que sirve como nucleófilo. El sitio activo contiene también un residuo histidina. El anillo de imidazol en la histidina sirve como base para generar un anión tiolato en el sitio activo cisteína, incrementando su nucleofilia. Cuando un sustrato es reconocido por la proteasa, el enlace amida a escindir se dirige al sitio activo, en donde el tiolato ataca el carbono de carbonilo formando un compuesto intermedio de acilo-enzima y escindiendo el enlace amida, liberando una amina. Subsiguientemente, el agua escinde las especies de acil-enzima regenerando la enzima y liberando el otro producto de escisión del sustrato, un ácido carboxílico.

Inhibidores de cisteína-proteasas contienen una funcionalidad que puede reaccionar reversible o irreversiblemente con la cisteína del sitio activo. Ejemplo de funcionalidades reactivas que han sido descritas (D. Rasnick, 1996, Perspectives in Drug Discovery and Design, 6, 47) en inhibidores de cisteína-proteasa incluyen peptidil-diazometanos, epóxidos, monofluoroalcanos y aciloximetanos, que irreversiblemente alquilan el cisteína-tiol. Otros inhibidores irreversibles

incluyen aceptores de Michael tal como ésteres peptidil-vinílicos y otros derivados de ácido carboxílico (S. Liu et al., J. Med Chem., 1992, 35, 1067) y vinil-sulfonas (J. T. Palmer et al., 1995, J. Med Chem., 38, 3193).

Funcionalidades reactivas que forman complejos reversibles con la cisteína del sitio activo incluyen peptidil--aldehídos (R.P. Hanzlik et al., 1991, Biochim. Biophys. Acta., 1073, 33), que son no selectivos, inhibiendo tanto la cisteína como las serina-proteasas así como otros compuestos nucleófilos. Peptidil-nitrilos (R.P. Hanzlik et al., 1990, Biochim. Biophys. Acta., 1035, 62) son menos reactivos que aldehídos y, por lo tanto, son más selectivos para las cisteínas-proteasas más nucleófilas. También se ha reseñado que diversas cetonas reactivas son inhibidores reversibles de cisteína-proteasas (D. Rasnick, 1996, ibid). Además de reaccionar con la cisteína nucleófila del sitio activo, cetonas reactivas pueden reaccionar con el agua formando un hemicetal que puede actuar como un inhibidor del estado de transición.

Se han reseñado ejemplos de inhibidores de catepsina S. J.L. Klaus et al. (documento WO 9640737) describieron inhibidores reversibles de cisteína-proteasas, incluida catepsina S, que contenían una etilen-diamina. En la patente de EE.UU. nº 5.776.718 expedida a Palmer et al. se describe, en su aspecto genérico más amplio, un inhibidor de proteasa que comprende un grupo que dirige a diana enlazado a través de una cadena de dos átomos de carbono a un grupo separador de electrones (GSE). Los compuestos de la presente solicitud son estructuralmente distintos y, así, están excluidos de la patente 5.776.718, poseyendo realizaciones particulares una actividad inesperadamente mayor que los compuestos más relacionados de la técnica anterior. Otros ejemplos de inhibidores de catepsina S han sido reseñados por E.T. Altmann et al, (documento WO 9924460, 1999) que describe dipéptido-nitrilos de los que se afirma que tienen actividad

como inhibidores de catepsinas B, K, L y S. La publicación WO no describe ningún compuesto que posea una estructura guanidino o amidino en la posición P3.

Peptidil-nitrilos adicionales han sido reseñados como inhibidores de proteasas. Por ejemplo, tanto los nitril s como los cetoheterociclos se describen por B.A. Rowe et al. (documento US 5.714.471) como inhibidores de proteasa útiles en el tratamiento de enfermedades neurodegenerativas. Los peptidil-nitrilos se reseñan por B. Malcolm et al. (documento WO 9222570) como inhibidores de picornavirus-proteasa. B.J. Gour-Salin (Can. J. Chem., 1991, 69, 1288) y T.C. Liang (Arch. Biochim. Biophys., 1987, 252, 626) describieron peptidil-nitrilos en calidad de inhibidores de papaína.

Un inhibidor reversible presenta una terapia más atractiva que los inhibidores irreversibles. Incluso compuestos con una elevada especificidad para una proteasa particular pueden unir enzimas no diana. Por lo tanto, un compuesto irreversible podría inactivar permanentemente una enzima no diana, aumentando la probabilidad de la toxicidad. Además de ello, cualesquiera efectos tóxicos que resultaran de la inactivación de la enzima diana serían mitigados por inhibidores reversibles y podrían ser fácilmente remediados mediante una dosificación modificada o una reducción de la dosificación. Finalmente, la modificación covalente de una enzima por parte de un inhibidor irreversible podría generar en potencia una respuesta de anticuerpo actuando en calidad de un hapteno.

A la vista de lo que antecede, existe una clara necesidad de compuestos que inhiban de forma reversible y selectiva cisteína-proteasas tales como catepsina S y catepsina K para las indicaciones en las que estas proteasas exacerban la enfermedad.

## BREVE DESCRIPCIÓN DE LA INVENCIÓN

Por lo tanto, es un objeto de esta invención proporcionar nuevos compuestos de acuerdo con las fórmulas (Ia) y (Ib) según se describe en esta memoria que inhiban reversiblemente las cisteínas-proteasas catepsinas S, K, F, L y B. Es un objeto adicional de la invención proporcionar métodos para tratar enfermedades y estados patológicos exacerbados por estas cisteína-proteasas tales como, pero no limitadas a artritis reumatoide, esclerosis múltiple, asma y osteoporosis. Es todavía un objeto adicional de la invención proporcionar nuevos procedimientos para la preparación de los nuevos compuestos antes mencionados.

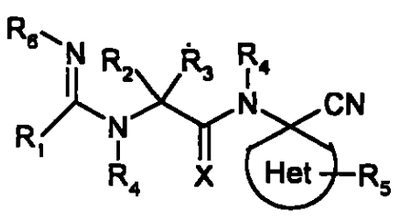
## DESCRIPCIÓN DETALLADA DE LA INVENCIÓN

Un mecanismo de acción propuesto de los inhibidores de cisteína-proteasas de esta invención es que los inhibidores contienen una funcionalidad que pueden reaccionar (reversible o irreversiblemente) con la cisteína del sitio activo. La funcionalidad reactiva está fijada a un péptido o un mímico de péptido que puede ser reconocido y alojado por la región de la proteasa que rodea al sitio activo. La naturaleza tanto de la funcionalidad reactiva como de la porción remanente del inhibidor determinan el grado de selectividad y la potencia hacia una proteasa particular.

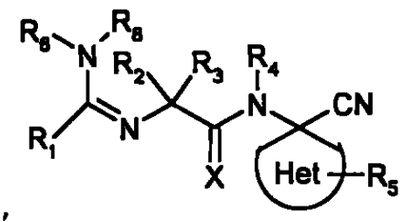
Dada la similitud de los sitios activos en las cisteína-proteasas, se puede anticipar que una clase dada de inhibidores podría tener actividad contra más de una cisteína-proteasa. También se puede esperar que, debido a diferencias estructurales entre cisteína-proteasas individuales, diferentes compuestos de la invención pueden tener diferentes potencias inhibidoras frente a cisteína-proteasas diferentes. Así, también puede esperarse que algunos de los compuestos de la invención sean lo más eficaces en tratar enfermedades mediadas por cisteína-proteasas a las que inhiben con la mayor potencia. La

actividad de compuestos particulares descritos en esta memoria frente a cisteína-proteasas tales como catepsinas S, K, F, L y B se puede determinar por los rastreos descritos en la sección titulada "Verificación de Propiedades Biológicas".

Por consiguiente, en un primer aspecto genérico de la invención, se proporcionan compuestos de fórmulas (Ia) y (Ib):




(Ia),




(Ib)

en donde:

Het es

azepanilo, piperidinilo, pirrolidinilo, azetidinilo, oxepanilo, tetrahidropiranilo, tetrahidrotiopiranilo, tetrahidrofuranilo, oxetanilo, azocanilo, oxocanilo, 1,3-diazocanilo, 1,4-diazocanilo, 1,5-diazocanilo, 1,3-dioxocanilo, 1,4-dioxocanilo, 1,5-dioxocanilo, 1,3-oxazocanilo, 1,4-oxazocanilo, 1,5-oxazocanilo, 1,3-diazepanilo, 1,4-diazepanilo, 1,3--dioxepanilo, 1,4-dioxepanilo, 1,3-oxazepanilo, 1,4-oxazepanilo, 1,2-tiazocanil-1,1-dióxido, 1,2,8-tiadiazocanil-1,1--dióxido, 1,2-tiazepanil-1,1-dióxido, 1,2,7-tiadiazepanil--1,1-dióxido, tetrahidrotiofenilo, hexahidropirimidinilo, hexahidropiridazinilo, piperazinilo, 1,4,5,6-tetrahidropirimidinilo, pirazolidinilo, dihidro-oxazolilo, dihidrotiazolilo, dihidroimidazolilo, isoxazolinilo, oxazolidinilo, 1,2-tiazinanil-1,1-dióxido, 1,2,6-tiadiazinanil-1,1-dióxido, isotiazolidinil-1,1-dióxido, imidazolidinil-2,4-diona, imidazolidinilo, morfolinilo, dioxanilo, tetrahidropiridinilo, tiomorfolinilo, tiazolidinilo, dihidropiranilo, ditianilo, decahidro-quinolinilo, decahidro-isoquinolinilo, 1,2,3,4-

tetrahidro-quinolinilo, indolinilo, octahidro-quinolizinilo, dihidro-indolizinilo, octahidro-indolizinilo, octahidro-indolilo, decahidroquinazolinilo, decahidroquinoxalinilo, 1,2,3,4-tetrahidroquinazolinilo ó 1,2,3,4-tetrahidroquinoxalinilo;

A es un biciclo C6-C10 puenteado, en donde uno o más átomos de carbono están opcionalmente reemplazados por un heteroátomo seleccionado de N, O y S;

estando cada uno opcionalmente sustituido con uno o más $R_6$;

$R_1$ es un enlace, hidrógeno, alquilo C1-10, alcoxi C1-10, ariloxi, cicloalquilo C3-8, cicloalquiloxi C3-8, arilo, bencilo, tetrahidronaftilo, indenilo, indanilo, alquil C1-10--sulfonil-alquilo C1-10, cicloalquil C3-8-sulfonil-alquilo C1-10, arilsulfonil-alquilo C1-10, heterociclilo seleccionado de azepanilo, azocanilo, pirrolidinilo, piperidinilo, morfolinilo, tiomorfolinilo, piperazinilo, indolinilo, piranilo, tetrahidropiranilo, tetrahidrotiopiranilo, tiopiranilo, furanilo, tetrahidrofuranilo, tienilo, pirrolilo, oxazolilo, isoxazolilo, tiazolilo, imidazolilo, piridinilo, pirimidinilo, pirazinilo, piridazinilo, tetrazolilo, pirazolilo, indolilo, benzofuranilo, benzotienilo, bencimidazolilo, benzotiazolilo, benzisoxazolilo, quinolinilo, tetrahidroquinolinilo, isoquinolinilo, tetrahidroisoquinolinilo, quinazolinilo, tetrahidroquinazolinilo, benzoxazolilo y quinoxalinilo, heterocicliloxi, en donde el resto heterociclilo se selecciona de los descritos en esta memoria y en este párrafo, hidroxi o amino; en donde $R_1$ está opcionalmente sustituido con uno o más $R_4$;

$R_4$ es un enlace, alquilo C1-10, cicloalquilo C3-8, arilo, tetrahidronaftilo, indenilo, indanilo, pirrolidinilo, piperidinilo, morfolinilo, tiomorfolinilo, piperazinilo, indolinilo, furanilo, tienilo, pirrolilo, oxazolilo, tiazolilo, imidazolilo, triazolilo, tetrazolilo, piridinilo, pirimidinilo, pirazinilo, indolilo, benzofuranilo, benzotienilo, bencimidazolilo, benzotia-

zolilo, benzoxazolilo, benzisoxazolilo, quinolinilo, isoquinolinilo, quinazolinilo, quinoxalinilo, alcoxi C1-10, alcanoílo C1-10, alcanoiloxi C1-10, ariloxi, benciloxi, alcoxi C1-10-carbonilo, ariloxicarbonilo, aroiloxi, carbamoílo, en donde el átomo de nitrógeno puede estar independientemente mono- o di-sustituido con alquilo C1-10, arilo, pirrolidinilo, piperidinilo, morfolinilo, tiomorfolinilo, piperazinilo, indolilo, furanilo, tienilo, pirrolilo, oxazolilo, tiazolilo, imidazolilo, triazolilo, tetrazolilo, piridinilo, pirimidinilo, pirazinilo, indolilo, benzofuranilo, benzotienilo, bencimidazolilo, benzotiazolilo, quinolinilo, isoquinolinilo, quinazolinilo o quinoxalinilo,

o $R_4$ es alcanoil C1-10-amino, aroilamino, alquiltio C1-10, en donde cualquier átomo de azufre puede estar oxidado en un sulfóxido o sulfona, ariltio, en donde el átomo de azufre puede estar oxidado en un sulfóxido o sulfona, ureido, en donde el átomo de nitrógeno puede estar sustituido, independientemente, con alquilo C1-10, arilo, pirrolidinilo, piperidinilo, morfolinilo, tiomorfolinilo, piperazinilo, indolinilo, furanilo, tienilo, pirrolilo, oxazolilo, tiazolilo, imidazolilo, triazolilo, tetrazolilo, piridinilo, pirimidinilo, pirazinilo, indolilo, benzofuranilo, benzotienilo, bencimidazolilo, benzotiazolilo, quinolinilo, isoquinolinilo, quinazolinilo o quinoxalinilo,

o $R_4$ es alcoxi C1-10-carbonilamino, ariloxicarbonilamino, alquil C1-10-carbamoiloxi, arilcarbamoiloxi, alquil C1-10-sulfonilamino, arilsulfonilamino, alquil C1-10--aminosulfonilo, arilaminosulfonilo, amino, en donde el átomo de nitrógeno puede estar independientemente mono- o di-sustituido con alquilo C1-10, arilo, pirrolidinilo, piperidinilo, morfolinilo, tiomorfolinilo, piperazinilo, indolinilo, furanilo, tienilo, pirrolilo, oxazolilo, tiazolilo, imidazolilo, triazolilo,

tetrazolilo, piridinilo, pirimidinilo, pirazinilo, indolilo, benzofuranilo, benzotienilo, bencimidazolilo, benzotiazolilo, quinolinilo, isoquinolinilo, quinazolinilo o quinoxalinilo,

o $R_a$ es halógeno, hidroxi, oxo, carboxi, ciano, nitro, carboxamida, amidino o guanidino, $R_a$ puede estar, además, opcionalmente sustituido con uno o más $R_h$; con la condición de que $R_1$ y $R_a$ no puedan ser simultáneamente un enlace;

$R_t$ es una cadena de carbonos C1-6 saturada o insaturada, ramificada o no ramificada, opcionalmente parcial o totalmente halogenada, en donde uno o más átomos de carbono están opcionalmente reemplazados por O, N, S(O), $S(O)_2$ o S, y en donde dicha cadena está opcionalmente sustituida de modo independiente con 1-2 grupos oxo, $-NH_2$, o uno más alquilo C1-4, pirrolidinilo, piperidinilo, morfolinilo, tiomorfolinilo, piperazinilo, indolinilo, furanilo, tienilo, pirrolilo, oxazolilo, tiazolilo, imidazolilo, triazolilo, tetrazolilo, piridinilo, pirimidinilo, pirazinilo, indolilo, benzofuranilo, benzotienilo, bencimidazolilo, benzotiazolilo, quinolinilo, isoquinolinilo, quinazolinilo o quinoxalinilo;

o $R_{..}$ es cicloalquilo C3-6, arilo, ariloxi, benciloxi, halógeno, hidroxi, oxo, carboxi, ciano, nitro, mono-alquil C1-5-amino, di-alquil C1-5--amino, carboxamida, amidino o guanidino;

$R_.$ es hidrógeno o alquilo C1-3;

$R_.$ es un enlace, hidrógeno, alquilo C1-10, alquileno C2-10, cicloalquilo C3-8, aril-alquilo C1-5 o arilo, en donde $R_3$ está opcionalmente sustituido con uno o más $R_c$;

$R_{..}$ es alquilo C1-10, cicloalquilo C3-8, arilo, indanilo, indenilo, biciclo[2.2.1]heptanilo, biciclo[2.2.2]-octanilo, biciclo[4.1.0]heptanilo, biciclo[3.1.0]-

hexanilo, biciclo[1.1.1]pentanilo, cubanilo, 1,2,3,4-tetrahidronaftilo, decahidronaftilo, pirrolidinilo, piperidinilo, morfolinilo, tiomorfolinilo, piperazinilo, indolinilo, furanilo, tetrahidrofuranilo, piranilo, tetrahidropiranilo, tetrahidrotiopiranilo, tienilo, pirrolilo, oxazolilo, tiazolilo, imidazolilo, pirazolilo, triazolilo, tetrazolilo, piridinilo, pirimidinilo, pirazinilo, indolilo, dihidrobenzofuranilo, octahidrobenzofuranilo, benzofuranilo, benzotienilo, bencimidazolilo, benzotiazolilo, tetrahidroquinolinilo, quinolinilo, tetrahidroisoquinolinilo, isoquinolinilo, quinazolinilo, quinoxalinilo, alcoxi C1-10, ariloxi, alcanoílo C1-10, aroílo, alcoxi C1-10-carbonilo, ariloxicarbonilo, alcanoiloxi C1-10, aroiloxi, carbamoílo, en donde el átomo de nitrógeno puede estar independientemente mono- o disustituido con alquilo C1-10, arilo, pirrolidinilo, piperidinilo, morfolinilo, tiomorfolinilo, piperazinilo, indolinilo, furanilo, tienilo, pirrolilo, oxazolilo, tiazolilo, imidazolilo, triazolilo, tetrazolilo, piridinilo, pirimidinilo, pirazinilo, indolilo, benzofuranilo, benzotienilo, bencimidazolilo, benzotiazolilo, quinolinilo, isoquinolinilo, quinazolinilo o quinoxalinilo,

o $R_2$ es alcanoil C1-10-amino, aroilamino, alquiltio C1-10, en donde el átomo de azufre puede estar oxidado en un sulfóxido o sulfona, ariltio, en donde el átomo de azufre puede estar oxidado en un sulfóxido o sulfona, ureido, en donde cualquier átomo de nitrógeno puede estar sustituido, independientemente, con alquilo C1-10, arilo, pirrolidinilo, piperidinilo, morfolinilo, tiomorfolinilo, piperazinilo, indolinilo, furanilo, tienilo, pirrolilo, oxazolilo, tiazolilo, imidazolilo, triazolilo, tetrazolilo, piridinilo, pirimidinilo, pirazinilo, indolilo, benzofuranilo, benzotienilo,

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bencimidazolilo, benzotiazolilo, quinolinilo, isoquinolinilo, quinazolinilo o quinoxalinilo,

o $R_c$ es alcoxi C1-10-carbonilamino, ariloxicarbonilamino, alquil C1-10-carbamoiloxi, arilcarbamoiloxi, alquil C1-10-sulfonilamino, arilsulfonilamino, alquil C1-10--aminosulfonilo, arilaminosulfonilo, amino, en donde el átomo de nitrógeno puede estar independientemente mono- o di-sustituido con alquilo C1-10, arilo, pirrolidinilo, piperidinilo, morfolinilo, tiomorfolinilo, piperazinilo, indolinilo, furanilo, tienilo, pirrolilo, oxazolilo, tiazolilo, imidazolilo, triazolilo, tetrazolilo, piridinilo, pirimidinilo, pirazinilo, indolilo, benzofuranilo, benzotienilo, bencimidazolilo, benzotiazolilo, quinolinilo, isoquinolinilo, quinazolinilo o quinoxalinilo,

o $R_c$ es halógeno, hidroxi, oxo, carboxi, ciano, nitro, aminidino o guanidino, $R_c$ puede estar, además, opcionalmente sustituido con uno o más $R_d$;

$R_c$ es alquilo C1-5, cicloalquilo C3-6, arilo, aril-alquilo C1-5, alcoxi C1-5, ariloxi, aril-alcoxi C1-5, aroílo, amino, halógeno, hidroxi, oxo, carboxi, ciano, nitro amidino o guanidino;

$R_c$ y $R_c$, junto con el carbono al que están fijados, forman opcionalmente un cicloalquilo no aromático de 5-7 miembros o un anillo heterocíclico;

cada $R_4$ es, independientemente, hidrógeno, hidroxi o alquilo C1-3;

$R_c$ es un enlace, hidrógeno, carbonilo, alquilo C1-10, alcoxi C1-10-alquilo C1-10, alquil C1-10-amino-alquilo C1-10, alquiltio C1-10-alquilo C1-10, en donde el átomo de azufre puede estar oxidado en un sulfóxido o sulfona, alcoxi C1-10, ariloxi, cicloalquilo C3-8, arilo, bencilo, tetrahidronaftilo, indenilo, indanilo, cicloalquil C3-7-sulfonil-alquil C1-5, arilsulfonil-alquilo C1-5, heterociclilo, seleccionado de pirrolidinilo, piperidinilo, morfolinilo, tiomorfolinilo,

piperazinilo, indolinilo, piranilo, tetrahidropiranilo, tiopiranilo, tetrahidrotiopiranilo, furanilo, tetrahidrofuranilo, tienilo, pirrolilo, oxazolilo, isoxazolilo, tiazolilo, imidazolilo, piridinilo, pirimidinilo, pirazinilo, piridazinilo, tetrazolilo, triazolilo, pirazolilo, indolilo, benzofuranilo, benzotienilo, bencimidazolilo, benzotiazolilo, quinolinilo, tetrahidroquinolinilo, isoquinolinilo, tetrahidroisoquinolinilo, quinazolinilo, tetrahidroquinazolinilo, benzoxazolilo y quinoxalinilo, heterocicliloxi, en donde el resto heterociclilo se selecciona de los descritos en esta memoria y en este párrafo, alcanoílo C1-10, aroílo, alcaniloxi C1-10, benciloxi, alcoxi C1-10-carbonilo, aril-alcoxi C1-5-carbonilo, ariloxicarbonilo, aroiloxi, carbamoílo, en donde el átomo de nitrógeno puede estar independientemente mono- o di-sustituido con alquilo C1-10, arilo, pirrolidinilo, piperidinilo, morfolinilo, tiomorfolinilo, piperazinilo, indolinilo, furanilo, tienilo, pirrolilo, oxazolilo, tiazolilo, imidazolilo, triazolilo, tetrazolilo, piridinilo, pirimidinilo, pirazinilo, indolilo, benzofuranilo, benzotienilo, bencimidazolilo, benzotiazolilo, quinolinilo, isoquinolinilo, quinazolinilo o quinoxalinilo,

o $R_4$ es alcanoil C1-10-amino, aroilamino, alquiltio C1-10, en donde el átomo de azufre puede estar oxidado en un sulfóxido o sulfona, ariltio, en donde el átomo de azufre puede estar oxidado en un sulfóxido o sulfona, ureido, en donde cualquier átomo de nitrógeno puede estar independientemente sustituido con alquilo C1-10, arilo, pirrolidinilo, piperidinilo, morfolinilo, tiomorfolinilo, piperazinilo, indolinilo, furanilo, tienilo, pirrolilo, oxazolilo, tiazolilo, imidazolilo, triazolilo, tetrazolilo, piridinilo, pirimidinilo, pirazinilo, indolilo, benzofuranilo, benzotienilo, bencimidazolilo, benzotiazolilo, quinolinilo, isoquinolinilo, quinazolinilo o quinoxalinilo,

o $R_4$ es alcoxi C1-10-carbonilamino, ariloxicarbonilamino, alquil C1-10-carbamoiloxi, arilcarbamoiloxi, alquil C1-10-

-sulfonilamino, arilsulfonilamino, alquil C1-10-aminosulfonilo, arilaminosulfonilo, amino, en donde el átomo de nitrógeno puede estar independientemente mono- o di-sustituido con alquilo C1-10, arilo, pirrolidinilo, piperidinilo, morfolinilo, tiomorfolinilo, piperazinilo, indolinilo, furanilo, tienilo, pirrolilo, oxazolilo, tiazolilo, imidazolilo, triazolilo, tetrazolilo, piridinilo, pirimidinilo, pirazinilo, indolilo, benzofuranilo, benzotienilo, bencimidazolilo, benzotiazolilo, quinolinilo, isoquinolinilo, quinazolinilo o quinoxalinilo,

o $R_1$ es halógeno, hidroxi, oxi, oxo, carboxi, ciano, nitro, carboxamida, amidino o guanidino, $R_5$ puede estar, además, opcionalmente sustituido con uno o más $R_6$;

$R_6$ es alquilo C1-10, alcoxi C1-10-alquilo C1-10, alquil C1-10-amino-alquilo C1-10, alquiltio C1-10-alquilo C1-10, en donde el átomo de azufre puede estar oxidado en un sulfóxido o sulfona, alcoxi C1-10, cicloalquilo C3-8, arilo, tetrahidronaftilo, indenilo, indanilo, pirrolidinilo, piperidinilo, morfolinilo, tiomorfolinilo, piperazinilo, indolinilo, tiopiranilo, tetrahidrotiopiranilo, piranilo, tetrahidropiranilo, tetrahidrofuranilo, furanilo, tienilo, pirrolilo, oxazolilo, tiazolilo, imidazolilo, triazolilo, tetrazolilo, piridinilo, pirimidinilo, pirazinilo, indolilo, benzofuranilo, benzotienilo, bencimidazolilo, benzotiazolilo, benzoxazolilo, benzisoxazolilo, quinolinilo, isoquinolinilo, quinazolinilo, quinoxalinilo, alcanoílo C1-10, aroílo, alcanoiloxi C1-10, ariloxi, benciloxi, alcoxi C1-10-carbonilo, ariloxi C1-3-carbonilo, ariloxicarbonilo, aroiloxi, carbamoílo, en donde el átomo de nitrógeno puede estar independientemente mono- o di-sustituido con alquilo C1-10, arilo, pirrolidinilo, piperidinilo, morfolinilo, tiomorfolinilo, piperazinilo, indolinilo, furanilo, tienilo, pirrolilo, oxazolilo, tiazolilo, imidazolilo,

triazolilo, tetrazolilo, piridinilo, pirimidinilo, pirazinilo, indolilo, benzofuranilo, benzotienilo, bencimidazolilo, benzotiazolilo, quinolinilo, isoquinolinilo, quinazolinilo o quinoxalinilo,

o $R_e$ es alcanoil C1-10-amino, aroilamino, alquilti C1-10, en donde el átomo de azufre puede estar oxidado en un sulfóxido o sulfona, ariltio, en donde el átomo de azufre puede estar oxidado en un sulfóxido o sulfona, ureido, en donde cualquier átomo de nitrógeno puede estar, independientemente, sustituido con alquilo C1-10, arilo, pirrolidinilo, piperidinilo, morfolinilo, tiomorfolinilo, piperazinilo, indolinilo, furanilo, tienilo, pirrolilo, oxazolilo, tiazolilo, imidazolilo, triazolilo, tetrazolilo, piridinilo, pirimidinilo, pirazinilo, indolilo, benzofuranilo, benzotienilo, bencimidazolilo, benzotiazolilo, quinolinilo, isoquinolinilo, quinazolinilo o quinoxalinilo,

o $R_e$ es alcoxi C1-10-carbonilamino, ariloxicarbonilamino, alquil C1-10-carbamoiloxi, arilcarbamoiloxi, alquil C1-10-sulfonilamino, arilsulfonilamino, alquil C1-10--aminosulfonilo, arilaminosulfonilo, amino, en donde el átomo de nitrógeno puede estar independientemente mono- o di-sustituido con alquilo C1-10, arilo, pirrolidinilo, piperidinilo, morfolinilo, tiomorfolinilo, piperazinilo, indolinilo, furanilo, tienilo, pirrolilo, oxazolilo, tiazolilo, imidazolilo, triazolilo, tetrazolilo, piridinilo, pirimidinilo, pirazinilo, indolilo, benzofuranilo, benzotienilo, bencimidazolilo, benzotiazolilo, quinolinilo, isoquinolinilo, quinazolinilo o quinoxalinilo,

o $R_e$ es halógeno, hidroxi, oxo, carboxi, ciano, nitro, carboxamida, amidino o guanidino, $R_e$ puede estar, además, opcionalmente sustituido con uno o más $R_f$;

$R_f$ es alquilo C1-5, cicloalquilo C3-6, tolilsulfonilo, alcoxi C1-5, arilo, ariloxi, benciloxi,

halógeno, hidroxi, oxo, carboxi, ciano, nitro, carboxamida, amidino o guanidino;

$R_3$ es

hidrógeno, hidroxi, nitrilo o

una cadena de carbonos C1-6, saturada o insaturada, ramificada o no ramificada, opcionalmente total o parcialmente halogenada, en donde uno o más átomos de C están opcionalmente reemplazados por O, NH, S(O), $S(O)_2$ o S, y en donde dicha cadena está opcionalmente sustituida de modo independiente con 1-2 grupos oxo, $-NH_2$, uno o más alquilo $C_{1-4}$, pirrolidinilo, piperidinilo, morfolinilo, tiomorfolinilo, piperazinilo, indolinilo, piranilo, tiopiranilo, furanilo, tienilo, pirrolilo, oxazolilo, isoxazolilo, tiazolilo, imidazolilo, piridinilo, pirimidinilo, pirazinilo, indolilo, benzofuranilo, benzotienilo, bencimidazolilo, benzotiazolilo, quinolinilo, isoquinolinilo, quinazolinilo, benzoxazolilo o quinoxalinilo;

en donde $R_2$ y $R_4$ en las fórmulas (Ia) o (Ib) forman opcionalmente un sistema de heteroanillo monocíclico de 4 a 8 miembros o policíclico de 7-12 miembros, cada uno de ellos aromático o no aromático, en donde cada heteroanillo está opcionalmente sustituido con uno o más $R_7$;

cada $R_2$ y $R_4$ son, independientemente:

una cadena de alquilo C1-5, opcionalmente interrumpida por uno o dos N, O o $S(O)_m$, y opcionalmente sustituida con 1-2 oxo, amino, hidroxi, halógeno, alquilo C1-4, pirrolidinilo, piperidinilo, morfolinilo, tiomorfolinilo, piperazinilo, indolinilo, piranilo, tiopiranilo, furanilo, tienilo, pirrolilo, oxazolilo, isoxazolilo, tiazolilo, imidazolilo, piridinilo, pirimidinilo, pirazinilo, indolilo, benzofuranilo, benzotienilo, bencimidazolilo, benzotiazolilo, quinolinilo, isoquinolinilo, quinazolinilo benzoxazolilo o quinoxalinilo,

arilo, ariloxi, aroílo, furanilo, tienilo, pirrolilo, imidazolilo, piridinilo, pirimidinilo, alcanoílo C1-5, alcoxi

C1-5-carbonilo, ariloxicarbonilo, benciloxicarbonilo, alcanoil C1-5-amino, aroilamino, alquiltio C1-5, arilti , alquil C1-5-sulfonilamino, arilsulfonilamino, alquil C1-5--aminosulfonilo, arilaminosulfonilo, cicloalquilo C3-6 y benciloxi,
estando cada uno de los antes mencionados opcionalmente halogenado,
halógeno, hidroxi, oxo, carboxi, nitrilo, nitro o $NH_2C(O)$-;
m es 0, 1 ó 2;
X es =O, =S o =N-$R_4$, en donde $R_4$ es como se define anteriormente, y
sus derivados farmacéuticamente aceptables.

En otra realización de la invención, se proporcionan nuevos compuestos de la fórmula (Ia) y fórmula (Ib) según se describe inmediatamente antes, y en donde:
Het es piperidinilo, pirrolidinilo, tetrahidropiranilo, tetrahidrotiopiranilo, azetidinilo, azepanilo, oxepanilo, tetrahidrofuranilo, oxetanilo, hexahidropirimidinilo, hexahidropiridazinilo, piperazinilo, 1,4,5,6-tetrahidropirimidinilo, octahidro-indolizinilo, octahidro-quinolizinilo, decahidro-quinolinilo, 1,2,3,4-tetrahidro-quinolinilo, dihidro-oxazolilo, 1,2-tiazinil-1,1-dióxido, 1,2,6-tiadiazinanil-1,1-dióxido, isotiazolidinil-1,1-dióxido, pirazolidinilo o un biciclo puenteado, elegido de aza-biciclo[3.2.1]octano, aza-biciclo[2.2.1]heptano, aza-biciclo[2.2.2]octano, aza-biciclo[3.2.2]nonano, aza-biciclo[2.1.1]hexano, aza-biciclo[3.1.1]heptano, aza-biciclo[3.3.2]decano y 2-oxa- ó 2-tia-5-aza-biciclo[2.2.1]heptano;
estando cada anillo opcionalmente sustituido con uno o más $R_1$;
$R_2$ es un enlace, hidrógeno, alquilo C1-7, alcoxi C1-7, cicloalquilo C3-7, ariloxi, fenilo, bencilo, naftilo, tetrahidronaftilo, alquil C1-7-sulfonil-alquilo C1-7, cicloalquil C3-7-sulfonil-alquilo C1-7, arilsulfonil-alquilo C1-7, pirrolidinilo, piperidinilo, morfolinilo, tiomorfolini-

lo, piperazinilo, indolinilo, piranilo, tiopiranilo, furanilo, tienilo, pirrolilo, oxazolilo, tiazolilo, imidazolilo, piridinilo, isoxazolilo, pirimidinilo, pirazinilo, piridazinilo, indolilo, quinolinilo, benzofuranilo, benzotienilo, bencimidazolilo, benzotiazolilo, benzisoxazolilo, benzoxazolilo o amino; en donde $R_1$ está opcionalmente sustituido con uno o más $R_4$;

$R_1$ es un enlace, alquilo C1-7, cicloalquilo C3-6, fenilo, naftilo, pirrolidinilo, piperidinilo, morfolinilo, tiomorfolinilo, piperazinilo, furanilo, tienilo, oxazolilo, tiazolilo, imidazolilo, triazolilo, tetrazolilo, piridinilo, pirimidinilo, pirazinilo, indolilo, benzofuranilo, benzotienilo, bencimidazolilo, benzotiazolilo, benzoxazolilo, quinolinilo, isoquinolinilo, quinazolinilo, quinoxalinilo, alcoxi C1-7, alcanoílo C1-7, alcanoiloxi C1-7, ariloxi, benciloxi, alcoxi C1-7-carbonilo, ariloxicarbonilo, aroiloxi, carbamoílo, en donde el átomo de nitrógeno puede estar independientemente mono- o di-sustituido con alquilo C1-7, arilo, pirrolidinilo, piperidinilo, morfolinilo, tiomorfolinilo, piperazinilo, furanilo, tienilo, oxazolilo, tiazolilo, imidazolilo, triazolilo, tetrazolilo, piridinilo, pirimidinilo, pirazinilo, indolilo, benzofuranilo, benzotienilo, bencimidazolilo, benzotiazolilo, quinolinilo, isoquinolinilo, quinazolinilo o quinoxalinilo,

o $R_1$ es alcanoil C1-7-amino, aroilamino, alquiltio C1-7, en donde el átomo de azufre puede estar oxidado en un sulfóxido o sulfona, ariltio, en donde el átomo de azufre puede estar oxidado en un sulfóxido o sulfona, ureido, en donde cualquier átomo de nitrógeno puede estar sustituido, independientemente, con alquilo C1-7, arilo, pirrolidinilo, piperidinilo, morfolinilo, tiomorfolinilo, piperazinilo, furanilo, tienilo, oxazolilo, tiazolilo, imidazolilo, triazolilo, tetrazo-

lilo, piridinilo, pirimidinilo, pirazinilo, indolilo, benzofuranilo, benzotienilo, bencimidazolilo, benzotiazolilo, quinolinilo, isoquinolinilo, quinazolinilo o quinoxalinilo,

o $R_n$ es alcoxi C1-7-carbonilamino, ariloxicarbonilamino, alquil C1-7-carbamoiloxi, arilcarbamoiloxi, alquil C1-7-sulfonilamino, arilsulfonilamino, alquil C1-7-aminosulfonilo, arilaminosulfonilo, amino, en donde el átomo de nitrógeno puede estar independientemente mono- o di-sustituido con alquilo C1-7, arilo, pirrolidinilo, piperidinilo, morfolinilo, tiomorfolinilo, piperazinilo, furanilo, tienilo, oxazolilo, tiazolilo, imidazolilo, triazolilo, tetrazolilo, piridinilo, pirimidinilo, pirazinilo, indolilo, benzofuranilo, benzotienilo, bencimidazolilo, benzotiazolilo, quinolinilo, isoquinolinilo, quinazolinilo o quinoxalinilo,

o $R_n$ es halógeno, hidroxi, oxo, carboxi, ciano, nitro, carboxamida, amidino o guanidino, $R_n$ puede estar, además, opcionalmente sustituido con uno o más $R_b$;

$R_b$ es alquilo C1-5, cicloalquilo C3-6, arilo, alcoxi C1-5, ariloxi, benciloxi, halógeno, hidroxi, oxo, carboxi, ciano, nitro, carboxamida, amidino o guanidino;

$R_c$ es hidrógeno o metilo o etilo;

$R_d$ es un enlace, hidrógeno, alquilo C1-5, alquileno C2-5, cicloalquilo C3-7, aril-alquilo C1-3 o arilo, en donde $R_d$ está opcionalmente sustituido con uno o más $R_e$;

$R_e$ es alquilo C1-5, cicloalquilo C3-7, arilo, indanilo, indenilo, biciclo[2.2.1]heptanilo, biciclo[2.2.2]-octanilo, biciclo[4.1.0]heptanilo, biciclo[3.1.0]hexanilo, biciclo[1.1.1]pentanilo, cubanilo, 1,2,3,4-tetrahidronaftilo, pirrolidinilo, piperidinilo, morfolinilo, tiomorfolinilo, piperazinilo, indolinilo, furanilo, tetrahidrofuranilo, piranilo, tetrahidropiranilo, tienilo, pirrolilo, oxazolilo, tiazolilo,

imidazolilo, pirazolilo, triazolilo, tetrazolilo, piridinilo, pirimidinilo, pirazinilo, indolilo, benzofuranilo, benzotienilo, bencimidazolilo, benzotiazolilo, quinolinilo, isoquinolinilo, quinazolinilo, quinoxalinilo, alcoxi C1-5, ariloxi, alcanoílo C1-5, aroílo, alcoxi C1-5-carbonilo, ariloxicarbonilo, alcanoiloxi C1-5, aroiloxi, carbamoílo, en donde el átomo de nitrógeno puede estar independientemente mono- o di-sustituido con alquilo C1-5, arilo, pirrolidinilo, piperidinilo, morfolinilo, tiomorfolinilo, piperazinilo, indolinilo, furanilo, tienilo, pirrolilo, oxazolilo, tiazolilo, imidazolilo, triazolilo, tetrazolilo, piridinilo, pirimidinilo, pirazinilo, indolilo, benzofuranilo, benzotienilo, bencimidazolilo, benzotiazolilo, quinolinilo, isoquinolinilo, quinazolinilo o quinoxalinilo,

o $R_{..}$ es alcanoil C1-5-amino, aroilamino, alquiltio C1-5, en donde el átomo de azufre puede estar oxidado en un sulfóxido o sulfona, ariltio, en donde el átomo de azufre puede estar oxidado en un sulfóxido o sulfona, ureido, en donde cualquier átomo de nitrógeno puede estar sustituido, independientemente, con alquilo C1-5, arilo, pirrolidinilo, piperidinilo, morfolinilo, tiomorfolinilo, piperazinilo, indolinilo, furanilo, tienilo, pirrolilo, oxazolilo, tiazolilo, imidazolilo, triazolilo, tetrazolilo, piridinilo, pirimidinilo, pirazinilo, indolilo, benzofuranilo, benzotienilo, bencimidazolilo, benzotiazolilo, quinolinilo, isoquinolinilo, quinazolinilo o quinoxalinilo,

o $R_{..}$ es alcoxi C1-5-carbonilamino, ariloxicarbonilamino, alquil C1-5-carbamoiloxi, arilcarbamoiloxi, alquil C1-5-sulfonilamino, arilsulfonilamino, alquil C1-5-aminosulfonilo, arilaminosulfonilo, amino, en donde el átomo de nitrógeno puede estar independientemente mono- o di-sustituido con alquilo C1-5, arilo, pirrolidinilo,

piperidinilo, morfolinilo, tiomorfolinilo, piperazinilo, indolinilo, furanilo, tienilo, pirrolilo, oxazolilo, tiazolilo, imidazolilo, triazolilo, tetrazolilo, piridinilo, pirimidinilo, pirazinilo, indolilo, benzofuranilo, benzotienilo, bencimidazolilo, benzotiazolilo, quinolinilo, isoquinolinilo, quinazolinilo o quinoxalinilo,

o $R_c$ es halógeno, hidroxi, oxo, carboxi, ciano, nitro, aminidino o guanidino, $R_c$ puede estar, además, opcionalmente sustituido con uno o más $R_d$;

$R_d$ es alquilo C1-5, cicloalquilo 3-6, arilo, aril-alquilo C1-4, alcoxi C1-5, ariloxi, aril-alcoxi C1-5, aroílo, halógeno, hidroxi, oxo o ciano;

$R_1$ es hidrógeno o metilo;

$R_2$ es un enlace, hidrógeno, carbonilo, alquilo C1-8, alcoxi C1-8-alquilo C1-8, alquil C1-8-amino-alquilo C1-8, alquiltio C1-8-alquilo C1-8, en donde el átomo de azufre puede estar oxidado en un sulfóxido o sulfona, alcoxi C1-8, ariloxi, cicloalquilo C3-7, arilo, bencilo, tetrahidronaftilo, indanilo, heterociclilo, seleccionado de pirrolidinilo, piperidinilo, morfolinilo, tiomorfolinilo, piperazinilo, indolinilo, piranilo, tetrahidropiranilo, tiopiranilo, tetrahidrotiopiranilo, furanilo, tetrahidrofuranilo, tienilo, oxazolilo, tiazolilo, imidazolilo, piridinilo, pirimidinilo, pirazinilo, tetrazolilo, triazolilo, pirazolilo, indolilo, benzofuranilo, benzotienilo, bencimidazolilo, benzotiazolilo, quinolinilo, isoquinolinilo, quinazolinilo, benzoxazolilo y quinoxalinilo, heterocicliloxi, en donde el resto heterociclilo se selecciona de los descritos en esta memoria en este párrafo, alcanoílo C1-7, aroílo, alcaniloxi C1-7, benciloxi, alcoxi C1-7-carbonilo, aril-alcoxi C1-4-carbonilo, ariloxicarbonilo, aroiloxi, carbamoílo, en donde el átomo de nitrógeno puede estar independientemente mono- o di-sustituido con alquilo C1-7, arilo, pirrolidinilo, piperidinilo, morfolinilo, tiomorfolinilo, piperazinilo, furanilo, tienilo, oxazolilo,

tiazolilo, imidazolilo, piridinilo, pirimidinilo, pirazinilo, indolilo, benzofuranilo, benzotienilo, bencimidazolilo, benzotiazolilo, quinolinilo, isoquinolinilo, quinazolinilo o quinoxalinilo,

o $R_4$ es alcanoil C1-7-amino, aroilamino, alquiltio C1-7, en donde el átomo de azufre puede estar oxidado en un sulfóxido o sulfona, ariltio, en donde el átomo de azufre puede estar oxidado en un sulfóxido o sulfona, ureido, en donde cualquier átomo de nitrógeno puede estar independientemente sustituido con alquilo C1-7, arilo, pirrolidinilo, piperidinilo, morfolinilo, tiomorfolinilo, piperazinilo, furanilo, tienilo, oxazolilo, tiazolilo, imidazolilo, piridinilo, pirimidinilo, pirazinilo, indolilo, benzofuranilo, benzotienilo, bencimidazolilo, benzotiazolilo, quinolinilo, isoquinolinilo, quinazolinilo o quinoxalinilo,

o $R_5$ es alcoxi C1-7-carbonilamino, ariloxicarbonilamino, alquil C1-7-carbamoiloxi, arilcarbamoiloxi, alquil C1-7-sulfonilamino, arilsulfonilamino, alquil C1-7-aminosulfonilo, arilaminosulfonilo, amino, en donde el átomo de nitrógeno puede estar independientemente mono- o di-sustituido con alquilo C1-7, arilo, pirrolidinilo, piperidinilo, morfolinilo, tiomorfolinilo, piperazinilo, furanilo, tienilo, pirrolilo, oxazolilo, tiazolilo, imidazolilo, piridinilo, pirimidinilo, pirazinilo, indolilo, benzofuranilo, benzotienilo, bencimidazolilo, benzotiazolilo, quinolinilo, isoquinolinilo, quinazolinilo o quinoxalinilo,

o $R_6$ es halógeno, hidroxi, oxi, oxo, carboxi, ciano, nitro o carboxamida, $R_4$ puede estar, además, opcionalmente sustituido con uno o más $R_9$;

$R_9$ es alquilo C1-7, alcoxi C1-7-alquilo C1-7, alquil C1-7-amino-alquilo C1-7, alquiltio C1-7-alquilo C1-7, en donde el átomo de azufre puede estar oxidado en un sulfóxido o sulfona, alcoxi C1-7, cicloalquilo C3-7, arilo, tetrahidronaftilo, indanilo, pirrolidinilo, piperidinilo, morfolinilo, tiomorfolinilo, pipera-

zinilo, tiopiranilo, tetrahidrotiopiranilo, tetrahidropiranilo, tetrahidrofuranilo, furanilo, tienilo, oxazolilo, tiazolilo, imidazolilo, piridinilo, pirimidinilo, pirazinilo, indolilo, benzofuranilo, benzotienilo, bencimidazolilo, benzotiazolilo, benzoxazolilo, quinolinilo, isoquinolinilo, quinazolinilo, quinoxalinilo, alcanoílo C1-5, aroílo, alcanoiloxi C1-5, ariloxi, benciloxi, alcoxi C1-5-carbonilo, ariloxicarbonilo, aroiloxi, carbamoílo, en donde el átomo de nitrógeno puede estar independientemente mono- o di-sustituido con alquilo C1-5, arilo, pirrolidinilo, piperidinilo, morfolinilo, tiomorfolinilo, piperazinilo, furanilo, tienilo, oxazolilo, tiazolilo, imidazolilo, piridinilo, pirimidinilo, pirazinilo, indolilo, benzofuranilo, benzotienilo, bencimidazolilo, benzotiazolilo, quinolinilo, isoquinolinilo, quinazolinilo o quinoxalinilo,

o $R_c$ es alcanoil C1-5-amino, aroilamino, alquiltio C1-5, en donde el átomo de azufre puede estar oxidado en un sulfóxido o sulfona, ariltio, en donde el átomo de azufre puede estar oxidado en un sulfóxido o sulfona, ureido, en donde cualquier átomo de nitrógeno puede estar independientemente sustituido con alquilo C1-5, arilo, pirrolidinilo, piperidinilo, morfolinilo, tiomorfolinilo, piperazinilo, furanilo, tienilo, oxazolilo, tiazolilo, imidazolilo, piridinilo, pirimidinilo, pirazinilo, indolilo, benzofuranilo, benzotienilo, bencimidazolilo, benzotiazolilo, quinolinilo, isoquinolinilo, quinazolinilo o quinoxalinilo,

o $R_c$ es alcoxi C1-5-carbonilamino, ariloxicarbonilamino, alquil C1-5-carbamoiloxi, arilcarbamoiloxi, alquil C1-5-sulfonilamino, arilsulfonilamino, alquil C1-5-aminosulfonilo, arilaminosulfonilo, amino, en donde el átomo de nitrógeno puede estar independientemente mono- o di-sustituido con alquilo C1-5, arilo, pirrolidinilo,

piperidinilo, morfolinilo, tiomorfolinilo, piperazinilo, furanilo, tienilo, oxazolilo, tiazolilo, imidazolilo, piridinilo, pirimidinilo, pirazinilo, indolilo, benzofuranilo, benzotienilo, bencimidazolilo, benzotiazolilo, quinolinilo, isoquinolinilo, quinazolinilo o quinoxalinilo,

o $R_6$ es halógeno, hidroxi, oxo, carboxi, ciano, nitro, carboxamida, amidino o guanidino, $R_6$ puede estar, además, opcionalmente sustituido con uno o más $R_7$;

$R_7$ es metilo, etilo, t-butilo, tolilsulfonilo, alcoxi C1-3, ciclopropilo, ciclohexilo, fenilo, naftilo, fenoxi, benciloxi, fluoro, cloro, bromo, hidroxi, oxo, carboxi, ciano, nitro o carboxamida;

$R_8$ es

hidrógeno, hidroxi, nitrilo o

una cadena de carbonos C1-6, saturada o insaturada, ramificada o no ramificada, opcionalmente total o parcialmente halogenada, en donde uno o más átomos de C están opcionalmente reemplazados por O, NH, S(O), $S(O)_2$ o S, y en donde dicha cadena está opcionalmente sustituida, de modo independiente, con 1-2 grupos oxo, $-NH_2$, uno o más alquilo C1-4, pirrolidinilo, piperidinilo, morfolinilo, tiomorfolinilo, piperazinilo, indolinilo, piranilo, tiopiranilo, furanilo, tienilo, pirrolilo, oxazolilo, isoxazolilo, tiazolilo, imidazolilo, piridinilo, pirimidinilo, pirazinilo, indolilo, benzofuranilo, benzotienilo, bencimidazolilo, benzotiazolilo, quinolinilo, isoquinolinilo, quinazolinilo, benzoxazolilo o quinoxalinilo;

$R_3$ y $R_4$ de la fórmula (Ia) o de la fórmula (Ib) forman opcionalmente un anillo heterocíclico monocíclico de 5, 6 ó 7 miembros, aromático o no aromático, opcionalmente sustituido con $R_7$;

o un anillo bicíclico con un anillo heterocíclico de 5, 6 ó 7 miembros, aromático o no aromático, condensado a un segundo anillo heterocíclico o carbocíclico de 5 - 7 miem-

bros, aromático o no aromático, en donde cada anillo está opcionalmente sustituido, de modo independiente, con uno o más $R_7$;

$R_7$ y $R_8$ son, independientemente, alquilo C1-5, cicloalquil C3-6, arilo, alcoxi C1-5, ariloxi, benciloxi, estando cada uno de los antes mencionados opcionalmente halogenado, o $R_8$ es halógeno, hidroxi, oxo, carboxi, nitrilo, nitro o $NH_2C(O)$-;

m es 0, 1 ó 2 y

X es O o S..

Todavía en otra realización de la invención, se proporcionan nuevos compuestos de las fórmulas (Ia) y (Ib) según se describe inmediatamente antes, y en donde:

Het es piperidinilo, pirrolidinilo, azetidinilo, azepanilo, oxepanilo, tetrahidropiranilo, tetrahidrotiopiranilo, tetrahidrofuranilo, oxetanilo, octahidro-indolizinilo, octahidro-quinolizinilo o aza-biciclo[3.2.1]octanilo, estando cada anillo opcionalmente sustituido con uno o más $R_7$;

$R_1$ es un enlace, hidrógeno, alquilo C1-5, alcoxi C1-5, cicloalquilo C3-6, ariloxi, fenilo, bencilo, naftilo, alquil C1-3-sulfonil-alquilo C1-3, cicloalquil C3-6-sulfonil-alquilo C1-3, arilsulfonil-alquilo C1-3, pirrolidinilo, piperidinilo, morfolinilo, tiomorfolinilo, piperazinilo, furanilo, tienilo, oxazolilo, tiazolilo, imidazolilo, piridinilo, isoxazolilo, pirimidinilo, pirazinilo, piridazinilo, indolilo, quinolinilo, benzofuranilo, benzotienilo, bencimidazolilo, benzotiazolilo, benzoxazolilo o amino; en donde $R_1$ está opcionalmente sustituido con uno o más $R_9$;

$R_9$ es un enlace, alquilo C1-3, ciclopropilo, ciclopentilo, ciclohexilo, fenilo, naftilo, pirrolidinilo, piperidinilo, morfolinilo, tiomorfolinilo, piperazinilo, furanilo, tienilo, oxazolilo, tiazolilo, imidazolilo, piridinilo, pirimidinilo, bencimidazolilo, benzotiazolilo, benzoxazolilo, alcoxi C1-3, alcanoílo

C1-3, alcanoiloxi C1-3, ariloxi, benciloxi, alcoxi C1-3-carbonilo, ariloxicarbonilo, aroiloxi, carbamoílo, en donde el átomo de nitrógeno puede estar independientemente mono- o di-sustituido con alquilo C1-3, arilo, pirrolidinilo, piperidinilo, morfolinilo, tiomorfolinilo, piperazinilo, tienilo, oxazolilo, tiazolilo, imidazolilo, piridinilo, pirimidinilo, bencimidazolilo o benzotiazolilo,

o $R_a$ es alcanoil C1-3-amino, aroilamino, alquiltio C1-3, en donde el átomo de azufre puede estar oxidado en un sulfóxido o sulfona, ariltio, en donde el átomo de azufre puede estar oxidado en un sulfóxido o sulfona, ureido, en donde cualquier átomo de nitrógeno puede estar sustituido, independientemente, con alquilo C1-3, arilo, pirrolidinilo, piperidinilo, morfolinilo, tiomorfolinilo o piperazinilo,

o $R_a$ es alcoxi C1-3-carbonilamino, ariloxicarbonilamino, alquil C1-3-carbamoiloxi, arilcarbamoiloxi, alquil C1-3-sulfonilamino, arilsulfonilamino, alquil C1-3-aminosulfonilo, arilaminosulfonilo, amino, en donde el átomo de nitrógeno puede estar independientemente mono- o di-sustituido con alquilo C1-3, arilo, pirrolidinilo, piperidinilo, morfolinilo, tiomorfolinilo o piperazinilo,

o $R_a$ es halógeno, hidroxi, oxo, carboxi, ciano, nitro, carboxamida, amidino o guanidino, $R_a$ puede estar, además, opcionalmente sustituido con uno o más $R_b$;

$R_b$ es alquilo C1-3, cicloalquilo C3-6, arilo, alcoxi C1-3, ariloxi, benciloxi, halógeno, hidroxi, oxo, carboxi, ciano, nitro, carboxamida, amidino o guanidino;

$R_c$ es hidrógeno o metilo;

$R_d$ es un enlace, hidrógeno, alquilo C1-5, alquileno C2-5, cicloalquilo C4-6 o aril-alquilo C1-2, en donde $R_d$ está opcionalmente sustituido con uno o más $R_e$;

$R_c$ es alquilo C1-4, cicloalquilo C5-6, fenilo, naftilo, indanilo, biciclo[2.2.1]heptanilo, biciclo[2.2.2]-octanilo, biciclo[4.1.0]heptanilo, biciclo[3.1.0]-hexanilo, biciclo[1.1.1]pentanilo, cubanilo, 1,2,3,4-tetrahidronaftilo, pirrolidinilo, piperidinilo, morfolinilo, tiomorfolinilo, indolinilo, furanilo, tetrahidrofuranilo, piranilo, tetrahidropiranilo, tienilo, pirrolilo, oxazolilo, tiazolilo, imidazolilo, pirazolilo, piridinilo, pirimidinilo, pirazinilo, indolilo, benzofuranilo, benzotienilo, bencimidazolilo, benzotiazolilo, quinolinilo, isoquinolinilo, quinazolinilo, quinoxalinilo, alcoxi C1-4, fenoxi, naftiloxi, alcanoílo C1-3, benzoílo, alcoxi C1-3-carbonilo, fenoxicarbonilo, alcanoiloxi C1-3, benzoiloxi, carbamoílo, en donde el átomo de nitrógeno puede estar independientemente mono- o di-sustituido con alquilo C1-5 o arilo,

o R es alcanoil C1-3-amino, benzoilamino, alquiltio C1-3, en donde el átomo de azufre puede estar oxidado en un sulfóxido o sulfona, feniltio, en donde el átomo de azufre puede estar oxidado en un sulfóxido o sulfona, ureido, en donde cualquier átomo de nitrógeno puede estar sustituido, independientemente, con alquilo C1-5 o arilo,

o $R_c$ es alcoxi C1-3-carbonilamino, ariloxicarbonilamino, alquil C1-3-carbamoiloxi, arilcarbamoiloxi, alquil C1-3-sulfonilamino, arilsulfonilamino, alquil C1-3-aminosulfonilo, arilaminosulfonilo, amino, en donde el átomo de nitrógeno puede estar independientemente mono- o di-sustituido con alquilo C1-5 o arilo,

o $R_c$ es halógeno, hidroxi, oxo, carboxi, ciano, nitro, amidino o guanidino, $R_c$ puede estar, además, opcionalmente sustituido con uno o más $R_d$;

$R_d$ es alquilo C1-3, cicloalquilo 3-6, fenilo, bencilo, alcoxi C1-3, fenoxi, fenil-alcoxi C1-3,

benzoílo, halógeno, hidroxi, oxo o ciano;

$R_4$ es hidrógeno;

$R_5$ es un enlace, hidrógeno, carbonilo, alquilo C1-6, alcoxi C1-6-alquilo C1-6, alquil C1-6-amino-alquilo C1-6, alquiltio C1-6-alquilo C1-6, en donde el átomo de azufre puede estar oxidado en un sulfóxido o sulfona, alcoxi C1-6, fenoxi, naftiloxi, cicloalquilo C3-6, fenilo, naftilo, bencilo, indanilo, heterociclilo, seleccionado de pirrolidinilo, piperidinilo, morfolinilo, tiomorfolinilo, piperazinilo, tetrahidropiranilo, tetrahidrotiopiranilo, furanilo, tetrahidrofuranilo, tienilo, oxazolilo, tiazolilo, imidazolilo, piridinilo, pirimidinilo, pirazolilo, benzofuranilo, benzotienilo, quinolinilo, isoquinolinilo y benzoxazolilo, heterocicliloxi, en donde el resto heterociclilo se selecciona de los descritos en esta memoria en este párrafo, alcanoílo C1-3, benzoílo, naftoílo, alcaniloxi C1-4, benciloxi, alcoxi C1-4-carbonilo, aril-alcoxi C1-2-carbonilo, fenoxicarbonilo, benzoiloxi, carbamoílo, en donde el átomo de nitrógeno puede estar independientemente mono- o di-sustituido con alquilo C1-3, fenilo, pirrolidinilo, piperidinilo, morfolinilo, piperazinilo, oxazolilo, tiazolilo, imidazolilo, piridinilo o pirimidinilo, o $R_5$ es alcanoil C1-4-amino, aroilamino, alquiltio C1-4, en donde el átomo de azufre puede estar oxidado en un sulfóxido o sulfona, ariltio, en donde el átomo de azufre puede estar oxidado en un sulfóxido o sulfona, ureido, en donde cualquier átomo de nitrógeno puede estar independientemente sustituido con alquilo C1-3, fenilo, naftilo, pirrolidinilo, piperidinilo, morfolinilo, piperazinilo, oxazolilo, tiazolilo, imidazolilo, piridinilo, pirimidinilo, pirazinilo, indolilo, benzofuranilo, benzotienilo, bencimidazolilo o benzotiazolilo,

o $R_5$ es alcoxi C1-4-carbonilamino, fenoxicarbonilamino, alquil C1-4-carbamoiloxi, fenilcarbamoiloxi, alquil C1-4-sulfonilamino, fenilsulfonilamino, alquil C1-3-aminosulfonilo, fenilaminosulfonilo, amino, en donde el átomo de nitrógeno

puede estar independientemente mono- o di-sustituido con alquilo C1-4, arilo, pirrolidinilo, piperidinilo, morfolinilo, tiomorfolinilo, piperazinilo, furanilo, tienilo, oxazolilo, tiazolilo, imidazolilo, piridinilo, pirimidinilo, bencimidazolilo o benzotiazolilo,

o $R_c$ es halógeno, hidroxi, oxo, carboxi, ciano, nitro o carboxamida, $R_b$ puede estar, además, opcionalmente sustituido con uno o más $R_e$;

$R_c$ es alquilo C1-4, alcoxi C1-4, cicloalquilo C3-7, fenilo, naftilo, indanilo, pirrolidinilo, piperidinilo, morfolinilo, tiomorfolinilo, piperazinilo, tetrahidrotiopiranilo, tetrahidropiranilo, tetrahidrofuranilo, tienilo, oxazolilo, tiazolilo, imidazolilo, piridinilo, pirimidinilo, pirazinilo, indolilo, bencimidazolilo, benzotiazolilo, benzoxazolilo, quinolinilo, isoquinolinilo, quinazolinilo, quinoxalinilo, alcanoílo C1-4, aroílo, alcanoiloxi C1-4, fenoxi, naftiloxi, benciloxi, alcoxi C1-4-carbonilo, fenoxicarbonilo, benzoiloxi, carbamoílo, en donde el átomo de nitrógeno puede estar independientemente mono- o di-sustituido con alquilo C1-3, fenilo, naftilo, pirrolidinilo, piperidinilo, morfolinilo, tiomorfolinilo, piperazinilo, furanilo, tienilo, oxazolilo, tiazolilo, imidazolilo, piridinilo, pirimidinilo, bencimidazolilo o benzotiazolilo,

o $R_e$ es alcanoil C1-4-amino, benzoilamino, alquiltio C1-4, en donde el átomo de azufre puede estar oxidado en un sulfóxido o sulfona, feniltio, en donde el átomo de azufre puede estar oxidado en un sulfóxido o sulfona, ureido, en donde cualquier átomo de nitrógeno puede estar independientemente sustituido con alquilo C1-3, fenilo, naftilo, pirrolidinilo, piperidinilo, morfolinilo, tiomorfolinilo, piperazinilo, furanilo, tienilo, oxazolilo, tiazolilo, imidazolilo, piridinilo, pirimidinilo, bencimidazolilo o benzotiazolilo,

o $R_c$ es alcoxi C1-4-carbonilamino, fenoxicarbonilamino,

alquil C1-4-carbamoiloxi, fenilcarbamoiloxi, alquil C1-4-sulfonilamino, fenilsulfonilamino, alquil C1-4-aminosulfonilo, fenilaminosulfonilo, amino, en donde el átomo de nitrógeno puede estar independientemente mono- o di-sustituido con alquilo C1-3, fenilo, naftilo, pirrolidinilo, piperidinilo, morfolinilo, tiomorfolinilo, piperazinilo, furanilo, tienilo, oxazolilo, tiazolilo, imidazolilo, piridinilo, pirimidinilo, bencimidazolilo o benzotiazolilo,

o $R_2$ es halógeno, hidroxi, oxo, carboxi, ciano, nitro o carboxamida, $R_2$ puede estar, además, opcionalmente sustituido con uno o más $R_3$;

$R_3$ es metilo, etilo, t-butilo, tolilsulfonilo, metoxi, ciclopropilo, fenilo, fenoxi, benciloxi, fluoro, cloro, bromo, hidroxi, oxo, carboxi o carboxamida;

$R_1$ y $R_4$ de la fórmula (Ia) o de la fórmula (Ib) forman opcionalmente un anillo heterocíclico monocíclico de 5 ó 6 miembros, aromático o no aromático, opcionalmente sustituido con $R_5$;

o un anillo bicíclico con un anillo heterocíclico de 5, ó ó 7 miembros, aromático o no aromático, condensado a un segundo anillo heterocíclico o carbocíclico de 5 - 6 miembros, aromático o no aromático, en donde cada anillo está opcionalmente sustituido, de modo independiente, con uno o más $R_6$;

$R_5$ y $R_6$ son, independientemente, alquilo C1-4, cicloalquilo C5-6, alcoxi C1-4, halógeno, hidroxi, oxo, carboxi, nitrilo, nitro o $NH_2C(O)$-;

y

X es O.

Todavía en otra realización de la invención, se proporcionan nuevos compuestos de las fórmulas (Ia) y (Ib) según se describe inmediatamente antes, y en donde:

Het es piperidinilo, pirrolidinilo, azetidinilo, azepanilo,

oxepanilo, tetrahidropiranilo, oxetanilo o tetrahidrotiopiranilo, estando cada anillo opcionalmente sustituido con uno o más $R_s$;

$R_r$ es un enlace, hidrógeno, alquilo C1-5, alcoxi C1-5, cicloalquilo C3-6, ariloxi, fenilo, bencilo, naftilo, pirrolidinilo, piperidinilo, morfolinilo, tiomorfolinilo, piperazinilo, furanilo, tienilo, oxazolilo, tiazolilo, imidazolilo, piridinilo, pirimidinilo, pirazinilo, piridazinilo, indolilo, quinolinilo, benzofuranilo, benzotienilo, benzoxazolilo o amino; en donde $R_r$ está opcionalmente sustituido con uno o más $R_a$;

$R_r$ es un enlace, alquilo C1-3, ciclopropilo, ciclohexilo, fenilo, pirrolidinilo, piperidinilo, morfolinilo, tiomorfolinilo, piperazinilo, tienilo, imidazolilo, alcoxi C1-3, alcanoílo C1-3, alcanoiloxi C1-3, ariloxi, benciloxi, alcoxi C1-3-carbonilo, ariloxicarbonilo, aroiloxi, carbamoílo, en donde el átomo de nitrógeno puede estar independientemente mono- o di-sustituido con alquilo C1-3, arilo, pirrolidinilo, piperidinilo, morfolinilo, tiomorfolinilo o piperazinilo,

o $R_a$ es alcanoil C1-3-amino, aroilamino, alquiltio C1-3, en donde el átomo de azufre puede estar oxidado en un sulfóxido o sulfona, ariltio, en donde el átomo de azufre puede estar oxidado en un sulfóxido o sulfona, ureido, en donde cualquier átomo de nitrógeno puede estar sustituido, independientemente, con alquilo C1-3, arilo, pirrolidinilo, piperidinilo, morfolinilo, tiomorfolinilo o piperazinilo,

o $R_a$ es alcoxi C1-3-carbonilamino, ariloxicarbonilamino, alquil C1-3-carbamoiloxi, arilcarbamoiloxi, alquil C1-3-sulfonilamino, arilsulfonílamino, alquil C1-3-aminosulfonilo, arilaminosulfonilo, amino, en donde el átomo de nitrógeno puede estar independientemente mono- o di-sustituido con alquilo C1-3, arilo, pirrolidinilo, piperidinilo, morfolinilo, tiomorfolinilo o piperazini-

lo,

o $R_a$ es halógeno, hidroxi, oxo, carboxi, ciano, nitro, carboxamida, amidino o guanidino, $R_a$ puede estar, además, opcionalmente sustituido con uno o más $R_b$;

$R_b$ es metilo, etilo, n-propilo, i-propilo, ciclopropilo, ciclopentilo, ciclohexilo, fenilo, metoxi, etoxi, n-propoxi, i-propoxi, fenoxi, benciloxi, fluoro, cloro, bromo, yodo, hidroxi, oxo, carboxi, ciano, nitro o carboxamida;

$R_1$ es hidrógeno;

$R_2$ es un enlace, alquilo C1-3, alquileno C2-4, cicloalquilo C5-6, bencilo o naftilmetilo, en donde $R_1$ está opcionalmente sustituido con uno o más $R_2$;

$R_2$ es alquilo C1-3, cicloalquilo C5-6, fenilo, naftilo, indanilo, biciclo[2.2.1]heptanilo, biciclo[2.2.2]-octanilo, biciclo[4.1.0]heptanilo, biciclo[3.1.0]-hexanilo, biciclo[1.1.1]pentanilo, cubanilo, 1,2,3,4-tetrahidronaftilo, furanilo, tetrahidropiranilo, tienilo, oxazolilo, tiazolilo, imidazolilo, pirimidinilo, indolilo, benzofuranilo, benzotienilo, benzotiazolilo, alcoxi C1-3, fenoxi, naftiloxi, alcanoílo C1-2, benzoílo, alcoxi C1-2-carbonilo, fenoxicarbonilo, alcanoiloxi C1-2, benzoiloxi, carbamoílo, en donde el átomo de nitrógeno puede estar independientemente mono- o di-sustituido con alquilo C1-3 o arilo,

o $R_2$ es alcanoil C1-2-amino, benzoilamino, alquiltio C1-2, en donde el átomo de azufre puede estar oxidado en un sulfóxido o sulfona, feniltio, en donde el átomo de azufre puede estar oxidado en un sulfóxido o sulfona, ureido, en donde cualquier átomo de nitrógeno puede estar sustituido, independientemente, con alquilo C1-3 o arilo,

o $R_2$ es alcoxi C1-2-carbonilamino, fenoxicarbonilamino, alquil C1-2-carbamoiloxi, arilcarbamoiloxi, alquil C1-2-sulfonilamino, fenilsulfonilamino, alquil C1-2-

aminosulfonilo, fenilaminosulfonilo, amino, en donde el átomo de nitrógeno puede estar independientemente mono- o di-sustituido con alquilo C1-3 o arilo,
o $R_c$ es halógeno, hidroxi, oxo, carboxi o ciano, $R_c$ puede estar, además, opcionalmente sustituido con uno o más $R_d$;

$R_d$ es metilo, ciclopropilo, ciclohexilo, fenilo, bencilo, metoxi, fenoxi, benciloxi, benzoílo, fluoro, cloro, oxo o ciano;

R. es un enlace, hidrógeno, carbonilo, alquilo C1-5, alcoxi C1-5-alquilo C1-5, alquil C1-5-amino-alquilo C1-5, alquiltio C1-5-alquilo C1-5, en donde el átomo de azufre puede estar oxidado en un sulfóxido o sulfona, alcoxi C1-5, fenoxi, cicloalquilo C3-6, fenilo, naftilo, bencilo, indanilo, heterociclilo, seleccionado de pirrolidinilo, piperidinilo, morfolinilc, tiomorfolinilo, piperazinilo, tetrahidropiranilo, oxazolilo, tiazolilo, imidazolilo, piridinilo, pirimidinilo, bencimidazolilo y benzotiazolilo, heterocicliloxi, en donde el resto heterociclilo se selecciona de los descritos en esta memoria en este párrafo, alcanoílo C1-3, benzoílo, naftoílo, alcaniloxi C1-3, benciloxi, alcoxi C1-3-carbonilo, benciloxicarbonilo, fenoxicarbonilo, benzoiloxi, carbamoílo, en donde el átomo de nitrógeno puede estar independientemente mono- o di-sustituido con alquilo C1-3, fenilo, pirrolidinilo, piperidinilo, morfolinilo, piperazinilo, oxazolilo, tiazolilo, imidazolilo, piridinilo o pirimidinilo,
o R. es alcanoil C1-3-amino, aroilamino, alquiltio C1-3, en donde el átomo de azufre puede estar oxidado en un sulfóxido o sulfona, feniltio, en donde el átomo de azufre puede estar oxidado en un sulfóxido o sulfona, ureido, en donde cualquier átomo de nitrógeno puede estar independientemente sustituido con alquilo C1-3, fenilo, pirrolidinilo, piperidinilo, morfolinilo, piperazinilo, oxazolilo, tiazolilo, imidazolilo, piridinilo, pirimidinilo, benzofuranilo, benzotienilo, bencimidazolilo o benzotiazolilo,

o $R_c$ es alcoxi C1-3-carbonilamino, fenoxicarbonilamino, alquil C1-3-carbamoiloxi, fenilcarbamoiloxi, alquil C1-3-sulfonilamino, fenilsulfonilamino, alquil C1-3-aminosulfonilo, fenilaminosulfonilo, amino, en donde el átomo de nitrógeno puede estar independientemente mono- o di-sustituido con alquilo C1-3, fenilo, pirrolidinilo, piperidinilo, morfolinilo, tiomorfolinilo, piperazinilo, oxazolilo, tiazolilo, imidazolilo, piridinilo, pirimidinilo, bencimidazolilo o benzotiazolilo,

o $R_c$ es halógeno, hidroxi, oxo, carboxi, ciano o carboxamida,

$R_c$ puede estar, además, opcionalmente sustituido con uno o más $R_e$;

$R_e$ es alquilo C1-3, alcoxi C1-3, cicloalquilo C3-7, fenilo, naftilo, indanilo, pirrolidinilo, piperidinilo, morfolinilo, piperazinilo, tetrahidropiranilo, indolilo, tienilo, oxazolilo, tiazolilo, imidazolilo, piridinilo, pirimidinilo, bencimidazolilo, benzotiazolilo, benzoxazolilo, alcanoílo C1-3, aroílo, alcanoiloxi C1-3, fenoxi, benciloxi, alcoxi C1-3-carbonilo, fenoxicarbonilo, benzoiloxi, carbamoílo, en donde el átomo de nitrógeno puede estar independientemente mono- o di-sustituido con alquilo C1-3, fenilo, pirrolidinilo, piperidinilo, morfolinilo, piperazinilo, oxazolilo, tiazolilo, imidazolilo, piridinilo, pirimidinilo, bencimidazolilo o benzotiazolilo,

o $R_e$ es alcanoil C1-3-amino, benzoilamino, alquiltio C1-3, en donde el átomo de azufre puede estar oxidado en un sulfóxido o sulfona, feniltio, en donde el átomo de azufre puede estar oxidado en un sulfóxido o sulfona, ureido, en donde cualquier átomo de nitrógeno puede estar independientemente sustituido con alquilo C1-3, fenilo, naftilo, pirrolidinilo, piperidinilo, morfolinilo, piperazinilo, oxazolilo, tiazolilo, imidazolilo, piridinilo, pirimidinilo, bencimidazolilo o benzotiazolilo,

o $R_e$ es alcoxi C1-3-carbonilamino, fenoxicarbonilamino, alquil C1-3-carbamoiloxi, fenilcarbamoiloxi, alquil C1-3-sulfonilamino, fenilsulfonilamino, alquil C1-3-aminosulfonilo, fenilaminosulfonilo, amino, en donde el átomo de nitrógeno puede estar independientemente mono- o di-sustituido con alquilo C1-3, fenilo, naftilo, pirrolidinilo, piperidinilo, morfolinilo, piperazinilo, oxazolilo, tiazolilo, imidazolilo, piridinilo, pirimidinilo, bencimidazolilo o benzotiazolilo,

o $R_e$ es halógeno, hidroxi, oxo, carboxi, ciano o carboxamida, $R_e$ puede estar, además, opcionalmente sustituido con uno o más $R_f$;

y

$R_f$ es metilo, fenilo, tolilsulfonilo, metoxi, fenoxi, benciloxi, fluoro, cloro, bromo, hidroxi, oxo, carboxi o carboxamida;

$R_f$ y $R_f$ de la fórmula (Ia) o de la fórmula (Ib) forman un anillo heterocíclico con 5 ó 6 miembros, aromático o no aromático, condensado a un segundo anillo de heteroarilo, heterociclo o de fenilo; en donde cada anillo está opcionalmente sustituido, de modo independiente, con uno o dos $R_g$.

Todavía en otra realización de la invención, se proporcionan nuevos compuestos de las fórmulas (Ia) y (Ib) según se describe inmediatamente antes, y en donde:

Het es piperidinilo, pirrolidinilo, azetidinilo, azepanilo o tetrahidropiranilo, estando cada anillo opcionalmente sustituido con uno o más $R_g$;

$R_f$ es un enlace, metilo, etilo, i-propilo, metoxi, etoxi, ciclopropilo, ciclopentilo, ciclohexilo, fenoxi, fenilo, bencilo, naftilo, pirrolidinilo, piperidinilo, morfolinilo, tiomorfolinilo, piperazinilo, furanilo, tienilo, tiazolilo, imidazolilo, piridinilo, pirazinilo o amino; en donde $R_f$ está opcionalmente sustituido con uno o más $R_g$;

$R_g$ es un enlace, metilo, etilo, ciclopropilo, fenilo, pirrolidinilo, piperidinilo, morfolinilo, tiomorfolini-

lo, piperazinilo, tienilo, imidazolilo, metoxi, acetilo, acetoxi, fenoxi, benciloxi, metoxicarbonilo, fenoxicarbonilo, benzoiloxi, carbamoílo, en donde el átomo de nitrógeno puede estar independientemente mono- o di-sustituido con metilo, etilo o fenilo,

o $R_n$ es acetilamino, benzoilamino, metiltio, feniltio, en donde el átomo de azufre puede estar oxidado en un sulfóxido o sulfona, ureido, en donde cualquier átomo de nitrógeno puede estar sustituido, independientemente, con metilo, etilo o fenilo,

o $R_n$ es metoxicarbonilamino, fenoxicarbonilamino, metilcarbamoiloxi, fenilcarbamoiloxi, metilsulfonilamino, fenilsulfonilamino, metilaminosulfonilo, fenilaminosulfonilo, amino, en donde el átomo de nitrógeno puede estar independientemente mono- o di-sustituido con metilo o fenilo,

o $R_n$ es fluoro, cloro, bromo, yodo, hidroxi, oxo, carboxi, ciano, nitro o carboxamida, $R_n$ puede estar, además, opcionalmente sustituido con uno o más $R_o$;

$R_o$ es metilo, ciclopropilo, fenilo, metoxi, fenoxi, benciloxi, fluoro, cloro, hidroxi, oxo, carboxi o carboxamida;

$R_m$ es un enlace, alquilo C1-3, alquileno C2-4, cicloalquilo C5-6, bencilo o naftilmetilo, en donde $R_m$ está opcionalmente sustituido con uno o más $R_p$;

$R_p$ es metilo, etilo, n-propilo, i-propilo, cicloalquilo C5-6, indanilo, biciclo[2.2.1]heptanilo, biciclo[2.2.2]octanilo, biciclo[4.1.0]heptanilo, biciclo[3.1.0]hexanilo, biciclo[1.1.1]pentanilo, cubanilo, 1,2,3,4-tetrahidronaftilo, tienilo, oxazolilo, tiazolilo, indolilo, benzofuranilo, benzotienilo, benzotiazolilo, metoxi, etoxi, fenoxi, acetilo, benzoílo, metoxicarbonilo, fenoxicarbonilo, acetoxi, benzoiloxi, carbamoílo, en donde el átomo de nitrógeno puede estar independientemente mono- o di-sustituido

con metilo, etilo o arilo,

o $R_c$ es acetilamino, benzoilamino, metiltio, en donde el átomo de azufre puede estar oxidado en un sulfóxido o sulfona, feniltio, en donde el átomo de azufre puede estar oxidado en un sulfóxido o sulfona, ureido, en donde cualquier átomo de nitrógeno puede estar sustituido, independientemente, con metilo, etilo o arilo,

o $R_c$ es metoxicarbonilamino, fenoxicarbonilamino, metilcarbamoiloxi, fenilcarbamoiloxi, metilsulfonilamino, fenilsulfonilamino, metilaminosulfonilo, fenilaminosulfonilo, amino, en donde el átomo de nitrógeno puede estar independientemente mono- o di-sustituido con metilo, etilo o fenilo,

o R es fluoro, cloro u oxo, $R_c$ puede estar, además, opcionalmente sustituido con uno o más $R_d$;

$R_d$ es metilo, ciclopropilo, fenilo, metoxi, fluoro, cloro u oxo;

$R_a$ es un enlace, hidrógeno, carbonilo, alquilo C1-4, alcoxi C1-4-alquilo C1-4, alquil C1-4-amino-alquilo C1-4, alquiltio C1-4-alquilo C1-4, en donde el átomo de azufre puede estar oxidado en un sulfóxido o sulfona, alcoxi C1-4, fenoxi, ciclopropilo, ciclopentilo, ciclohexilo, fenilo, naftilo, bencilo, indanilo, heterociclilo, seleccionado de pirrolidinilo, piperidinilo, morfolinilo, piperazinilo, tetrahidropiranilo, oxazolilo, tiazolilo, imidazolilo, piridinilo, pirimidinilo, bencimidazolilo y benzotiazolilo, heterocicliloxi, en donde el resto heterociclilo se selecciona de los descritos en esta memoria en este párrafo, alcanoílo C1-2, benzoílo, naftoílo, alcaniloxi C1-2, benciloxi, alcoxi C1-2-carbonilo, benciloxicarbonilo, fenoxicarbonilo, benzoiloxi, carbamoílo, en donde el átomo de nitrógeno puede estar independientemente mono- o di-sustituido con alquilo C1-2, fenilo, pirrolidinilo, piperidinilo, morfolinilo, piperazinilo, oxazolilo, tiazolilo, imidazolilo, piridinilo o

pirimidinilo,
o $R_t$ es alcanoil C1-2-amino, benzoilamino, alquiltio C1-2, en donde el átomo de azufre puede estar oxidado en un sulfóxido o sulfona, feniltio, en donde el átomo de azufre puede estar oxidado en un sulfóxido o sulfona, ureido, en donde cualquier átomo de nitrógeno puede estar independientemente sustituido con alquilo C1-2, fenilo, pirrolidinilo, piperidinilo, morfolinilo, piperazinilo, oxazolilo, tiazolilo, imidazolilo, piridinilo, pirimidinilo, bencimidazolilo o benzotiazolilo,
o $R_t$ es alcoxi C1-2-carbonilamino, fenoxicarbonilamino, alquil C1-2-carbamoiloxi, fenilcarbamoiloxi, alquil C1-2-sulfonilamino, fenilsulfonilamino, alquil C1-2-aminosulfonilo, fenilaminosulfonilo, amino, en donde el átomo de nitrógeno puede estar independientemente mono- o di-sustituido con alquilo C1-2, fenilo, pirrolidinilo, piperidinilo, morfolinilo, piperazinilo, oxazolilo, tiazolilo, imidazolilo, piridinilo o pirimidinilo,
o $R_t$ es fluoro, cloro, bromo, hidroxi, oxo, carboxi o carboxamida, $R_t$ puede estar, además, opcionalmente sustituido con uno o más $R_e$;

$R_e$ es alquilo C1-3, alcoxi C1-2, cicloalquilo C3-6, fenilo, naftilo, indanilo, pirrolidinilo, piperidinilo, morfolinilo, piperazinilo, tetrahidropiranilo, indolilo, tienilo, oxazolilo, tiazolilo, imidazolilo, piridinilo, pirimidinilo, bencimidazolilo, benzotiazolilo, benzoxazolilo, alcanoílo C1-2, aroílo, alcanoiloxi C1-2, fenoxi, benciloxi, alcoxi C1-2-carbonilo, fenoxicarbonilo, benzoiloxi, carbamoílo, en donde el átomo de nitrógeno puede estar independientemente mono- o di-sustituido con alquilo C1-2, fenilo, pirrolidinilo, piperidinilo, morfolinilo, piperazinilo, oxazolilo, tiazolilo, imidazolilo, piridinilo o pirimidinilo,
o $R_e$ es alcanoil C1-2-amino, benzoilamino, alquiltio C1-2, en donde el átomo de azufre puede estar oxidado

en un sulfóxido o sulfona, feniltio, en donde el átomo de azufre puede estar oxidado en un sulfóxido o sulfona, ureido, en donde cualquier átomo de nitrógeno puede estar independientemente sustituido con alquilo C1-2, fenilo, pirrolidinilo, piperidinilo, morfolinilo, piperazinilo, oxazolilo, tiazolilo, imidazolilo, piridinilo o pirimidinilo,

o $R_6$ es alcoxi C1-2-carbonilamino, fenoxicarbonilamino, alquil C1-2-carbamoiloxi, fenilcarbamoiloxi, alquil C1-2-sulfonilamino, fenilsulfonilamino, alquil C1-2-aminosulfonilo, fenilaminosulfonilo, amino, en donde el átomo de nitrógeno puede estar independientemente mono- o di-sustituido con alquilo C1-2, fenilo, naftilo, pirrolidinilo, piperidinilo, morfolinilo, piperazinilo, oxazolilo, tiazolilo, imidazolilo, piridinilo o pirimidinilo,

o $R_6$ es fluoro, cloro, bromo, hidroxi, oxo, carboxi o carboxamida, $R_6$ puede estar, además, opcionalmente sustituido con uno o más $R_7$;

$R_7$ es metilo, fenilo, tolilsulfonilo, metoxi, fenoxi, benciloxi, fluoro, cloro, hidroxi, oxo, carboxi o carboxamida;

$R_4$ y $R_5$ de la fórmula (Ia) o de la fórmula (Ib) forman un anillo bicíclico con un anillo heterocíclico de 5 - 6 miembros, aromático o no aromático, condensado a un anillo de fenilo; en donde cada anillo está opcionalmente sustituido, de modo independiente, con uno o dos $R_7$.

Todavía en otra realización de la invención, se proporcionan nuevos compuestos de la fórmula (Ia) o de la fórmula (Ib) según se describe inmediatamente antes, y en donde:

Het es piperidin-4-ilo, piperidín-3-ilo, pirrolidin-3-ilo, azetidin-3-ilo, azepan-3-ilo, azepan-4-ilo o tetrahidropiran-4-ilo, estando cada anillo opcionalmente sustituido con uno o más $R_7$;

$R_3$ es un enlace, metilo, etilo, i-propilo, metoxi, ciclopro-

pilo, ciclohexilo, fenoxi, fenilo, bencilo, naftilo, pirrolidinilo, piperidinilo, morfolinilo, tiomorfolinilo, piperazinilo, furanilo, tienilo, tiazolilo, imidazolilo, piridinilo, pirazinilo o amino; en donde $R_1$ está opcionalmente sustituido con uno o más $R_a$;

$R_a$ es metilo, fenilo, tienilo, metoxi, acetilo, acetoxi, fenoxi, benciloxi, metoxicarbonilo, benzoiloxi, carbamoílo, en donde el átomo de nitrógeno puede estar independientemente mono- o di-sustituido con metilo o fenilo,

o $R_a$ es acetilamino, metiltio, feniltio, en donde el átomo de azufre puede estar oxidado en un sulfóxido o sulfona, ureido, en donde cualquier átomo de nitrógeno puede estar sustituido, independientemente, con metilo o fenilo,

o $R_a$ es metoxicarbonilamino, metilcarbamoiloxi, fenilcarbamoiloxi, metilsulfonilamino, fenilsulfonilamino, amino, en donde el átomo de nitrógeno puede estar independientemente mono- o di-sustituido con metilo o fenilo,

o $R_a$ es fluoro, cloro, hidroxi, oxo, carboxi, ciano, nitro o carboxamida;

$R_b$ es un enlace, metilo, etilo, n-propilo, propenilo, butenilo, i-butenilo, ciclohexilo, bencilo o naftilmetilo, en donde $R_b$ está opcionalmente sustituido con uno o más $R_c$;

$R_c$ es metilo, etilo, n-propilo, i-propilo, ciclohexilo, indanilo, biciclo[2.2.1]heptanilo, biciclo[2.2.2]-octanilo, biciclo[4.1.0]heptanilo, biciclo[3.1.0]-hexanilo, biciclo[1.1.1]pentanilo, cubanilo, 1,2,3,4-tetrahidronaftilo, metoxi, fenoxi, acetilo, benzoílo, metoxicarbonilo, fenoxicarbonilo, acetoxi, benzoiloxi, metiltio, en donde el átomo de azufre puede estar oxidado en un sulfóxido o sulfona, fluoro, cloro u oxo;

$R_d$ es un enlace, hidrógeno, carbonilo, alquilo C1-4, alcoxi C1-2-alquilo C1-2, alquil C1-2-amino-alquilo C1-2, alquiltio

C1-2-alquilo C1-2, en donde el átomo de azufre puede estar oxidado en un sulfóxido o sulfona, alcoxi C1-2, fenoxi, ciclopropilo, ciclopentilo, ciclohexilo, fenilo, bencilo, heterociclilo, seleccionado de pirrolidinilo, piperidinilo, morfolinilo, tetrahidropiranilo, piridinilo y pirimidinilo, heterocicliloxi, en donde el resto heterociclilo se selecciona de los descritos en esta memoria en este párrafo, acetilo, benzoílo, benzoílo, acetiloxi, benciloxi, metoxicarbonilo, etoxicarbonilo, benciloxicarbonilo, benzoiloxi, carbamoílo, en donde el átomo de nitrógeno puede estar independientemente mono- o di-sustituido con metilo, etilo o fenilo,

o R es acetilamino, benzoilamino, metiltio, en donde el átomo de azufre puede estar oxidado en un sulfóxido o sulfona, feniltio, en donde el átomo de azufre puede estar oxidado en un sulfóxido o sulfona, ureido, en donde cualquier átomo de nitrógeno puede estar independientemente sustituido con metilo, etilo o fenilo,

o R es metoxicarbonilamino, etoxicarbonilamino, fenoxicarbonilamino, metilcarbamoiloxi, fenilcarbamoiloxi, fenilsulfonilamino, metilaminosulfonilo, fenilaminosulfonilo, amino, en donde el átomo de nitrógeno puede estar independientemente mono- o di-sustituido con metilo, etilo o fenilo,

o R es fluoro, cloro, hidroxi, oxo, carboxi o carboxamida, $R_c$ puede estar, además, opcionalmente sustituido con uno o más $R_e$;

$R_e$ es metilo, metoxi, etoxi, ciclopropilo, ciclopentilo, ciclohexilo, fenilo, naftilo, indanilo, piperidinilo, morfolinilo, indolilo, tienilo, piridinilo, acetilo, benzoílo, acetiloxi, fenoxi, benciloxi, metoxicarbonilo, etoxicarbonilo, carbamoílo, en donde el átomo de nitrógeno puede estar independientemente mono- o di-sustituido con metilo, etilo o fenilo,

o $R_e$ es acetilamino, benzoilamino, metiltio, en donde el átomo de azufre puede estar oxidado en un sulfóxido o sulfona, feniltio, en donde el átomo de azufre puede

estar oxidado en un sulfóxido o sulfona, ureido, en donde cualquier átomo de nitrógeno puede estar independientemente sustituido con metilo, etilo o fenilo,

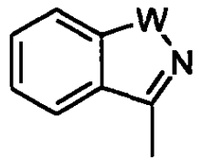
o $R_e$ es metoxicarbonilamino, etoxicarbonilamino, fenoxicarbonilamino, metilcarbamoiloxi, fenilcarbamoiloxi, metilsulfonilamino, fenilsulfonilamino, metilaminosulfonilo, fenilaminosulfonilo, amino, en donde el átomo de nitrógeno puede estar independientemente mono- o disustituido con metilo, etilo o fenilo,

o $R_e$ es fluoro, cloro, hidroxi, oxo, carboxi o carboxamida, $R_e$ puede estar, además, opcionalmente sustituido con uno o más $R_f$;

y

$R_g$ es metilo, fenilo, tolilsulfonilo, fenoxi, benciloxi, fluoro, cloro u oxo;

$R_3$ y $R_4$ de la fórmula (Ia) o de la fórmula (Ib) forman el anillo bicíclico




en donde W es $-S(O)_n-$, -O-(C(O)- o -N-C(O)-, n es 0, 1 ó 2 y en donde cada anillo está opcionalmente sustituido, de modo independiente, con uno o dos $R_7$.

En una realización adicional de la invención, se proporcionan nuevos compuestos de las fórmulas (Ia) y (Ib) según se describe inmediatamente antes, y en donde:

Het es piperidin-4-ilo, piperidin-3-ilo, pirrolidin-3-ilo, azetidin-3-ilo o tetrahidropiran-4-ilo, estando cada anillo sustituido con uno o más $R_8$;

$R_8$ es i-propilo, benciloxi, ciclohexilo, fenilo, 4-(acetilamino)-fenilo, 4-(metanosulfonilámino)-fenilo, 4-metoxifenilo, 3-fenoxifenilo, 4-clorofenilo, 4-fluorofenilo, 2-fluorofenilo, 2-fluoro-4-clorofenilo, naftilo, tienilmetilo, piperidinilo, morfolinilo, pirrolidinilo, piperazinilo, furanilo, tienilo, 5-clorotienilo, piridin-4-ilo, pirazinilo, metilami-

no, etilamino, dimetilamino o dietilamino;

$R_3$ es etilo, n-propilo, propenilo, butenilo, i-butenilo, bencilo o naftilmetilo, en donde $R_3$ está opcionalmente sustituido con uno o más $R_7$;

$R_7$ es metilo, ciclohexilo, ciclopentilo, indanilo, 1,2,3,4-tetrahidronaftilo, metoxi, metiltio, en donde el átomo de azufre puede estar oxidado en un sulfóxido o sulfona, fluoro, cloro u oxo;

$R_8$ es un enlace, carbonilo, metilo, etilo, n-propilo, n-butilo, t-butilo, i-propilo, i-butilo, ciclopropilo, ciclopentilo, ciclohexilo, fenilo, bencilo, piperidinilo, tetrahidropiranilo, pirimidinilo, acetilo, benzoílo, etoxicarbonilo, benciloxicarbonilo, metilsulfonilamino, fenilsulfonilamino, metilamino, dimetilamino, fluoro, oxo o carboxi, $R_8$ puede estar, además, opcionalmente sustituido con uno o más $R_9$;

$R_9$ es metilo, ciclopropilo, ciclopentilo, ciclohexilo, fenilo, naftilo, indanilo, tienilo, 5-metiltienilo, metoxi, fenoxi, benciloxi, piperidinilo, piridinilo, indolilo, 1-(tolil-sulfonil)-indolilo, carbamoílo, en donde el átomo de nitrógeno puede estar independientemente mono- o di-sustituido con metilo, fenilo o bencilo,

o $R_9$ es hidroxi, fluoro, cloro, oxo, dimetilamino o trifluorometilo;

y

n es 2.

En otra realización de la invención, se proporcionan nuevos compuestos de las fórmulas (Ia) y (Ib) según se describe para el aspecto genérico más amplio antes, y en donde:

$R_1$ y $R_2$ permanecen acíclicos,

Het es piperidinilo, pirrolidinilo, azetidinilo, azepanilo, oxepanilo o tetrahidropiranilo, oxetanilo o tetrahidrotiopiranilo, estando cada anillo sustituido con uno o más $R_5$;

$R_5$ es un enlace, alquilo C1-5, alcoxi C1-5, cicloalquilo

C3-6, ariloxi, fenilo, bencilo, naftilo, pirrolidinilo, piperidinilo, morfolinilo, tiomorfolinilo, piperazinilo, furanilo, tienilo, oxazolilo, tiazolilo, imidazolilo, piridinilo, pirimidinilo, pirazinilo, piridazinilo, indolilo, quinolinilo, benzofuranilo, benzotienilo, bencimidazolilo, benzotiazolilo, benzoxazolilo o amino; en donde $R_1$ está opcionalmente sustituido con uno o más $R_a$;

$R_a$ es un enlace, alquilo C1-3, ciclopropilo, ciclohexilo, fenilo, pirrolidinilo, piperidinilo, morfolinilo, tiomorfolinilo, piperazinilo, tienilo, imidazolilo, alcoxi C1-3, alcanoílo C1-3, alcanoiloxi C1-3, ariloxi, benciloxi, alcoxi C1-3-carbonilo, ariloxicarbonilo, aroiloxi, carbamoílo, en donde el átomo de nitrógeno puede estar independientemente mono- o di-sustituido con alquilo C1-3, arilo, pirrolidinilo, piperidinilo, morfolinilo, tiomorfolinilo o piperazinilo,

o $R_a$ es alcanoil C1-3-amino, aroilamino, alquiltio C1-3, en donde el átomo de azufre puede estar oxidado en un sulfóxido o sulfona, ariltio, en donde el átomo de azufre puede estar oxidado en un sulfóxido o sulfona, ureido, en donde cualquier átomo de nitrógeno puede estar sustituido, independientemente, con alquilo C1-3, arilo, pirrolidinilo, piperidinilo, morfolinilo, tiomorfolinilo o piperazinilo,

o $R_a$ es alcoxi C1-3-carbonilamino, ariloxicarbonilamino, alquil C1-3-carbamoiloxi, arilcarbamoiloxi, alquil C1-3-sulfonilamino, arilsulfonilamino, alquil C1-3-aminosulfonilo, arilaminosulfonilo, amino, en donde el átomo de nitrógeno puede estar independientemente mono- o di-sustituido con alquilo C1-3, arilo, pirrolidinilo, piperidinilo, morfolinilo, tiomorfolinilo o piperazinilo,

o $R_a$ es halógeno, hidroxi, oxo, carboxi, ciano, nitro, carboxamida, amidino o guanidino, $R_a$ puede estar, además, opcionalmente sustituido con uno o más $R_b$;

$R_c$ es metilo, etilo, n-propilo, i-propilo, ciclopropilo, ciclopentilo, ciclohexilo, fenilo, metoxi, etoxi, n-propoxi, i-propoxi, fenoxi, benciloxi, fluoro, cloro, bromo, yodo, hidroxi, oxo, carboxi, ciano, nitro o carboxamida;

$R_a$ es hidrógeno;

$R_b$ es un enlace, alquilo C1-3, alquileno C2-4, cicloalquilo C5-6, bencilo o naftilmetilo, en donde $R_b$ está opcionalmente sustituido con uno o más $R_c$;

$R_c$ es alquilo C1-3, cicloalquilo C5-6, fenilo, naftilo, biciclo[2.2.1]heptanilo, biciclo[2.2.2]octanilo, biciclo[4.1.0]heptanilo, biciclo[3.1.0]hexanilo, biciclo[1.1.1]pentanilo, cubanilo, 1,2,3,4-tetrahidronaftilo, furanilo, tetrahidropiranilo, tienilo, oxazolilo, tiazolilo, imidazolilo, pirimidinilo, indolilo, benzofuranilo, benzotienilo, benzotiazolilo, alcoxi C1-3, fenoxi, naftiloxi, alcanoílo C1-2, benzoílo, alcoxi C1-2-carbonilo, fenoxicarbonilo, alcanoiloxi C1-2, benzoiloxi, carbamoílo, en donde el átomo de nitrógeno puede estar independientemente mono- o di-sustituido con alquilo C1-3 o arilo,

o $R_c$ es alcanoil C1-2-amino, benzoilamino, alquiltio C1-2, en donde el átomo de azufre puede estar oxidado en un sulfóxido o sulfona, feniltio, en donde el átomo de azufre puede estar oxidado en un sulfóxido o sulfona, ureido, en donde cualquier átomo de nitrógeno puede estar sustituido, independientemente, con alquilo C1-3 o arilo,

o $R_c$ es alcoxi C1-2-carbonilamino, fenoxicarbonilamino, alquil C1-2-carbamoiloxi, arilcarbamoiloxi, alquil C1-2-sulfonilamino, fenilsulfonílamino, alquil C1-2-aminosulfonilo, fenilaminosulfonilo, amino, en donde el átomo de nitrógeno puede estar independientemente mono- o di-sustituido con alquilo C1-3 o fenilo,

o $R_c$ es halógeno, hidroxi, oxo, carboxi o ciano, $R_c$

puede estar, además, opcionalmente sustituido con uno o más $R_d$;

$R_d$ es metilo, ciclopropilo, ciclohexilo, fenilo, bencilo, metoxi, fenoxi, benciloxi, benzoílo, fluoro, cloro, oxo o ciano;

$R_1$ es hidrógeno;

$R_2$ es un enlace, hidrógeno, carbonilo, alquilo C1-5, alcoxi C1-5-alquilo C1-5, alquil C1-5-amino-alquilo C1-5, alquiltio C1-5-alquilo C1-5, en donde el átomo de azufre puede estar oxidado en un sulfóxido o sulfona, alcoxi C1-5, fenoxi, cicloalquilo C3-6, fenilo, naftilo, bencilo, indanilo, heterociclilo, seleccionado de pirrolidinilo, piperidinilo, morfolinilo, tiomorfolinilo, piperazinilo, tetrahidropiranilo, oxazolilo, tiazolilo, imidazolilo, piridinilo, pirimidinilo, bencimidazolilo y benzotiazolilo, heterocicliloxi, en donde el resto heterociclilo se selecciona de los descritos en esta memoria en este párrafo, alcanoílo C1-3, benzoílo, naftoílo, alcanoiloxi C1-3, benciloxi, alcoxi C1-3-carbonilo, benciloxicarbonilo, fenoxicarbonilo, carbamoílo, en donde el átomo de nitrógeno puede estar independientemente mono- o disustituido con alquilo C1-3, fenilo, pirrolidinilo, piperidinilo, morfolinilo, piperazinilo, oxazolilo, tiazolilo, imidazolilo, piridinilo o pirimidinilo,

o $R_2$ es alcanoil C1-3-amino, aroilamino, alquiltio C1-3, en donde el átomo de azufre puede estar oxidado en un sulfóxido o sulfona, feniltio, en donde el átomo de azufre puede estar oxidado en un sulfóxido o sulfona, ureido, en donde cualquier átomo de nitrógeno puede estar independientemente sustituido con alquilo C1-3, fenilo, pirrolidinilo, piperidinilo, morfolinilo, piperazinilo, oxazolilo, tiazolilo, imidazolilo, piridinilo, pirimidinilo, benzofuranilo, benzotienilo, bencimidazolilo o benzotiazolilo,

o $R_2$ es alcoxi C1-3-carbonilamino, fenoxicarbonilamino, alquil C1-3-carbamoiloxi, fenilcarbamoiloxi, alquil C1-3-sulfonilamino, fenilsulfonilamino, alquil C1-3-aminosulfoni-

lo, fenilaminosulfonilo, amino, en donde el átomo de nitrógeno puede estar independientemente mono- o di-sustituido con alquilo C1-3, fenilo, pirrolidinilo, piperidinilo, morfolinilo, tiomorfolinilo, piperazinilo, oxazolilo, tiazolilo, imidazolilo, piridinilo, pirimidinilo, bencimidazolilo o benzotiazolilo,

o $R_2$ es halógeno, hidroxi, oxo, carboxi, ciano o carboxamida, $R_2$ puede estar, además, opcionalmente sustituido con uno o más $R_4$;

$R_4$ es alquilo C1-3, alcoxi C1-3, cicloalquilo C3-7, fenilo, naftilo, indanilo, pirrolidinilo, piperidinilo, morfolinilo, piperazinilo, tetrahidropiranilo, indolilo, tienilo, oxazolilo, tiazolilo, imidazolilo, piridinilo, pirimidinilo, bencimidazolilo, benzotiazolilo, benzoxazolilo, alcanoílo C1-3, aroílo, alcanoiloxi C1-3, fenoxi, benciloxi, alcoxi C1-3-carbonilo, fenoxicarbonilo, benzoiloxi, alcoxi C1-3-carbonilo, fenoxicarbonilo, benzoiloxi, carbamoilo, en donde el átomo de nitrógeno puede estar independientemente mono- o di-sustituido con alquilo C1-3, fenilo, pirrolidinilo, piperidinilo, morfolinilo, piperazinilo, oxazolilo, tiazolilo, imidazolilo, piridinilo, pirimidinilo, bencimidazolilo o benzotiazolilo,

o $R_4$ es alcanoil C1-3-amino, benzoilamino, alquiltio C1-3, en donde el átomo de azufre puede estar oxidado en un sulfóxido o sulfona, feniltio, en donde el átomo de azufre puede estar oxidado en un sulfóxido o sulfona, ureido, en donde cualquier átomo de nitrógeno puede independientemente sustituido con alquilo C1-3, fenilo, pirrolidinilo, piperidinilo, morfolinilo, piperazinilo, indolilo, oxazolilo, tiazolilo, imidazolilo, piridinilo, pirimidinilo, bencimidazolilo o benzotiazolilo,

o $R_4$ es alcoxi C1-3-carbonilamino, fenoxicarbonilamino, alquil C1-3-carbamoiloxi, fenilcarbamoiloxi, alquil

C1-3-sulfonilamino, fenilsulfonilamino, alquil C1-3-aminosulfonilo, fenilaminosulfonilo, amino, en donde el átomo de nitrógeno puede estar independientemente mono- o di-sustituido con alquilo C1-3, fenilo, naftilo, pirrolidinilo, piperidinilo, morfolinilo, piperazinil , oxazolilo, tiazolilo, imidazolilo, piridinilo, pirimidinilo, bencimidazolilo o benzotiazolilo,

o $R_6$ es halógeno, hidroxi, oxo, carboxi, ciano o carboxamida, $R_5$ puede estar, además, opcionalmente sustituido con uno o más $R_7$;

$R_7$ es metilo, fenilo, tolilsulfonilo, metoxi, fenoxi, benciloxi, fluoro, cloro, bromo, hidroxi, oxo, carboxi o carboxamida;

$R_8$ es

hidroxi, nitrilo o

una cadena de carbonos C1-5, saturada o insaturada, ramificada o no ramificada, opcionalmente total o parcialmente halogenada, en donde uno o más átomos de C están opcionalmente reemplazados por O, NH o $S(O)_2$, y en donde dicha cadena está opcionalmente sustituida de modo independiente con 1-2 grupos oxo, $-NH_2$, uno o más alquilo $C_{1-4}$, pirrolidinilo, piperidinilo, morfolinilo, tiomorfolinilo, piperazinilo, indolinilo, piranilo, tiopiranilo, furanilo, tienilo, pirrolilo, oxazolilo, isoxazolilo, tiazolilo, imidazolilo, piridinilo, pirimidinilo, pirazinilo, indolilo, benzofuranilo, benzotienilo, bencimidazolilo, benzotiazolilo, quinolinilo, isoquinolinilo, quinazolinilo, benzoxazolilo o quinoxalinilo;

y

X es O.

En otra realización de la invención, se proporcionan nuevos compuestos de las fórmulas (Ia) y (Ib) según se describe inmediatamente antes, y en donde:

$R_5$ es un enlace, metilo, etilo, i-propilo, metoxi, etoxi, ciclopropilo, ciclopentilo, ciclohexilo, fenoxi, fenilo,

bencilo, naftilo, pirrolidinilo, piperidinilo, morfolinilo, tiomorfolinilo, piperazinilo, furanilo, tienilo, tiazolilo, imidazolilo, piridinilo, pirazinilo o amino; en donde $R_1$ está opcionalmente sustituido con uno o más $R_a$;

$R_1$ es un enlace, metilo, etilo, ciclopropilo, fenilo, pirrolidinilo, piperidinilo, morfolinilo, tiomorfolinilo, piperazinilo, tienilo, imidazolilo, metoxi, acetilo, acetoxi, fenoxi, benciloxi, metoxicarbonilo, fenoxicarbonilo, benzoiloxi, carbamoílo, en donde el átomo de nitrógeno puede estar independientemente mono- o di-sustituido con metilo, etilo o fenilo,

o $R_1$ es acetilamino, benzoilamino, metiltio, feniltio, en donde el átomo de azufre puede estar oxidado en un sulfóxido o sulfona, ureido, en donde cualquier átomo de nitrógeno puede estar sustituido, independientemente, con metilo, etilo o fenilo,

o $R_1$ es metoxicarbonilamino, fenoxicarbonilamino, metilcarbamoiloxi, fenilcarbamoiloxi, metilsulfonilamino, fenilsulfonilamino, metilaminosulfonilo, fenilaminosulfonilo, amino, en donde el átomo de nitrógeno puede estar independientemente mono- o di-sustituido con metilo o fenilo,

o $R_1$ es fluoro, cloro, bromo, yodo, hidroxi, oxo, carboxi, ciano, nitro o carboxamida, $R_a$ puede estar, además, opcionalmente sustituido con uno o más $R_b$;

$R_b$ es metilo, ciclopropilo, fenilo, metoxi, fenoxi, benciloxi, fluoro, cloro, hidroxi, oxo, carboxi o carboxamida;

$R_2$ es un enlace, alquilo C1-3, alquileno C2-4, cicloalquilo C5-6, bencilo o naftilmetilo, en donde $R_3$ está opcionalmente sustituido con uno o más $R_c$;

$R_c$ es metilo, etilo, n-propilo, i-propilo, cicloalquilo C5-6, indanilo, biciclo[2.2.1]heptanilo, biciclo[2.2.2]octanilo, biciclo[4.1.0]heptanilo, biciclo[3.1.0]hexanilo, biciclo[1.1.1]pentanilo, cubanilo,

1,2,3,4-tetrahidronaftilo, tienilo, oxazolilo, tiazolilo, indolilo, benzofuranilo, benzotienilo, benzotiazolilo, metoxi, etoxi, fenoxi, acetilo, benzoílo, metoxicarbonilo, fenoxicarbonilo, acetoxi, benzoiloxi, carbamoílo, en donde el átomo de nitrógeno puede estar independientemente mono- o di-sustituido con metilo, etilo o arilo,

o $R_{..}$ es acetilamino, benzoilamino, metiltio, en donde el átomo de azufre puede estar oxidado en un sulfóxido o sulfona, feniltio, en donde el átomo de azufre puede estar oxidado en un sulfóxido o sulfona, ureido, en donde cualquier átomo de nitrógeno puede estar sustituido, independientemente, con metilo, etilo o arilo,

o $R_{..}$ es metoxicarbonilamino, fenoxicarbonilamino, metilcarbamoiloxi, fenilcarbamoiloxi, metilsulfonilamino, fenilsulfonilamino, metilaminosulfonilo, fenilaminosulfonilo, amino, en donde el átomo de nitrógeno puede estar independientemente mono- o di-sustituido con metilo, etilo o fenilo,

o $R_{..}$ es fluoro, cloro u oxo, $R_{..}$ puede estar, además, opcionalmente sustituido con uno o más $R_{3}$;

$R_{3}$ es metilo, ciclopropilo, fenilo, metoxi, fluoro, cloro u oxo;

$R_{..}$ es un enlace, hidrógeno, carbonilo, alquilo C1-4, alcoxi C1-4-alquilo C1-4, alquil C1-4-amino-alquilo C1-4, alquiltio C1-4-alquilo C1-4, en donde el átomo de azufre puede estar oxidado en un sulfóxido o sulfona, alcoxi C1-4, fenoxi, ciclopropilo, ciclopentilo, ciclohexilo, fenilo, naftilo, bencilo, indanilo, heterociclilo, seleccionado de pirrolidinilo, piperidinilo, morfolinilo, piperazinilo, tetrahidropiranilo, oxazolilo, tiazolilo, imidazolilo, piridinilo, pirimidinilo, bencimidazolilo y benzotiazolilo, heterocicliloxi, en donde el resto heterociclilo se selecciona de los descritos en esta memoria en este párrafo, alcanoílo C1-2,

benzoílo, naftoílo, alcanoiloxi C1-2, benciloxi, alcoxi C1-2-carbonilo, benciloxicarbonilo, fenoxicarbonilo, benzoiloxi, carbamoílo, en donde el átomo de nitrógeno puede estar independientemente mono- o di-sustituido con alquilo C1-2, fenilo, pirrolidinilo, piperidinilo, morfolinilo, piperazinilo, oxazolilo, tiazolilo, imidazolilo, piridinilo o pirimidinilo,

o $R_s$ es alcanoil C1-2-amino, benzoilamino, alquiltio C1-2, en donde el átomo de azufre puede estar oxidado en un sulfóxido o sulfona, feniltio, en donde el átomo de azufre puede estar oxidado en un sulfóxido o sulfona, ureido, en donde cualquier átomo de nitrógeno puede estar independientemente sustituido con alquilo C1-2, fenilo, pirrolidinilo, piperidinilo, morfolinilo, piperazinilo, oxazolilo, tiazolilo, imidazolilo, piridinilo, pirimidinilo, bencimidazolilo o benzotiazolilo,

o $R_s$ es alcoxi C1-2-carbonilamino, fenoxicarbonilamino, alquil C1-2-carbamoiloxi, fenilcarbamoiloxi, alquil C1-2-sulfonilamino, fenilsulfonilamino, alquil C1-2-aminosulfonilo, fenilaminosulfonilo, amino, en donde el átomo de nitrógeno puede estar independientemente mono- o di-sustituido con alquilo C1-2, fenilo, pirrolidinilo, piperidinilo, morfolinilo, piperazinilo, oxazolilo, tiazolilo, imidazolilo, piridinilo o pirimidinilo,

o $R_s$ es fluoro, cloro, bromo, hidroxi, oxo, carboxi o carboxamida, $R_t$ puede estar, además, opcionalmente sustituido con uno o más $R_u$;

$R_u$ es alquilo C1-3, alcoxi C1-2, cicloalquilo C3-6, fenilo, naftilo, indanilo, pirrolidinilo, piperidinilo, morfolinilo, piperazinilo, tetrahidropiranilo, indolilo, tienilo, oxazolilo, tiazolilo, imidazolilo, piridinilo, pirimidinilo, bencimidazolilo, benzotiazolilo, benzoxazolilo, alcanoílo C1-2, aroílo, alcanoiloxi C1-2, fenoxi, benciloxi, alcoxi C1-2-carbonilo, fenoxicarbonilo, benzoiloxi, carbamoílo, en donde el átomo de nitrógeno puede estar independiente-

mente mono- o di-sustituido con alquilo C1-2, fenilo, pirrolidinilo, piperidinilo, morfolinilo, piperazinil , oxazolilo, tiazolilo, imidazolilo, piridinilo o pirimidinilo,

o $R_e$ es alcanoil C1-2-amino, benzoilamino, alquiltio C1-2, en donde el átomo de azufre puede estar oxidado en un sulfóxido o sulfona, feniltio, en donde el átomo de azufre puede estar oxidado en un sulfóxido sulfona, ureido, en donde cualquier átomo de nitrógeno puede estar independientemente sustituido con alquilo C1-2, fenilo, pirrolidinilo, piperidinilo, morfolinilo, piperazinilo, oxazolilo, tiazolilo, imidazolilo, piridinilo o pirimidinilo,

o $R_e$ es alcoxi C1-2-carbonilamino, fenoxicarbonilamino, alquil C1-2-carbamoiloxi, fenilcarbamoiloxi, alquil C1-2-sulfonilamino, fenilsulfonilamino, alquil C1-2-aminosulfonilo, fenilaminosulfonilo, amino, en donde el átomo de nitrógeno puede estar independientemente mono- o di-sustituido con alquilo C1-2, fenilo, naftilo, pirrolidinilo, piperidinilo, morfolinilo, piperazinilo, oxazolilo, tiazolilo, imidazolilo, piridinilo o pirimidinilo,

o $R_e$ es fluoro, cloro, bromo, hidroxi, oxo, carboxi o carboxamida, $R_e$ puede estar, además, opcionalmente sustituido con uno o más $R_i$;

$R_i$ es metilo, fenilo, tolilsulfonilo, metoxi, fenoxi, benciloxi, fluoro, cloro, hidroxi, oxo, carboxi o carboxamida; y

$R_r$ es nitrilo o

una cadena de carbonos C1-5, saturada o insaturada, ramificada o no ramificada, opcionalmente parcial o totalmente halogenada, en donde uno o más átomos de C están opcionalmente reemplazados por O, NH o $S(O)_2$ y en donde dicha cadena está opcionalmente sustituida, de modo independiente, con oxo, $-NH_2$, piperidinilo, morfolinilo, tiomorfolinilo,

piperazinilo, piridinilo, pirimidinilo o pirazinilo.

Todavía en otra realización de la invención, se proporcionan nuevos compuestos de la fórmula (Ia) o de la fórmula (Ib) según se describe inmediatamente antes, y en donde:

Het es piperidin-4-ilo, piperidin-3-ilo, pirrolidin-3-ilo, azetidin-3-ilo, azepan-3-ilo, azepan-4-ilo o tetrahidropiran-4-ilo, estando cada anillo opcionalmente sustituido con uno o más $R_c$;

$R_b$ es un enlace, metilo, etilo, i-propilo, metoxi, ciclopropilo, ciclohexilo, fenoxi, fenilo, bencilo, naftilo, pirrolidinilo, piperidinilo, morfolinilo, tiomorfolinilo, piperazinilo, furanilo, tienilo, tiazolilo, imidazolilo, piridinilo, pirazinilo o amino; en donde $R_b$ está opcionalmente sustituido con uno o más $R_1$;

$R_1$ es metilo, fenilo, tienilo, metoxi, acetilo, acetoxi, fenoxi, benciloxi, metoxicarbonilo, benzoiloxi, carbamoílo, en donde el átomo de nitrógeno puede estar independientemente mono- o di-sustituido con metilo o fenilo,

o $R_1$ es acetilamino, metiltio, feniltio, en donde el átomo de azufre puede estar oxidado en un sulfóxido o sulfona, ureido, en donde cualquier átomo de nitrógeno puede estar sustituido, independientemente, con metilo o fenilo,

o $R_1$ es metoxicarbonilamino, metilcarbamoiloxi, fenilcarbamoiloxi, metilsulfonilamino, fenilsulfonilamino, amino, en donde el átomo de nitrógeno puede estar independientemente mono- o di-sustituido con metilo o fenilo,

o $R_1$ es fluoro, cloro, hidroxi, oxo, carboxi, ciano o carboxamida;

$R_c$ es un enlace, metilo, etilo, n-propilo, propenilo, butenilo, i-butenilo, ciclohexilo, bencilo o naftilmetilo, en donde $R_c$ está opcionalmente sustituido con uno o más $R_c$;

$R_c$ es metilo, etilo, n-propilo, i-propilo, ciclohexilo,

ciclopentilo, indanilo, biciclo[2.2.1]heptanilo, biciclo[2.2.2]octanilo, biciclo[4.1.0]heptanilo, biciclo-[3.1.0]hexanilo, biciclo[1.1.1]pentanilo, cubanilo, 1,2,3,4-tetrahidronaftilo, metoxi, fenoxi, acetilo, benzoílo, metoxicarbonilo, fenoxicarbonilo, acetoxi, benzoiloxi, metiltio, en donde el átomo de azufre puede estar oxidado en un sulfóxido o sulfona, feniltio, en donde el átomo de azufre puede estar oxidado en un sulfóxido o sulfona, fluoro, cloro u oxo;

y

en donde la configuración en el estereocentro definido por $R_2$ y R. cuando son diferentes, y el carbono al que está unidos se define como L; y

R. es un enlace, hidrógeno, carbonilo, alquilo C1-4, alcoxi C1-2-alquilo C1-2, alquil C1-2-amino-alquilo C1-2, alquiltio C1-2-alquilo C1-2, en donde el átomo de azufre puede estar oxidado en un sulfóxido o sulfona, alcoxi C1-2, fenoxi, ciclopropilo, ciclopentilo, ciclohexilo, fenilo, bencilo, heterociclilo, seleccionado de pirrolidinilo, piperidinilo, morfolinilo, tetrahidropiranilo, piridinilo y pirimidinilo, heterocicliloxi, en donde el resto heterociclilo se selecciona de los descritos en esta memoria en este párrafo, acetilo, benzoílo, acetiloxi, benciloxi, metoxicarbonilo, etoxicarbonilo, benciloxicarbonilo, benzoiloxi, carbamoílo, en donde el átomo de nitrógeno puede estar independientemente mono- o disustituido con metilo, etilo o fenilo,

o R. es acetilamino, benzoilamino, metiltio, en donde el átomo de azufre puede estar oxidado en un sulfóxido o sulfona, feniltio, en donde el átomo de azufre puede estar oxidado en un sulfóxido o sulfona, ureido, en donde cualquier átomo de nitrógeno puede estar independientemente sustituido con metilo, etilo o fenilo,

o R. es metoxicarbonilamino, etoxicarbonilamino, fenoxicarbonilamino, metilcarbamoiloxi, fenilcarbamoiloxi, metilsulfonilamino, fenilsulfonilamino, metilaminosulfonilo, fenilami-

nosulfonilo, amino, en donde el átomo de nitrógeno puede estar independientemente mono- o di-sustituido con metilo, etilo o fenilo,

o $R_4$ es fluoro, cloro, hidroxi, oxo, carboxi o carboxamida, $R_5$ puede estar, además, opcionalmente sustituido con uno o más $R_6$;

$R_6$ es metilo, metoxi, etoxi, ciclopropilo, ciclopentilo, ciclohexilo, fenilo, naftilo, indanilo, piperidinilo, morfolinilo, indolilo, tienilo, piridinilo, acetilo, benzoílo, acetiloxi, fenoxi, benciloxi, metoxicarbonilo, etoxicarbonilo, carbamoílo, en donde el átomo de nitrógeno puede estar independientemente mono- o di-sustituido con metilo, etilo o fenilo,

o $R_6$ es acetilamino, benzoilamino, metiltio, en donde el átomo de azufre puede estar oxidado en un sulfóxido o sulfona, feniltio, en donde el átomo de azufre puede estar oxidado en un sulfóxido o sulfona, ureido, en donde cualquier átomo de nitrógeno puede estar independientemente sustituido con metilo, etilo o fenilo,

o $R_6$ es metoxicarbonilamino, etoxicarbonilamino, fenoxicarbonilamino, metilcarbamoiloxi, fenilcarbamoiloxi, metilsulfonilamino, fenilsulfonilamino, metilaminosulfonilo, fenilaminosulfonilo, amino, en donde el átomo de nitrógeno puede estar independientemente mono- o di-sustituido con metilo, etilo o fenilo,

o $R_6$ es fluoro, cloro, hidroxi, oxo, carboxi o carboxamida, $R_6$ puede estar, además, opcionalmente sustituido con uno o más $R_7$;

$R_7$ es metilo, fenilo, tolilsulfonilo, fenoxi, benciloxi, fluoro, cloro u oxo;

$R_4$ es

nitrilo o

una cadena de carbonos C1-5, saturada o insaturada, ramificada o no ramificada, opcionalmente parcial o totalmente halogenada, en donde uno o más átomos de C están opcionalmen-

te reemplazados por O, NH o $S(O)_2$ y en donde dicha cadena está opcionalmente sustituida, de modo independiente, con oxo, $-NH_2$, morfolinilo o piperazinilo.

Todavía en otra realización de la invención, se proporcionan nuevos compuestos de las fórmulas (Ia) o (Ib) según se describe inmediatamente antes, y en donde:

Het es piperidin-4-ilo, piperidin-3-ilo, pirrolidin-3-ilo, azetidin-3-ilo o tetrahidropiran-4-ilo, estando cada anillo opcionalmente sustituido con uno o más $R_3$;

$R_1$ es i-propilo, benciloxi, ciclohexilo, fenilo, 4-(acetilamino)-fenilo, 4-(metanosulfonilamino)-fenilo, 4-metoxifenilo, 3-fenoxifenilo, 4-clorofenilo, 4-fluorofenilo, 2-fluorofenilo, 2-fluoro-4-clorofenilo, naftilo, tienilmetilo, piperidinilo, morfolinilo, pirrolidinilo, piperazinilo, furanilo, tienilo, 5-clorotienilo, piridin-4-ilo, pirazinilo, metilamino, etilamino, dimetilamino o dietilamino;

$R_2$ es etilo, n-propilo, propenilo, butenilo, i-butenilo, bencilo o naftilmetilo, en donde $R_2$ está opcionalmente sustituido con uno o más $R_5$;

$R_3$ es metilo, ciclohexilo, ciclopentilo, indanilo, 1,2,3,4-tetrahidronaftilo, metoxi, metiltio, en donde el átomo de azufre puede estar oxidado en un sulfóxido o sulfona, fluoro o cloro;

$R_4$ es un enlace, carbonilo, metilo, etilo, n-propilo, n-butilo, t-butilo, i-propilo, i-butilo, ciclopropilo, ciclopentilo, ciclohexilo, fenilo, bencilo, piperidinilo, tetrahidropiranilo, pirimidinilo, acetilo, benzoílo, etoxicarbonilo, benciloxicarbonilo, metilsulfonilamino, fenilsulfonilamino, metilamino, dimetilamino, fluoro, oxo o carboxi, $R_5$ puede estar, además, opcionalmente sustituido con uno o más $R_6$;

$R_6$ es metilo, ciclopropilo, ciclopentilo, ciclohexilo, fenilo, naftilo, indanilo, tienilo, 5-metiltienilo, metoxi, fenoxi, benciloxi, piperidinilo, piridinilo, indolilo, 1-(tolil-sulfonil)-indolilo, carbamoílo, en donde el átomo de nitrógeno puede estar independiente-

mente mono- o di-sustituido con metilo, fenilo o bencilo,

o $R_c$ es hidroxi, fluoro, cloro, oxo, dimetilamino o trifluorometilo;

y

$R_a$ es acetilo, alquil C1-3-aminocarbonilo o alcoxi C1-3-carbonilo.

Todavía en una realización adicional de la invención, se proporcionan nuevos compuestos de las fórmulas (Ia) o (Ib) según se describe inmediatamente antes, y en donde:

Het es piperidin-4-ilo o pirrolidin-3-ilo;

$R_b$ es morfolin-4-ilo, p-fluorenilo o p-metoxifenilo;

$R_c$ es metilo, propilo, n-pentilo o ciclohexilo

y

$R_a$ es acetilo, etilaminocarbonilo o etoxicarbonilo.

La actividad de compuestos particulares descritos en esta memoria contra catepsina K se puede determinar sin una experimentación excesiva mediante un experto ordinario en la técnica a través de la técnica, la guía proporcionada a lo largo de esta memoria y por las pantallas descritas en la sección titulada "Determinación de Propiedades Biológicas".

Se postula que el siguiente aspecto subgenérico de los compuestos de las fórmula (Ia) y (Ib) posee actividad de catepsina K:

La realización más amplia de las fórmulas (Ia) y (Ib) según se describe inmediatamente antes, y en donde

Het es piperidinilo, pirrolidinilo, azetidinilo, azepanilo, oxepanilo, tetrahidropiranilo, oxetanilo o tetrahidrotiopiranilo, estando cada anillo opcionalmente sustituido con uno o más $R_c$;

$R_b$ es un enlace, alquilo C1-4, alcoxi C1-4, ciclopropilo, ciclohexilo, fenoxi, naftiloxi, fenilo, bencilo, naftilo, pirrolidinilo, piperidinilo, morfolinilo, tiomorfolinilo, piperazinilo, furanilo, tienilo, oxazolilo, tiazolilo, imidazolilo, piridinilo, pirimidinilo, pirazinilo, piridazi-

nilo, indolilo, quinolinilo, benzofuranilo, benzotienilo, benzoxazolilo o amino; en donde $R_1$ está opcionalmente sustituido con uno o más $R_4$;

$R_4$ es metilo, etilo, propilo, i-propilo, ciclopropilo, ciclohexilo, fenilo, pirrolidinilo, piperidinilo, morfolinilo, tiomorfolinilo, piperazinilo, tienilo, imidazolilo, metoxi, etoxi, acetilo, acetoxi, fenoxi, naftiloxi, benciloxi, metoxicarbonilo, etoxicarbonilo, fenoxicarbonilo, naftiloxicarbonilo, benzoiloxi, carbamoílo, en donde el átomo de nitrógeno puede estar independientemente mono- o di-sustituido con metilo, etilo, fenilo, naftilo, pirrolidinilo, piperidinilo, morfolinilo, tiomorfolinilo o piperazinilo,

o $R_4$ es acetilamino, benzoilamino, metiltio, en donde el átomo de azufre puede estar oxidado en un sulfóxido o sulfona, etiltio, en donde el átomo de azufre puede estar oxidado en un sulfóxido o sulfona, feniltio, en donde el átomo de azufre puede estar oxidado en un sulfóxido o sulfona, ureido, en donde cualquier átomo de nitrógeno puede estar sustituido, independientemente, con metilo, etilo, fenilo, naftilo, pirrolidinilo, piperidinilo, morfolinilo, tiomorfolinilo o piperazinilo,

o $R_4$ es metoxicarbonilamino, etoxicarbonilamino, fenoxicarbonilamino, alquil C1-2-carbamoiloxi, fenilcarbamoiloxi, naftilcarbamoiloxi, alquil C1-2-sulfonilamino, fenilsulfonilamino, naftilsulfonilamino, alquil C1-2-aminosulfonilo, fenilaminosulfonilo, naftilaminosulfonilo, amino, en donde el átomo de nitrógeno puede estar independientemente mono- o di-sustituido con metilo, etilo, fenilo, naftilo, pirrolidinilo, piperidinilo, morfolinilo, tiomorfolinilo o piperazinilo,

o $R_4$ es halógeno, hidroxi, oxo, carboxi, ciano, nitro, carboxamida, amidino o guanidino, $R_4$ puede estar,

además, opcionalmente sustituido con uno o más $R_b$;

$R_t$ es metilo, etilo, ciclopropilo, ciclohexilo, fenilo, metoxi, etoxi, fenoxi, benciloxi, fluoro, cloro, bromo, hidroxi, oxo, carboxi, ciano, nitro o carboxamida;

$R_s$ es hidrógeno o metilo;

$R_r$ es un enlace, metilo, etilo, n-propilo, i-propilo, n-butilo, i-butilo, n-pentilo, propenilo, i-butenilo, ciclohexilo, bencilo o naftilmetilo, en donde $R_j$ está opcionalmente sustituido con uno o más $R_z$;

$R_z$ es metilo, etilo, ciclohexilo, fenilo, naftilo, biciclo[3.1.0]hexanilo, biciclo[1.1.1]pentanilo, cubanilo, furanilo, tetrahidropiranilo, tienilo, oxazolilo, tiazolilo, imidazolilo, pirimidinilo, metoxi, etoxi, fenoxi, acetilo, benzoílo, metoxicarbonilo, fenoxicarbonilo, acetoxi, benzoiloxi, carbamoílo, en donde el átomo de nitrógeno puede estar independientemente mono- o di-sustituido con metilo o fenilo,

o $R_z$ es acetilamino, benzoilamino, metiltio, en donde el átomo de azufre puede estar oxidado en un sulfóxido o sulfona, feniltio, en donde el átomo de azufre puede estar oxidado en un sulfóxido o sulfona, ureido, en donde cualquier átomo de nitrógeno puede estar sustituido, independientemente, con metilo o fenilo,

o $R_z$ es metoxicarbonilamino, fenoxicarbonilamino, metilcarbamoiloxi, fenilcarbamoiloxi, metilsulfonilamino, fenilsulfonilamino, metilaminosulfonilo, fenilaminosulfonilo, amino, en donde el átomo de nitrógeno puede estar independientemente mono- o di-sustituido con metilo o fenilo,

o $R_z$ es cloro, fluoro, hidroxi, oxo, carboxi o ciano;

$R_y$ y $R_{y'}$ junto con el carbono al que están unidos, forman opcionalmente un anillo seleccionado de ciclopentilo, ciclohexilo, cicloheptilo, tetrahidropiranilo, tetrahidrotiopiranilo, tetrahidrofuranilo, pirrolidinilo, piperidinilo, pipera-

zinilo, morfolinilo o tetrahidrotiofenilo;

$R_1$ es hidrógeno;

R es un enlace, hidrógeno, carbonilo, alquilo C1-5, alcoxi C1-5-alquilo C1-5, alquil C1-5-amino-alquilo C1-5, alquiltio C1-5-alquilo C1-5, en donde el átomo de azufre puede estar oxidado en un sulfóxido o sulfona, alcoxi C1-5, fenoxi, naftiloxi, ciclopropilo, ciclopentilo, ciclohexilo, fenilo, naftilo, bencilo, heterociclilo, seleccionado de pirrolidinilo, piperidinilo, morfolinilo, tetrahidropiranilo, piridinilo y pirimidinilo, heterocicliloxi, en donde el resto heterociclilo se selecciona de los descritos en esta memoria en este párrafo, acetilo, benzoílo, acetiloxi, benciloxi, metoxicarbonilo, etoxicarbonilo, benciloxicarbonilo, benzoiloxi, carbamoílo, en donde el átomo de nitrógeno puede estar independientemente mono- o di-sustituido con metilo, etilo o fenilo,

o R es acetilamino, benzoilamino, feniltio, en donde el átomo de azufre puede estar oxidado en un sulfóxido o sulfona, ureido, en donde cualquier átomo de nitrógeno puede estar independientemente sustituido con metilo, etilo o fenilo,

o R es metoxicarbonilamino, etoxicarbonilamino, fenoxicarbonilamino, metilcarbamoiloxi, fenilcarbamoiloxi, fenilsulfonilamino, fenilaminosulfonilo, amino, en donde el átomo de nitrógeno puede estar independientemente mono- o di-sustituido con metilo, etilo o fenilo,

o R es fluoro, cloro, hidroxi, oxo, carboxi o carboxamida, $R_4$ puede estar, además, opcionalmente sustituido con uno o más $R_2$;

$R_2$ es metilo, etilo, metoxi, etoxi, ciclopropilo, ciclopentilo, ciclohexilo, fenilo, naftilo, indanilo, piperidinilo, morfolinilo, indolilo, tienilo, piridinilo, metoxi, etoxi, acetilo, benzoílo, acetiloxi, fenoxi, benciloxi, metoxicarbonilo, etoxicarbonilo, carbamoílo, en donde el átomo de nitrógeno puede estar

independientemente mono- o di-sustituido con metilo, etilo o fenilo,

o $R_e$ es acetilamino, benzoilamino, metiltio, en donde el átomo de azufre puede estar oxidado en un sulfóxido o sulfona, feniltio, metiltio, en donde el átomo de azufre puede estar oxidado en un sulfóxido o sulfona, ureido, en donde cualquier átomo de nitrógeno puede estar independientemente sustituido con metilo, etilo o fenilo,

o $R_e$ es metoxicarbonilamino, etoxicarbonilamino, fenoxicarbonilamino, metilcarbamoiloxi, fenilcarbamoiloxi, metilsulfonilamino, fenilsulfonilamino, metilaminosulfonilo, fenilaminosulfonilo, amino, en donde el átomo de nitrógeno puede estar independientemente mono- o di-sustituido con metilo, etilo o fenilo,

o $R_e$ es fluoro, cloro, hidroxi, oxo, carboxi o carboxamida, $R_e$ puede estar, además, opcionalmente sustituido con uno o más $R_f$;

$R_f$ es metilo, fenilo, tolilsulfonilo, fenoxi, benciloxi, fluoro, cloro u oxo.

Inhibidores de catepsina K preferidos son los que se describen inmediatamente antes, y en donde:

$R_d$ es un enlace, metilo, etilo, n-propilo, i-propilo, metoxi, etoxi, benciloxi, ciclopropilo, ciclohexilo, fenoxi, naftiloxi, fenilo, bencilo, naftilo, pirrolidinilo, piperidinilo, morfolinilo, tiomorfolinilo, piperazinilo, furanilo, tienilo, oxazolilo, tiazolilo, imidazolilo, piridinilo, pirimidinilo, pirazinilo, piridazinilo, indolilo, quinolinilo, benzofuranilo, benzotienilo, bencimidazolilo, benzotiazolilo, benzoxazolilo o amino; en donde $R_d$ está opcionalmente sustituido con uno o más $R_g$;

$R_g$ es metilo, ciclopropilo, fenilo, halógeno, hidroxi, oxo, carboxi, ciano, nitro o carboxamida;

$R_c$ es un enlace, metilo, etilo, n-propilo, i-propilo, n-butilo, i-butilo, n-pentilo, propenilo, i-butenilo, bencilo o

naftilmetilo, en donde $R_3$ está opcionalmente sustituido con uno o más $R_c$;

$R_c$ es metilo, etilo, ciclohexilo, ciclopentilo, fenilo, furanilo, tetrahidropiranilo, tienilo, oxazolilo, tiazolilo, metoxi, fenoxi, acetilo, benzoílo, metoxicarbonilo, fenoxicarbonilo, acetoxi, benzoiloxi, carbamoílo, en donde el átomo de nitrógeno puede estar independientemente mono- ó di-sustituido con metilo o fenilo,

o $R_c$ es acetilamino, benzoilamino, metiltio, metoxicarbonilamino, metilcarbamoiloxi, metilsulfonilamino, metilaminosulfonilo, amino, en donde el átomo de nitrógeno puede estar independientemente mono- o di-sustituido con metilo,

o $R_c$ es fluoro u oxo;

$R_a$ y $R_b$, junto con el carbono al que están unidos, forman opcionalmente un anillo seleccionado de cilopentilo, ciclohexilo, cicloheptilo, tetrahidropiranilo, tetrahidrotiopiranilo, tetrahidrofuranilo, pirrolidinilo o piperidinilo;

$R_d$ es metilo, etilo, n-propilo, n-butilo, n-pentilo, 2-pentilo, 3-pentilo, fenetilo, fenpropilo, 2.2-dimetilpropilo, t-butilo, i-propilo, i-butilo, ciclopropilo, ciclopentilo, ciclohexilo, ciclopropilmetilo, ciclopentilmetilo, ciclohexilmetilo, fenilo, bencilo, 2-metilbencilo, 3-metilbencilo, 4-metilbencilo, 2,6-dimetilbencilo, 2,5-dimetilbencilo, 2,4-dimetilbencilo, 2,3-dimetilbencilo, 3,4-dimetilbencilo, 3,5-dimetilbencilo, 2,4,6-trimetilbencilo, 2-metoxibencilo, 3-metoxibencilo, 4-metoxibencilo, 2-fenoxibencilo, 3-fenoxibencilo, 4-fenoxibencilo, 2-benciloxibencilo, 3-benciloxibencilo, 4-benciloxibencilo, 2-fluorobencilo, 3-fluorobencilo, 4-fluorobencilo, 2,6-difluorobencilo, 2,5-difluorobencilo, 2,4-difluorobencilo, 2,3-difluorobencilo, 3,4-difluorobencilo, 3,5-difluorobencilo, 2,4,6-trifluorobencilo, 2-trifluorometilbencilo, 3-trifluorometilbencilo, 4-trifluorometilbencilo, naftilmetilo, indanilmetilo, piridinilmetilo, indolilmetilo,

tienilmetilo, 5-metiltienilmetilo, piperidinilo, piperidincarbonilo, piridinilcarbonilo, tetrahidropiranilo, pirimidinilo, acetilo, benzoílo, etoxicarbonilo, benciloxicarbonilo, t-butoxicarbonilo, metilcarbamoílo, fenilcarbamoílo, bencilcarbamoílo, metilsulfonilamino, fenilsulfonilamino, metilamino, dimetilamino, fluoro, oxo o carboxi.

Inhibidores de catepsina K más preferidos son los que se describen inmediatamente antes, y en donde:

$R_1$ es metoxi, benciloxi, ciclohexilo, fenoxi, naftiloxi, fenilo, bencilo, naftilo, pirrolidinilo, piperidinilo, morfolinilo, tiomorfolinilo, piperazinilo, furanilo, tienilo, oxazolilo, tiazolilo, imidazolilo, piridinilo, pirimidinilo, pirazinilo, indolilo, quinolinilo, benzofuranilo, benzotienilo, bencimidazolilo, benzotiazolilo, benzoxazolilo o amino; en donde $R_1$ está opcionalmente sustituido con uno o más $R_4$;

$R_4$ es metilo, fenilo, fluoro, cloro, hidroxi, oxo, carboxi o carboxamida;

$R_2$ es un enlace, metilo, etilo, n-propilo, i-propilo, n-butilo, i-butilo, n-pentilo, propenilo, i-butenilo o bencilo, en donde $R_2$ está opcionalmente sustituido con uno o más $R_5$;

$R_5$ es metilo, etilo, ciclohexilo, ciclopentilo, fenilo, furanilo, tetrahidropiranilo, tienilo, oxazolilo, tiazolilo, metoxi, fenoxi, acetilo, benzoílo, metoxicarbonilo, acetilamino, metiltio, metilsulfonilamino o fluoro;

$R_2$ y $R_3$, junto con el carbono al que están unidos, forman opcionalmente un anillo seleccionado de cilopentilo, ciclohexilo, cicloheptilo, tetrahidropiranilo, tetrahidrotiopiranilo o tetrahidrofuranilo;

$R_3$ es metilo, etilo, n-propilo, n-butilo, fenetilo, fenpropilo, t-butilo, i-propilo, i-butiló, ciclopropilo, ciclohexilo, ciclopropilmetilo, ciclohexilmetilo, fenilo, bencilo, 2-metoxibencilo, 3-metoxibencilo, 4-metoxibencilo, 4-fluorobencilo, 3,5-difluorobencilo, 4-trifluorometilbencilo, naftilmetilo, piridinilmetilo, indolilmetilo, tienilmetilo, acetilo,

benzoílo, etoxicarbonilo, benciloxicarbonilo, t-butoxicarbonilo, fenilcarbamoílo, fenilsulfonilamino o fluoro.

Inhibidores de catepsina K más preferidos son los que se describen inmediatamente antes, y en donde:

Het es pirrolidinilo, piperidinilo o tetrahidropiranilo;

$R_1$ es benciloxi, fenoxi, naftiloxi, fenilo, naftilo, pirrolidinilo, piperidinilo, morfolinilo, tiomorfolinilo, piperazinilo, piridinilo, indolilo, quinolinilo, benzofuranilo, benzotienilo, bencimidazolilo, benzotiazolilo, benzoxazolilo o fenilamino;

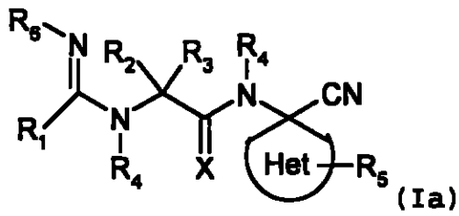
$R_2$ es n-propilo, i-butilo, propenilo, i-butenilo ó 2,2-dimetilpropilo;

$R_2$ y $R_3$, junto con el carbono al que están unidos, forman opcionalmente un anillo seleccionado de cilopentilo, ciclohexilo o cicloheptilo;

$R_4$ es metilo, etilo, n-propilo, fenetilo, t-butilo, i-propilo, i-butilo, ciclohexilo, ciclohexilmetilo, bencilo, 4-fluorobencilo, naftilmetilo, acetilo, benzoílo o benciloxicarbonilo.

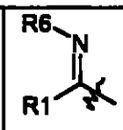
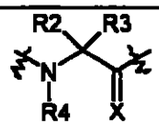
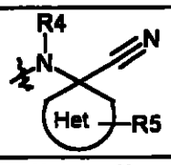
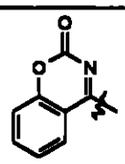
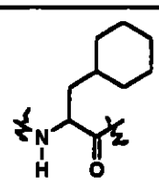
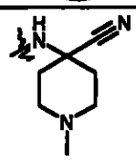
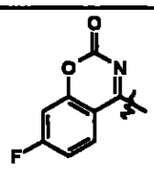
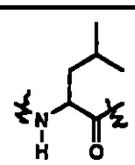
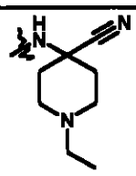
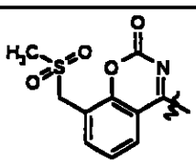
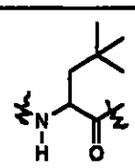
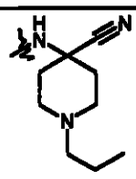
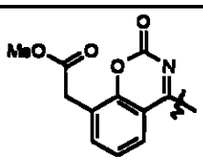
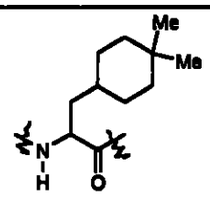
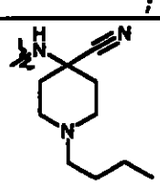
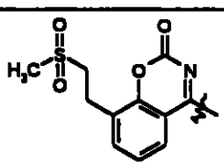
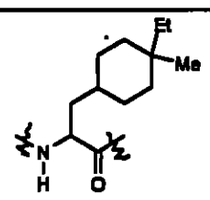
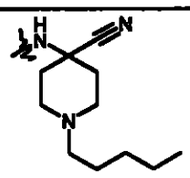
En la siguiente Tabla I se proporcionan compuestos adicionales de fórmula (Ia), constituidos por los componentes A, B y C. Cualquiera y todas las combinaciones de componentes, A, B y C dentro de las limitaciones estructurales de la fórmula (Ia) comprenden un compuesto de la invención y sus derivados farmacéuticamente aceptables. Estos compuestos se pueden sintetizar por los esquemas generales, métodos descritos en la sección experimental de este documento y métodos análogos conocidos por los expertos en la técnica sin una experimentación excesiva. Compuestos preferidos poseerán deseablemente una actividad de inhibición de catepsina S en un análisis basado en células según se describe en Riese, R.J. et al., Immunity, 1996, 4, 357-366, incorporado en esta memoria como referencia.

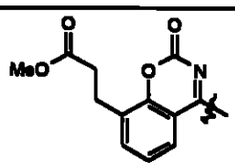
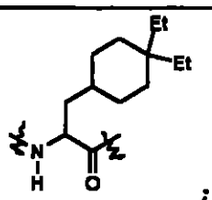
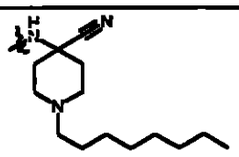
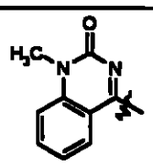
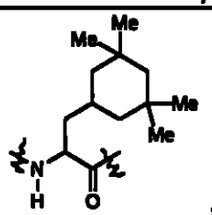
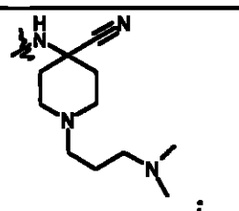
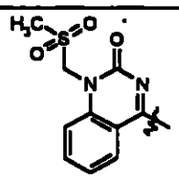
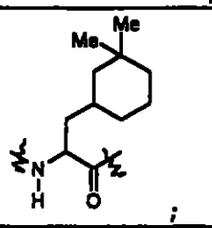
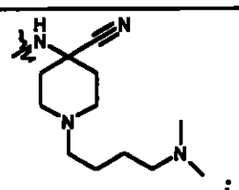
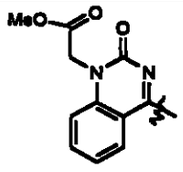
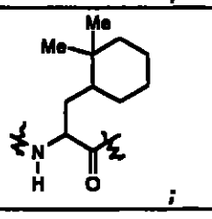
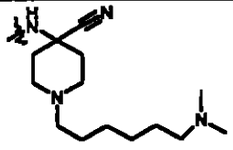
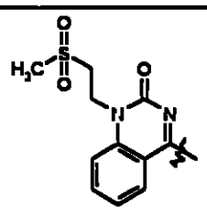
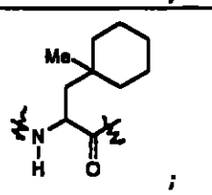
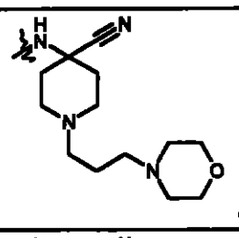
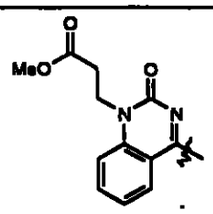
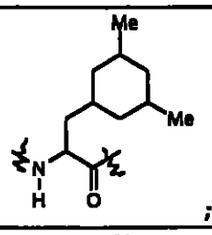
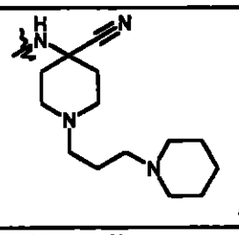
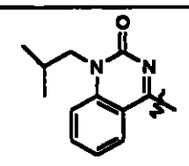
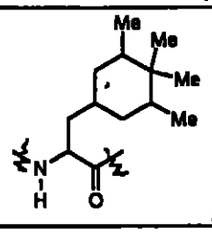
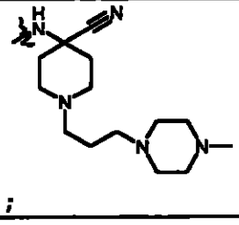
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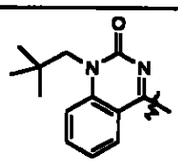
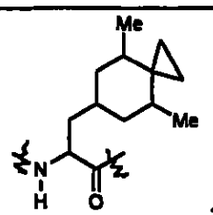
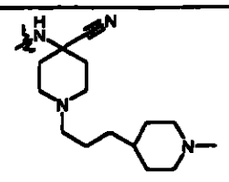
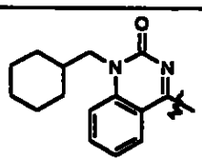
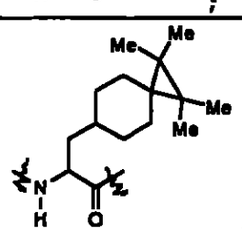
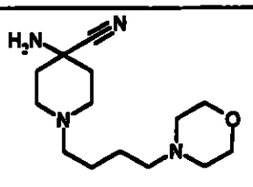
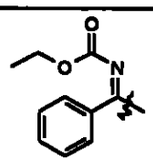
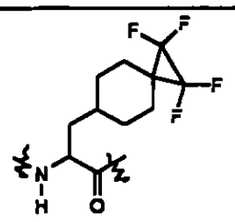
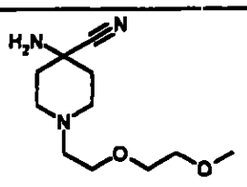
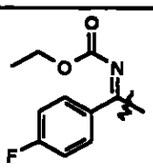
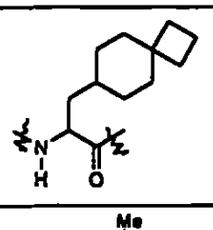
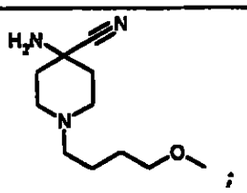
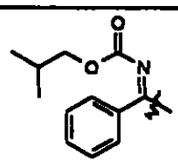
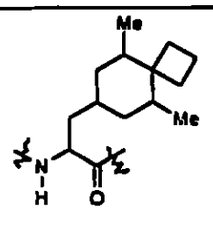
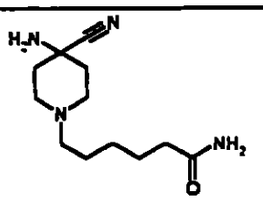
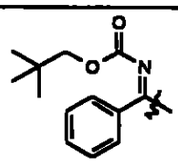
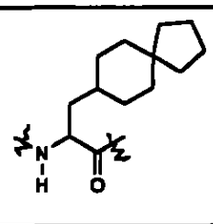
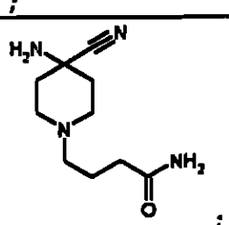
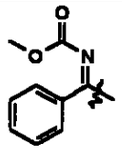
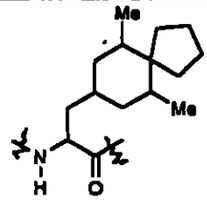
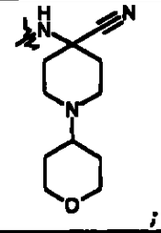


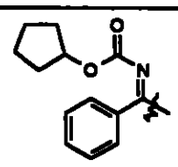
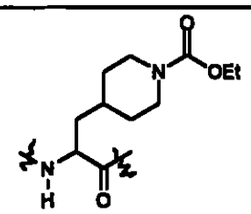
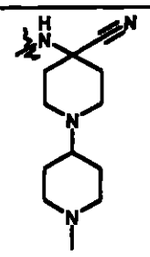
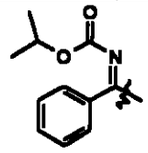
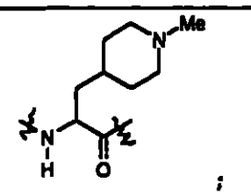
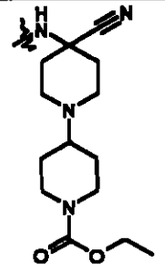
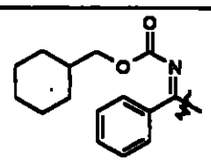
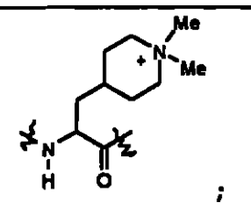
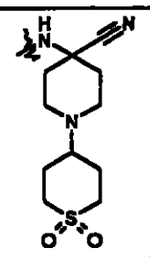
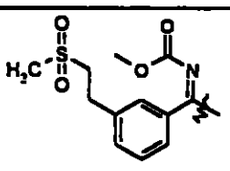
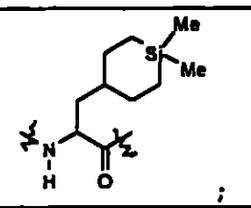
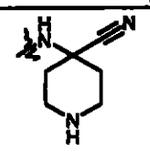
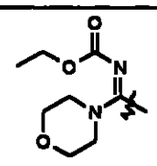
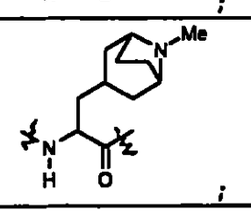
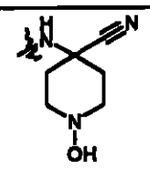
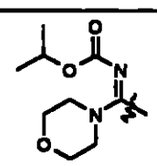
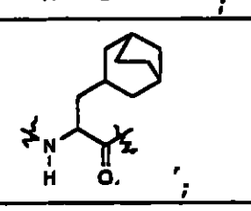
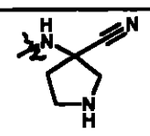
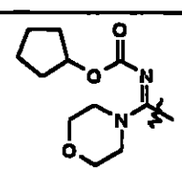
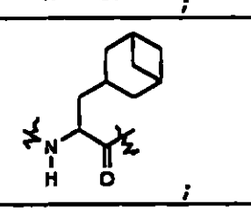
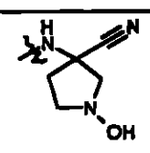
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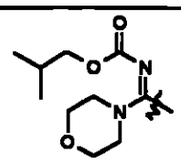
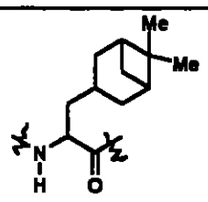
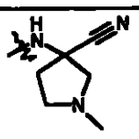
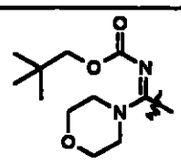
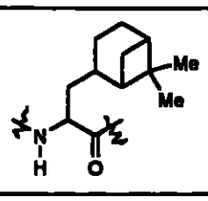
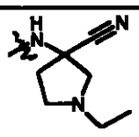
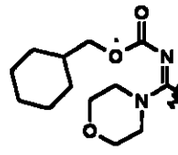
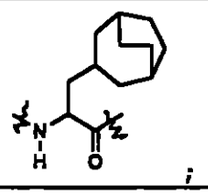
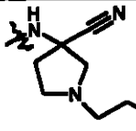
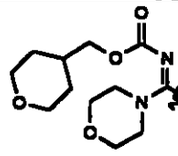
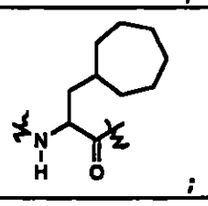
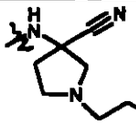
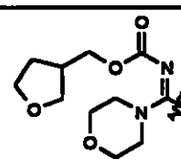
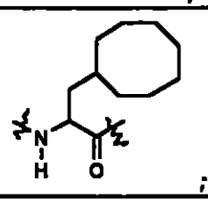
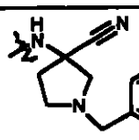
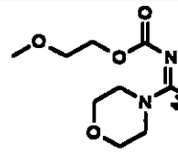
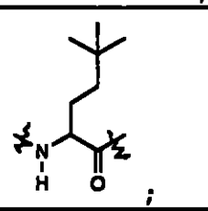
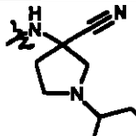
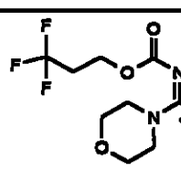
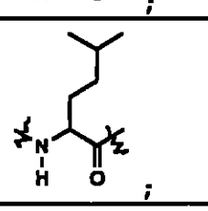
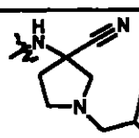
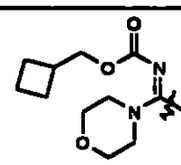
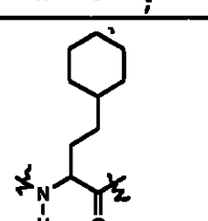
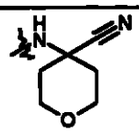
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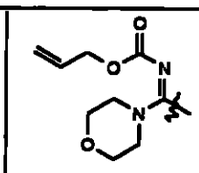
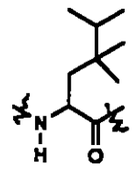
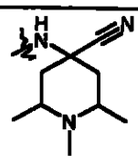
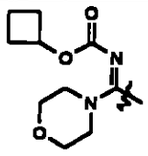
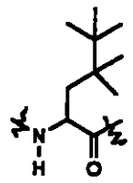
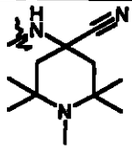
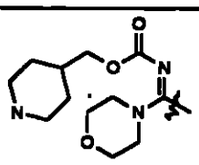
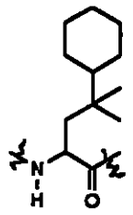
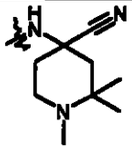
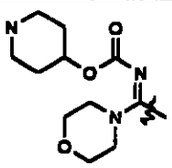
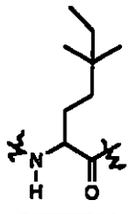
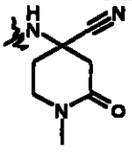
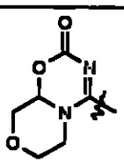
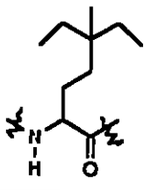
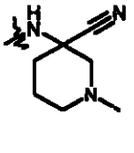
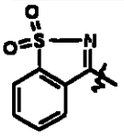
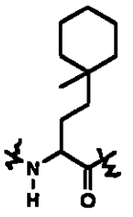
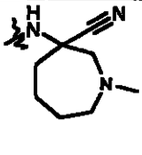
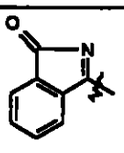
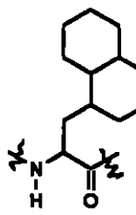
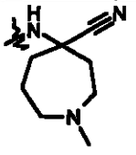
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|---|---|---|---|---|---|
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| A2 |  ; | B2 |  ; | C2 |  ; |
| A3 |  ; | B3 |  ; | C3 |  ; |
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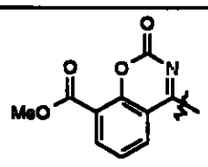
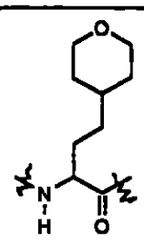
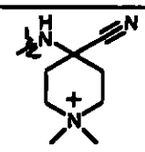
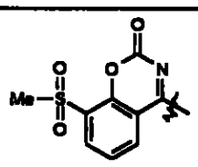
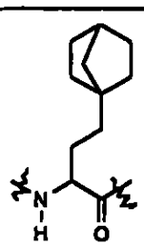
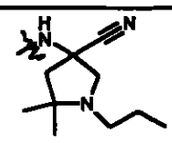
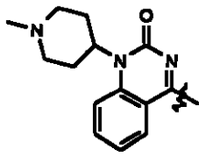
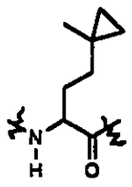
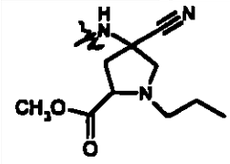
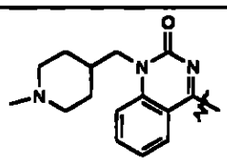
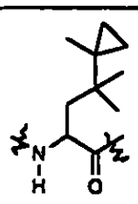
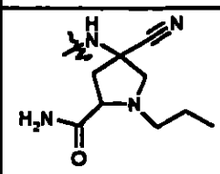
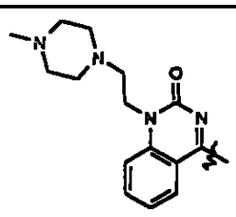
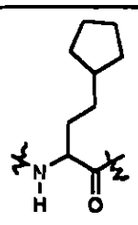
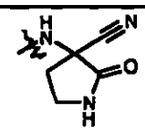
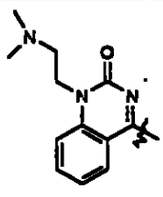
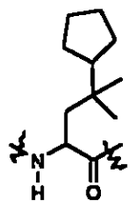
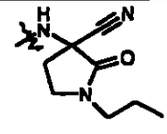
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| A6 |  | B6 |  | C6 |  |
| A7 |  | B7 |  | C7 |  |
| A8 |  | B8 |  | C8 |  |
| A9 |  | B9 |  | C9 |  |
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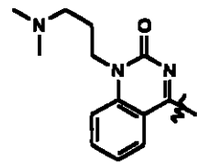
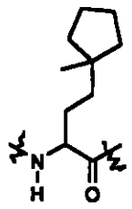
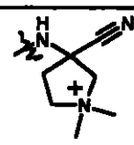
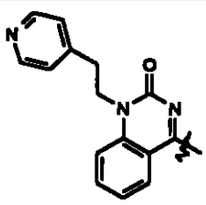
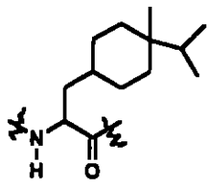
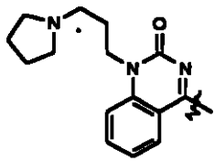
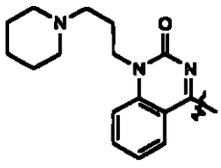
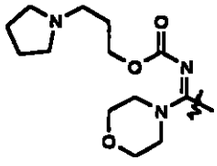
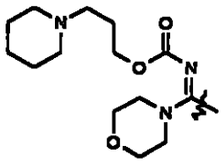
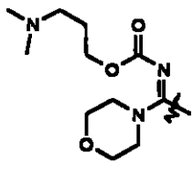
| | | | | | |
|---|---|---|---|---|---|
| A13 |  ; | B13 |  ; | C13 |  ; |
| A14 |  ; | B14 |  ; | C14 |  ; |
| A15 |  ; | B15 |  ; | C15 |  ; |
| A16 |  ; | B16 |  ; | C16 |  ; |
| A17 |  ; | B17 |  ; | C17 |  ; |
| A18 |  ; | B18 |  ; | C18 |  ; |
| A19 |  ; | B19 |  ; | C19 |  ; |

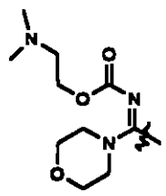
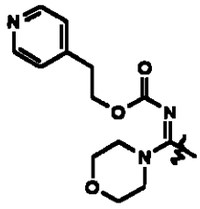
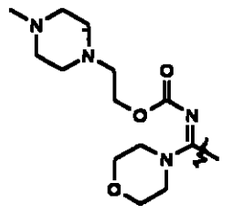
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| A20 |  ; | B20 |  ; | C20 |  ; |
| A21 |  ; | B21 |  ; | C21 |  ; |
| A22 |  ; | B22 |  ; | C22 |  ; |
| A23 |  ; | B23 |  ; | C23 |  ; |
| A24 |  ; | B24 |  ; | C24 |  ; |
| A25 |  ; | B25 |  ; | C25 |  ; |
| A26 |  ; | B26 |  ; | C26 |  ; |

| | | | | | |
|---|---|---|---|---|---|
| A27 |  ; | B27 |  ; | C27 |  ; |
| A28 |  ; | B28 |  ; | C28 |  ; |
| A29 |  ; | B29 |  ; | C29 |  ; |
| A30 |  ; | B30 |  ; | C30 |  ; |
| A31 |  ; | B31 |  ; | C31 |  ; |
| A32 |  ; | B32 |  ; | C32 |  ; |
| A33 |  ; | B33 |  ; | C33 |  ; |
| A34 |  ; | B34 |  ; | C34 |  ; |

| | | | | | |
|---|---|---|---|---|---|
| A35 |  ; | B35 |  ; | C35 |  ; |
| A36 |  ; | B35 |  ; | C36 |  ; |
| A37 |  ; | B37 |  ; | C37 |  ; |
| A38 |  ; | B38 |  ; | C38 |  ; |
| A39 |  ; | B39 |  ; | C39 |  ; |
| A40 |  ; | B40 |  ; | C40 |  ; |
| A41 |  ; | B41 |  ; | C41 |  ; |

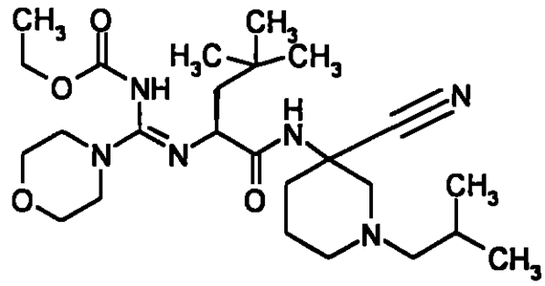
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|---|---|---|---|---|---|
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| A43 |  ; | B43 |  ; | C43 |  ; |
| A44 |  ; | B44 |  ; | C44 |  ; |
| A45 |  ; | B45 |  ; | C45 |  ; |
| A46 |  ; | B46 |  ; | C46 |  ; |
| A47 |  ; | B47 |  ; | C47 |  ; |

| | | | | | |
|---|---|---|---|---|---|
| A48 |  ; | B48 |  ; | C48 |  ; |
| A49 |  ; | B49 |  ; | | |
| A50 |  ; | | | | |
| A51 |  ; | | | | |
| A52 |  ; | | | | |
| A53 |  ; | | | | |
| A54 |  ; | | | | |

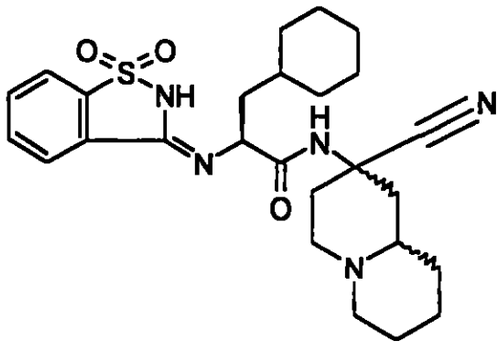
| | | | | | |
|---|---|---|---|---|---|
| A55 |  ; | | | | |
| A56 |  ; | | | | |
| A57 |  | | | | |

y sus derivados farmacéuticamente aceptables.

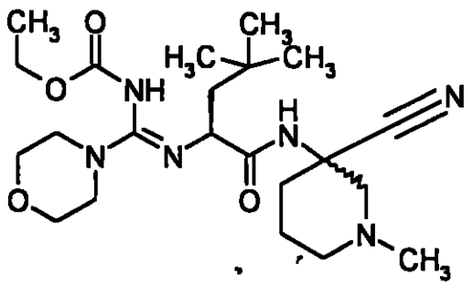
En otra realización de la invención se proporcionan los siguientes compuestos de las fórmula (Ia) y (Ib) que han sido sintetizados utilizando los esquemas generales, métodos descritos en la sección experimental de este documento y métodos análogos conocidos por los expertos en la técnica sin una experimentación indebida. Los compuestos poseen una actividad de inhibición deseable de catepsina S en un análisis basado en células referenciado anteriormente, según se describe en Riese, R.J. et al., Immunity, 1996, 4, 357-366, incorporado en esta memoria como referencia.



Éster etílico de ácido {[1-(3-ciano-1-isobutil-piperidin-3-il-carbamoil)-3,3-dimetil-butilamino]-morfolin-4-il-metileno}-carbámico; MS: 493 (M+1)



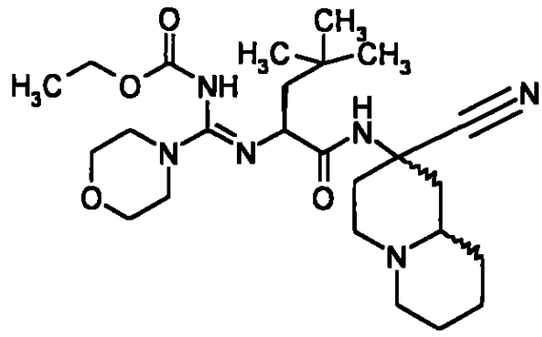
N-(2-ciano-octahidro-quinolizin-2-il)-3-ciclohexil-2-(1,1-dioxo-1H-1λ-benzo-3-ilamino)-propionamida; MS: 498 (M+1)



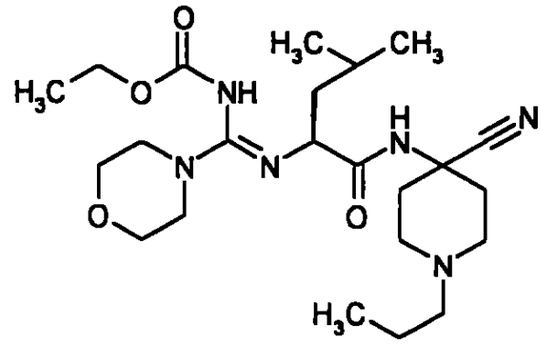
Éster etílico de ácido {[1-3-ciano-1-metil-piperidin-3-il-carbamoil)-3,3-dimetil-butilamino]-morfolin-4-il-metileno}-

458
459

carbámico; MS: 451 (M+1)

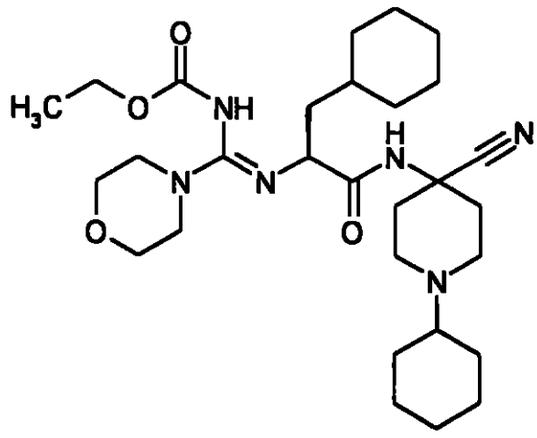


Éster etílico de ácido {[1-(2-ciano-octahidro-quinolizin-2--ilcarbamoil)-3,3-dimetil-butilamino]-morfolin-4-il-metileno}-carbámico; MS: 491 (M+1)

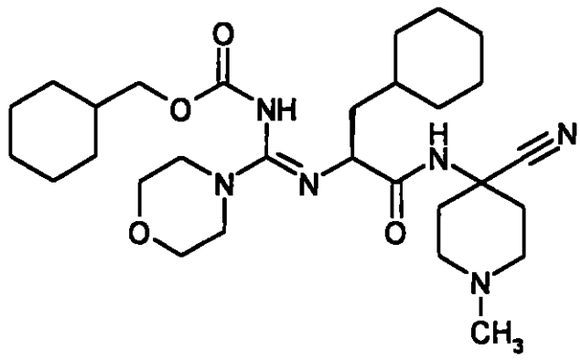


Éster etílico de ácido {[1-(4-ciano-1-propil-piperidin-4-ilcarbamoil)-3-metil-butilamino]-morfolin-4-il-metileno}-carbámico; MS: 465 (M+1)

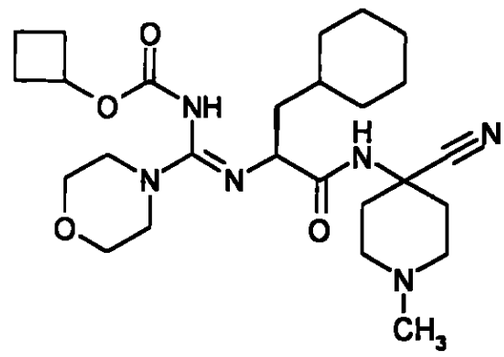
459
460



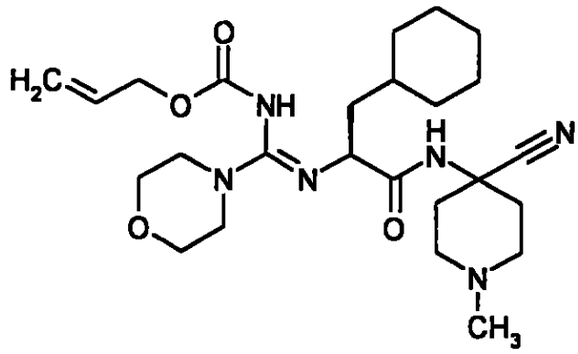
Éster etílico de ácido {[1-(4-ciano-1-ciclohexil-piperidin-4-ilcarbamoil)-2-ciclohexil-etilamino]-morfolin-4-il-metileno}-carbámico; MS: 545 (M+1)



Éster ciclohexilmetílico de ácido {[1-(4-ciano-1-metil-piperidin-4-ilcarbamoil)-2-ciclohexil-etilamino]-morfolin-4-il-metileno}-carbámico; MS: 545 (M+1)

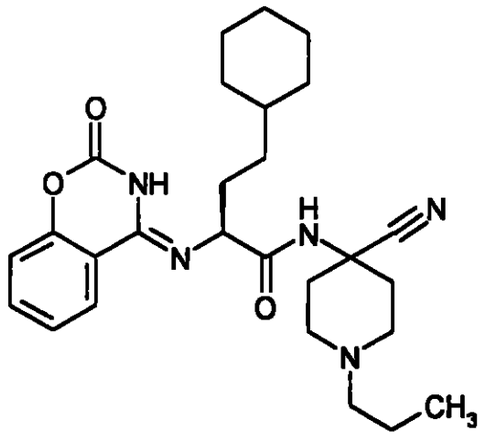


Éster ciclobutílico de ácido {[1-(4-ciano-1-metil-piperidin-4-ilcarbamoil)-2-ciclohexil-etilamino]-morfolin-4-il-metileno}-carbámico; MS: 503 (M+1)

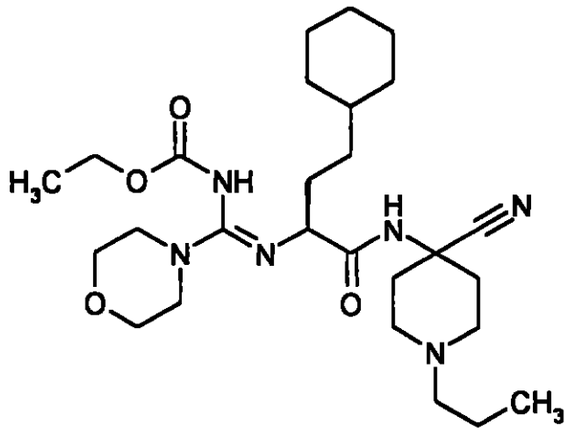


Éster alílico de ácido {[1-(4-ciano-1-metil-piperidin-4-il-carbamoil)-2-ciclohexil-etilamino]-morfolin-4-il-metileno}--carbámico; MS: 489 (M+1)

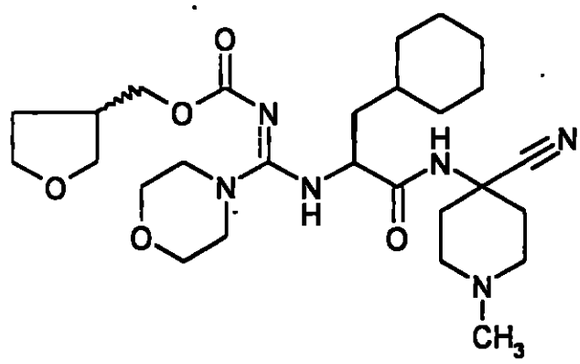
461
462



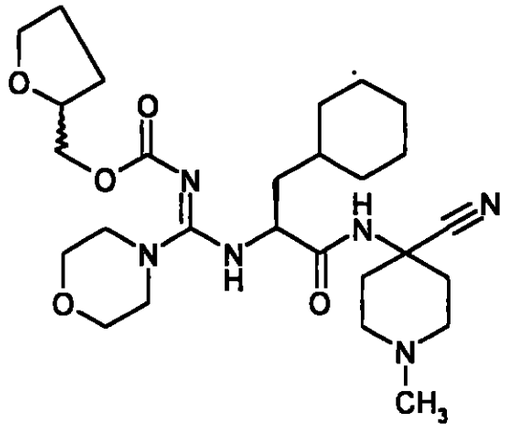
N-(4-ciano-1-propil-piperidin-4-il)-4-ciclohexil-2-(2-oxo-2,3-dihidro-benzo[e][1,3]oxazin-4-ilidenamino)-butiramida; MS: 480 (M+1)



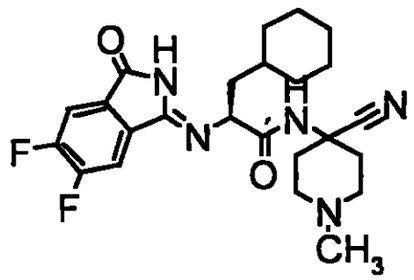
Éster de ácido {[1-(4-ciano-1-propil-piperidin-4-ilcarbamoil)-3-ciclohexil-propilamino]-morfolin-4-il-metileno}carbámico; MS: 519 (M+1)



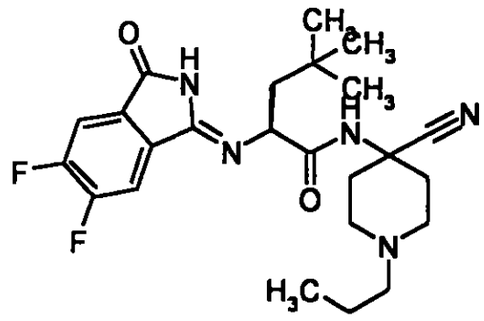
Éster tetrahidro-furan-3-ilmetílico de ácido {[1-(4-ciano-1-metil-piperidin-4-ilcarbamoil)-2-ciclohexil-etilamino]-morfolin-4-il-metileno}-carbámico; MS: 533 (M+1)



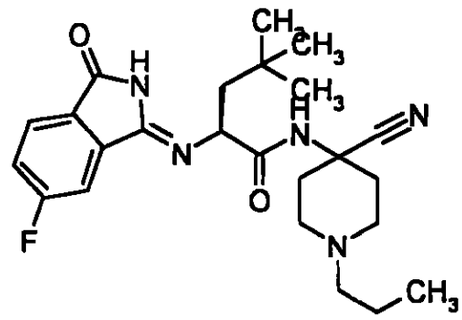
Éster tetrahidro-furan-2-ilmetílico de ácido {[1-(4-ciano-1-metil-piperidin-4-ilcarbamoil)-2-ciclohexil-etilamino]-morfolin-4-il-metileno}-carbámico; MS: 533 (M+1)



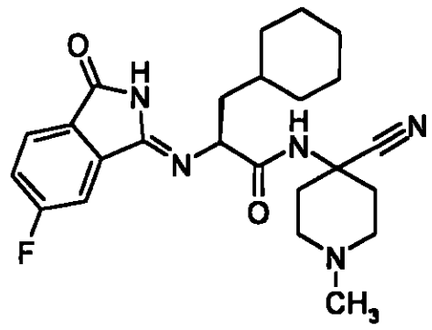
N-(4-ciano-1-metil-piperidin-4-il)-3-ciclohexil-2-(5,6-difluoro-3-oxo-2,3-dihidro-isoindol-1-ilidenamino)-propionamida; MS: 458 (M+1)



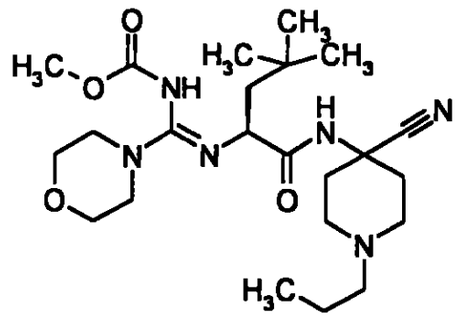
(4-ciano-1-propil-piperidin-4-il)-amida de ácido 2-(5,6-difluoro-3-oxo-2,3-dihidro-isoindol-1-ilidenamino)-4,4-dimetil-pentanoico; MS: 460 (M+1)



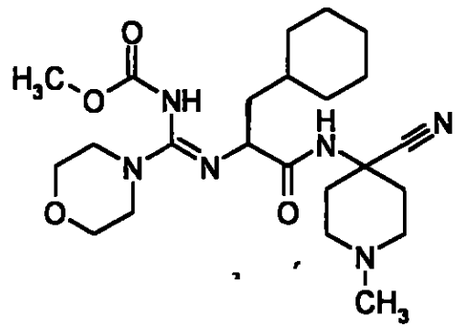
(4-ciano-1-propil-piperidin-4-il)-amida de ácido 2-(6-fluoro-3-oxo-2,3-dihidro-isoindol-1-ilidenamino)-4,4-dimetil-pentanoico; MS: 442 (M+1)



N-(4-ciano-1-metil-piperidin-4-il)-3-ciclohexil-2-(6-fluoro-3-oxo-2,3-dihidro-isoindol-1-ilidenamino)-propionamida; MS: 440 (M+1)

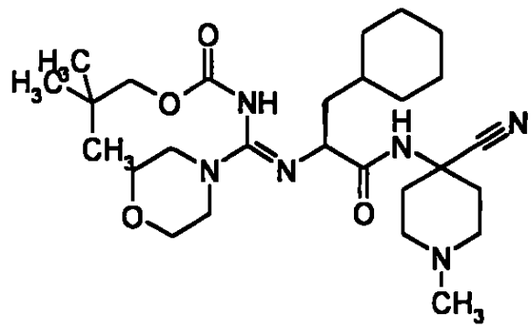


Éster metílico de ácido {[1-(4-ciano-1-propil-piperidin-4-il-carbamoil)-3,3-dimetil-butilamino]-morfolin-4-il-metil}-carbámico; MS: 465 (M+1)

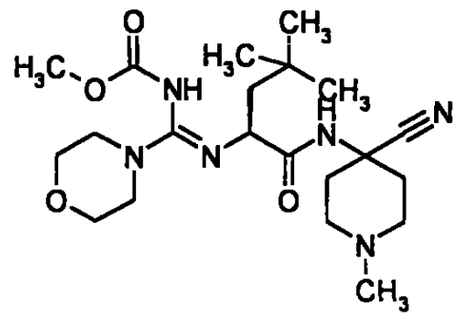


Éster metílico de ácido {[1-(4-ciano-1-metil-piperidin-4-il-

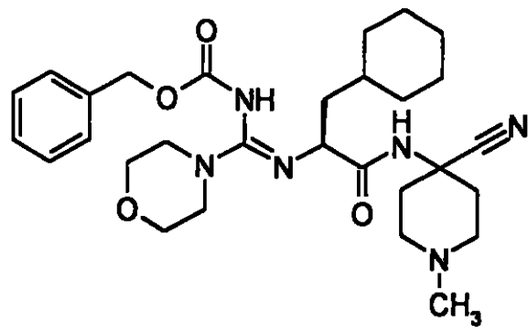
carbamoil)-2-ciclohexil-etilimino]-morfolin-4-il-metil}-carbámico; MS: 463 (M+1)



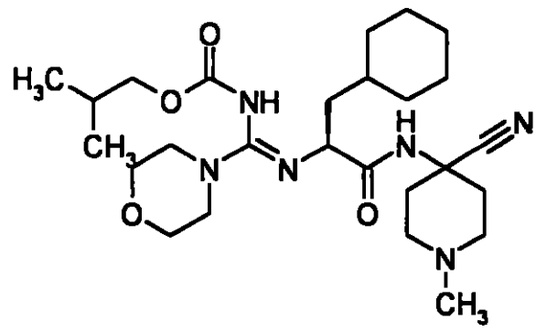
Éster 2,2-dimetil-propílico de ácido {[1-(4-ciano-1-metil--piperidin-4-ilcarbamoil)-2-ciclohexil-etilimino]-morfolin-4-il-metil}-carbámico; MS: 519 (M+1)



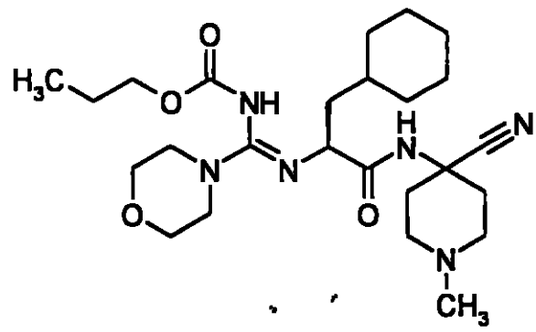
Éster metílico de ácido {[1-(4-ciano-1-metil-piperidin-4-il-carbamoil)-3,3-dimetil-butilimino]-morfolin-4-il-metil}-carbámico; MS: 437 (M+1)



Éster bencílico de ácido {[1-(4-ciano-1-metil-piperidin-4-il-carbamoil)-2-ciclohexil-etilimino]-morfolin-4-il-metil}-carbámico; MS: 539 (M+1)

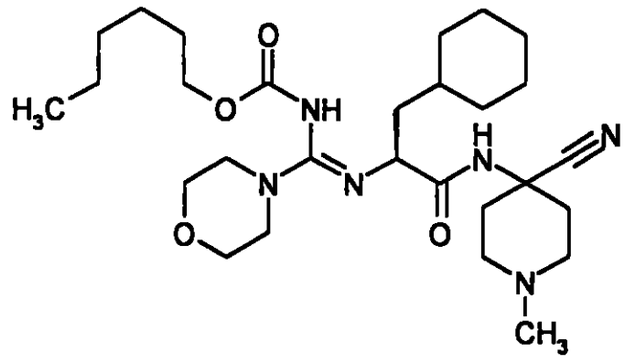


Éster isobutílico de ácido {[1-(4-ciano-1-metil-piperidin-4-ilcarbamoil}-2-ciclohexil-etilimino]-morfolin-4-il-metil}-carbámico; MS: 505 (M+1)

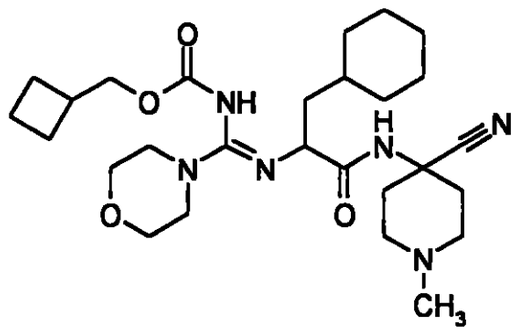


Éster propílico de ácido {[1-(4-ciano-1-metil-piperidin-4-il-carbamoil)-2-ciclohexil-etilimino]-morfolin-4-il-metil}-car-

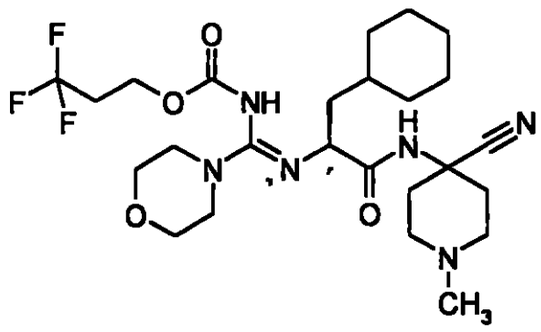
bámico; MS: 491 (M+1)



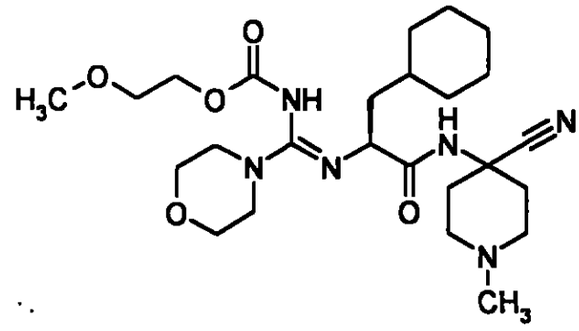
Éster hexílico de ácido {[1-(4-ciano-1-metil-piperidin-4-il-carbamoil)-2-ciclohexil-etilimino]-morfolin-4-il-metil}-carbámico; MS: 533 (M+1)



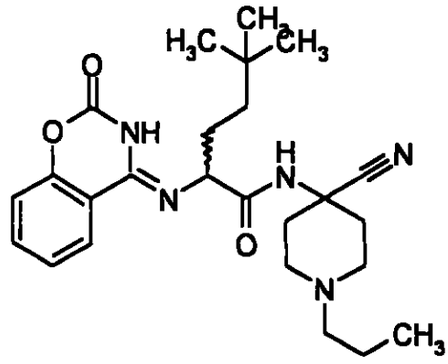
Éster ciclobutilmetílico de ácido {[1-(4-ciano-1-metil-piperidin-4-ilcarbamoil)-2-ciclohexil-etilimino]-morfolin-4-il--metil}-carbámico; MS: 517 (M+1)



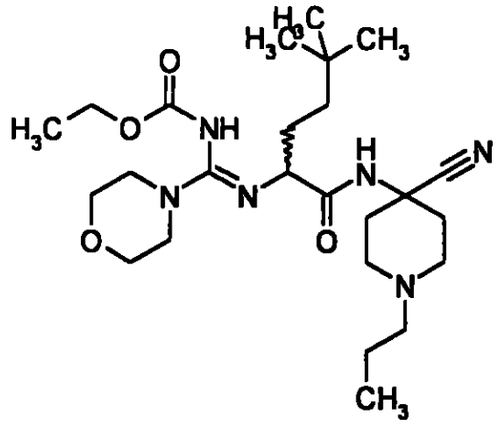
Éster 3,3,3-trifluoro-propílico de ácido {[1-(4-ciano-1-metil-piperidin-4-ilcarbamoil)-2-ciclohexil-etilimino]-morfolin-4-il-metil}-carbámico; MS: 545 (M+1)



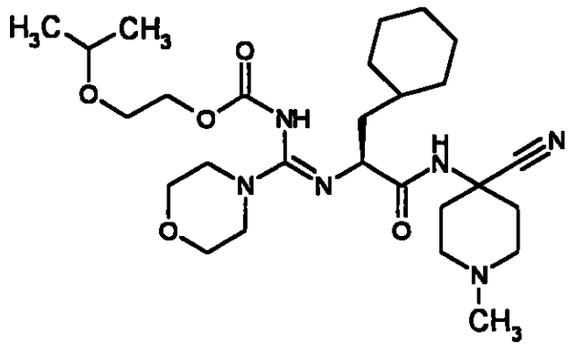
Éster 2-metoxi-etílico de ácido {[1-(4-ciano-1-metil-piperidin-4-ilcarbamoil)-2-ciclohexil-etilimino]-morfolin-4-il-metil}-carbámico; MS: 507 (M+1)



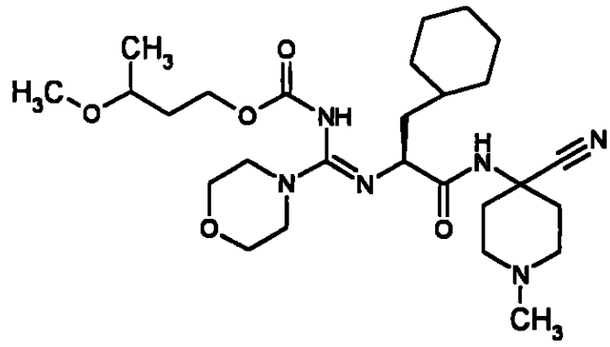
(4-ciano-1-propil-piperidin-4-il)-amida de ácido 5,5-dimetil-2-(2-oxo-2,3-dihidro-benzo[e][1,3]oxazin-4-ilidenamino)-hexanoico; MS: 454 (M+1)



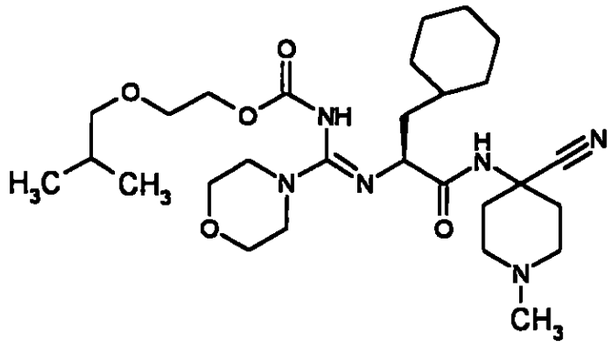
Éster etílico de ácido {[1-(4-ciano-1-propil-piperidin-4-il-carbamoil)-4,4-dimetil-pentilimino]-morfolin-4-il-metil}-carbámico; MS: 493 (M+1)



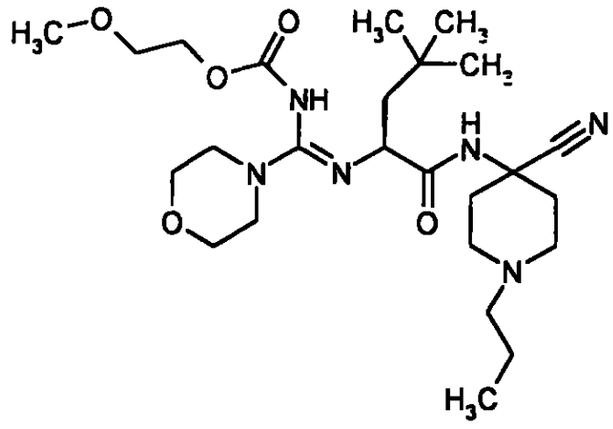
Éster 2-isopropoxi-etílico de ácido {[1-(4-ciano-1-metil-piperidin-4-ilcarbamoil)-2-ciclohexil-etilimino]-morfolin-4-il-metil}-carbámico; MS: 534 (M+1)



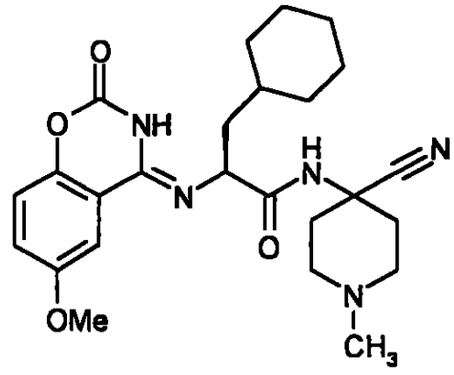
Éster 3-metoxi-butílico de ácido {[1-(4-ciano-1-metil-piperidin-4-ilcarbamoil)-2-ciclohexil-etilimino]-morfolin-4-il-metil}-carbámico; MS: 534 (M+1)



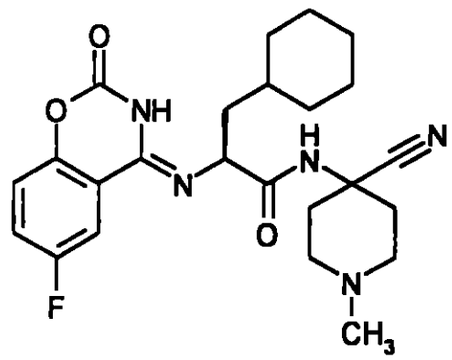
Éster 2-isobutoxi-etílico de ácido {[1-(4-ciano-1-metil-piperidin-4-ilcarbamoil)-2-ciclohexil-etilimino]-morfolin-4-il-metil}-carbámico; MS: 549 (M+1)



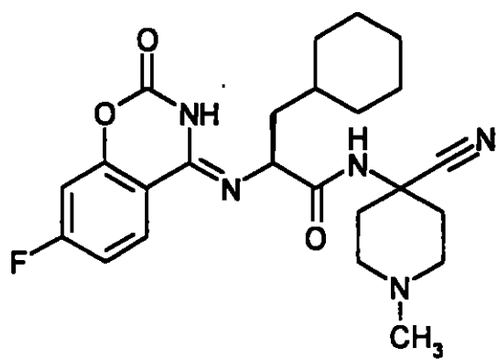
Éster 2-metoxi-etílico de ácido {[1-(4-ciano-1-propil-piperidin-4-ilcarbamoil)-3,3-dimetil-butilimino]-morfolin-4-il-metil}-carbámico; MS: 509 (M+1)



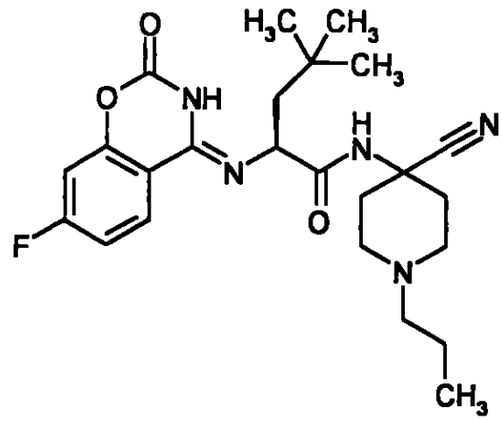
N-(4-ciano-1-metil-piperidin-4-il)-4-ciclohexil-2-(6-metoxi-2-oxo-2,3-dihidro-benzo[e][1,3]oxazin-4-ilidenamino)-butiramida; MS: 468 (M+1)



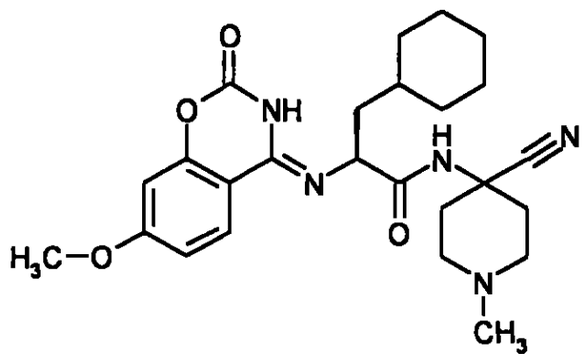
N-(4-ciano-1-metil-piperidin-4-il)-4-ciclohexil-2-(6-fluoro-2-oxo-2,3-dihidro-benzo[e][1,3]oxazin-4-ilidenamino)-butiramida; MS: 456 (M+1)



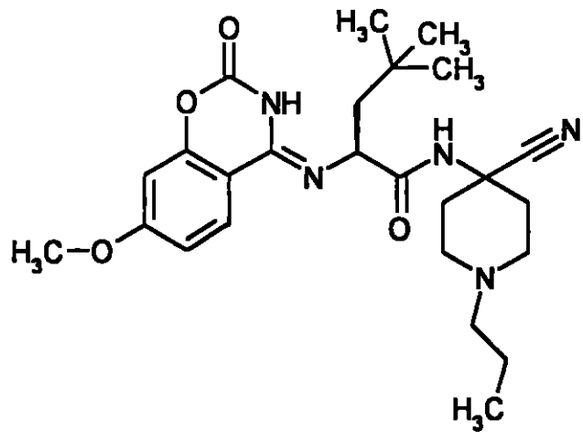
N-(4-ciano-1-metil-piperidin-4-il)-4-ciclohexil-2-(7-fluoro-2-oxo-2,3-dihidro-benzo[e][1,3]oxazin-4-ilidenamino)-butiramida; MS: 456 (M+1)



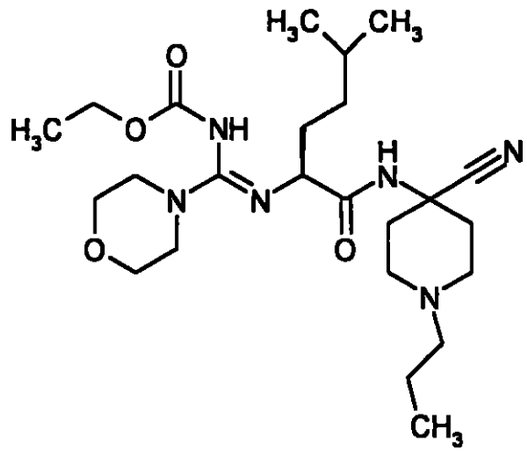
'4-ciano-1-propil-piperidin-4-il)-amida de ácido 2-(7-fluoro-2-oxo-2,3-dihidro-benzo[e][1,3]oxazin-4-ilidenamino)-5,5-dimetil-hexanoico; MS: 458 (M+1)



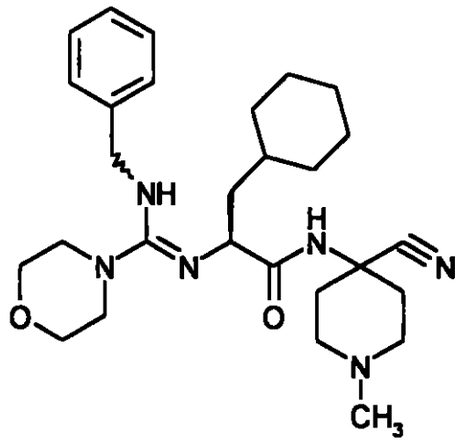
N-(4-ciano-1-metil-piperidin-4-il)-4-ciclohexil-2-(7-metoxi-2-oxo-2,3-dihidro-benzo[e][1,3]oxazin-4-ilidenamino)-butiramida; MS: 468 (M+1)



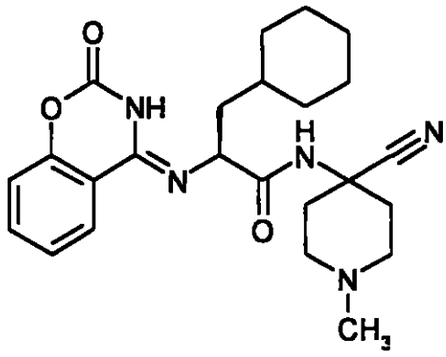
(4-ciano-1-propil-piperidin-4-il)-amida de ácido 2-(7-metoxi-2-oxo-2,3-dihidro-benzo[e][1,3]oxazin-4-ilidenamino)-5,5-dimetil-hexanoico; MS: 470 (M+1)



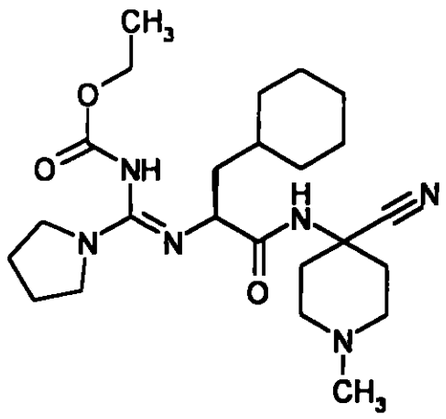
Éster etílico de ácido {[1-(4-ciano-1-propil-piperidin-4-il-carbamoil)-5-metil-hexilimino]-morfolin-4-il-metil}-carbámico; MS: 479 (M+1)



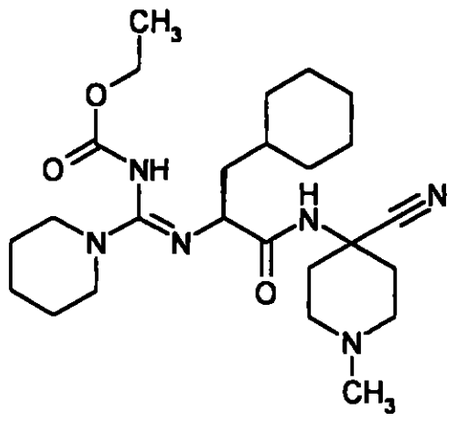
2-[(N-bencil-morfolin-4-carboximidoil)-amino]-N-(4-ciano-1-metil-piperidin-4-il)-3-ciclohexil-propionamida; MS: 495 (M+1)



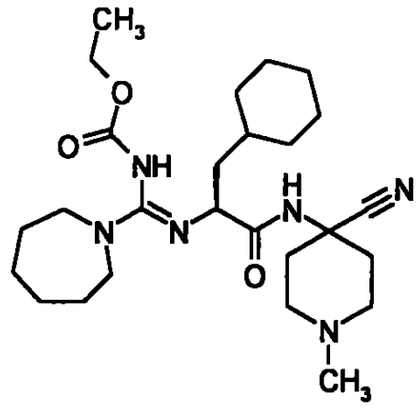
N-(4-ciano-1-metil-piperidin-4-il)-3-ciclohexil-2-(2-oxo-2,3-dihidro-benzo[e][1,3]oxazin-4-ilidenamino)-propionamida; MS: 438 (M+1)



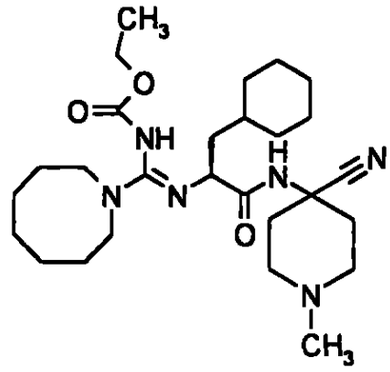
Éster etílico de ácido {[1-(4-ciano-1-metil-piperidin-4-il-carbamoil)-2-ciclohexil-etilimino]-pirrolidin-1-il-metil}-carbámico; MS: 461 (M+1)



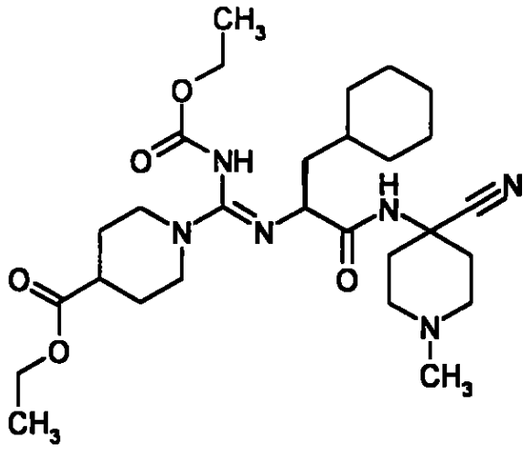
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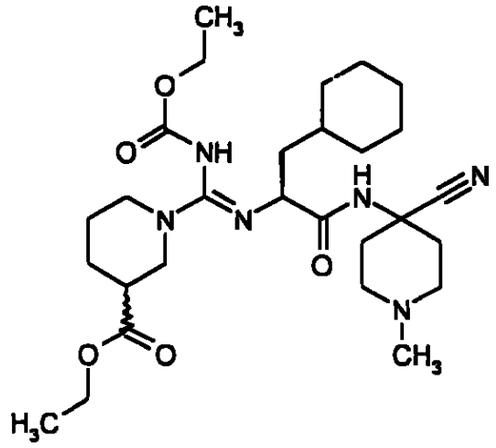
Éster etílico de ácido {azepan-1-il-[1-(4-ciano-1-metil-piperidin-4-ilcarbamoil)-2-ciclohexil-etilimino]-metil}-carbámico; MS: 489 (M+1)



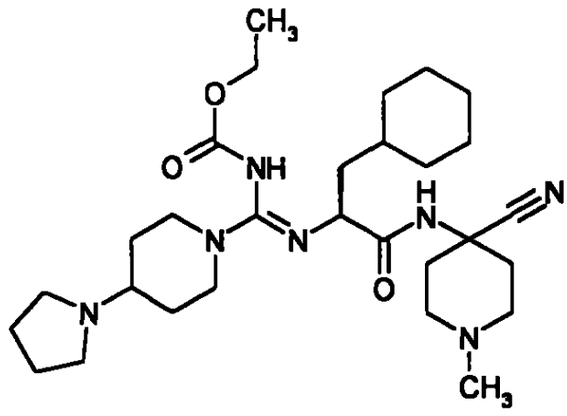
Éster etílico de ácido {azocan-1-il-[1-(4-ciano-1-metil-piperidin-4-ilcarbamoil)-2-ciclohexil-etilimino]-metil}-carbámico; MS: 503 (M+1)



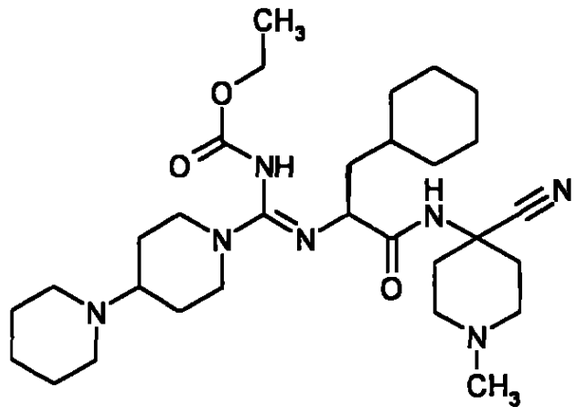
Éster etílico de ácido 1-{[1-(4-ciano-1-metil-piperidin-4-il-carbamoil)-2-ciclohexil-etilimino]-etoxicarbonilamino-metil}-piperidina-4-carboxílico; MS: 547 (M+1)



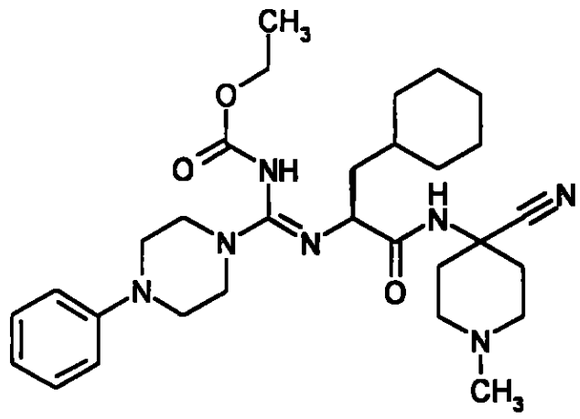
Éster etílico de ácido 1-{[1-(4-ciano-1-metil-piperidin-4-il-carbamoil)-2-ciclohexil-etilimino]-etoxicarbonilamino-metil}-piperidina-3-carboxílico; MS: 547 (M+1)



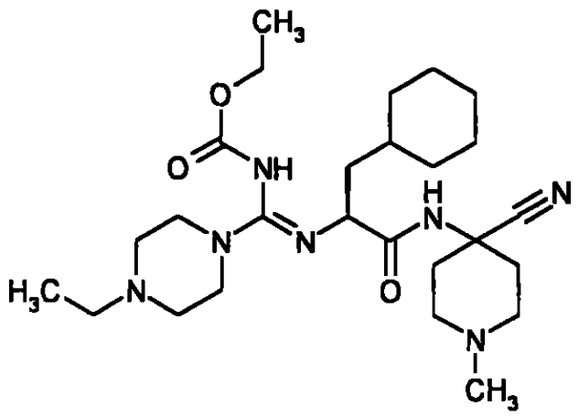
Éster etílico de ácido [[1-(4-ciano-1-metil-piperidin-4-il-carbamoil)-2-ciclohexil-etilimino]-(4-pirrolidin-1-il-piperidin-1-il)-metil]-carbámico; MS: 544 (M+1)



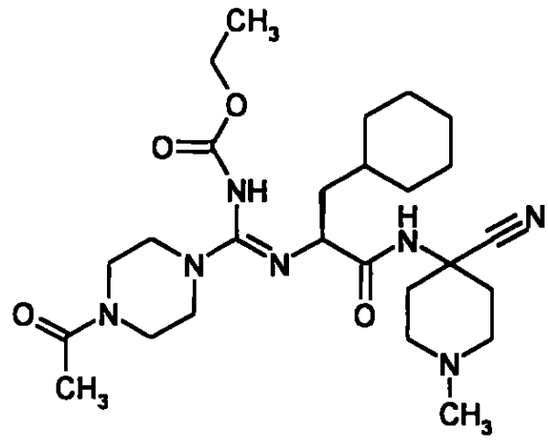
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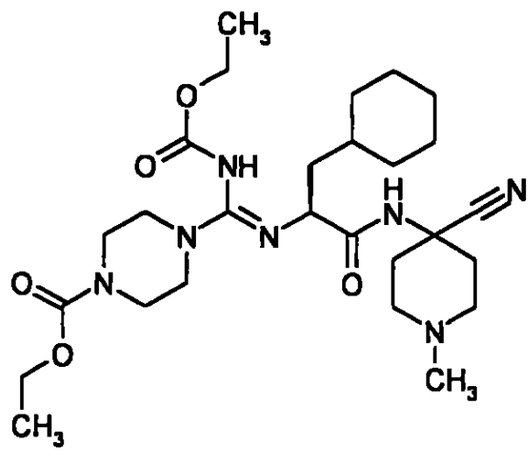
Éster etílico de ácido [[1-(4-ciano-1-metil-piperidin-4-il-carbamoil)-2-ciclohexil-etilimino]-(4-fenilpiperazin-1-il)-metil]-carbámico; MS: 552 (M+1)



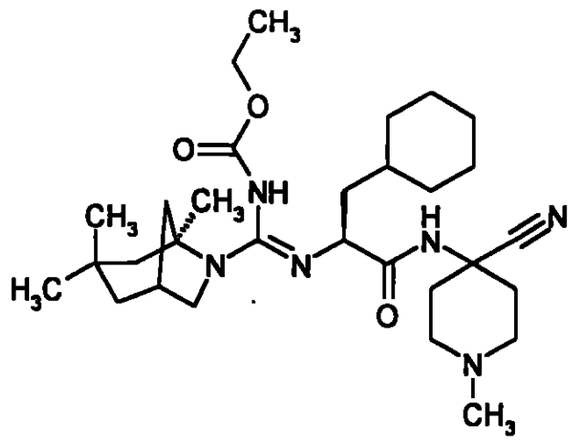
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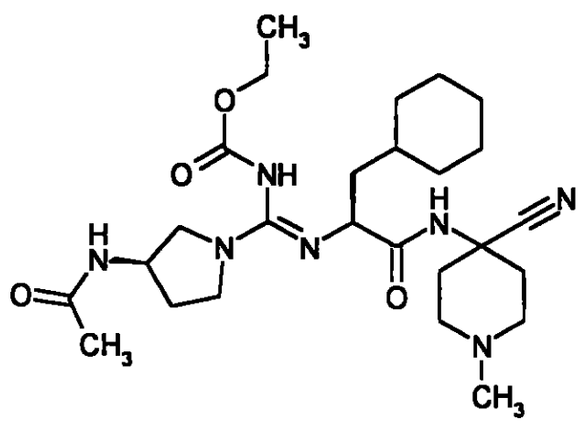
Éster etílico de ácido {(4-acetil-piperazin-1-il)-[1-(4-ciano-1-metil-piperidin-4-ilcarbamoil)-2-ciclohexil-etilimino]-metil}-carbámico; MS: 518 (M+1)



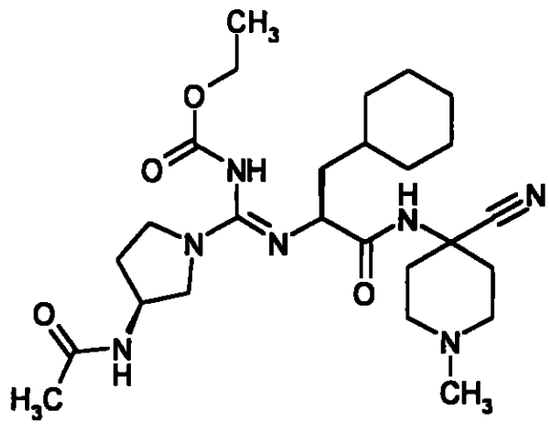
Éster etílico de ácido 4-{[1-(4-ciano-1-metil-piperidin-4-il-carbamoil)-2-ciclohexil-etilimino]-etoxicarbonilamino-metil}-piperazina-1-carboxílico; MS: 548 (M+1)



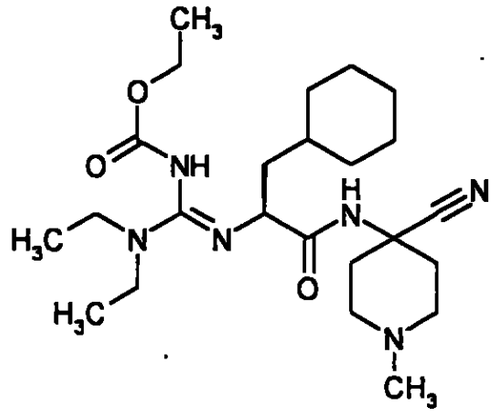
Éster etílico de ácido [[1-(4-ciano-1-metil-piperidin-4-il-carbamoil)-2-ciclohexil-etilimino]-(3,3,5-trimetil-6-aza-biciclo[3.2.1]oct-6-il)-metil]-carbámico; MS: 543 (M+1)



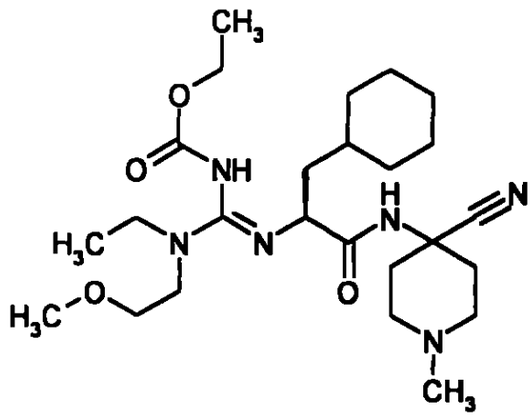
Éster etílico de ácido {(3-acetilamino-pirrolidin-1-il)-[1-(4-ciano-1-metil-piperidin-4-ilcarbamoil)-2-ciclohexil-etilimino]-metil}-carbámico; MS: 518 (M+1)



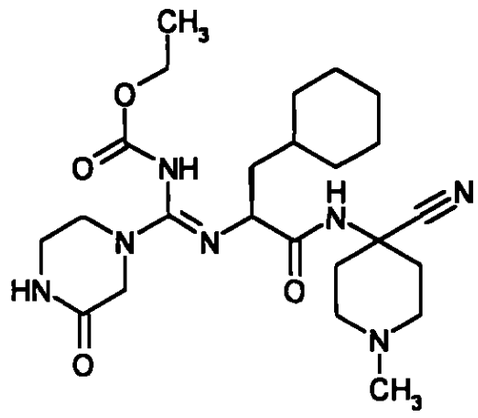
Éster etílico de ácido {(3-acetilamino-pirrolidin-1-il)-[1-(4-ciano-1-metil-piperidin-4-ilcarbamoil)-2-ciclohexil-etilimino]-metil}-carbámico; MS: 518 (M+1)



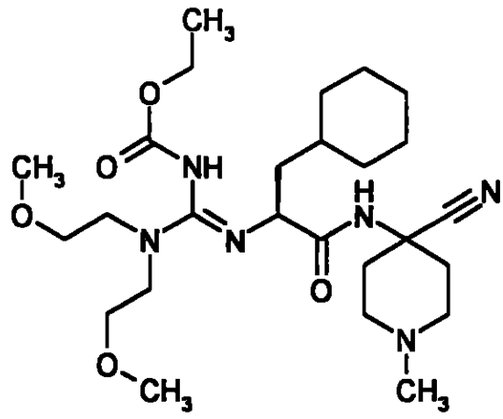
Éster etílico de ácido {(3-azapent-3-il)-[1-(4-ciano-1-metil-piperidin-4-ilcarbamoil)-2-ciclohexil-etilimino]-metil}-carbámico; MS: 463 (M+1)



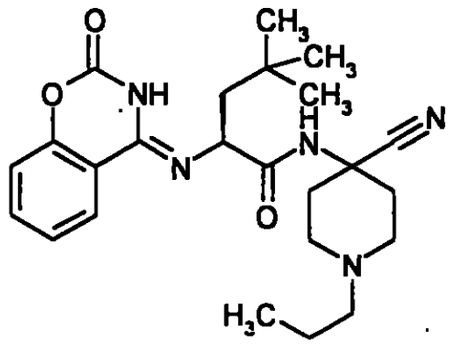
Éster etílico de ácido {(1-metoxi-3-azapent-3-il)-[1-(4-ciano-1-metil-piperidin-4-ilcarbamoil)-2-ciclohexil-etilimino]-metil}-carbámico; MS: 493 (M+1)



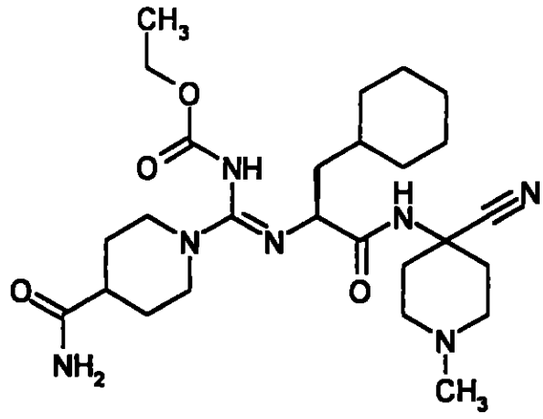
Éster etílico de ácido [[1-(4-ciano-1-metil-piperidin-4-il-carbamoil)-2-ciclohexil-etilimino]-(3-oxo-piperazin-1-il)-metil]-carbámico· MS: 490 (M+1)



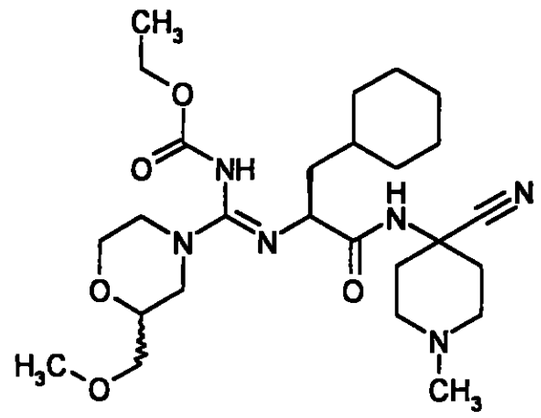
Éster etílico de ácido {(1,5-dimetoxi-3-azapent-3-il)-[1-(4-ciano-1-metil-piperidin-4-ilcarbamoil)-2-ciclohexil-etilimino]-metil}-carbámico; MS: 523 (M+1)



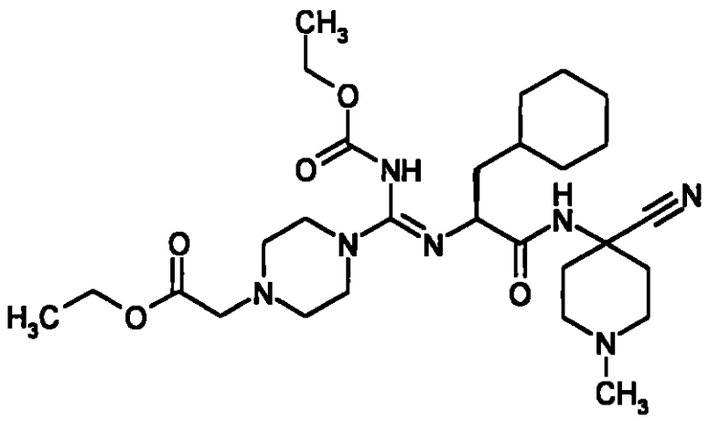
{4-ciano-1-propil-piperidin-4-il}-amida de ácido 4,4-dimetil-2-(2-oxo-2,3-dihidro-benzo[e][1,3]oxazin-4-ilidenamino)-pentanoico; MS: 440 (M+1)



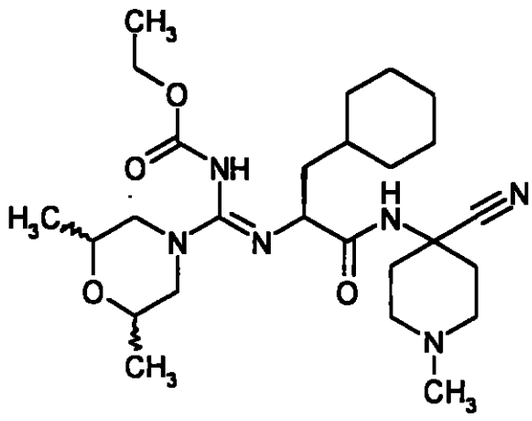
Éster etílico de ácido {(4-carbamoil-piperidin-1-il)-[1-(4-ciano-1-metil-piperidin-4-ilcarbamoil)-2-ciclohexil-etilimino]-metil}-carbámico; MS: 518 (M+1)



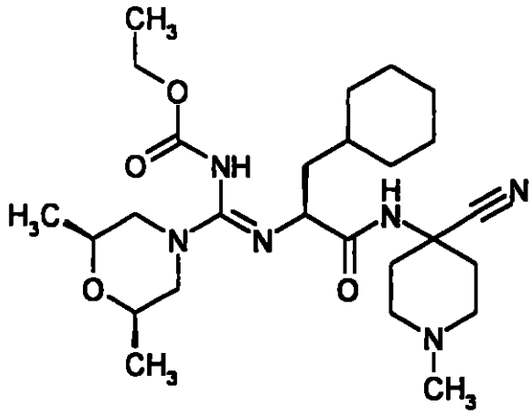
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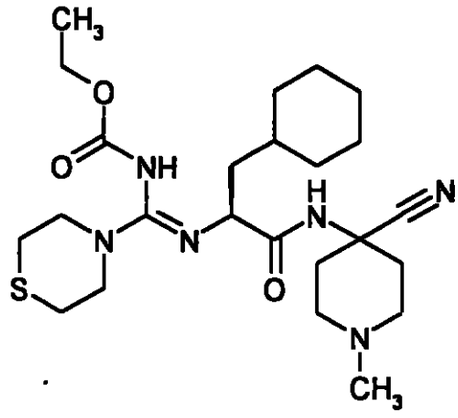
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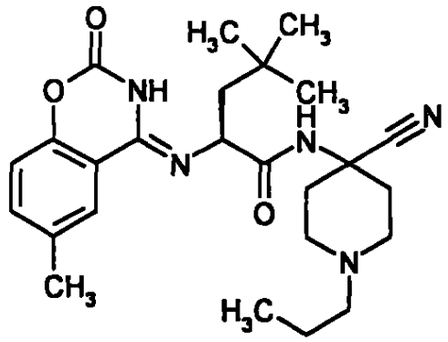
Éster etílico de ácido [[1-(4-ciano-1-metil-piperidin-4-il-carbamoil)-2-ciclohexil-etilimino]-(2,6-dimetil-morfolin-4-il)-metil]-carbámico; MS: 505 (M+1)



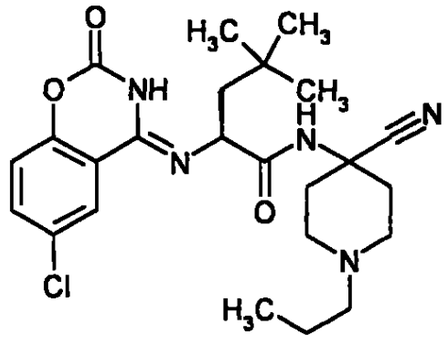
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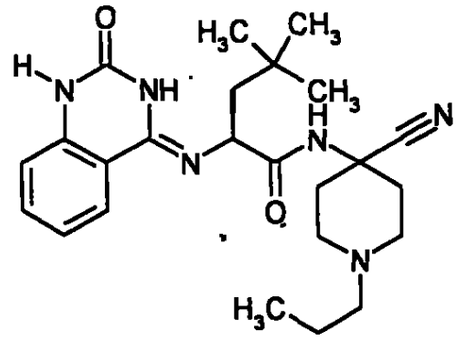
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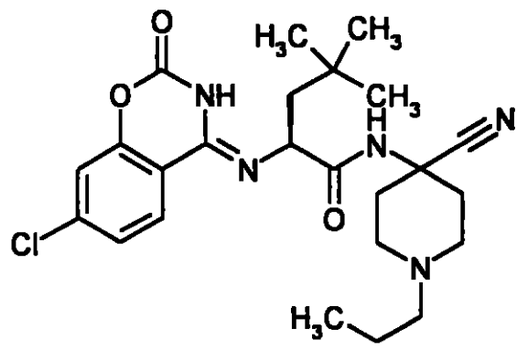
(4-ciano-1-propil-piperidin-4-il)-amida de ácido 4,4-dimetil-2-(6-metil-2-oxo-2,3-dihidro-benzo[e][1,3]oxazin-4-ilidenamino)-pentanoico; MS: 454 (M+1)



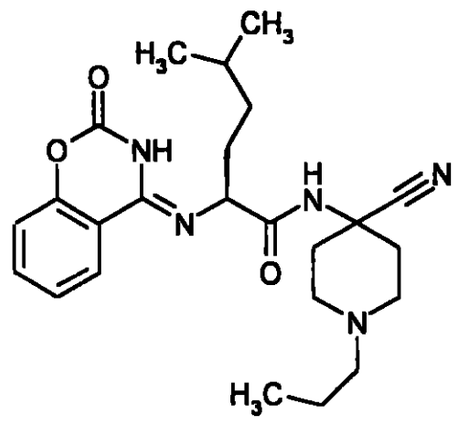
(4-ciano-1-propil-piperidin-4-il)-amida de ácido 2-(6-cloro-2-oxo-2,3-dihidro-benzo[e][1,3]oxazin-4-ilidenamino)-4,4-dimetil-pentanoico; MS: 475 (M+1)



(4-ciano-1-propil-piperidin-4-il)-amida de ácido 4,4-dimetil-2-(2-oxo-2,3-dihidro-1*H*-quinazolin-4-ilidenamino)-pentanoico; MS: 439 (M+1)

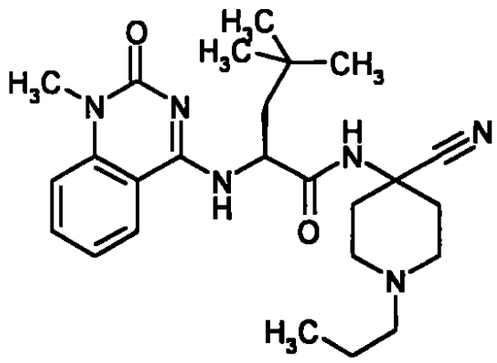


(4-ciano-1-propil-piperidin-4-il)-amida de ácido 2-(7-cloro-2-oxo-2,3-dihidro-benzo[e][1,3]oxazin-4-ilidenamino)-4,4-dimetil-pentanoico; MS: 475 (M+1)

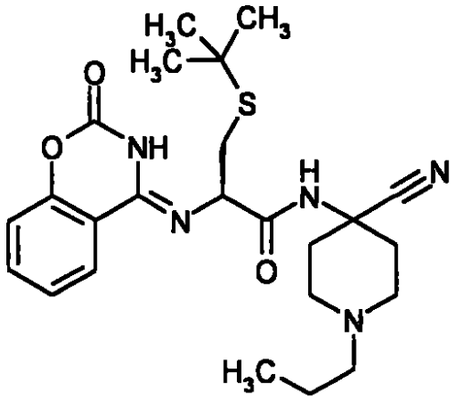


(4-ciano-1-propil-piperidin-4-il)-amida de ácido 5-metil-2-(2-oxo-2,3-dihidro-benzo[e][1,3]oxazin-4-ilidenamino)-hexanoico; MS: 440 (M+1)

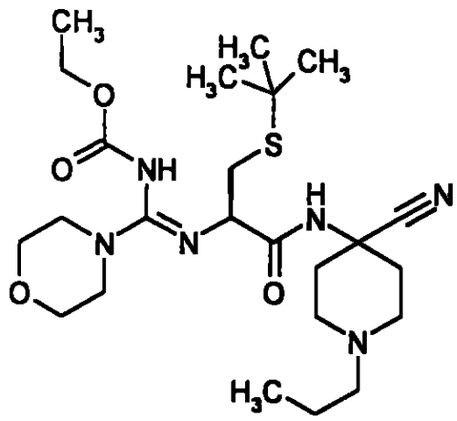
497
492



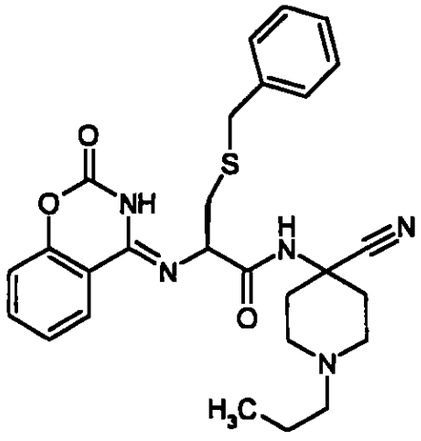
(4-ciano-1-propil-piperidin-4-il)-amida de ácido 4,4-dimetil-2-(1-metil-2-oxo-1,2-dihidro-quinazolin-4-ilamino)-pentanoico; MS: 453 (M+1)



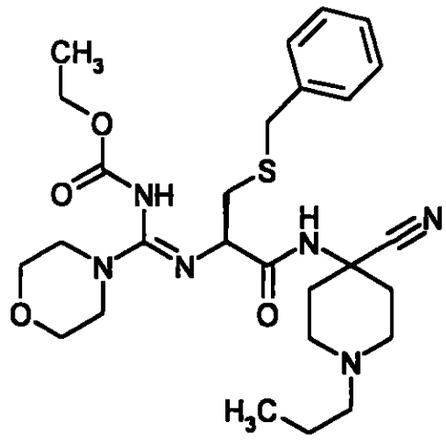
3-terc.-butilsulfanil-N-(4-ciano-1-propil-piperidin-4-il)-2-(2-oxo-2,3-dihidro-benzo[e][1,3]oxazin-4-ilidenamino)-propionamida; MS: 472 (M+1)



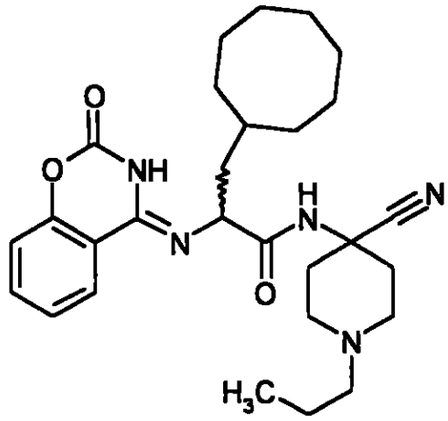
Éster etílico de ácido {[2-terc.-butilsulfanil-1-(4-ciano-1-propil-piperidin-4-ilcarbamoil)-etilimino]-morfolin-4-il-metil}-carbámico; MS: 511 (M+1)



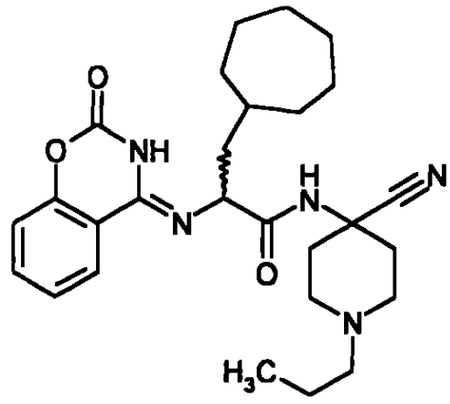
3-bencilsulfanil-N-(4-ciano-1-propil-piperidin-4-il)-2-(2-oxo-2,3-dihidro-benzo[e][1,3]oxazin-4-ilidenamino)-propionamida; MS: 506 (M+1)



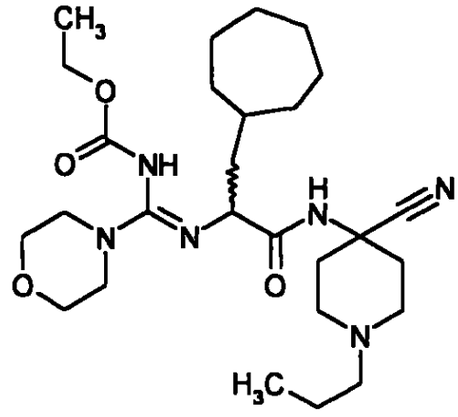
Éster etílico de ácido ({2-bencilsulfanil-1-(4-ciano-1-propil-piperidin-4-ilcarbamoil)-etilimino]-morfolin-4-il-metil}-carbámico; MS: 545 (M+1)



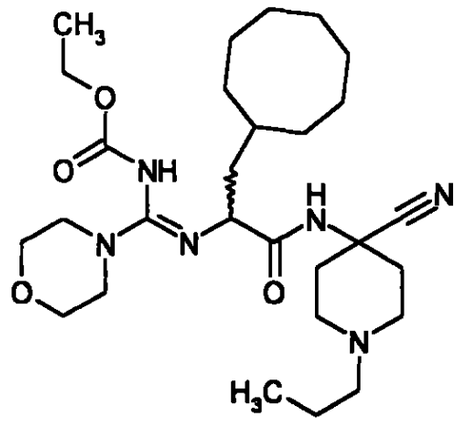
N-(4-ciano-1-propil-piperidin-4-il)-3-ciclooctil-(2-oxo-2,3-dihidro-benzo[e][1,3]oxazin-4-ilidenamino)-propionamida; MS: 494 (M+1)



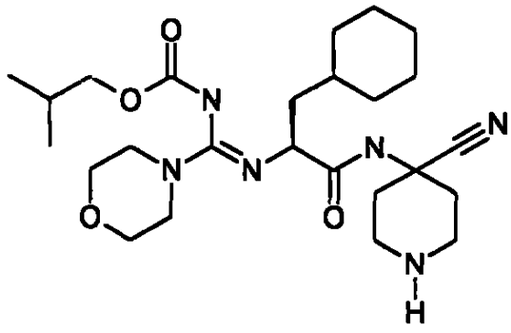
N-(4-ciano-1-propil-piperidin-4-il)-3-cicloheptil-2-(2-oxo-2,3-dihidro-benzo[e][1,3]oxazin-4-ilidenamino)-propionamida; MS: 480 (M+1)



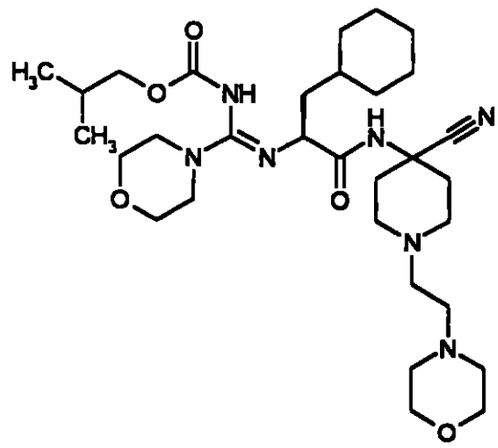
Éster etílico de ácido {[1-(4-ciano-1-propil-piperidin-4-il-carbamoil)-2-cicloheptil-etiliminc]-morfolin-4-il-metil}-carbámico; MS: 519 (M+1)



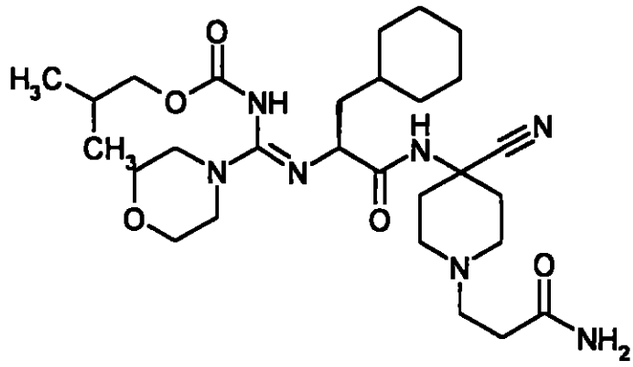
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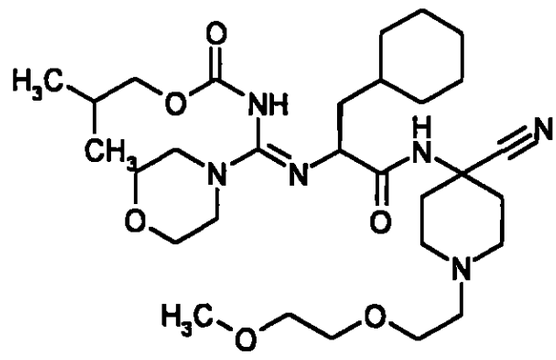
Éster isobutílico de ácido {[1-(4-ciano-piperidin-4-ilcarbamoil)-2-ciclohexil-etilamino]-morfolin-4-il-metileno}-carbámico; MS: 491 (M+1)



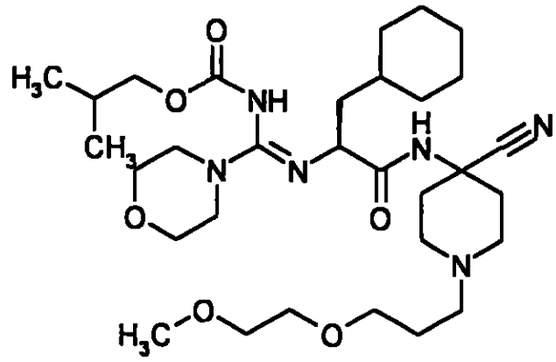
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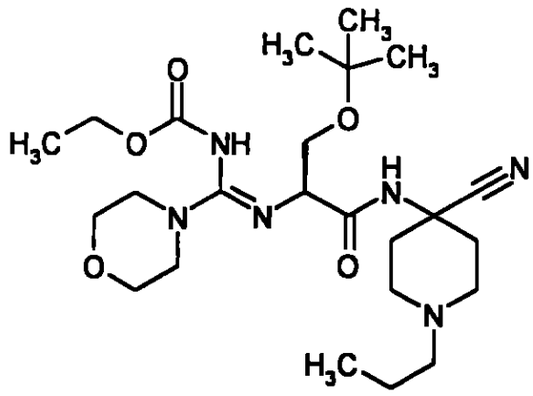
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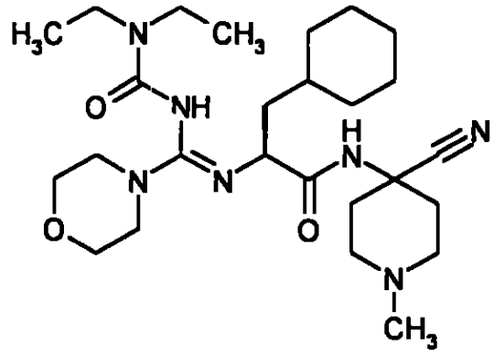
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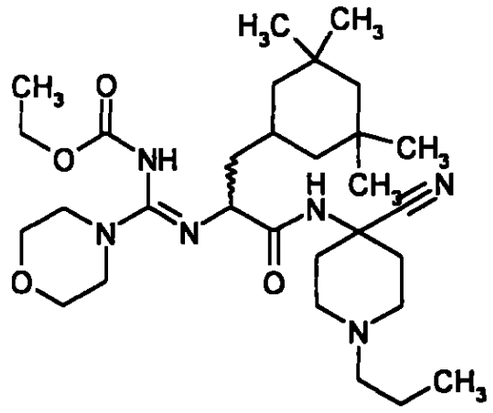
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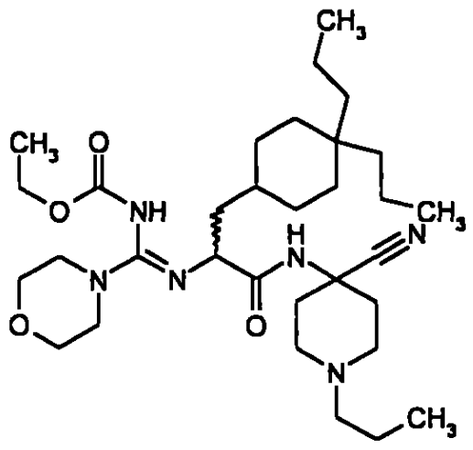
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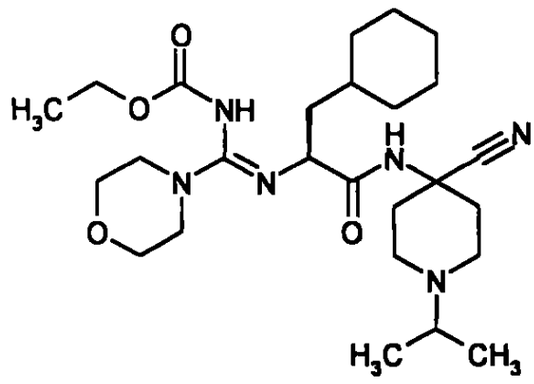
N-(4-ciano-1-metil-piperidin-4-il.-3-ciclohexil-2-{[dietil-carbamoilimino)-morfolin-4-il-metil]-amino}-propionamida; MS: 504 (M+1)



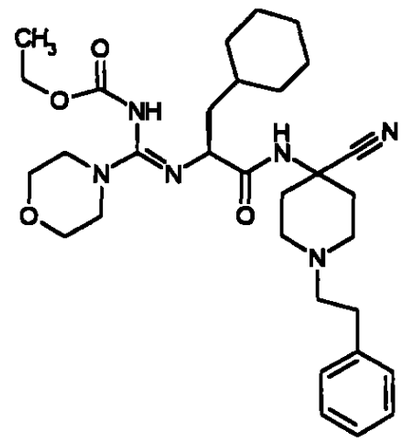
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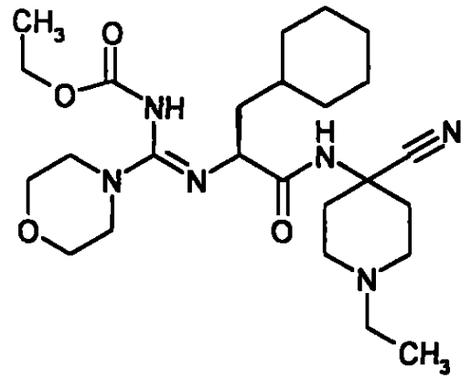
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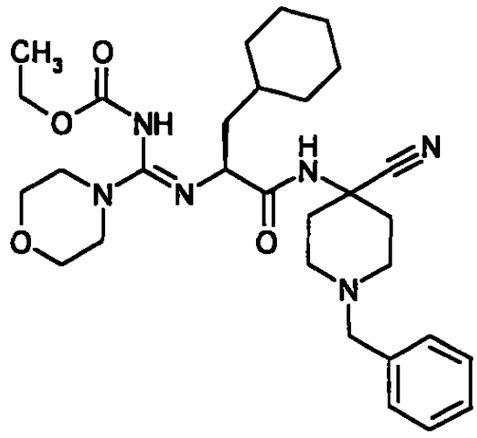
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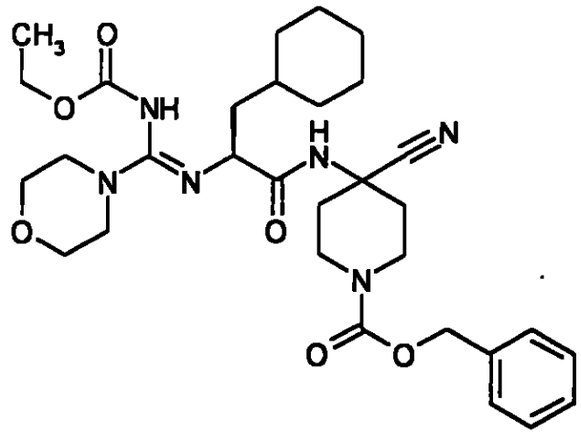
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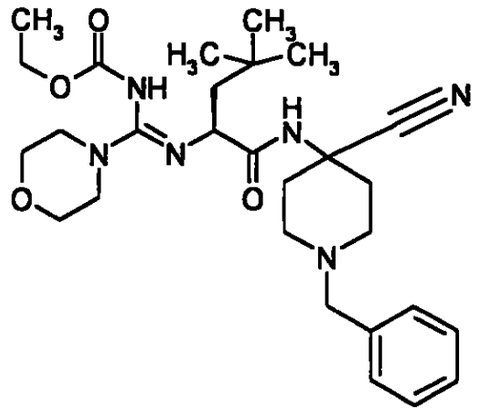
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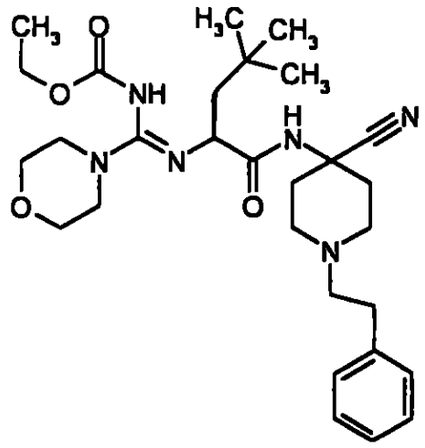
Éster etílico de ácido {[1-(1-bencil-4-ciano-piperidin-4-il-carbamoil)-2-ciclohexil-etilamino]-morfolin-4-il-metileno}-carbámico; MS: 553 (M+1)



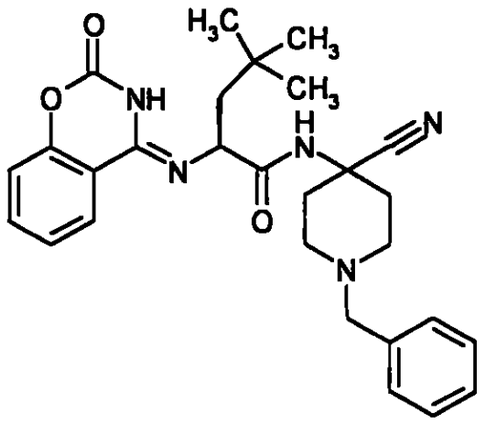
Éster bencílico de ácido 4-ciano-4-{3-ciclohexil-2-[(etoxi-carbonilimino-morfolin-4-il-metil)-amino]-propionilamino}-piperidina-1-carboxílico; MS: 597 (M+1)



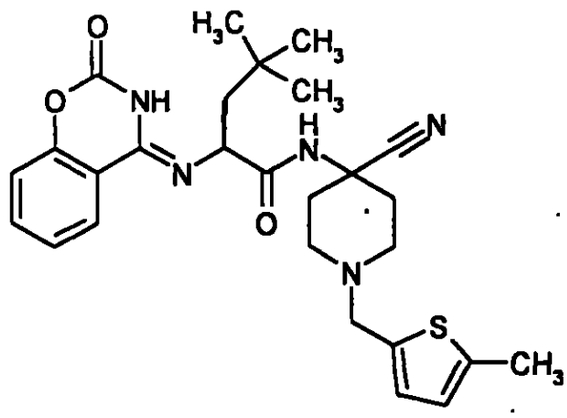
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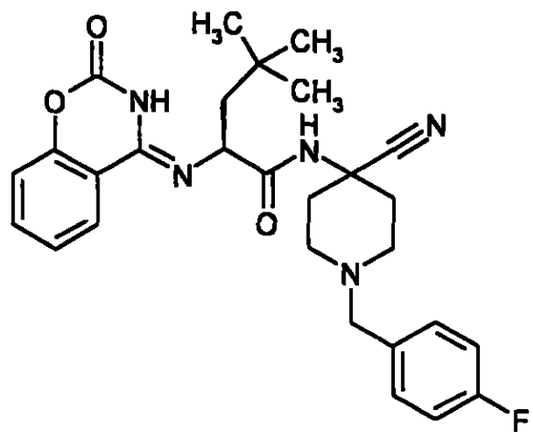
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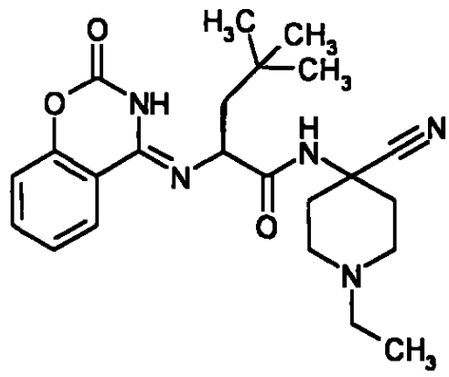
(1-bencil-4-ciano-piperidin-4-il)-amida de ácido 4,4-dimetil-2-(2-oxo-2H-benzo[e][1,3]oxazin-4-ilamino)-pentanoico; MS: 488 (M+1)



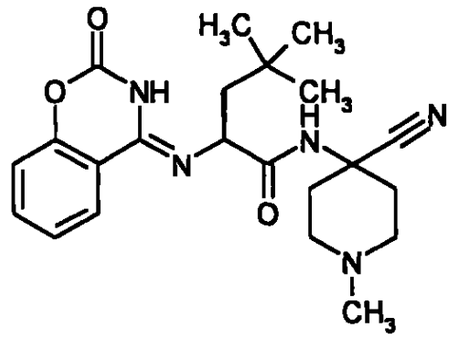
[4-ciano-1-(5-metil-tiofen-2-ilmetil)-piperidin-4-il]-amida de ácido 4,4-dimetil-2-(2-oxo-2H-benzo[e][1,3]oxazin-4-ilamino)-pentanoico; MS: 508 (M+1)



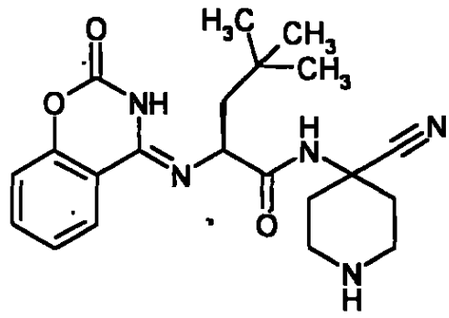
[4-ciano-1-(4-fluoro-bencil)-piperidin-4-il]-amida de ácido 4,4-dimetil-2-(2-oxo-2H-benzo[e][1,3]oxazin-4-ilamino)-pentanoico; MS: 506 (M+1)



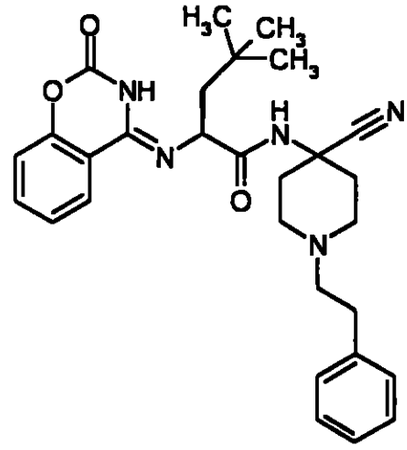
(4-ciano-1-etil-piperidin-4-il)-amida de ácido 4,4-dimetil-2-(2-oxo-2H-benzo[e][1,3]oxazin-4-ilamino)-pentanoico; MS: 426 (M+1)



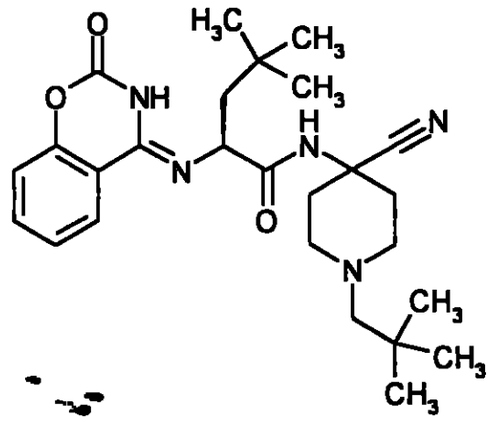
(4-ciano-1-metil-piperidin-4-il)-amida de ácido 4,4-dimetil-2-(2-oxo-2H-benzo[e][1,3]oxazin-4-ilamino)-pentanoico; MS: 412 (M+1)



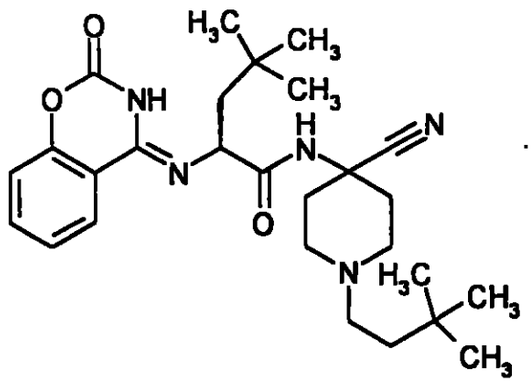
(4-ciano-piperidin-4-il)-amida de ácido 4,4-dimetil-2-(2-oxo-2H-benzo[e][1,3]oxazin-4-ilamino)-pentanoico; MS: 398 (M+1)



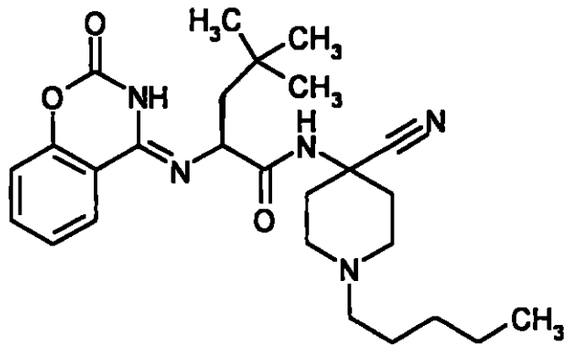
(4-ciano-1-fenetil-piperidin-4-il)-amida de ácido 4,4-dimetil-2-(2-oxo-2H-benzo[e][1,3]oxazin-4-ilamino)-pentanoico; MS: 502 (M+1)



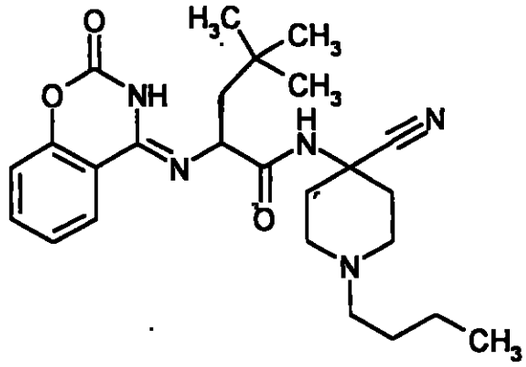
[4-ciano-1-(2,2-dimetil-propil)-piperidin-4-il]-amida de ácido 4,4-dimetil-2-(2-oxo-2H-benzo[e][1,3]oxazin-4-ilamino)pentanoico; MS: 468 (M+1)



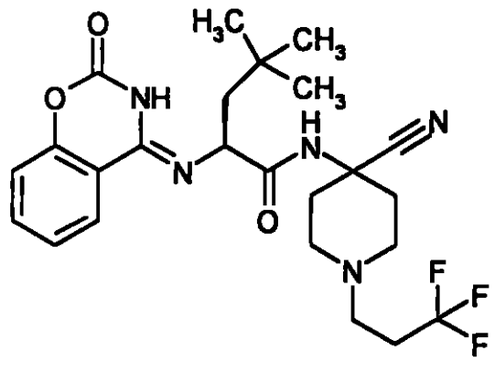
[4-ciano-1-(3,3-dimetil-butil)-piperidin-4-il]-amida de ácido 4,4-dimetil-2-(2-oxo-2H-benzo[e][1,3]oxazin-4-ilamino)-pentanoico; MS: 482 (M+1)



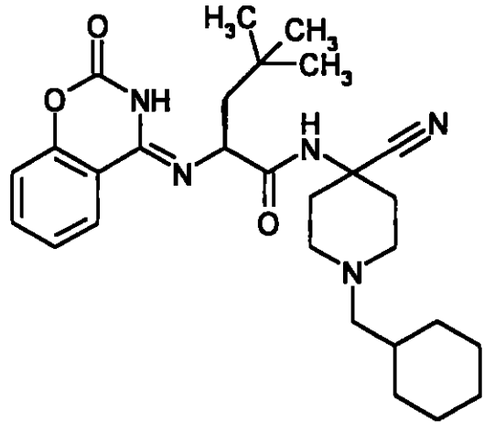
(4-ciano-1-pentil-piperidin-4-il)-amida de ácido 4,4-dimetil-2-(2-oxo-2H-benzo[e][1,3]oxazin-4-ilamino)-pentanoico; MS: 468 (M+1)



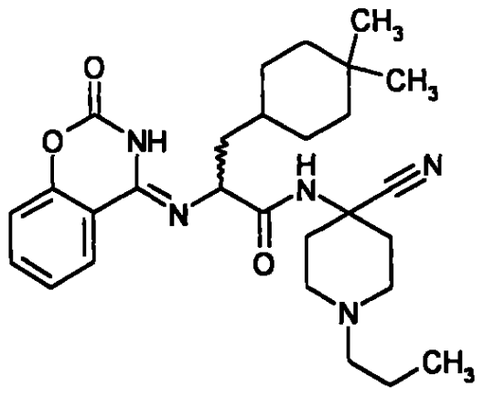
1-butil-4-ciano-piperidin-4-il)-amida de ácido 4,4-dimetil-2-(2-oxo-2H-benzo[e][1,3]oxazin-4-ilamino)-pentanoico; MS: 454 (M+1)



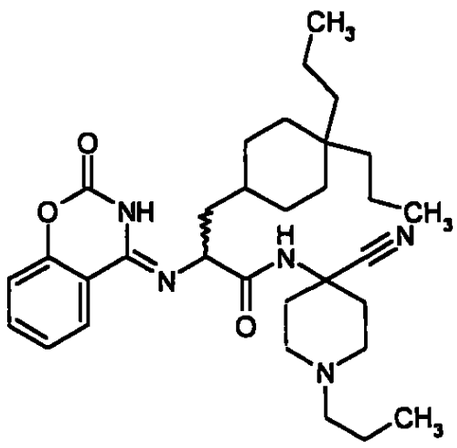
[4-ciano-1-(3,3,3-trifluoro-propil)-piperidin-4-il]-amida de ácido 4,4-dimetil-2-(2-oxo-2H-benzo[e][1,3]oxazin-4-ilamino)-pentanoico; MS: 494 (M+1)



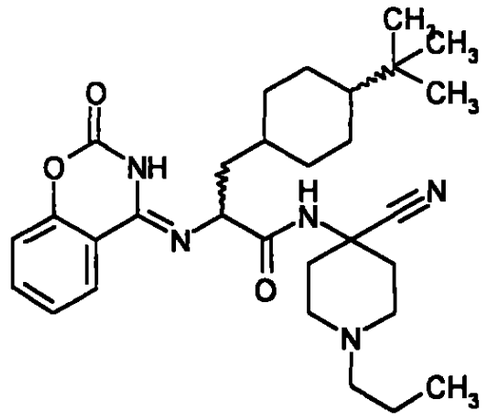
(4-ciano-1-ciclohexilmetil-piperidin-4-il)-amida de ácido 4,4-dimetil-2-(2-oxo-2H-benzo[e][1,3]oxazin-4-ilamino)-pentanoico; MS: 494 (M+1)



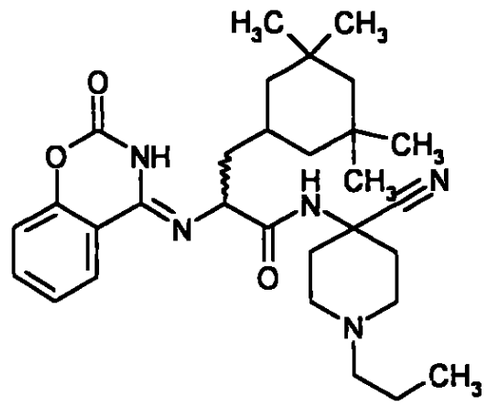
N-(4-ciano-1-propil-piperidin-4-il)-3-(4,4-dimetil-ciclohexil)-2-(2-oxo-2H-benzo[e][1,3]oxazin-4-ilamino)-propionamida; MS: 494 (M+1)



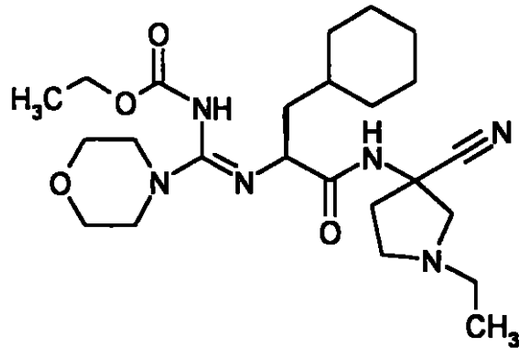
N-(4-ciano-1-propil-piperidin-4-il)-3-(4,4-dipropil-ciclohexil)-2-(2-oxo-2H-benzo[e][1,3]oxazin-4-ilamino)-propionamida; MS: 550 (M+1)



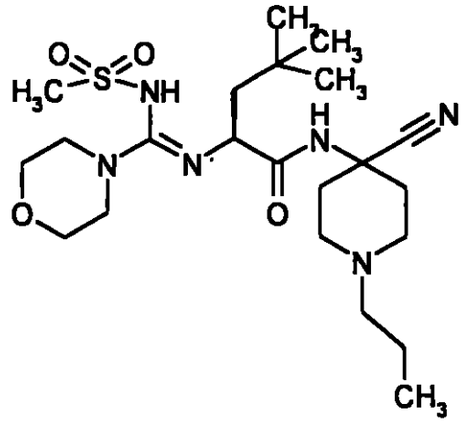
N-(4-ciano-1-propil-piperidin-4-il)-3-(4-terc.-butil-ciclohexil)-2-(2-oxo-2H-benzo[e][1,3]oxazin-4-ilamino)-propionamida; MS: 522 (M+1)



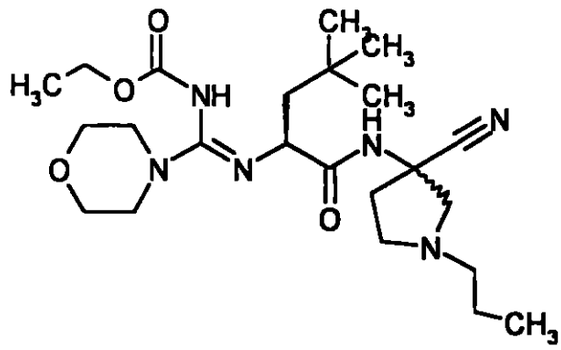
N-(4-ciano-1-propil-piperidin-4-il)-3-(3,3,5,5-tetrametil-ciclohexil)-2-(2-oxo-2H-benzo[e][1,3]oxazin-4-ilamino)-propionamida; MS: 522 (M+1)



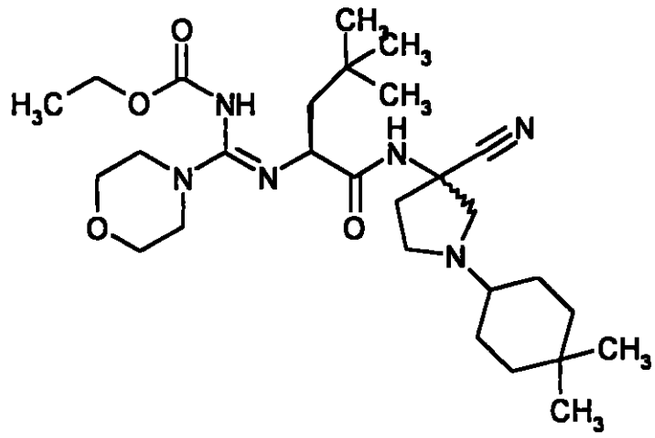
éster etílico de ácido {[1-(3-ciano-1-etil-pirrolidin-3-il-carbamoil)-2-ciclohexil-etilamino]-morfolin-4-il-metileno}-carbámico; MS: 477 (M+1)



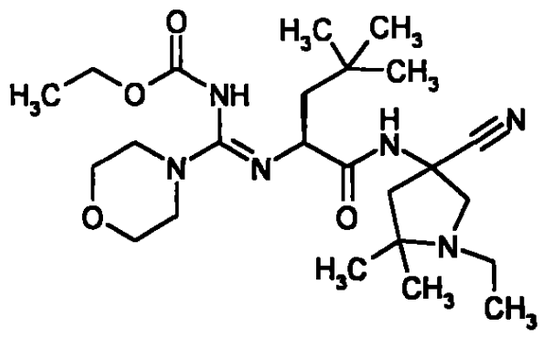
(4-ciano-1-propil-piperidin-4-il)-amida de ácido 2-[(metano-sulfonilimino-morfolin-4-il-metil)-amino]-4,4-dimetil-pentanoico; MS 485 (M+1)



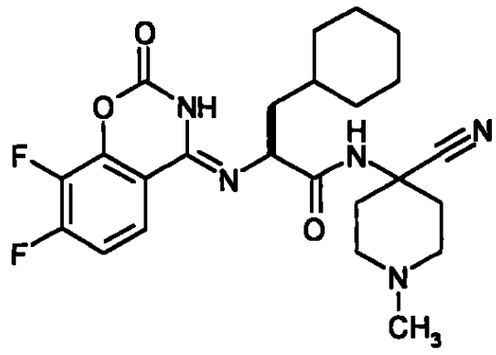
Éster etílico de ácido {[1-(3-ciano-1-propil-pirrolidin-3-ilcarbamoil)-3,3-dimetil-butilamino]-morfolin-4-il-metileno}-carbámico; MS: 465 (M+1)



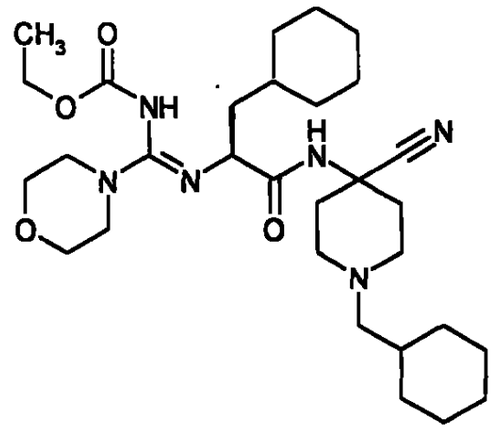
Éster etílico de ácido ({1-[3-ciano-1-(4,4-dimetil-ciclohexil)-pirrolidin-3-ilcarbamoil]-3,3-dimetil-butilamino}-morfolin-4-il-metileno)-carbámico; MS: 533 (M+1)



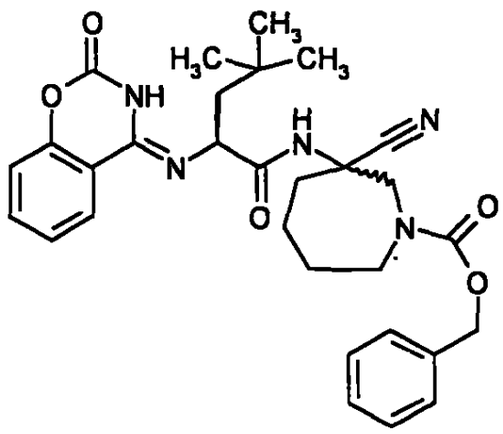
Éster etílico de ácido {[1-(3-ciano-1-etil-5,5-dimetil-pirrolidin-3-ilcarbamoil)-3,3-dimetil-butilamino]-morfolin-4-il-metileno}-carbámico; MS: 479 (M+1)



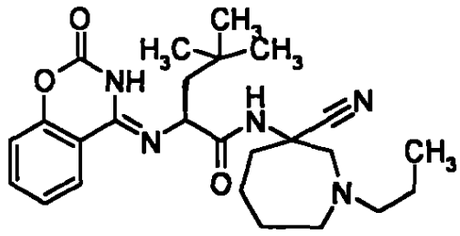
N-(4-ciano-1-metil-piperidin-4-il)-3-ciclohexil-2-(7,8-difluoro-2-oxo-2H-benzo[e][1,3]oxazin-4-ilamino)-propionamida; MS: 474 (M+1)



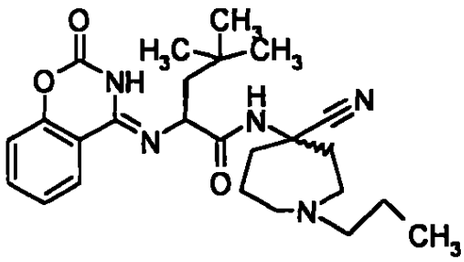
Éster etílico de ácido {[1-(4-ciano-1-ciclohexilmetil-piperidin-4-ilcarbamoil)-2-ciclohexil-etilamino]-morfolin-4-il-metileno}-carbámico; MS: 559 (M+1)



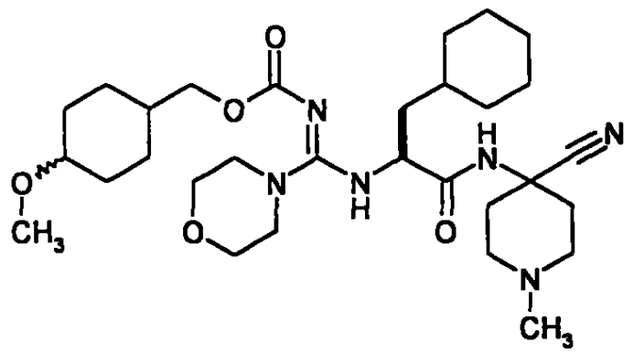
Éster bencílico de ácido 3-ciano-3-[4,4-dimetil-2-(2-oxo-2*H*-benzo[e][1,3]oxazin-4-ilamino)-pentanoilamino]-azepan-1-carboxílico; MS: 546 (M+1)



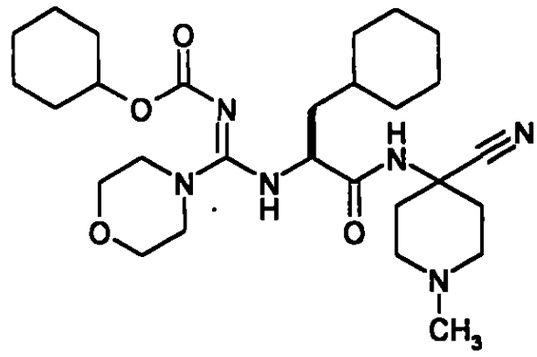
(3-ciano-1-propil-azepan-3-il)-amida de ácido 4,4-dimetil-2-(2-oxo-2*H*-benzo[e][1,3]oxazin-4-ilamino)-pentanoico; MS: 454 (M+1)



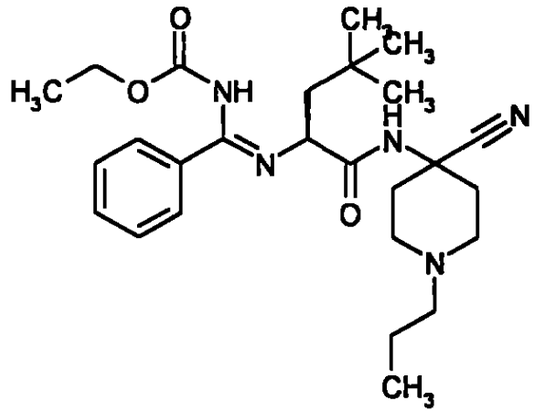
(4-ciano-1-propil-azepan-4-il)-amida de ácido 4,4-dimetil-2-(2-oxo-2*H*-benzo[e][1,3]oxazin-4-ilamino)-pentanoico; MS: 454 (M+1)



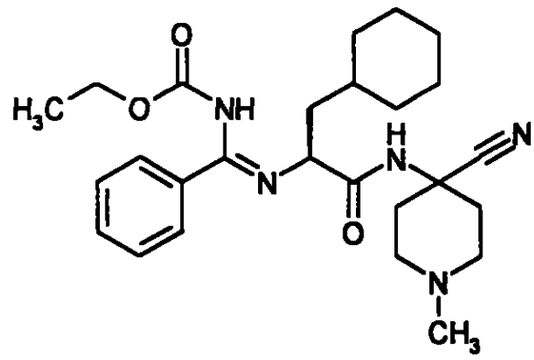
Éster 4-metoxi-ciclohexilmetílico de ácido {[1-(4-ciano-1-metil-piperidin-4-ilcarbamoil)-2-ciclohexil-etilamino]-morfolin-4-il-metileno}-carbámico; MS: 575 (M+1)



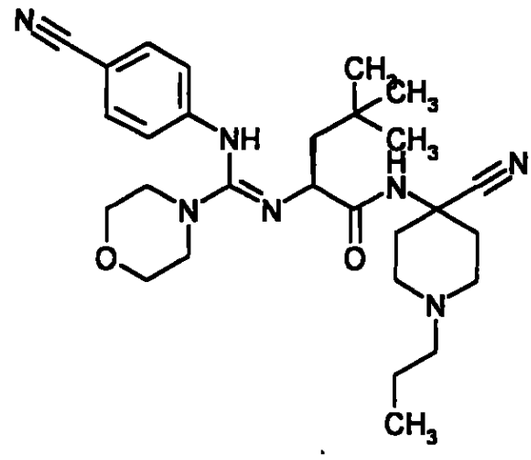
Ester ciclohexilico de ácido {[1-(4-ciano-1-metil-piperidin-4-ilcarbamoil)-2-ciclohexil-etilamino]-morfolin-4-il-metileno}-carbámico; MS: 531 (M+1)



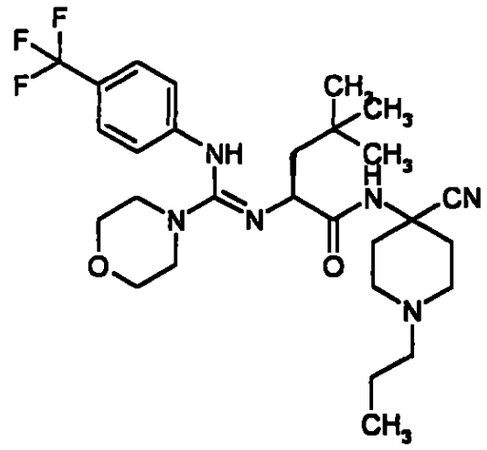
Éster etílico de ácido {[1-(4-ciano-1-propil-piperidin-4-ilcarbamoil)-3,3-dimetil-butilamino]-fenil-metileno}-carbámico; MS: 470 (M+1)



Éster etílico de ácido {[1-(4-ciano-1-metil-piperidin-4-ilcarbamoil)-2-ciclohexil-etilamino]-fenil-metileno}-carbámico; MS: 468 (M+1)

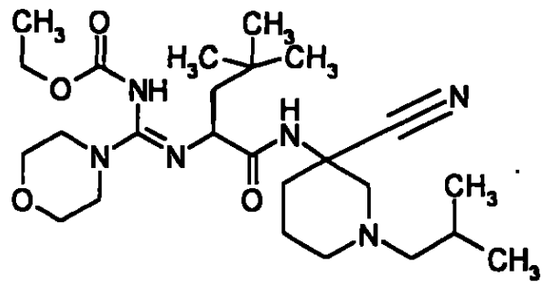


(4-ciano-1-propil-piperidin-4-il)-amida de ácido 2-{[N-(4-ciano-fenil)-morfolina-4-carboximidoil]-amino}-4,4-dimetil-pentanoico; MS: 508 (M+1)

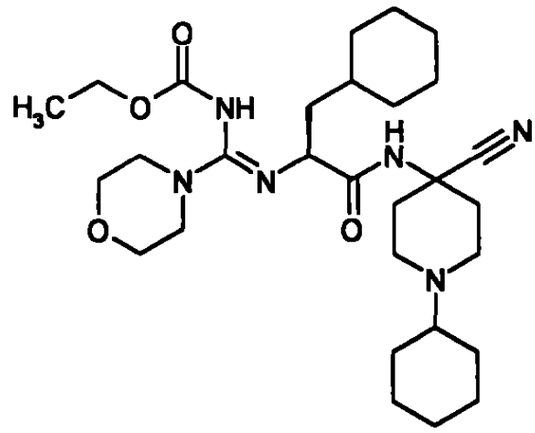


(4-ciano-1-propil-piperidin-4-il)-amida de ácido 4,4-dimetil-2-{[N-(4-trifluorometil-fenil)-morfolina-4-carboximidoil]-amino}-pentanoico; MS: 551 (M+1)

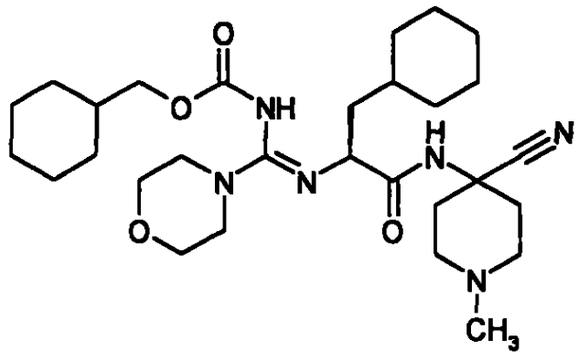
Los siguientes son compuestos preferidos de las fórmulas (Ia) y (Ib):



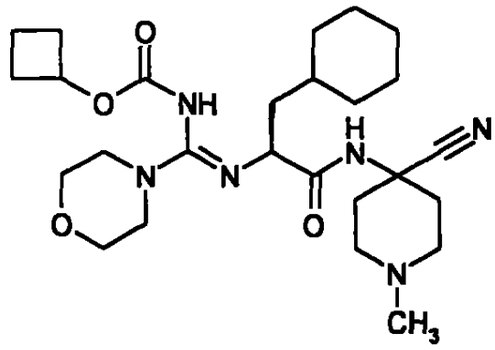
Éster etílico de ácido {[1-(3-ciano-1-isobutil-piperidin-3-il-carbamoil)-3,3-dimetil-butilamino]-morfolin-4-il-metileno}-carbámico; MS: 493 (M+1)



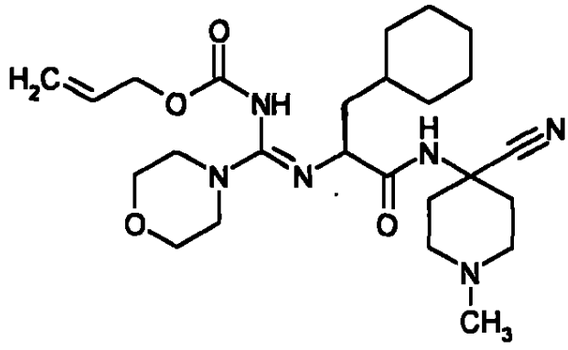
Éster etílico de ácido {[1-(4-ciano-1-ciclohexil-piperidin-4-ilcarbamoil)-2-ciclohexil-etilamino]-morfolin-4-il-metileno}-carbámico; MS: 545 (M+1)



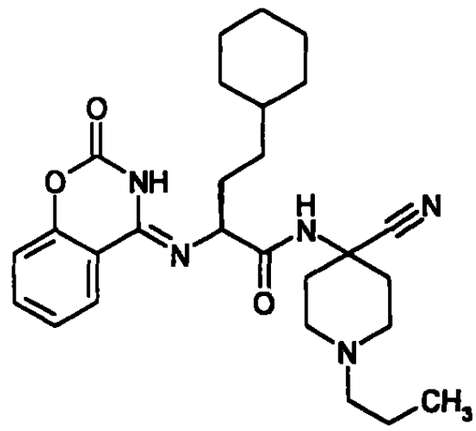
Éster ciclohexilmetílico de ácido {[1-(4-ciano-1-metil-piperidin-4-ilcarbamoil)-2-ciclohexil-etilamino]-morfolin-4-il-metileno}-carbámico; MS: 545 (M+1)



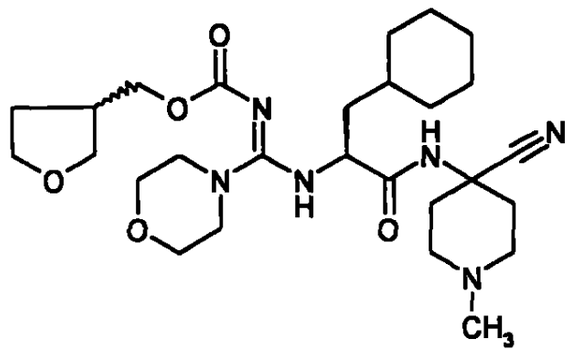
Éster ciclobutílico de ácido {[1-(4-ciano-1-metil-piperidin-4-ilcarbamoil)-2-ciclohexil-etilamino]-morfolin-4-il-metileno}-carbámico; MS: 503 (M+1)



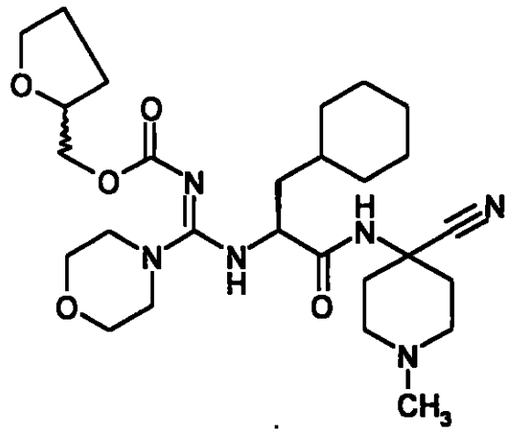
Éster alílico de ácido {[1-(4-ciano-1-metil-piperidin-4-ilcarbamoil)-2-ciclohexil-etilamino]-morfolin-4-il-metileno}-carbámico; MS: 489 (M+1)



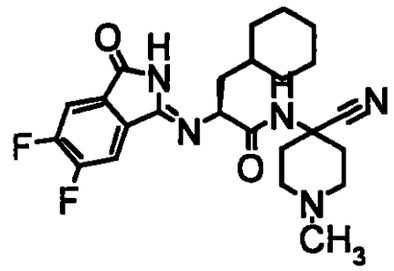
N-(4-ciano-1-propil-piperidin-4-il)-4-ciclohexil-2-(2-oxo-2,3-dihidro-benzo[e][1,3]oxazin-4-ilidenamino)-butiramida; MS: 480 (M+1)



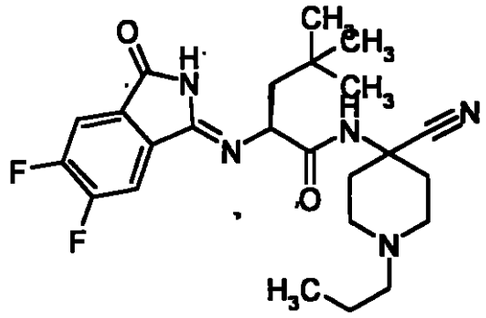
Éster tetrahidro-furan-3-ilmetílico de ácido {[1-(4-ciano-1-metil-piperidin-4-ilcarbamoil)-2-ciclohexil-etilamino]-morfolin-4-il-metileno}-carbámico; MS: 533 (M+1)



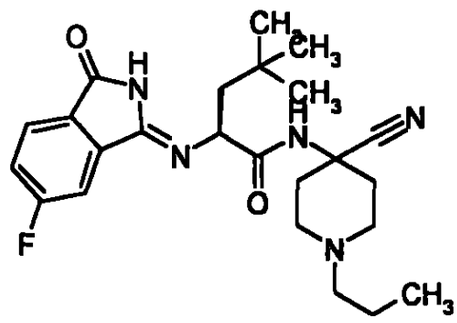
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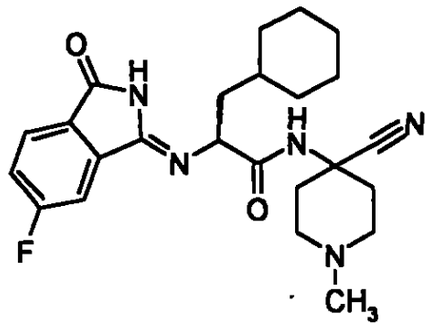
N-(4-ciano-1-metil-piperidin-4-il)-3-ciclohexil-2-(5,6-difluoro-3-oxo-2,3-dihidro-isoindol-1-ilidenamino)-propionamida; MS: 458 (M+1)



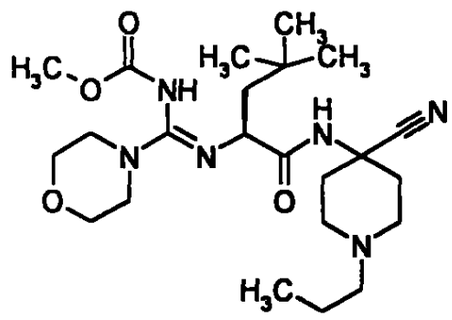
(4-ciano-1-propil-piperidin-4-il)-amida de ácido 2-(5,6-difluoro-3-oxo-2,3-dihidro-isoindol-1-ilidenamino)-4,4-dimetil-pentanoico; MS: 460 (M+1)



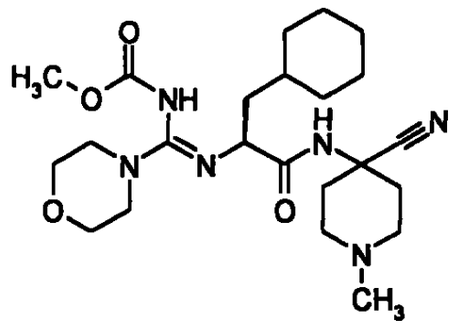
(4-ciano-1-propil-piperidin-4-il)-amida de ácido 2-(6-fluoro-3-oxo-2,3-dihidro-isoindol-1-ilidenamino)-4,4-dimetil-pentanoico; MS: 442 (M+1)



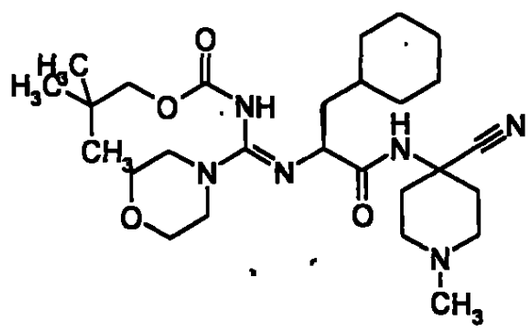
N-(4-ciano-1-metil-piperidin-4-il)-3-ciclohexil-2-(6-fluoro-3-oxo-2,3-dihidro-isoindol-1-ilidenamino)-propionamida; MS: 440 (M+1)



Éster metílico de ácido {[1-(4-ciano-1-propil-piperidin-4-ilcarbamoil)-3,3-dimetil-butilimino]-morfolin-4-il-metil}-carbámico; MS: 465 (M+1)

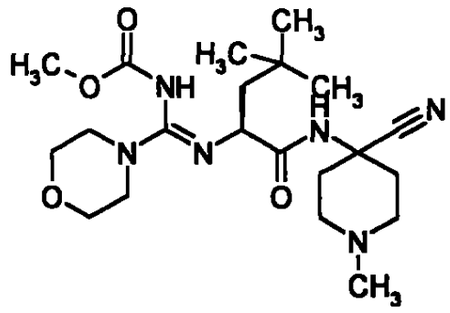


Éster metílico de ácido {[1-(4-ciano-1-metil-piperidin-4-ilcarbamoil)-2-ciclohexil-etilimino]-morfolin-4-il-metil}-carbámico; MS: 463 (M+1)

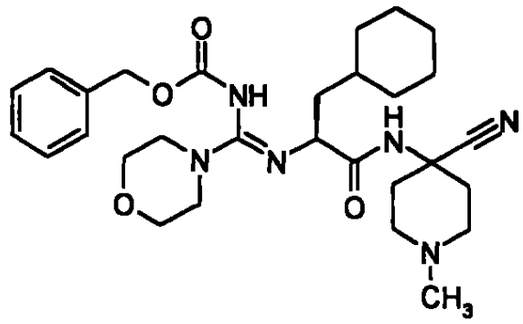


Éster 2,2-dimetil-propílico de ácido {[1-(4-ciano-1-metil-

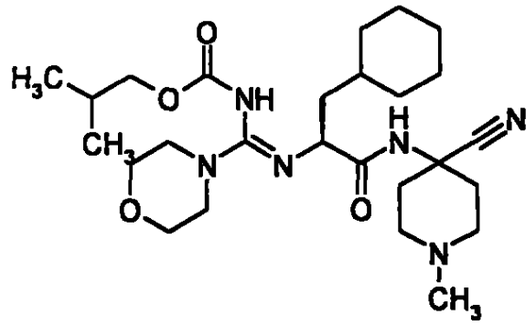
piperidin-4-ilcarbamoil)-2-ciclohexil-etilimino]-morfolin-4-il-metil}-carbámico; MS: 519 (M+1)



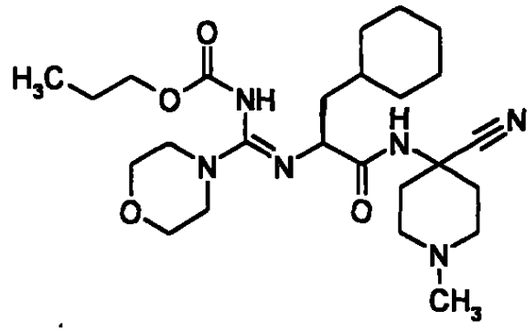
Éster metílico de ácido {[1-(4-ciano-1-metil-piperidin-4-ilcarbamoil)-3,3-dimetil-butilimino]-morfolin-4-il-metil}-carbámico; MS: 437 (M+1)



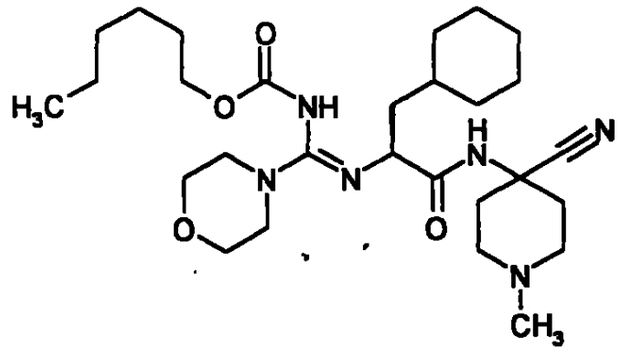
Éster bencílico de ácido {[1-(4-ciano-1-metil-piperidin-4-ilcarbamoil)-2-ciclohexil-etilimino]-morfolin-4-il-metil}-carbámico; MS: 539 (M+1)



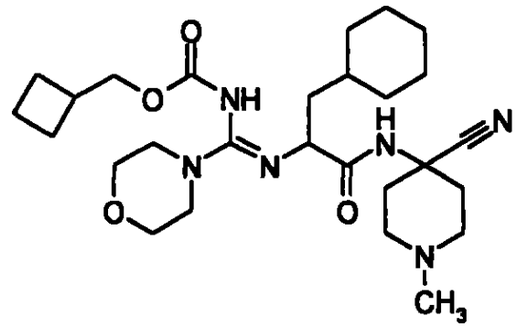
Éster isobutílico de ácido {[1-(4-ciano-1-metil-piperidin-4-ilcarbamoil)-2-ciclohexil-etilimino]-morfolin-4-il-metil}-carbámico; MS: 505 (M+1)



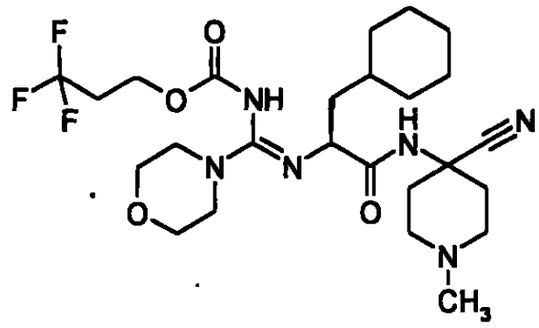
Éster propílico de ácido {[1-(4-ciano-1-metil-piperidin-4-ilcarbamoil)-2-ciclohexil-etilimino]-morfolin-4-il-metil}-carbámico; MS: 491 (M+1)



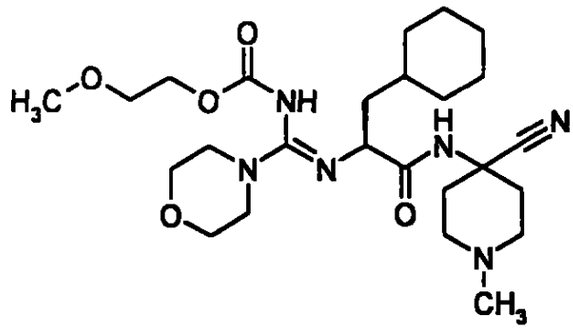
Éster hexílico de ácido {[1-(4-ciano-1-metil-piperidin-4-ilcarbamoil)-2-ciclohexil-etilimino]-morfolin-4-il-metil}-carbámico; MS: 533 (M+1)



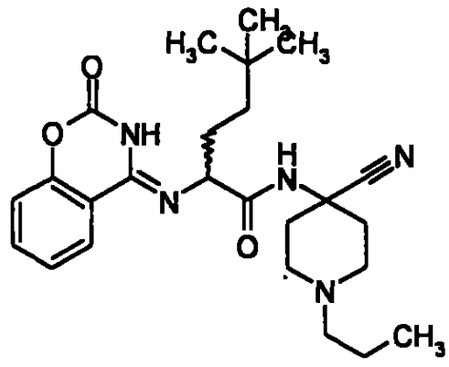
Éster ciclobutilmetílico de ácido {[1-(4-ciano-1-metil-piperidin-4-ilcarbamoil)-2-ciclohexil-etilimino]-morfolin-4-il-metil}-carbámico; MS: 517 (M+1)



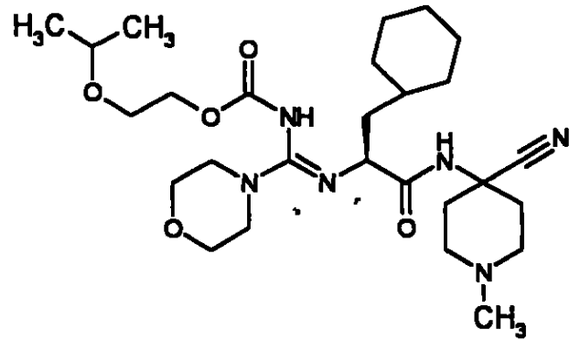
Éster 3,3,3-trifluoro-propílico de ácido {[1-(4-ciano-1-metil-piperidin-4-ilcarbamoil)-2-ciclohexil-etilimino]-morfolin-4-il-metil}-carbámico; MS: 545 (M+1)



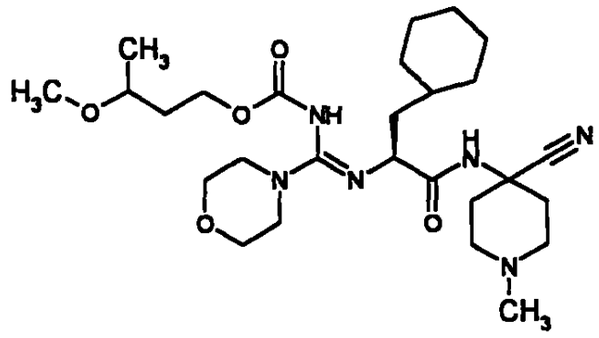
Éster 2-metoxi-etílico de ácido {[1-(4-ciano-1-metil-piperidin-4-ilcarbamoil)-2-ciclohexil-etilimino]-morfolin-4-il-metil}-carbámico; MS: 507 (M+1)



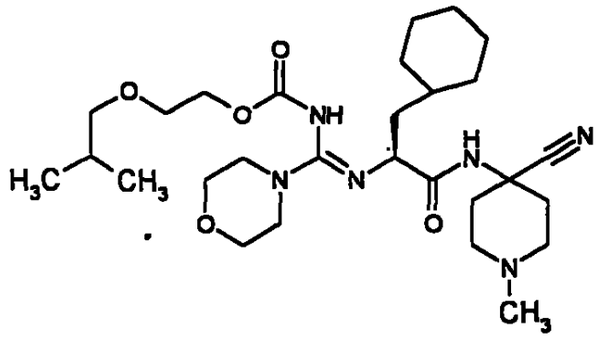
(4-ciano-1-propil-piperidin-4-il)-amida de ácido 5,5-dimetil-2-(2-oxo-2,3-dihidro-benzo[e][1,3]oxazin-4-ilidenamino)-hexanoico; MS: 454 (M+1)



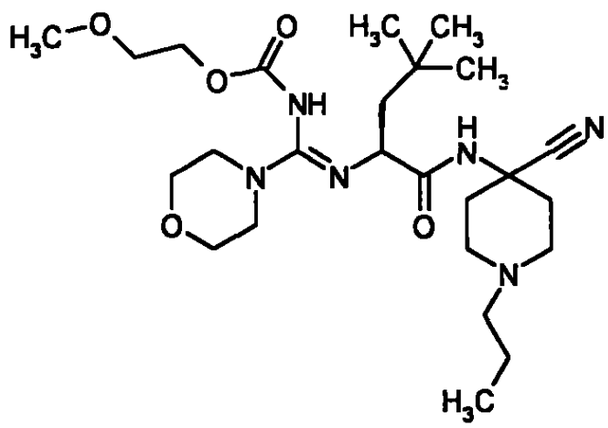
Éster 2-isopropoxi-etílico de ácido {[1-(4-ciano-1-metil-piperidin-4-ilcarbamoil)-2-ciclohexil-etilimino]-morfolin-4-il-metil}-carbámico; MS: 534 (M+1)



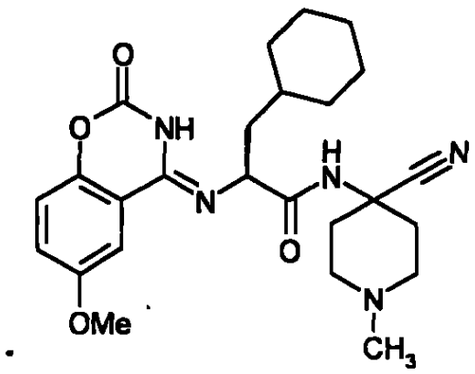
Éster 3-metoxi-butílico de ácido {[1-(4-ciano-1-metil-piperidin-4-ilcarbamoil)-2-ciclohexil-etilimino]-morfolin-4-il-metil}-carbámico; MS: 534 (M+1)



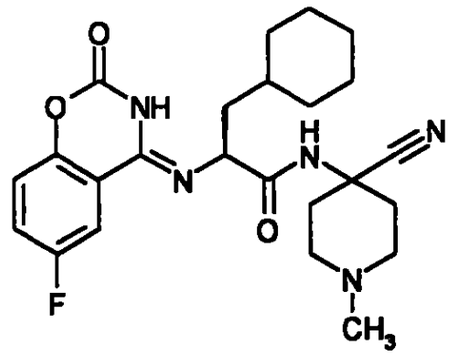
Éster 2-isobutoxi-etílico de ácido {[1-(4-ciano-1-metil-piperidin-4-ilcarbamoil)-2-ciclohexil-etilimino]-morfolin-4-il-metil}-carbámico; MS: 549 (M+1)



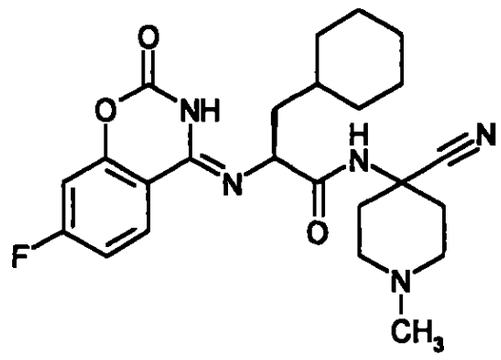
Éster 2-metoxi-etílico de ácido {[1-(4-ciano-1-propil-piperidin-4-ilcarbamoil)-3,3-dimetil-butilimino]-morfolin-4-il-metil}-carbámico; MS: 509 (M+1)



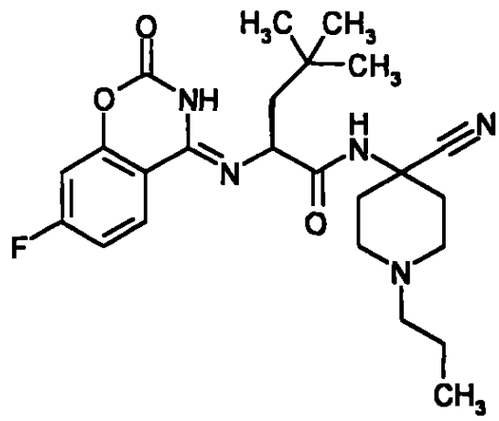
N-(4-ciano-1-metil-piperidin-4-il)-4-ciclohexil-2-(6-metoxi-2-oxo-2,3-dihidro-benzo[e][1,3]oxazin-4-ilidenamino)-butiramida; MS: 468 (M+1)



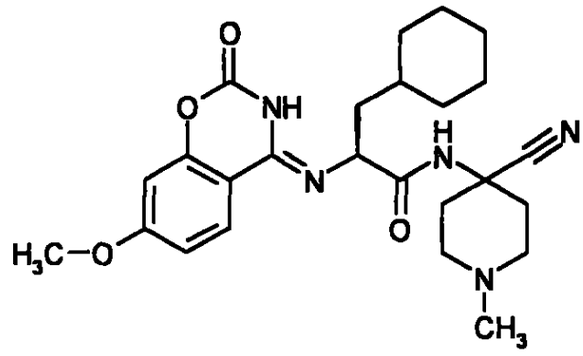
N-(4-ciano-1-metil-piperidin-4-il)-4-ciclohexil-2-(6-fluoro-2-oxo-2,3-dihidro-benzo[e][1,3]oxazin-4-ilidenamino)-butiramida; MS: 456 (M+1)



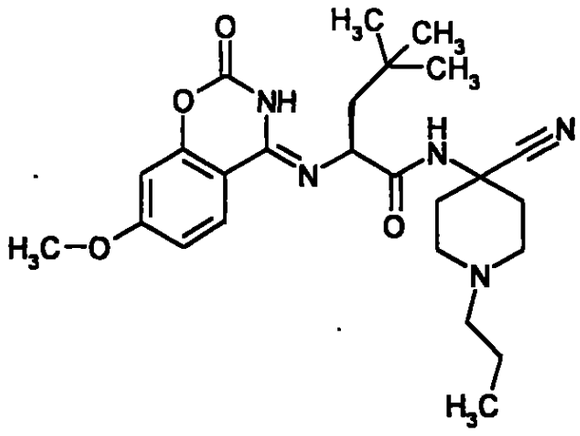
N-(4-ciano-1-metil-piperidin-4-il)-4-ciclohexil-2-(7-fluoro-2-oxo-2,3-dihidro-benzo[e][1,3]oxazin-4-ilidenamino)-butiramida; MS: 456 (M+1)



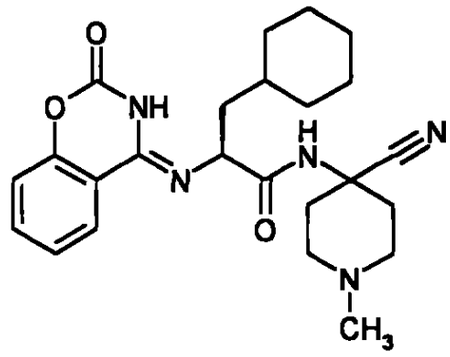
(4-ciano-1-propil-piperidin-4-il)-amida de ácido 2-(7-fluoro-2-oxo-2,3-dihidro-benzo[e][1,3]oxazin-4-ilidenamino)-5,5-dimetil-hexanoico; MS: 458 (M+1)



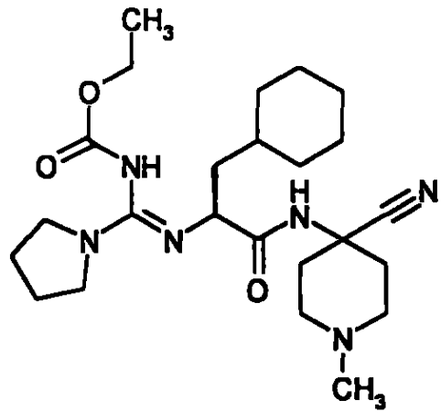
N-(4-ciano-1-metil-piperidin-4-il)-4-ciclohexil-2-(7-metoxi-2-oxo-2,3-dihidro-benzo[e][1,3]oxazin-4-ilidenamino)-butiramida; MS: 468 (M+1)



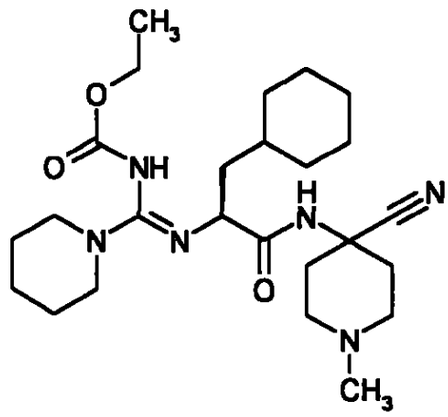
(4-ciano-1-propil-piperidin-4-il)-amida de ácido 2-(7-metoxi-2-oxo-2,3-dihidro-benzo[e][1,3]oxazin-4-ilidenamino)-5,5-dimetil-hexanoico; MS: 470 (M+1)



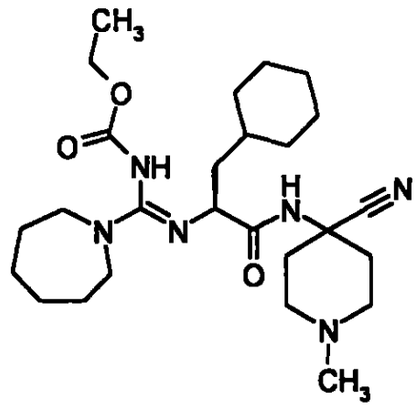
N-(4-ciano-1-metil-piperidin-4-il)-3-ciclohexil-2-(2-oxo-2,3-dihidro-benzo[e][1,3]oxazin-4-ilidenamino)-propionamida; MS: 438 (M+1)



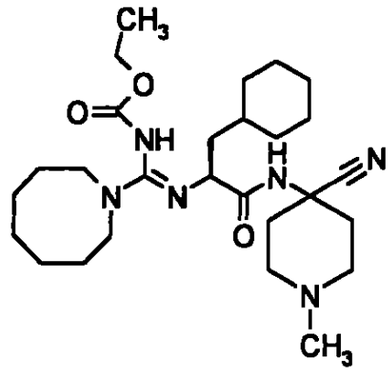
Éster etílico de ácido {[1-(4-ciano-1-metil-piperidin-4-il-carbamoil)-2-ciclohexil-etilimino]-pirrolidin-1-il-metil}-carbámico; MS: 461 (M+1)



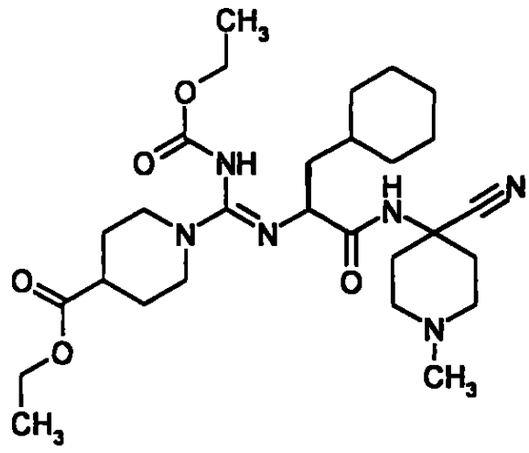
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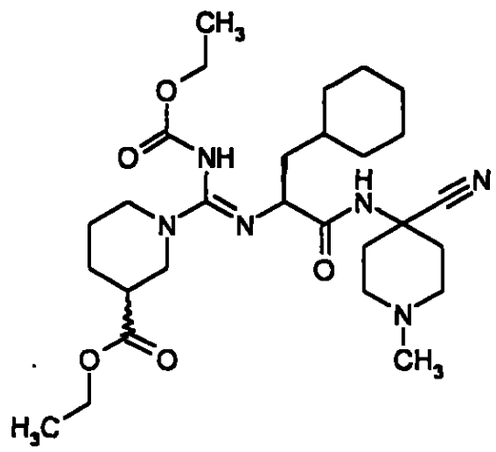
Éster etílico de ácido {azepan-1-il-[1-(4-ciano-1-metil-piperidin-4-ilcarbamoil)-2-ciclohexil-etilimino]-metil}-carbámico; MS: 489 (M+1)



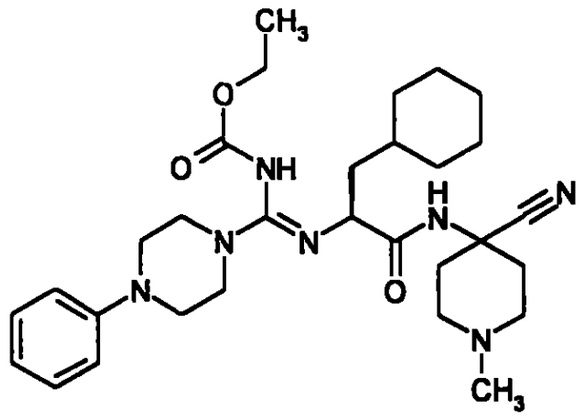
Éster etílico de ácido {azocan-1-il-[1-(4-ciano-1-metil-piperidin-4-ilcarbamoil)-2-ciclohexil-etilimino]-metil}-carbámico; MS: 503 (M+1)



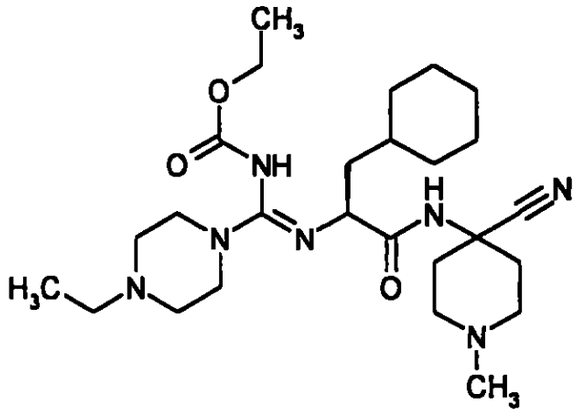
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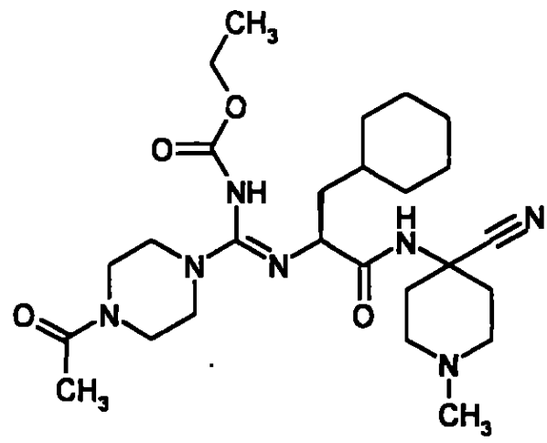
Éster etílico de ácido 1-{[1-(4-ciano-1-metil-piperidin-4-ilcarbamoil)-2-ciclohexil-etilimino]-etoxicarbonilamino-metil}-piperidina-3-carboxílico; MS: 547 (M+1)



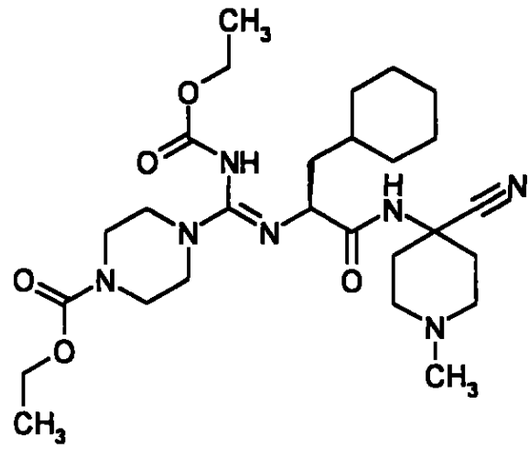
Éster etílico de ácido [[1-(4-ciano-1-metil-piperidin-4-ilcarbamoil)-2-ciclohexil-etilimino]-(4-fenil-piperazin-1-il-metil]-carbámico; MS: 552 (M+1)



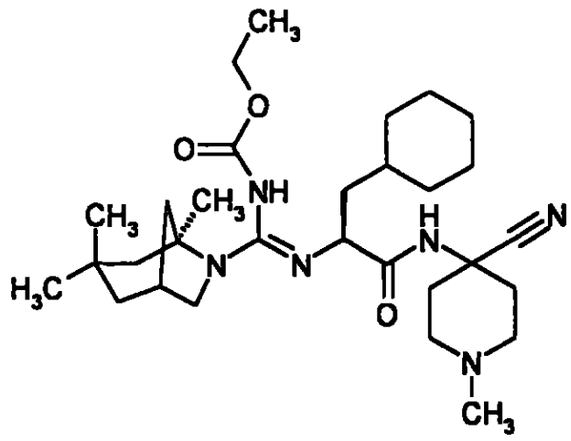
Éster etílico de ácido [[1-(4-ciano-1-metil-piperidin-4-ilcarbamoil)-2-ciclohexil-etilimino]-(4-etil-piperazin-1-il)-metil]-carbámico; MS: 504 (M+1)



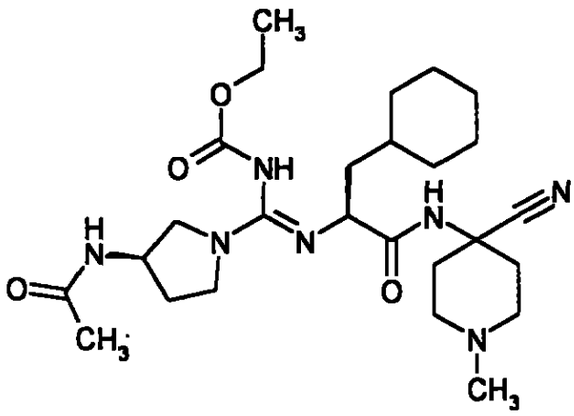
Éster etílico de ácido {(4-acetil-piperazin-1-il)-[1-(4-ciano-1-metil-piperidin-4-ilcarbamoil)-2-ciclohexil-etilimino]-metil}-carbámico; MS: 518 (M+1)



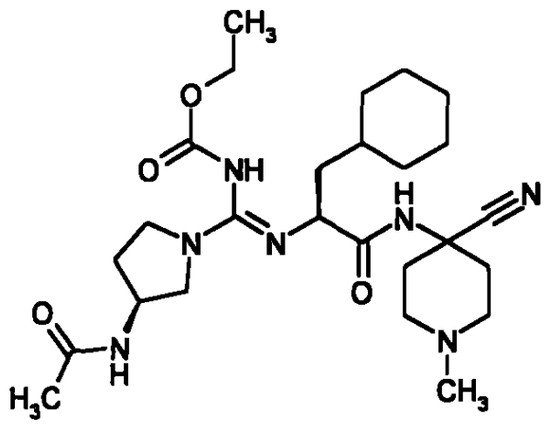
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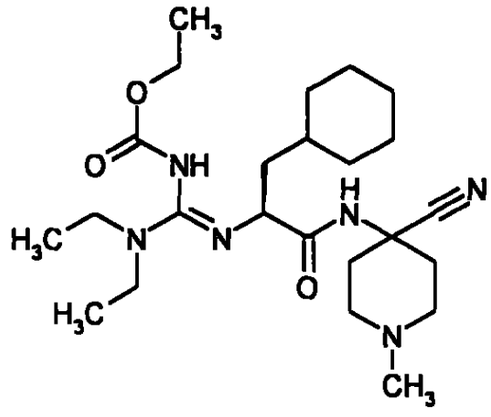
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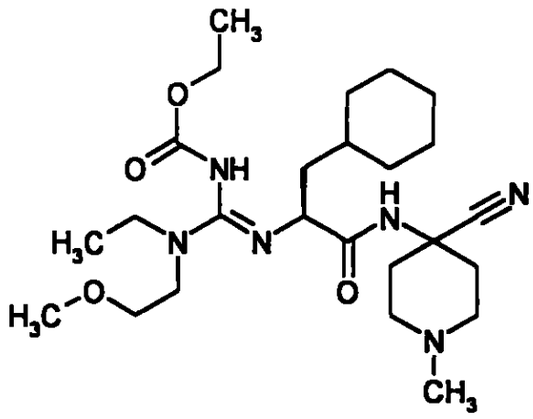
Éster etílico de ácido {(3-acetilamino-pirrolidin-1-il)-[1-(4-ciano-1-metil-piperidin-4-ilcarbamoil)-2-ciclohexil-etilimino]-metil}-carbámico; MS: 518 (M+1)



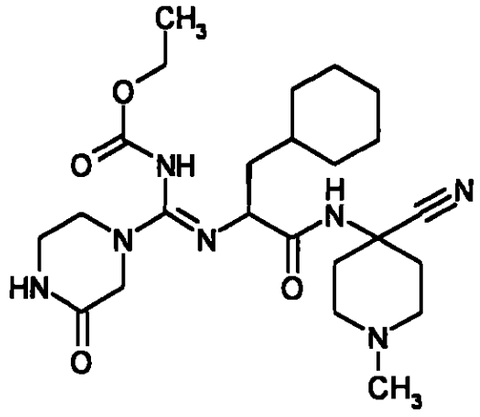
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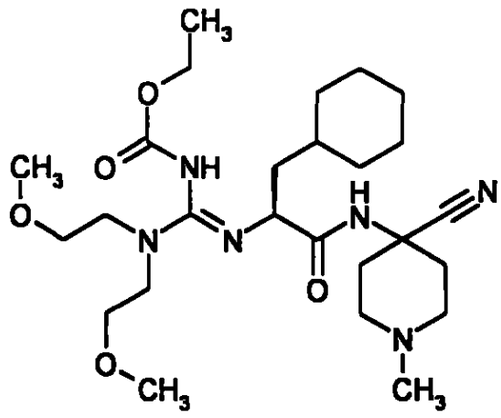
Éster etílico de ácido {(3-azapent-3-il)-[1-(4-ciano-1-metil-piperidin-4-ilcarbamoil)-2-ciclohexil-etilimino]-metil}-carbámico; MS: 463 (M+1)



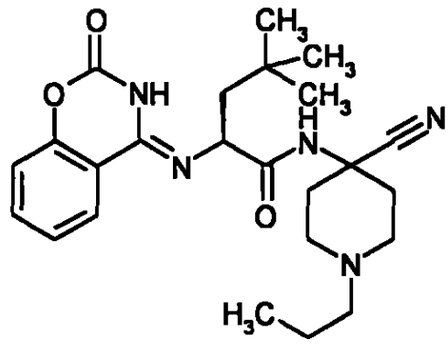
Éster etílico de ácido {(1-metoxi-3-azapent-3-il)-[1-(4-ciano-1-metil-piperidin-4-ilcarbamoil)-2-ciclohexil-etilimino]-metil}-carbámico; MS: 493 (M+1)



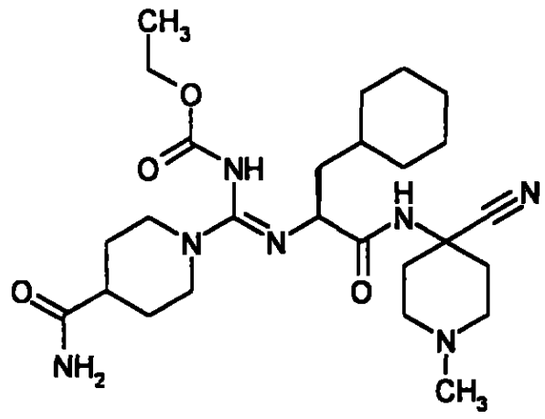
Éster etílico de ácido {[1-(4-ciano-1-metil-piperidin-4-il-carbamoil)-2-ciclohexil-etilimino]-(3-oxo-piperazin-1-il)-metil}-carbámico; MS: 490 (M+1)



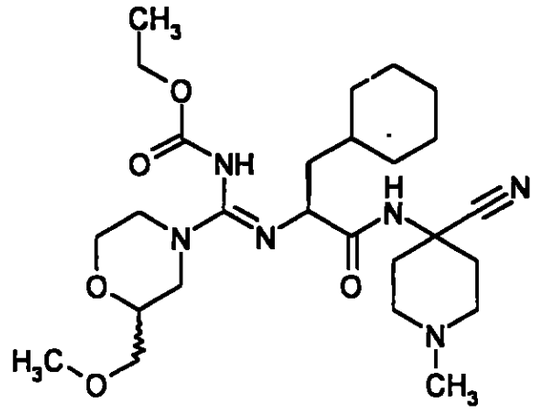
Éster etílico de ácido {(1,5-dimetoxi-3-azapent-3-il)-[1-(4-ciano-1-metil-piperidin-4-ilcarbamoil)-2-ciclohexil-etilimino]-metil}-carbámico; MS: 523 (M+1)



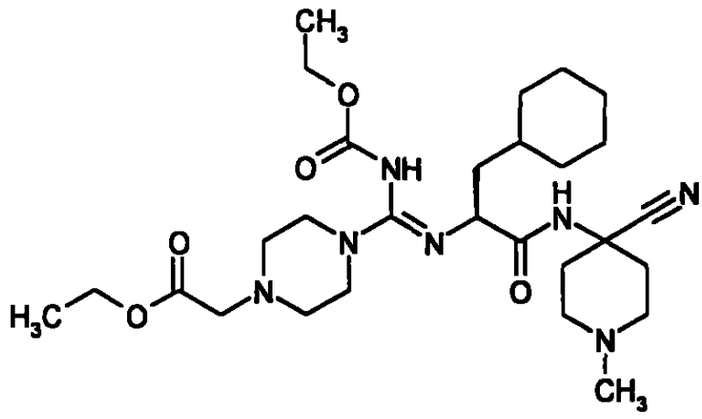
(4-ciano-1-propil-piperidin-4-il)-amida de ácido 4,4-dimetil-2-(2-oxo-2,3-dihidro-benzo[e][1,3]oxazin-4-ilidenamino)-pentanoico; MS: 440 (M+1)



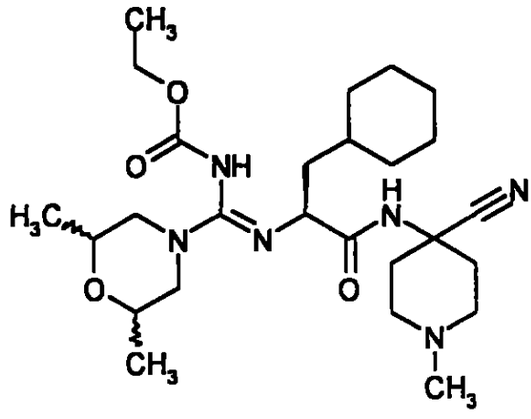
Éster etilico de ácido {(4-carbamoil-piperidin-1-il)-[1-(4-ciano-1-metil-piperidin-4-ilcarbamoil)-2-ciclohexil-etilimino]-metil}-carbámico; MS: 518 (M+1)



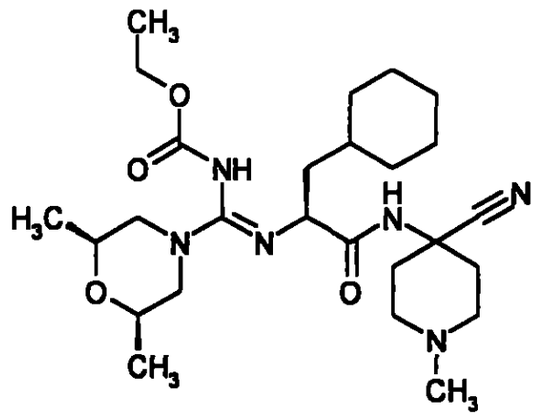
Éster etilico de ácido [[1-(4-ciano-1-metil-piperidin-4-il-carbamoil)-2-ciclohexil-etilimino]-(2-metoximetil-morfolin-4-il)-metil]-carbámico; MS: 521 (M+1)



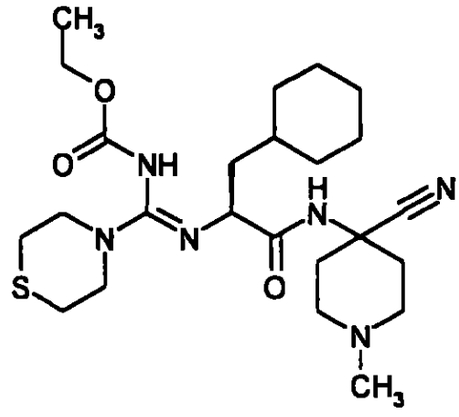
Éster etílico de ácido (4-{[1-(4-ciano-1-metil-piperidin-4-ilcarbamoil)-2-ciclohexil-etilimino]-etoxicarbonilamino-metil}-piperazin-1-il)-metil]-acético; MS: 562 (M+1)



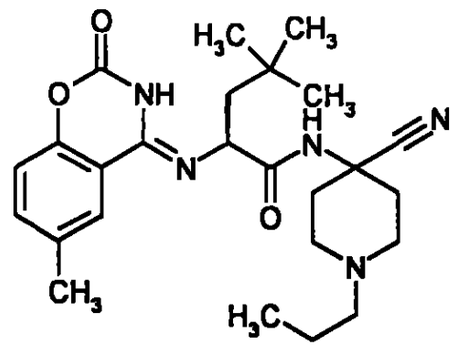
Éster etílico de ácido [[1-(4-ciano-1-metil-piperidin-4-il-carbamoil)-2-ciclohexil-etilimino]-(2,6-dimetil-morfolin-4-il)-metil]-carbámico; MS: 505 (M+1)



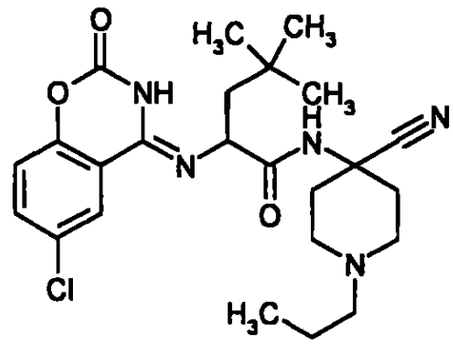
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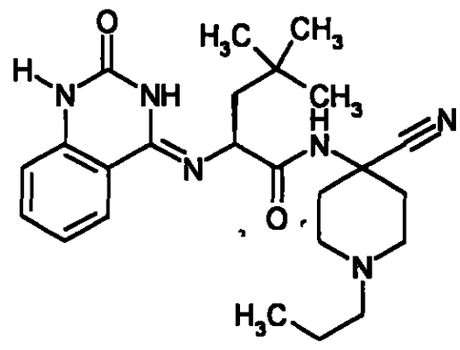
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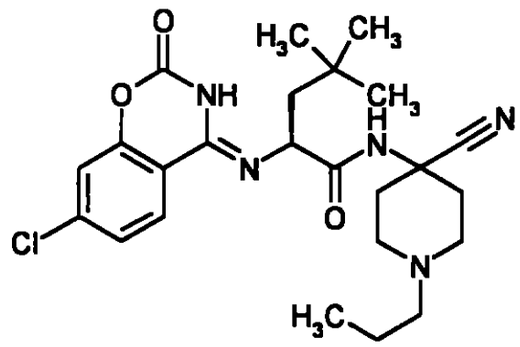
(4-ciano-1-propil-piperidin-4-il)-amida de ácido 4,4-dimetil-2-(6-metil-2-oxo-2,3-dihidro-benzo[e][1,3]oxazin-4-ilidenamino)-pentanoico; MS: 454 (M+1)



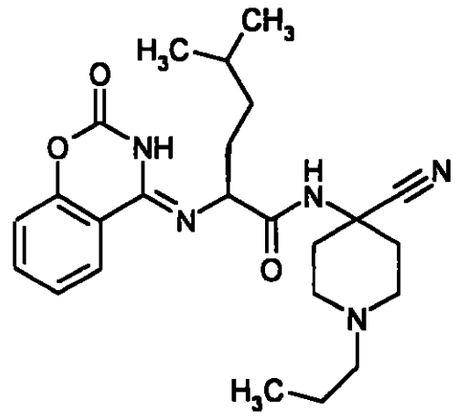
(4-ciano-1-propil-piperidin-4-il)-amida de ácido 2-(6-cloro-2-oxo-2,3-dihidro-benzo[e][1,3]oxazin-4-ilidenamino)-4,4-dimetil-pentanoico; MS: 475 (M+1)



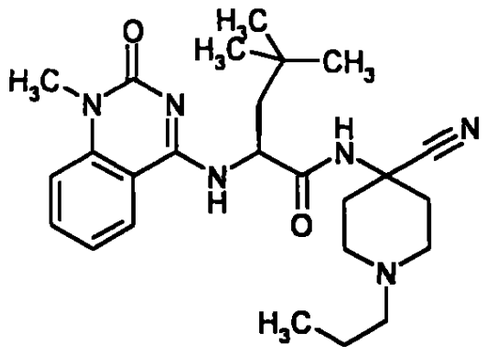
(4-ciano-1-propil-piperidin-4-il)-amida de ácido 4,4-dimetil-2-(2-oxo-2,3-dihidro-1H-quinazolin-4-ilidenamino)-pentanoico; MS: 439 (M+1)



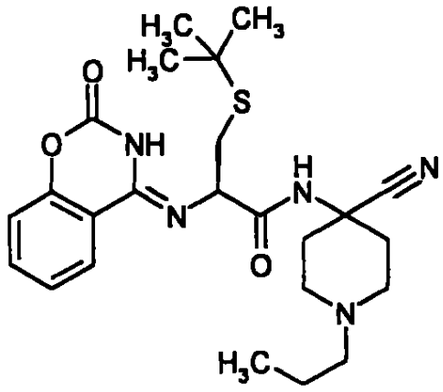
(4-ciano-1-propil-piperidin-4-il)-amida de ácido 2-(7-cloro-2-oxo-2,3-dihidro-benzo[e][1,3]oxazin-4-ilidenamino)-4,4-dimetil-pentanoico; MS: 475 (M+1)



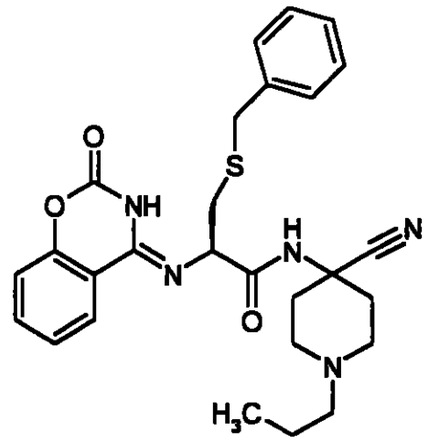
(4-ciano-1-propil-piperidin-4-il)-amida de ácido 5-metil-2-(2-oxo-2,3-dihidro-benzo[e][1,3]oxazin-4-ilidenamino)-hexanoico; MS: 440 (M+1)



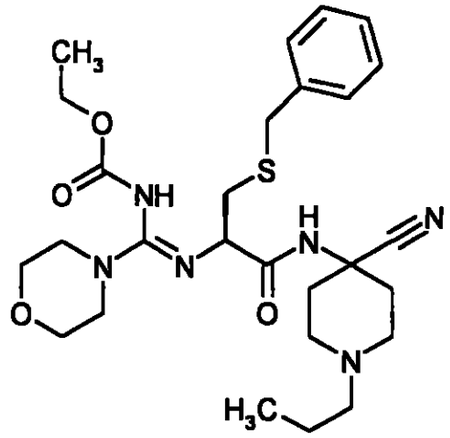
(4-ciano-1-propil-piperidin-4-il)-amida de ácido 4,4-dimetil-2-(1-metil-2-oxo-1,2-dihidro-quinazolin-4-ilamino)-pentanoico; MS: 453 (M+1)



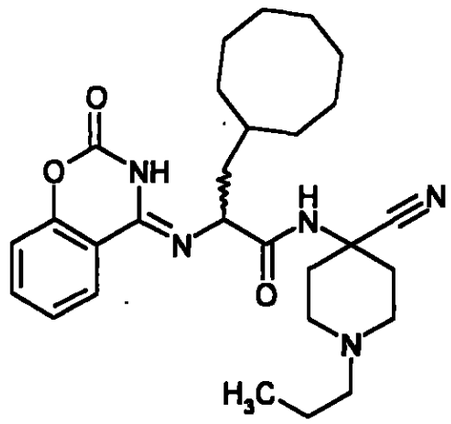
3-terc.-butilsulfanil-N-(4-ciano-1-propil-piperidin-4-il)-2-(2-oxo-2,3-dihidro-benzo[e][1,3]oxazin-4-iliden amino)-propionamida; MS: 472 (M+1)



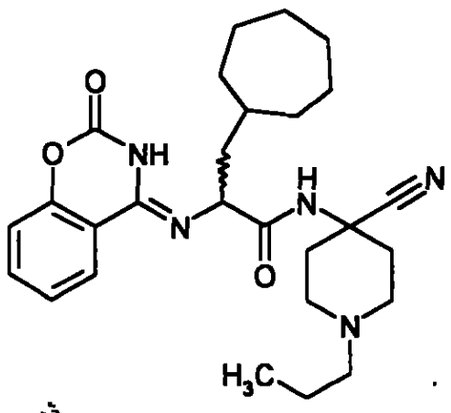
3-bencilsulfanil-N-(4-ciano-1-propil-piperidin-4-il)-2-(2-oxo-2,3-dihidro-benzo[e][1,3]oxazin-4-ilidenamino)-propionamida; MS: 506 (M+1)



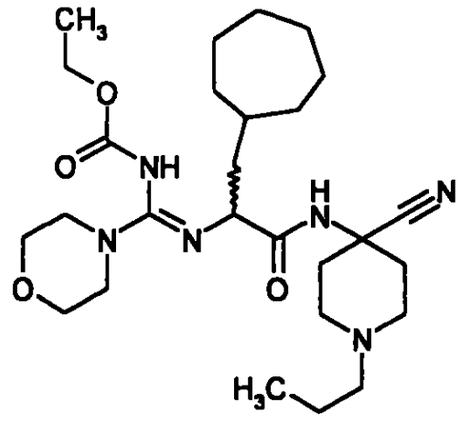
Éster etílico de ácido {[2-bencilsulfanil-1-(4-ciano-1-propil-piperidin-4-ilcarbamoil)-etilimino]-morfolin-4-il-metil}-carbámico; MS: 545 (M+1)



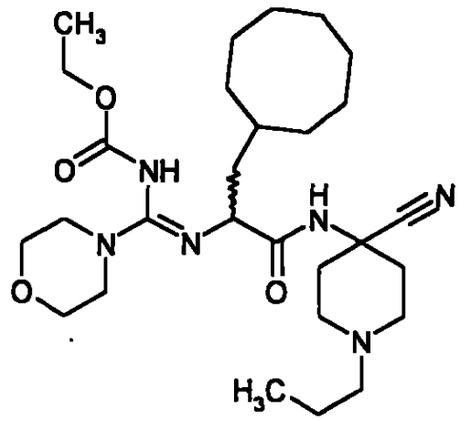
N-(4-ciano-1-propil-piperidin-4-il)-3-ciclooctil-2-(2-oxo-2,3-dihidro-benzo[e][1,3]oxazin-4-ilidenamino)-propionamida; MS: 494 (M+1)



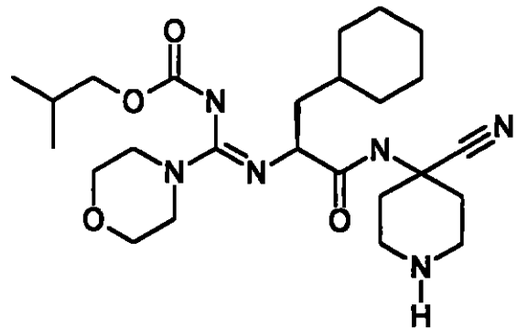
N-(4-ciano-1-propil-piperidin-4-il)-3-cicloheptil-2-(2-oxo-2,3-dihidro-benzo[e][1,3]oxazin-4-ilidenamino)-propionamida; MS: 480 (M+1)



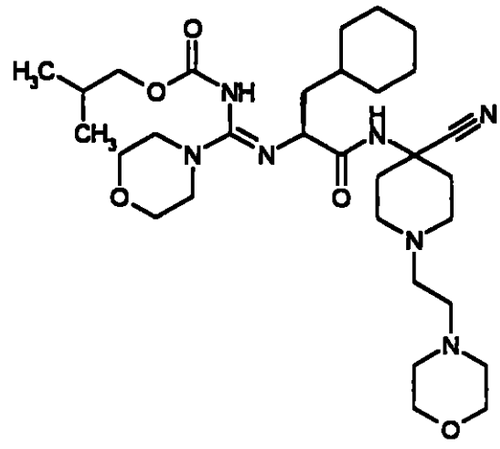
Éster etílico de ácido {[1-(4-ciano-1-propil-piperidin-4-il-carbamoil)-2-cicloheptil-etilimino]-morfolin-4-il-metil}-carbámico; MS: 519 (M+1)



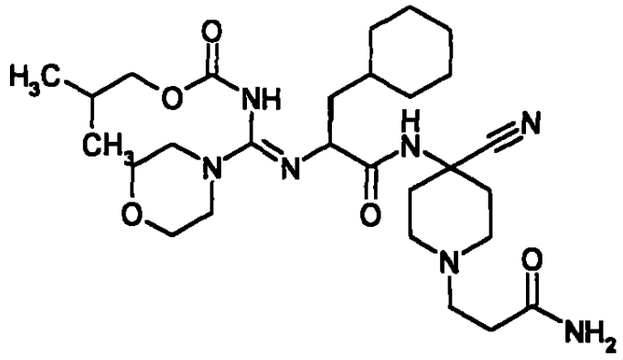
Éster etílico de ácido {[1-(4-ciano-1-propil-piperidin-4-il-carbamoil)-2-ciclooctil-etilimino]-morfolin-4-il-metil}-carbámico; MS: 533 (M+1)



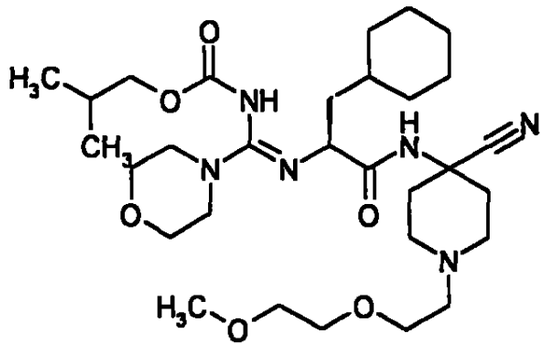
Éster isobutílico de ácido {[1-(4-ciano-piperidin-4-il-carbamoil)-2-ciclohexil-etilamino]-morfolin-4-il-metileno}-carbámico; MS: 491 (M+1)



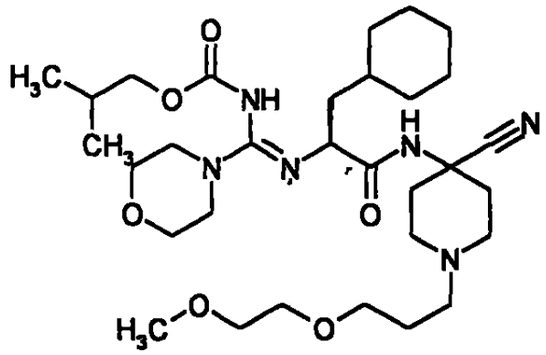
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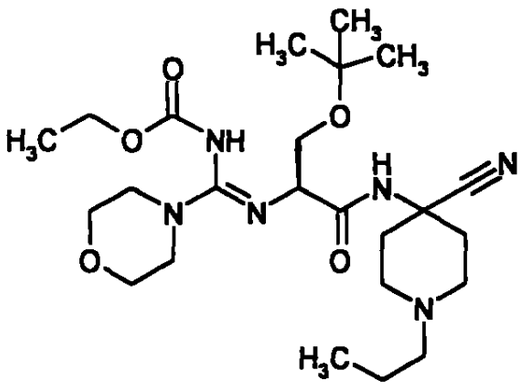
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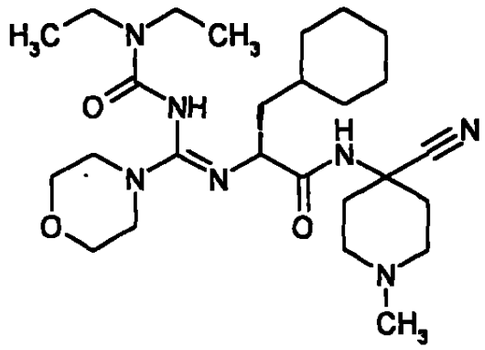
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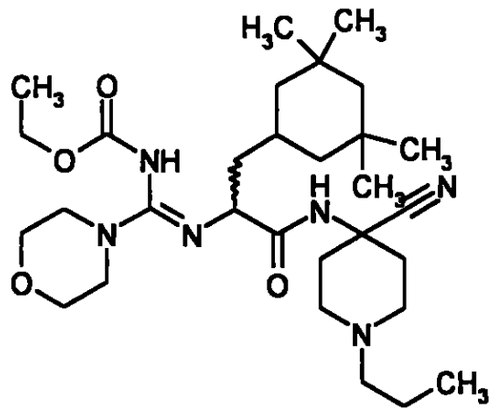
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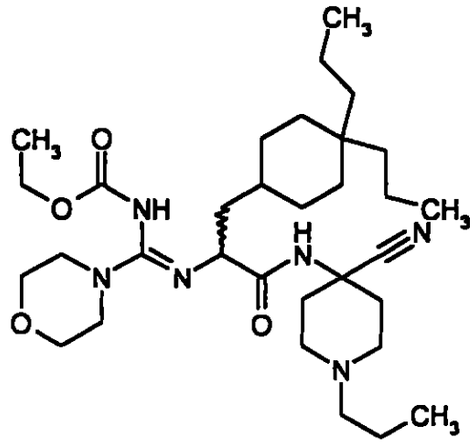
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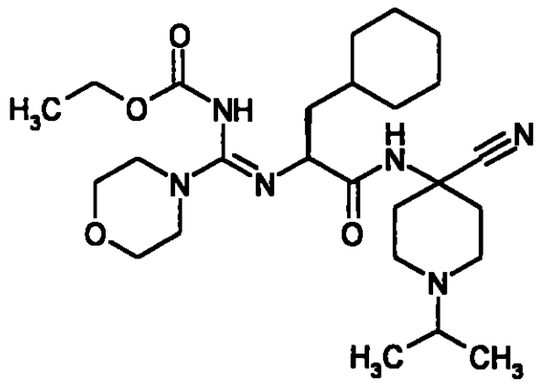
N-(4-ciano-1-metil-piperidin-4-il)-3-ciclohexil-2-{[dietil-carbamoilimino)-morfolin-4-il-metil]-amino}-propionamida; MS: 504 (M+1)



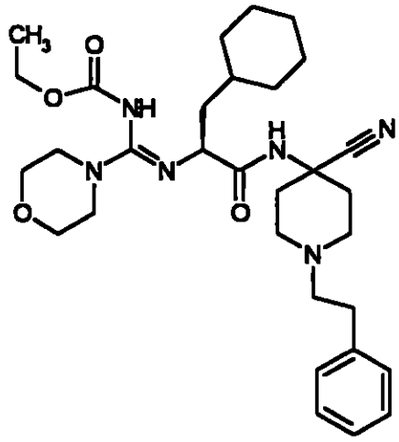
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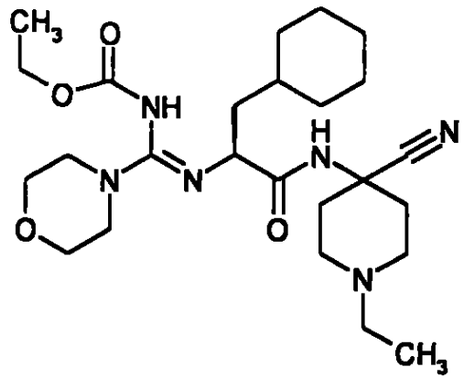
Éster etílico de ácido {[1-(4-ciano-1-propil-piperidin-4-ilcarbamoil)-2-(4,4-dipropil-ciclohexil)-etilamino]-morfolin-4-il-metileno}-carbámico; MS: 589 (M+1)



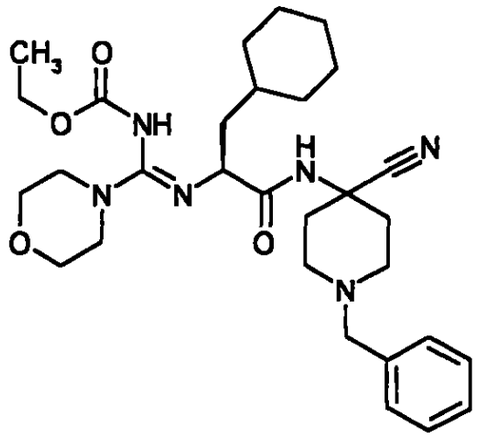
Éster etílico de ácido {[1-(4-ciano-1-isopropil-piperidin-4-ilcarbamoil)-2-ciclohexil-etilamino]-morfolin-4-il-metileno}-carbámico; MS: 505 (M+1)



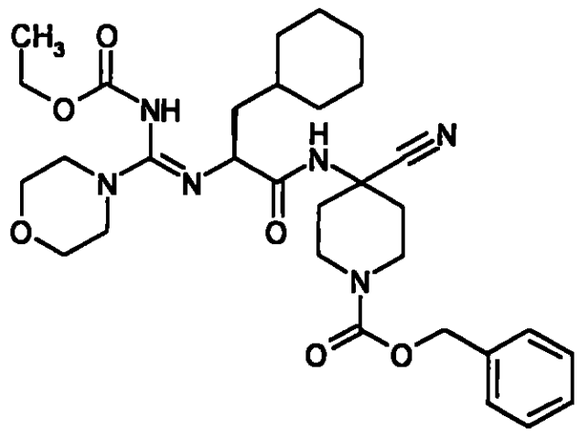
Éster etílico de ácido {[1-(4-ciano-1-fenetil-piperidin-4-ilcarbamoil)-2-ciclohexil-etilamino]-morfolin-4-il-metileno}-carbámico; MS: 567 (M+1)



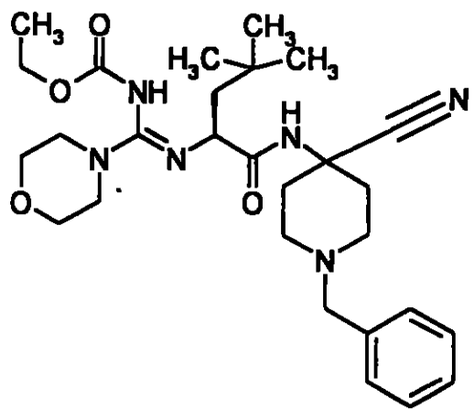
Éster etílico de ácido {[1-(4-ciano-1-etil-piperidin-4-ilcarbamoil)-2-ciclohexil-etilamino]-morfolin-4-il-metileno}-carbámico; MS: 491 (M+1)



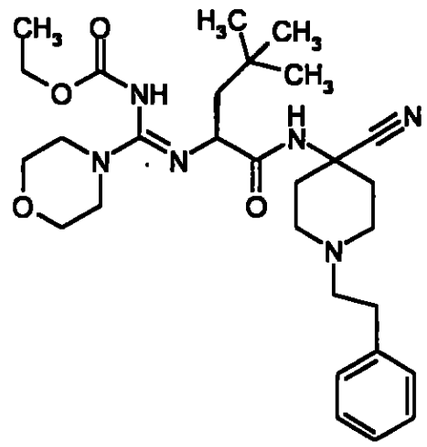
Éster etílico de ácido {[1-(1-bencil-4-ciano-piperidin-4-ilcarbamoil)-2-ciclohexil-etilamino]-morfolin-4-il-metileno}-carbámico; MS: 553 (M+1)



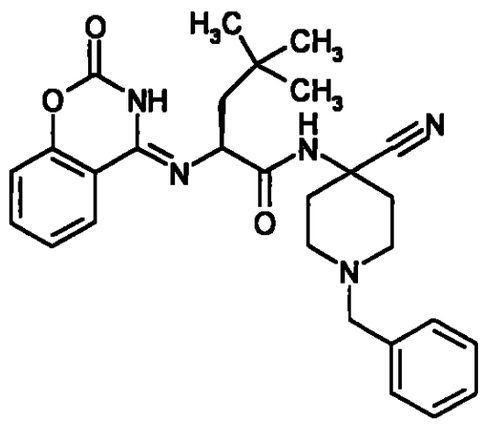
Éster bencílico de ácido 4-ciano-4-{3-ciclohexil-2-[(etoxi-carbonilimino-morfolin-4-il-metil)-amino]-propionilamino}-piperidina-1-carboxílico; MS: 597 (M+1)



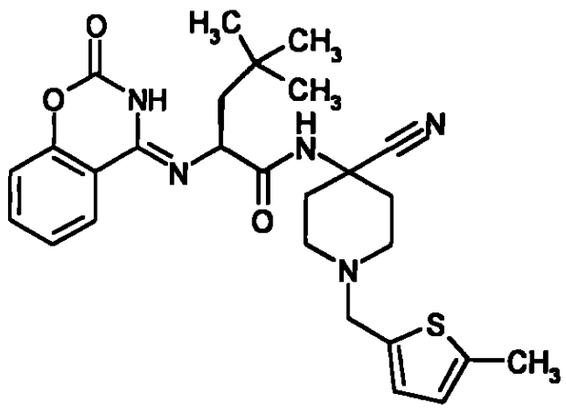
Éster etílico de ácido {[1-(1-bencil-4-ciano-piperidin-4-ilcarbamoil)-3,3-dimetil-butilamino]-morfolin-4-il-metileno}-carbámico; MS: 527 (M+1)



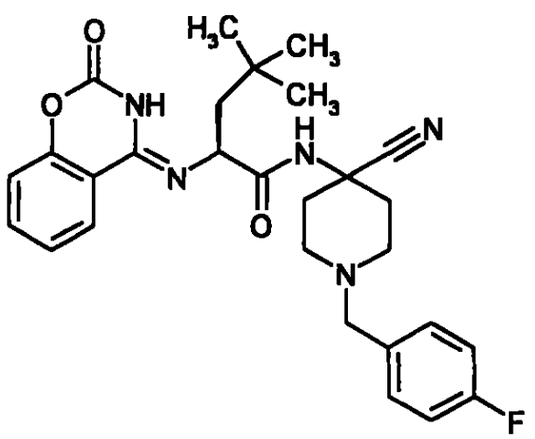
Éster etílico de ácido {[1-(4-ciano-1-fenetil-piperidin-4-ilcarbamoil)-3,3-dimetil-butilamino]-morfolin-4-il-metileno}-carbámico; MS: 541 (M+1)



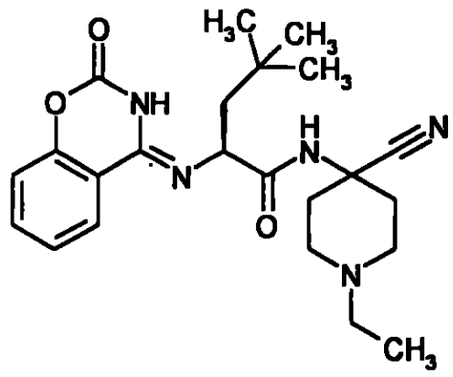
(1-bencil-4-ciano-piperidin-4-il)-amida de ácido 4,4-dimetil-2-(2-oxo-2H-benzo[e][1,3]oxazin-4-ilamino)-pentanoico; MS: 488 (M+1)



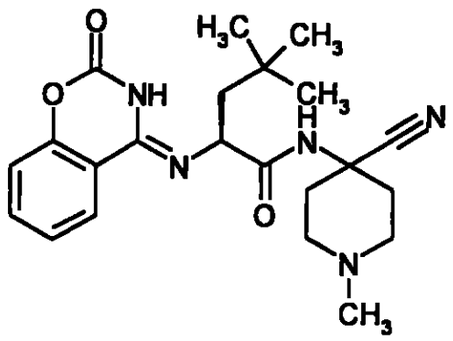
[4-ciano-1-(5-metil-tiofen-2-ilmetil)-piperidin-4-il]-amida de ácido 4,4-dimetil-2-(2-oxo-2H-benzo[e][1,3]oxazin-4-il-amino)-pentanoico; MS: 508 (M+1)



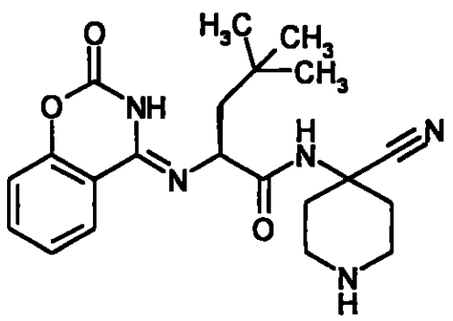
[4-ciano-1-(4-fluoro-bencil)-piperidin-4-il]-amida de ácido 4,4-dimetil-2-(2-oxo-2H-benzo[e][1,3]oxazin-4-ilamino)-pentanoico; MS: 506 (M+1)



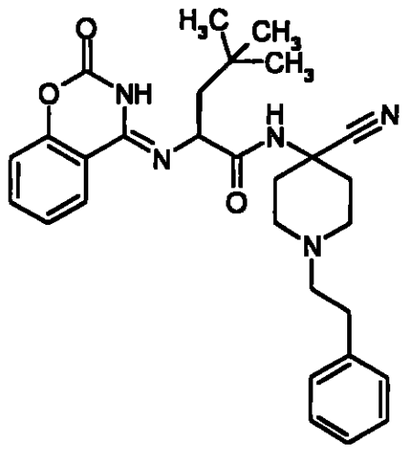
(4-ciano-1-etil-piperidin-4-il)-amida de ácido 4,4-dimetil-2-(2-oxo-2H-benzo[e][1,3]oxazin-4-ilamino)-pentanoico; MS: 426 (M+1)



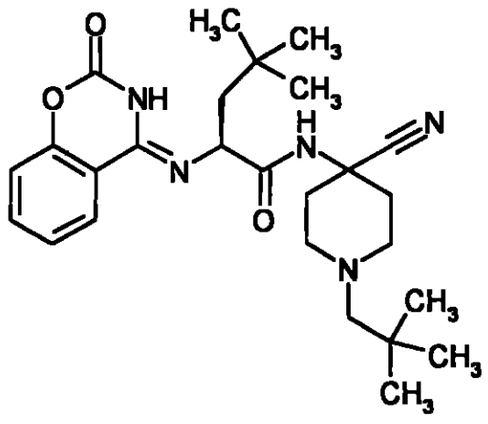
(4-ciano-1-metil-piperidin-4-il)-amida de ácido 4,4-dimetil-2-(2-oxo-2H-benzo[e][1,3]oxazin-4-ilamino)-pentanoico; MS: 412 (M+1)



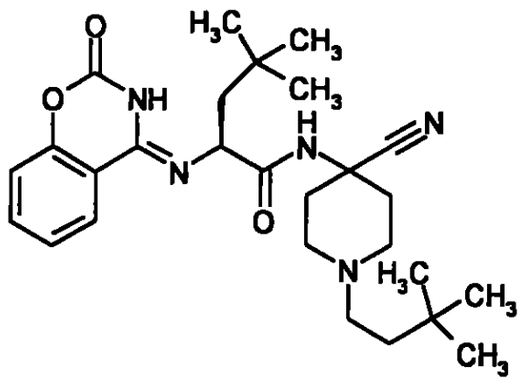
(4-ciano-piperidin-4-il)-amida de ácido 4,4-dimetil-2-(2-oxo-2H-benzo[e][1,3]oxazin-4-ilamino)-pentanoico; MS: 398 (M+1)



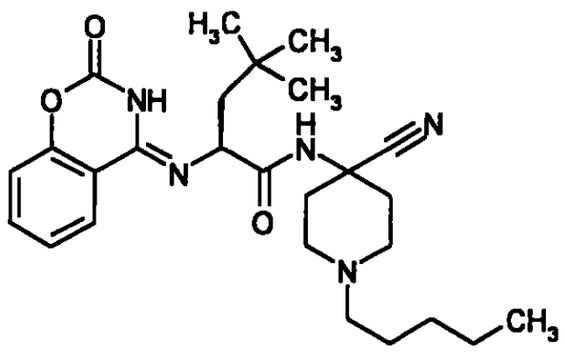
(4-ciano-1-fenetil-piperidin-4-il)-amida de ácido 4,4-dimetil-2-(2-oxo-2H-benzo[e][1,3]oxazin-4-ilamino)-pentanoico; MS: 502 (M+1)



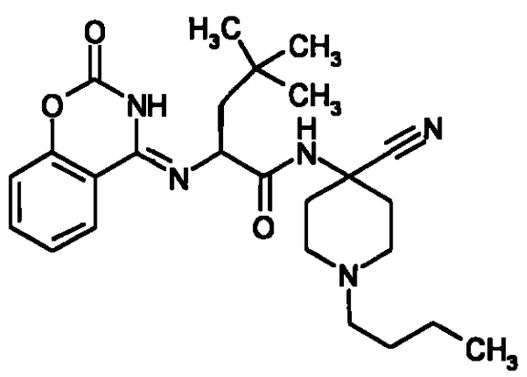
[4-ciano-1-(2,2-dimetil-propil)-piperidin-4-il]-amida de ácido 4,4-dimetil-2-(2-oxo-2H-benzo[e][1,3]oxazin-4-ilamino)-pentanoico; MS: 468 (M+1)



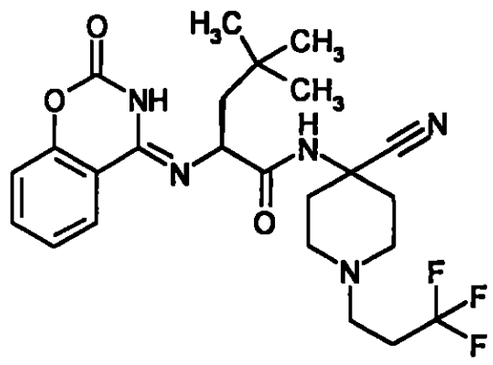
[4-ciano-1-(3,3-dimetil-butil)-piperidin-4-il]-amida de ácido 4,4-dimetil-2-(2-oxo-2H-benzo[e][1,3]oxazin-4-ilamino)-pentanoico; MS: 482 (M+1)



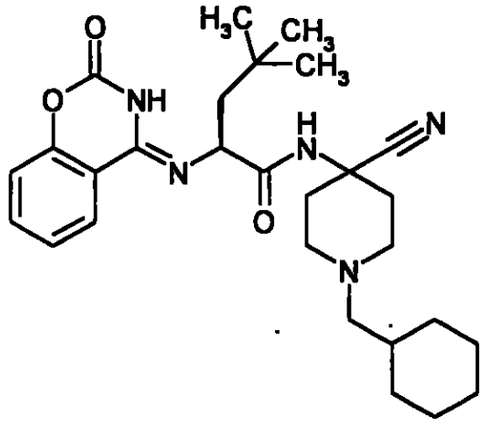
(4-ciano-1-pentil-piperidin-4-il)-amida de ácido 4,4-dimetil-2-(2-oxo-2H-benzo[e][1,3]oxazin-4-ilamino)-pentanoico; MS: 468 (M+1)



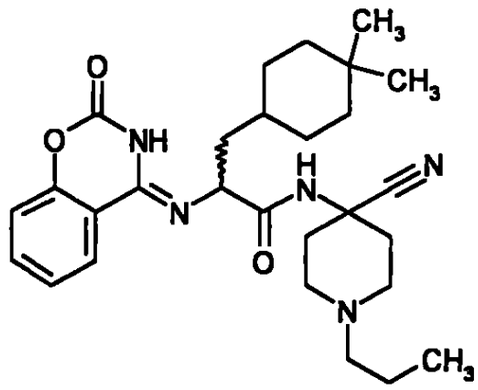
(1-butil-4-ciano-piperidin-4-il)-amida de ácido 4,4-dimetil-2-(2-oxo-2H-benzo[e][1,3]oxazin-4-ilamino)-pentanoico; MS: 454 (M+1)



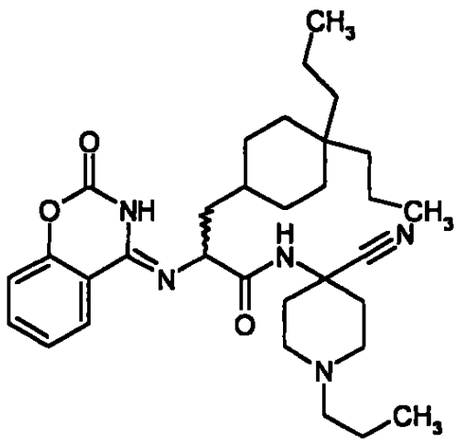
[4-ciano-1-(3,3,3-trifluoro-propil)-piperidin-4-il]-amida de ácido 4,4-dimetil-2-(2-oxo-2H-benzo[e][1,3]oxazin-4-ilamino)-pentanoico; MS: 494 (M+1)



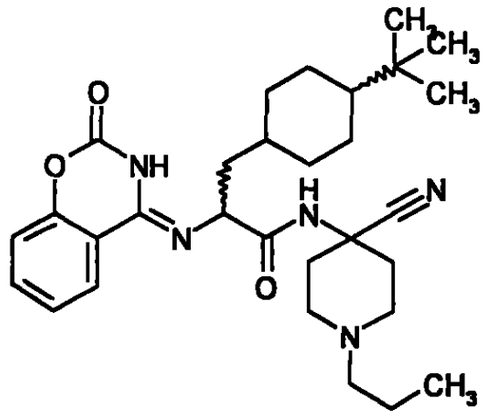
(4-ciano-1-ciclohexilmetil-piperidin-4-il)-amida de ácido 4,4-dimetil-2-(2-oxo-2H-benzo[e][1,3]oxazin-4-ilamino)-pentanoico; MS: 494 (M+1)



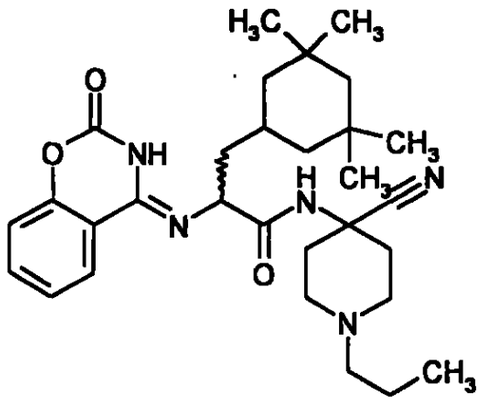
N-(4-ciano-1-propil-piperidin-4-il)-3-(4,4-dimetil-ciclohexil)-2-(2-oxo-2H-benzo[e][1,3]oxazin-4-ilamino)-propionamida; MS: 494 (M+1)



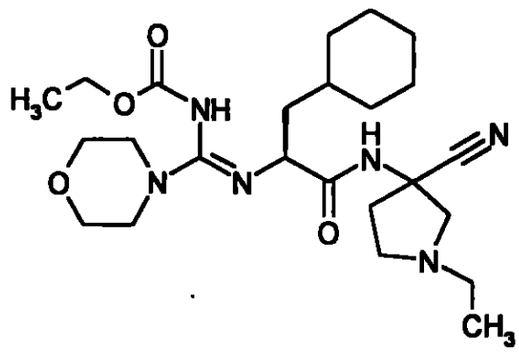
N-(4-ciano-1-propil-piperidin-4-il)-3-(4,4-dipropil-ciclohexil)-2-(2-oxo-2H-benzo[e][1,3]oxazin-4-ilamino)-propionamida; MS: 550 (M+1)



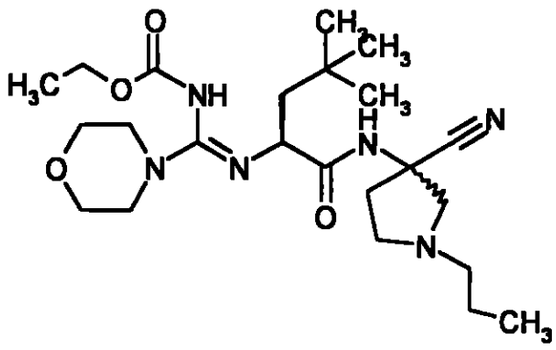
N-(4-ciano-1-propil-piperidin-4-il)-3-(4-terc.-butil-ciclohexil)-2-(2-oxo-2H-benzo[e][1,3]oxazin-4-ilamino)-propionamida; MS: 522 (M+1)



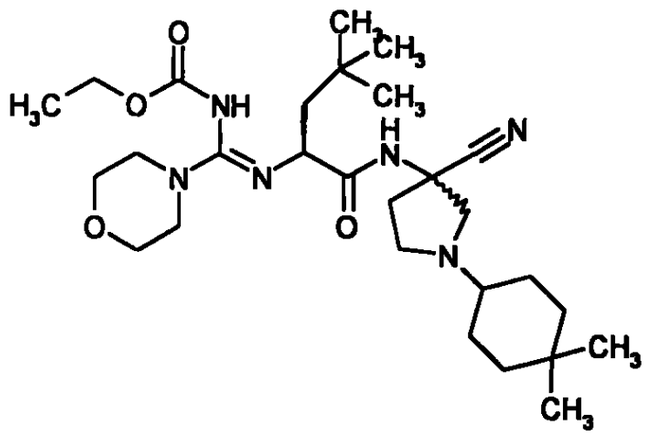
N-(4-ciano-1-propil-piperidin-4-il)-3-(3,3,5,5-tetrametil-ciclohexil)-2-(2-oxo-2H-benzo[e][1,3]oxazin-4-ilamino)-propionamida; MS: 522 (M+1)



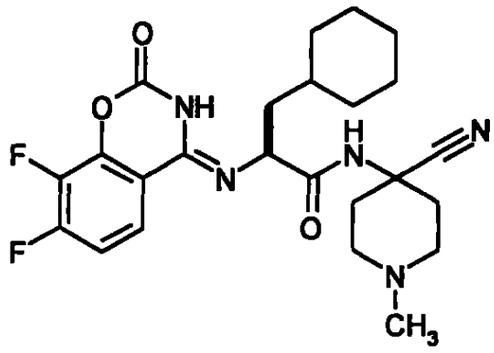
Éster etílico de ácido {[1-(3-ciano-1-etil-pirrolidin-3-ilcarbamoil)-2-ciclohexil-etilamino]-morfolin-4-il-metileno}-carbámico; MS: 477 (M+1)



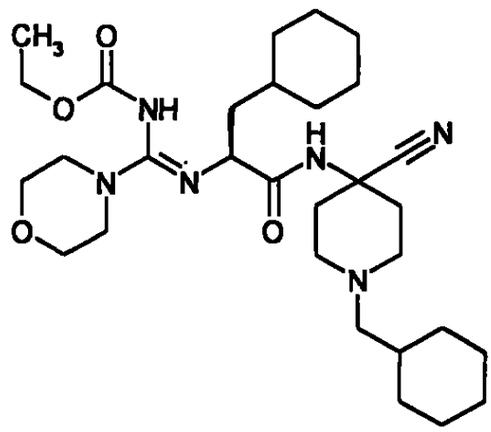
Éster etílico de ácido {[1-(3-ciano-1-propil-pirrolidin-3-ilcarbamoil)-3,3-dimetil-butilamino]-morfolin-4-il-metileno}-carbámico; MS: 465 (M+1)



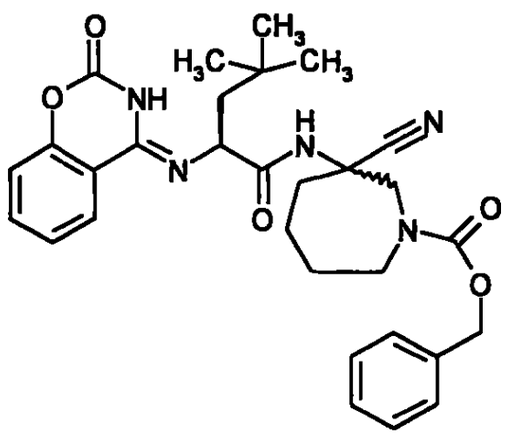
Éster etílico de ácido ((1-[3-ciano-1-(4,4-dimetil-ciclohexil)-pirrolidin-3-ilcarbamoil]-3,3-dimetil-butilamino}-morfolin-4-il-metileno)-carbámico; MS: 533 (M+1)



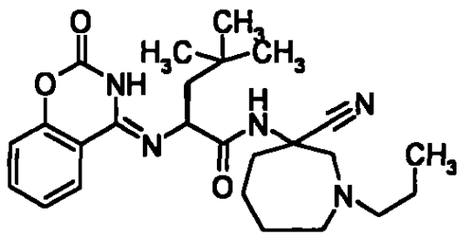
N-(4-ciano-1-metil-piperidin-4-il)-3-ciclohexil-2-(7,8-difluoro-2-oxo-2H-benzo[e][1,3]oxazin-4-ilamino)-propionamida; MS: 474 (M+1)



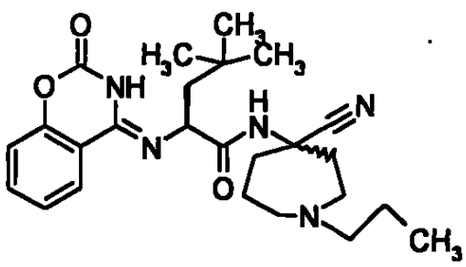
Éster etílico de ácido {[1-(4-ciano-1-ciclohexilmetil-piperidin-4-ilcarbamoil)-2-ciclohexil-etilamino]-morfolin-4-il-metileno}-carbámico; MS: 559 (M+1)



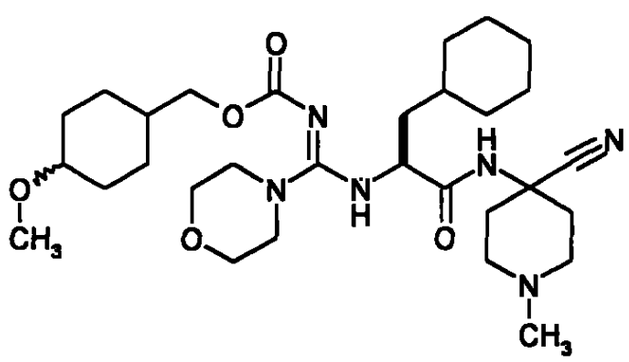
Éster bencílico de ácido 3-ciano-3-[4,4-dimetil-2-(2-oxo-2*H*-benzo[e][1,3]oxazin-4-ilamino)-pentanoilamino]-azepan-1-carboxílico; MS: 546 (M+1)



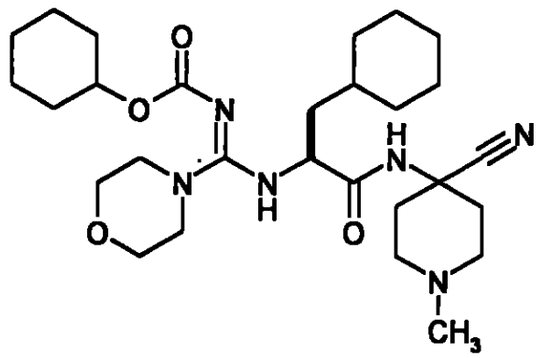
(3-ciano-1-propil-azepan-3-il)-amida de ácido 4,4-dimetil-2-(2-oxo-2H-benzo[e][1,3]oxazin-4-ilamino)-pentanoico; MS: 454 (M+1)



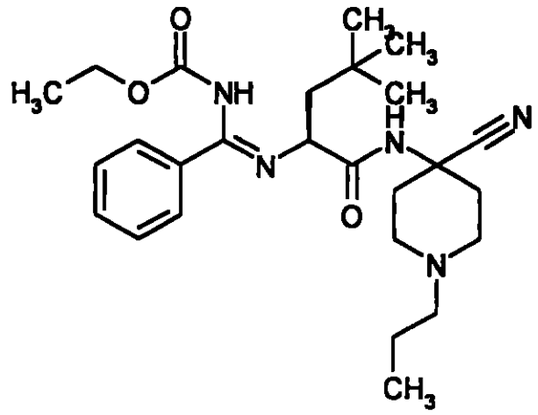
(4-ciano-1-propil-azepan-4-il)-amida de ácido 4,4-dimetil-2-(2-oxo-2H-benzo[e][1,3]oxazin-4-ilamino)-pentanoico; MS: 454 (M+1)



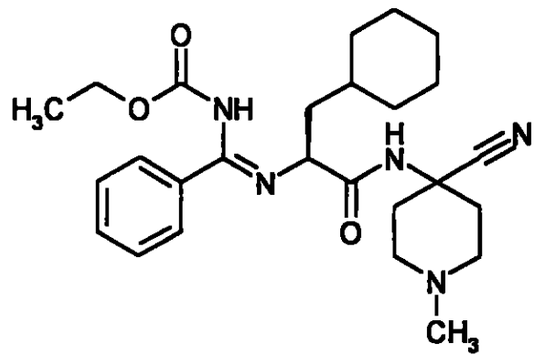
Éster 4-metoxi-ciclohexilmetílico de ácido {[1-(4-ciano-1-metil-piperidin-4-ilcarbamoil)-2-ciclohexil-etilamino]-morfolin-4-il-metileno}-carbámico; MS: 575 (M+1)



Éster ciclohexílico de ácido {[1-(4-ciano-1-metil-piperidin-4-ilcarbamoil)-2-ciclohexil-etilamino]-morfolin-4-il-metileno}-carbámico; MS: 531 (M+1)

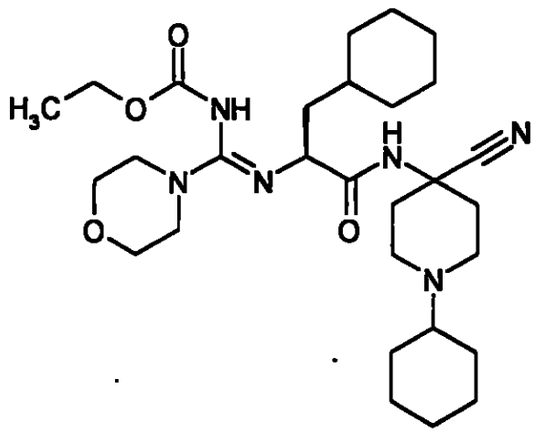


Éster etílico de ácido {[1-(4-ciano-1-propil-piperidin-4-ilcarbamoil)-3,3-dimetil-butilamino]-fenil-metileno}-carbámico; MS: 470 (M+1)

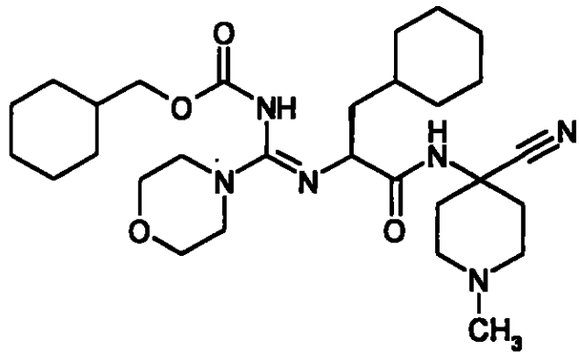


Éster etílico de ácido {[1-(4-ciano-1-metil-piperidin-4-ilcarbamoil)-2-ciclohexil-etilamino]-fenil-metileno}-carbámico; MS: 468 (M+1)

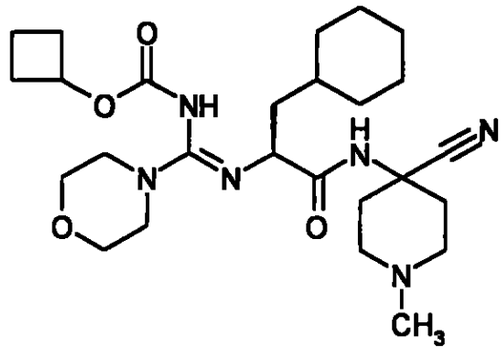
Compuestos más preferidos de fórmulas (Ia) y (Ib) se eligen de los siguientes:



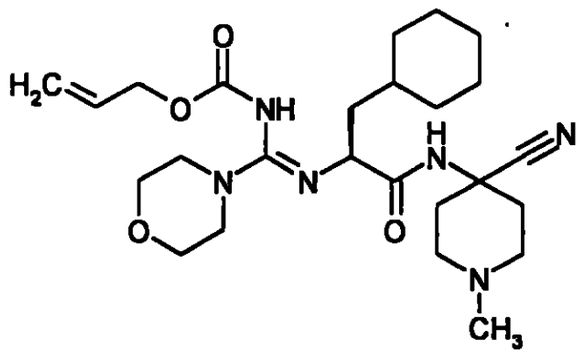
Éster etílico de ácido {[1-(4-ciano-1-ciclohexil-piperidin-4-ilcarbamoil)-2-ciclohexil-etilamino]-morfolin-4-il-metileno}-carbámico; MS: 545 (M+1)



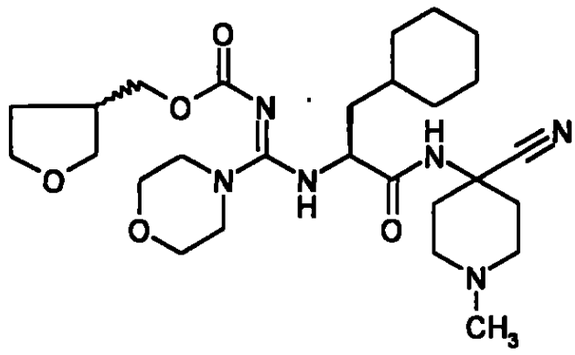
Éster ciclohexilmetílico de ácido {[1-(4-ciano-1-metil-piperidin-4-ilcarbamoil)-2-ciclohexil-etilamino]-morfolin-4-il-metileno}-carbámico; MS: 545 (M+1)



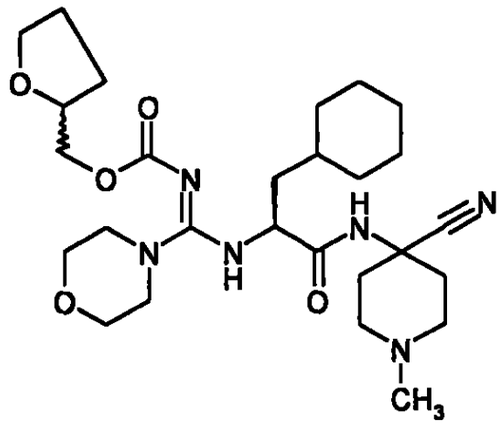
Éster ciclobutílico de ácido {[1-(4-ciano-1-metil-piperidin-4-ilcarbamoil)-2-ciclohexil-etilamino]-morfolin-4-il-metileno}-carbámico; MS: 503 (M+1)



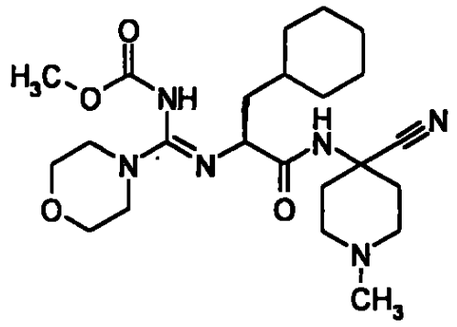
Éster alílico de ácido {[1-(4-ciano-1-metil-piperidin-4-il-carbamoil)-2-ciclohexil-etilamino]-morfolin-4-il-metileno}-carbámico; MS: 489 (M+1)



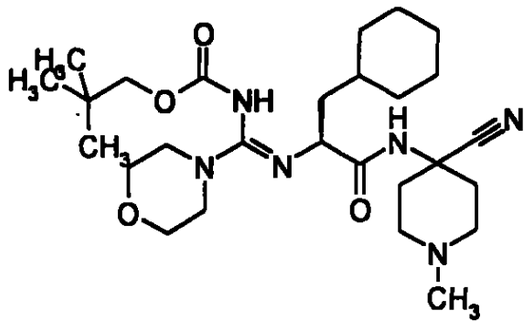
Éster tetrahidro-furan-3-ilmetílico de ácido {[1-(4-ciano-1-metil-piperidin-4-ilcarbamoil)-2-ciclohexil-etilamino]-morfolin-4-il-metileno}-carbámico; MS: 533 (M+1)



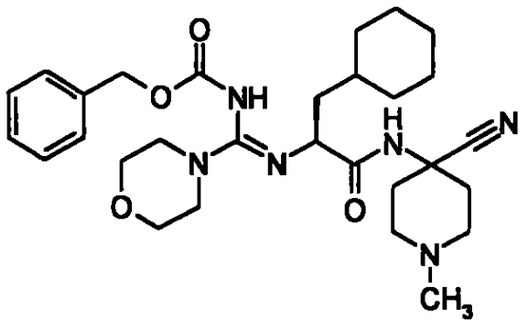
Éster tetrahidro-furan-2-ilmetílico de ácido {[1-(4-ciano-1-metil-piperidin-4-ilcarbamoil)-2-ciclohexil-etilamino]-morfolin-4-il-metileno}-carbámico; MS: 533 (M+1)



Éster metílico de ácido {[1-(4-ciano-1-metil-piperidin-4-il-carbamoil)-2-ciclohexil-etilimino]-morfolin-4-il-metil}-carbámico; MS: 463 (M+1)

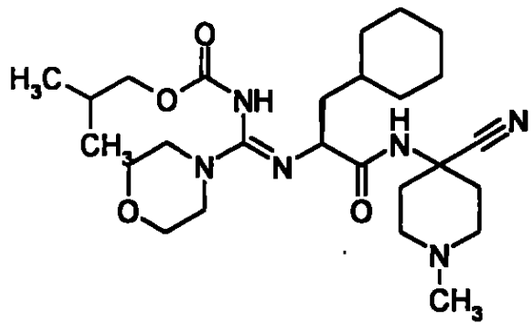


Éster 2,2-dimetil-propílico de ácido {[1-(4-ciano-1-metil-piperidin-4-ilcarbamoil)-2-ciclohexil-etilimino]-morfolin-4-il-metil}-carbámico; MS: 519 (M+1)

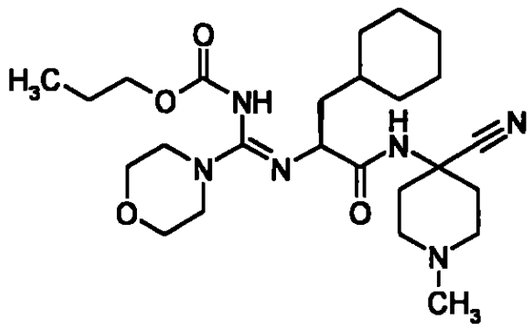


Éster bencílico de ácido {[1-(4-ciano-1-metil-piperidin-4-il-

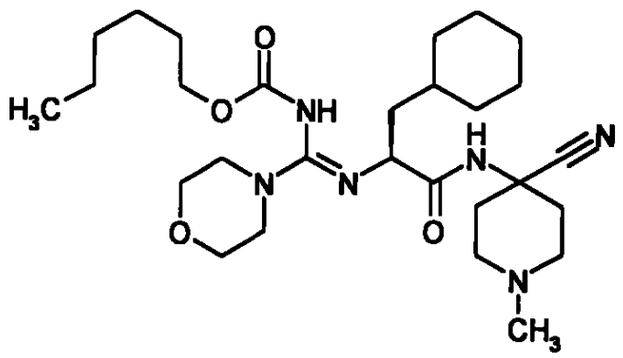
carbamoil)-2-ciclohexil-etilimino]-morfolin-4-il-metil}-carbámico; MS: 539 (M+1)



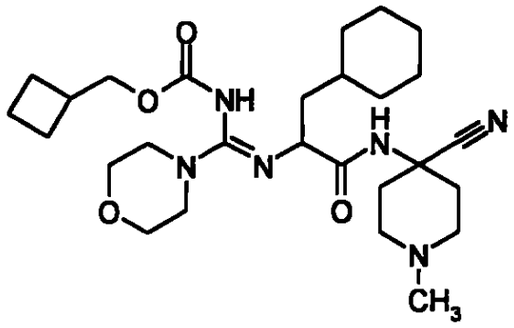
Éster isobutílico de ácido {[1-(4-ciano-1-metil-piperidin-4-ilcarbamoil)-2-ciclohexil-etilimino]-morfolin-4-il-metil}-carbámico; MS: 505 (M+1)



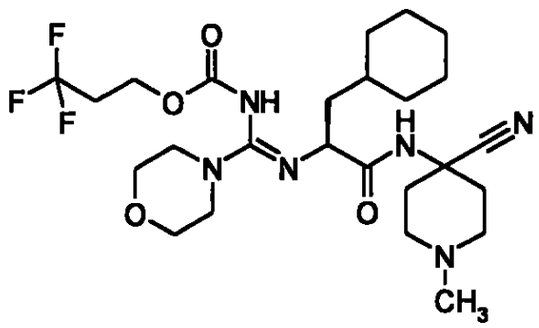
Éster propílico de ácido {[1-(4-ciano-1-metil-piperidin-4-ilcarbamoil)-2-ciclohexil-etilimino]-morfolin-4-il-metil}-carbámico; MS: 491 (M+1)



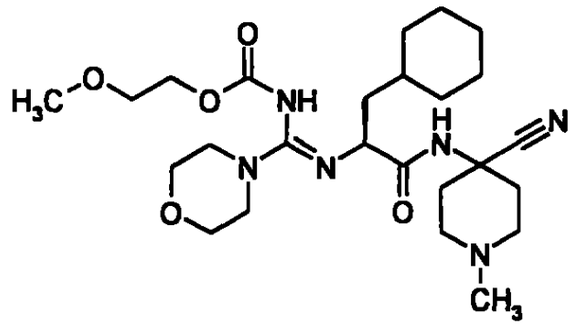
Éster hexílico de ácido {[1-(4-ciano-1-metil-piperidin-4-il-carbamoil)-2-ciclohexil-etilimino]-morfolin-4-il-metil}-carbámico; MS: 533 (M+1)



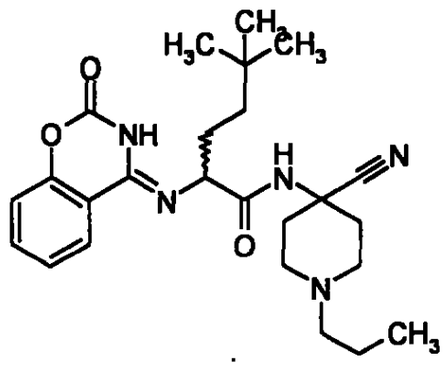
Éster ciclobutilmetílico de ácido {[1-(4-ciano-1-metil-piperidin-4-ilcarbamoil)-2-ciclohexil-etilimino]-morfolin-4-il-metil}-carbámico; MS: 517 (M+1)



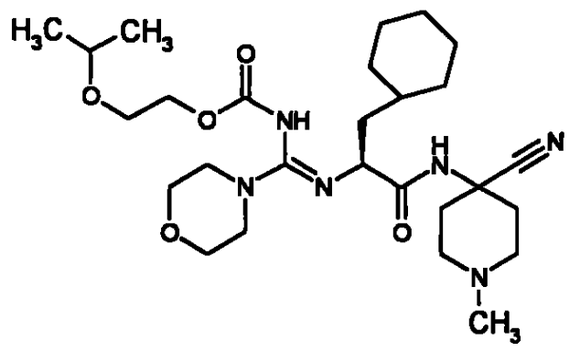
Éster 3,3,3-trifluoro-propilico de ácido {[1-(4-ciano-1-metil-piperidin-4-ilcarbamoil)-2-ciclohexil-etilimino]-morfolin-4-il-metil}-carbámico; MS: 545 (M+1)



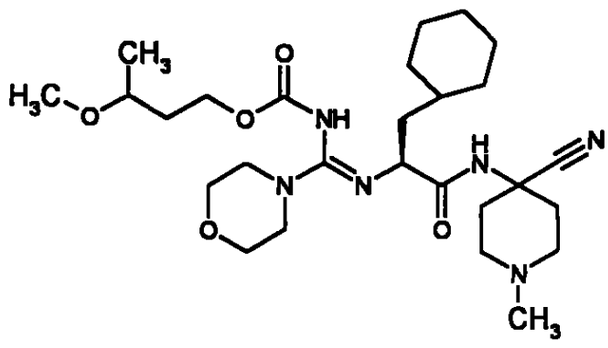
Éster 2-metoxi-etílico de ácido {[1-(4-ciano-1-metil-piperidin-4-ilcarbamoil)-2-ciclohexil-etilimino]-morfolin-4-il-metil}-carbámico; MS: 507 (M+1)



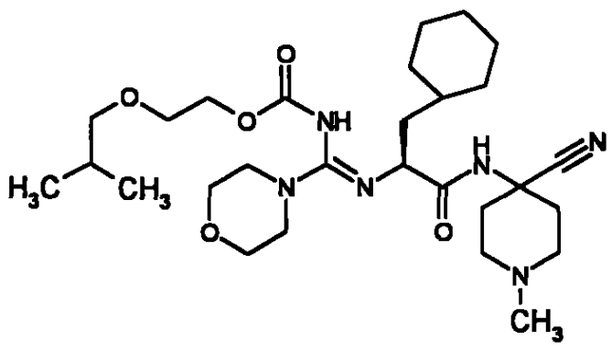
(4-ciano-1-propil-piperidin-4-il)-amida de ácido 5,5-dimetil-2-(2-oxo-2,3-dihidro-benzo[e][1,3]oxazin-4-ilidenamino)-hexanoico; MS: 454 (M+1)



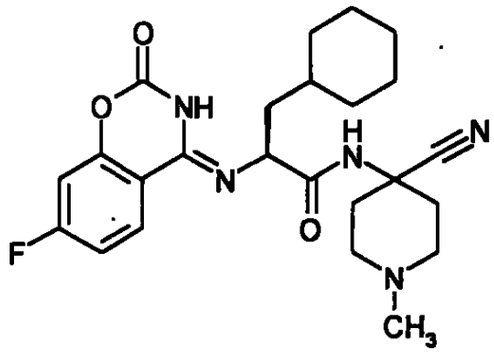
Éster 2-isopropoxi-etílico de ácido {[1-(4-ciano-1-metil-piperidin-4-ilcarbamoil)-2-ciclohexil-etilimino]-morfolin-4-il-metil}-carbámico; MS: 534 (M+1)



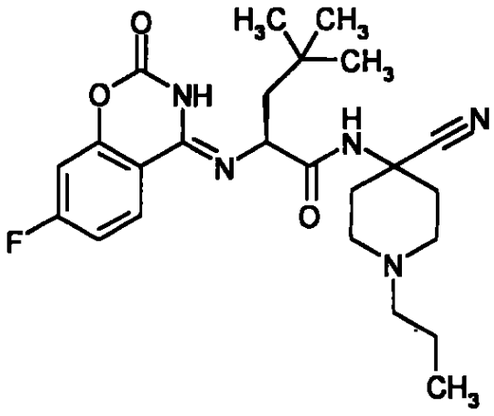
Éster 3-metoxi-butílico de ácido {[1-(4-ciano-1-metil-piperidin-4-ilcarbamoil)-2-ciclohexil-etilimino]-morfolin-4-il-metil}-carbámico; MS: 534 (M+1)



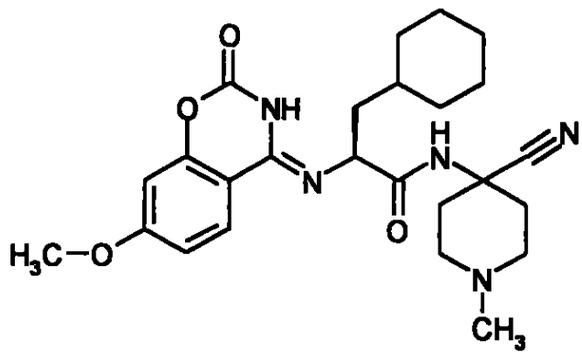
Éster 2-isobutoxi-etílico de ácido {[1-(4-ciano-1-metil-piperidin-4-ilcarbamoil)-2-ciclohexil-etilimino]-morfolin-4-il-metil}-carbámico; MS: 549 (M+1)



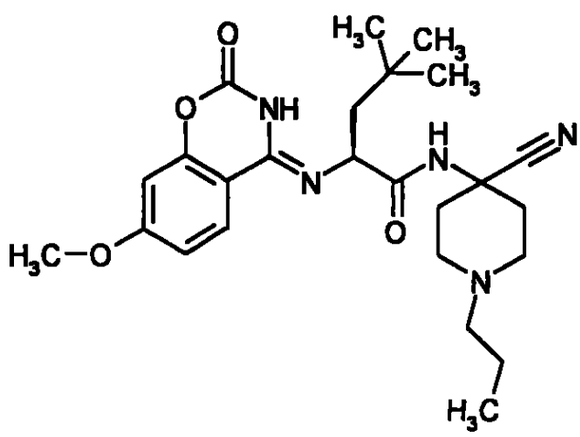
N-(4-ciano-1-metil-piperidin-4-il)-4-ciclohexil-2-(7-fluoro-2-oxo-2,3-dihidro-benzo[e][1,3]oxazin-4-ilidenamino)-butiramida; MS: 456 (M+1)



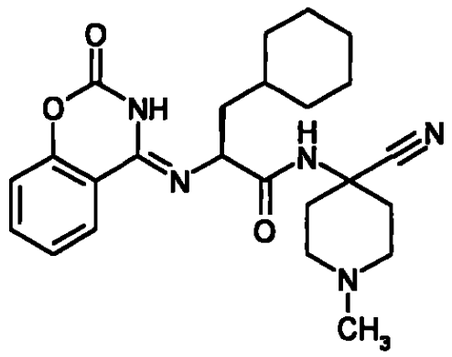
(4-ciano-1-propil-piperidin-4-il)-amida de ácido 2-(7-fluoro-2-oxo-2,3-dihidro-benzo[e][1,3]oxazin-4-ilidenamino)-5,5-dimetil-hexanoico; MS: 458 (M+1)



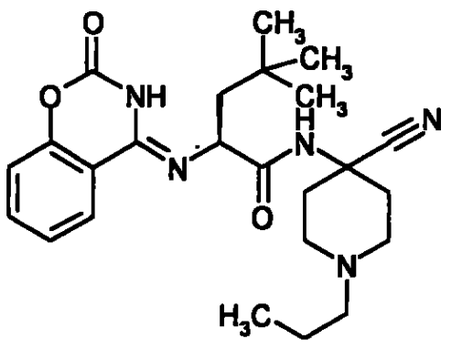
N-(4-ciano-1-metil-piperidin-4-il)-4-ciclohexil-2-(7-metoxi-2-oxo-2,3-dihidro-benzo[e][1,3]oxazin-4-ilidenamino)-butiramida; MS: 468 (M+1)



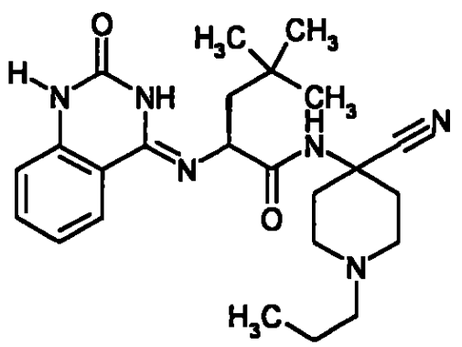
(4-ciano-1-propil-piperidin-4-il)-amida de ácido 2-(7-metoxi-2-oxo-2,3-dihidro-benzo[e][1,3]oxazin-4-ilidenamino)-5,5-dimetil-hexanoico; MS: 470 (M+1)



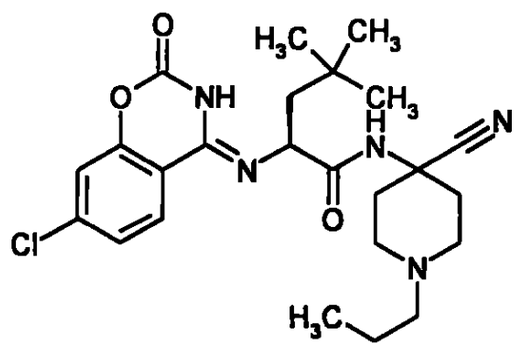
N-(4-ciano-1-metil-piperidin-4-il)-3-ciclohexil-2-(2-oxo-2,3-dihidro-benzo[e][1,3]oxazin-4-ilidenamino)-propionamida; MS: 438 (M+1)



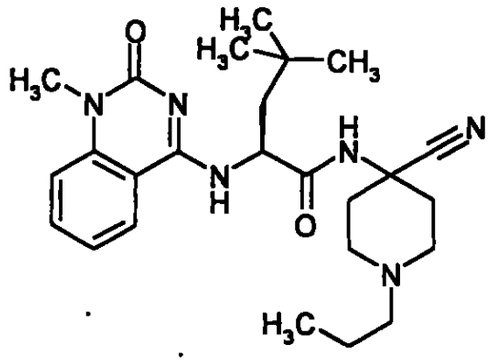
(4-ciano-1-propil-piperidin-4-il)-amida de ácido 4,4-dimetil-2-(2-oxo-2,3-dihidro-benzo[e][1,3]oxazin-4-ilidenamino)-pentanoico; MS: 440 (M+1)



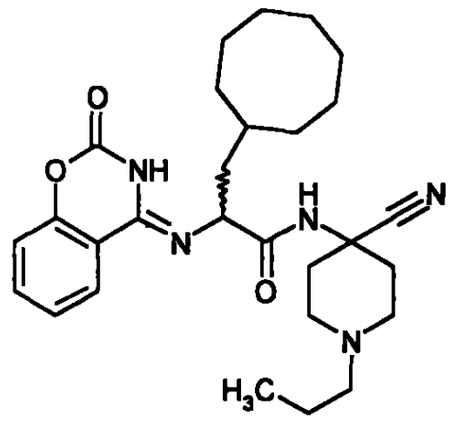
(4-ciano-1-propil-piperidin-4-il)-amida de ácido 4,4-dimetil-2-(2-oxo-2,3-dihidro-1*H*-quinazolin-4-ilidenamino)-pentanoico; MS: 439 (M+1)



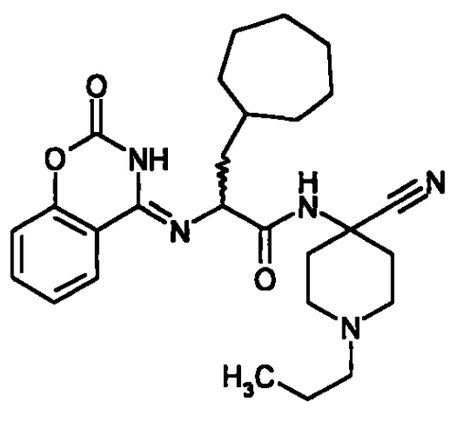
(4-ciano-1-propil-piperidin-4-il)-amida de ácido 2-(7-cloro-2-oxo-2,3-dihidro-benzo[e][1,3]oxazin-4-ilidenamino)-4,4-dimetil-pentanoico; MS: 475 (M+1)



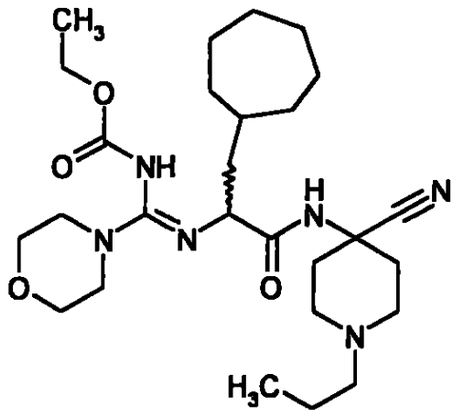
(4-ciano-1-propil-piperidin-4-il)-amida de ácido 4,4-dimetil-2-(1-metil-2-oxo-1,2-dihidro-quinazolin-4-ilidenamino)-pentanoico; MS: 453 (M+1)



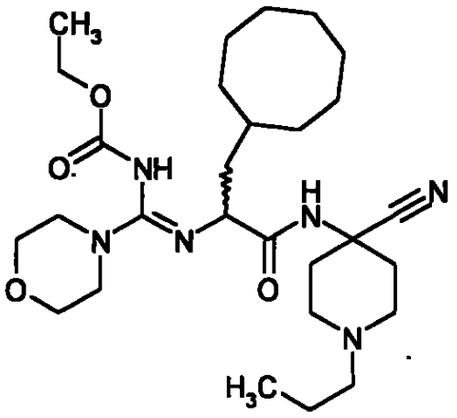
N-(4-ciano-1-propil-piperidin-4-il)-3-ciclooctil-2-(2-oxo-2,3-dihidro-benzo[e][1,3]oxazin-4-ilidenamino)-propionamida;
MS: 494 (M+1)



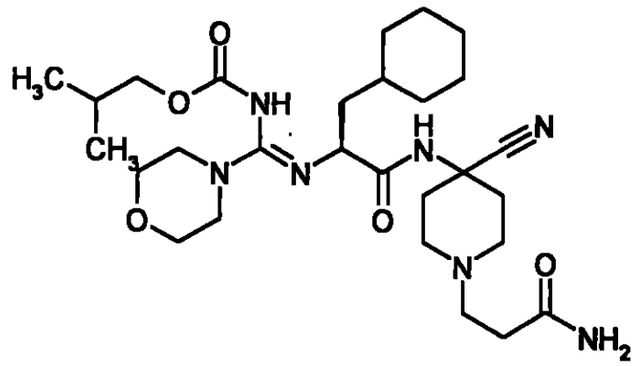
N-(4-ciano-1-propil-piperidin-4-il)-3-cicloheptil-2-(2-oxo-2,3-dihidro-benzo[e][1,3]oxazin-4-ilidenamino)-propionamida;
MS: 480 (M+1)



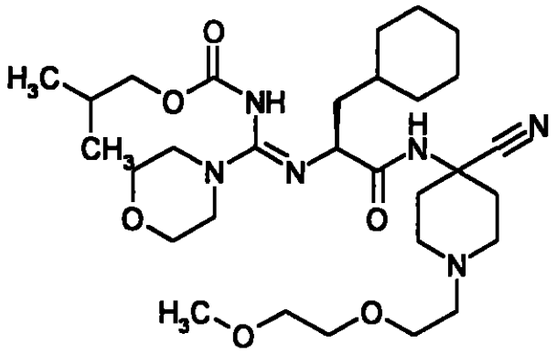
Éster etílico de ácido {[1-(4-ciano-1-propil-piperidin-4-ilcarbamoil)-2-cicloheptil-etilimino]-morfolin-4-il-metil}-carbámico; MS: 519 (M+1)



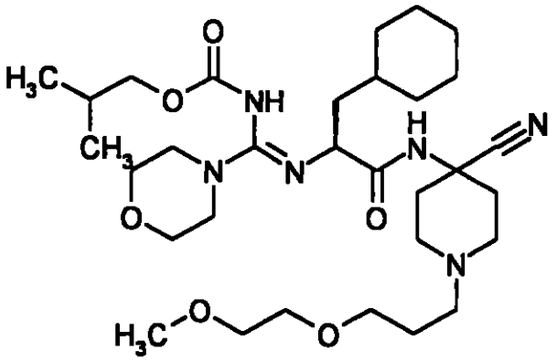
Éster etílico de ácido {[1-(4-ciano-1-propil-piperidin-4-ilcarbamoil)-2-ciclooctil-etilimino]-morfolin-4-il-metil}-carbámico; MS: 533 (M+1)



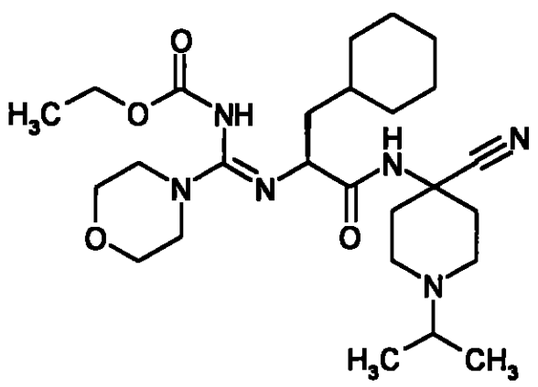
Éster isobutílico de ácido ({1-[1-(2-carbamoil-etil)-4-ciano-piperidin-4-ilcarbamoil)-2-ciclohexil-etilamino]-morfolin-4-il-metileno)-carbámico; MS: 562 (M+1)



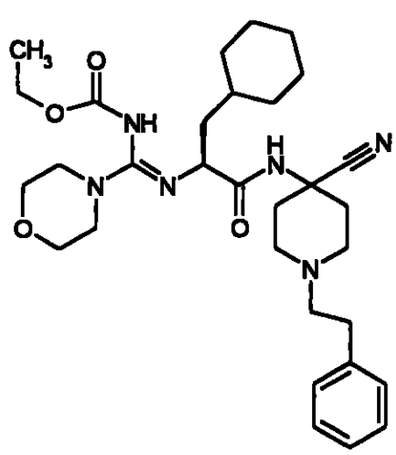
Éster isobutílico de ácido [(1-{4-ciano-1-[2-(2-metoxil-etoxi)-etil]-piperidin-4-ilcarbamoil}-2-ciclohexil-etilamino)-morfolin-4-il-metileno]-carbámico; MS: 593 (M+1)



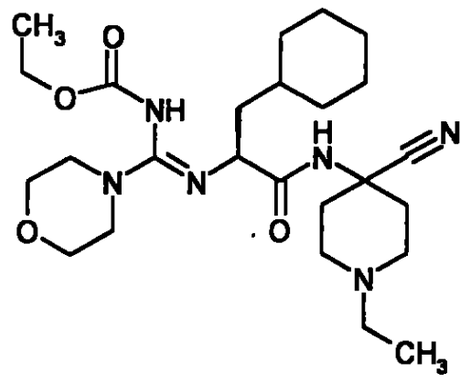
Éster isobutílico de ácido [(1-{4-ciano-1-[3-(2-metoxil-etoxi)-propil]-piperidin-4-ilcarbamoil}-2-ciclohexil-etilamino)-morfolin-4-il-metileno]-carbámico; MS: 607 (M+1)



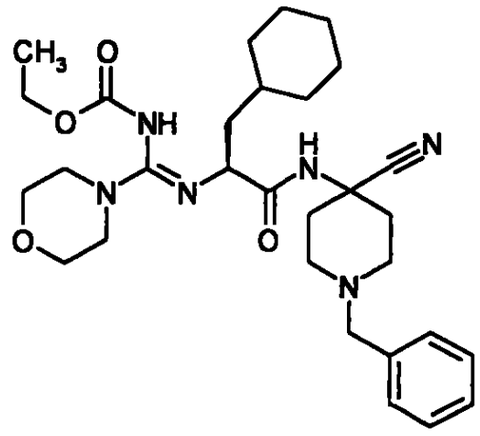
Éster etílico de ácido {[1-(4-ciano-1-isopropil-piperidin-4-ilcarbamoil)-2-ciclohexil-etilamino]-morfolin-4-il-metileno}-carbámico; MS: 505 (M+1)



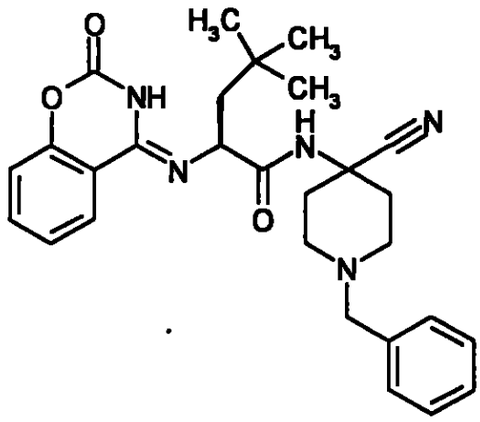
Éster etílico de ácido {[1-(4-ciano-1-fenetil-piperidin-4-ilcarbamoil)-2-ciclohexil-etilamino]-morfolin-4-il-metileno}-carbámico; MS: 567 (M+1)



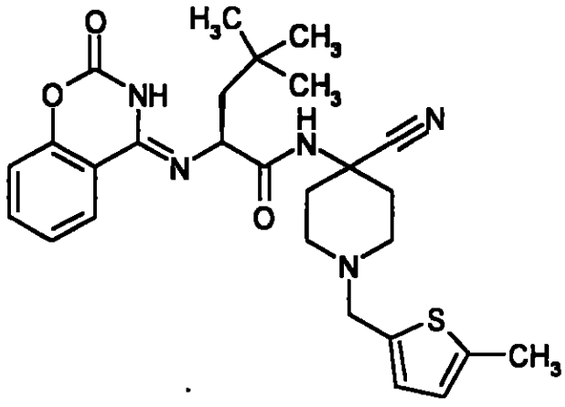
Éster etílico de ácido {[1-(4-ciano-1-etil-piperidin-4-ilcarbamoil)-2-ciclohexil-etilamino]-morfolin-4-il-metileno}-carbámico; MS: 491 (M+1)



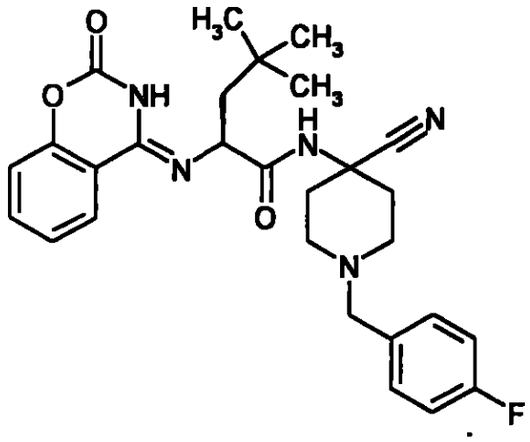
Éster etílico de ácido {[1-(1-bencil-4-ciano-piperidin-4-ilcarbamoil)-2-ciclohexil-etilamino]-morfolin-4-il-metileno}-carbámico; MS: 553 (M+1)



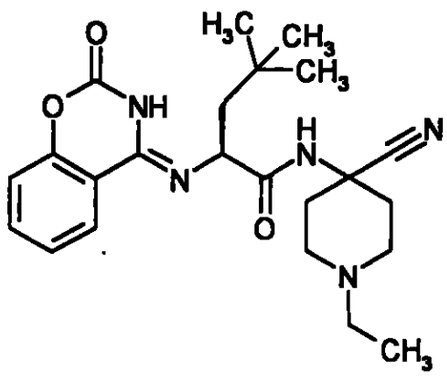
(1-bencil-4-ciano-piperidin-4-il)-amida de ácido 4,4-dimetil-2-(2-oxo-2H-benzo[e][1,3]oxazin-4-ilamino)-pentanoico; MS: 488 (M+1)



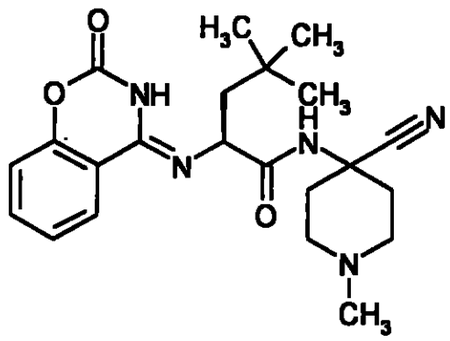
[4-ciano-1-(5-metil-tiofen-2-ilmetil)-piperidin-4-il]-amida de ácido 4,4-dimetil-2-(2-oxo-2H-benzo[e][1,3]oxazin-4-ilamino)-pentanoico; MS: 508 (M+1)



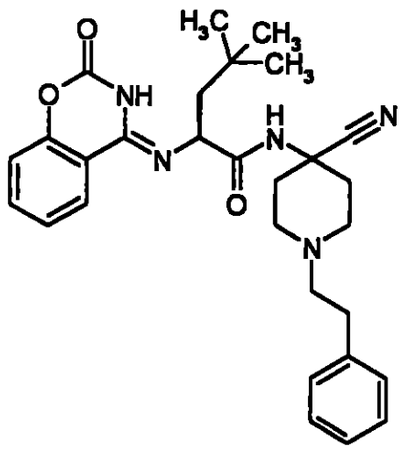
[4-ciano-1-(4-fluoro-bencil)-piperidin-4-il]-amida de ácido 4,4-dimetil-2-(2-oxo-2H-benzo[e][1,3]oxazin-4-ilamino)-pentanoico; MS: 506 (M+1)



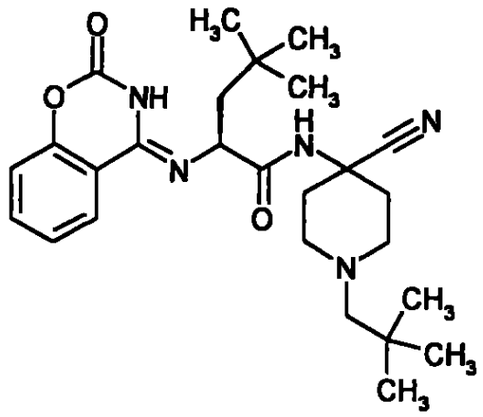
(4-ciano-1-etil-piperidin-4-il)-amida de ácido 4,4-dimetil-2-(2-oxo-2H-benzo[e][1,3]oxazin-4-ilamino)-pentanoico; MS: 426 (M+1)



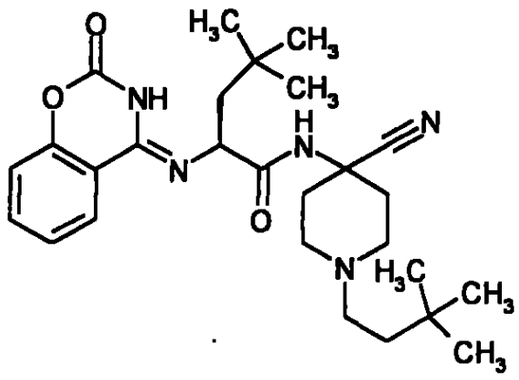
(4-ciano-1-metil-piperidin-4-il)-amida de ácido 4,4-dimetil-2-(2-oxo-2H-benzo[e][1,3]oxazin-4-ilamino)-pentanoico; MS: 412 (M+1)



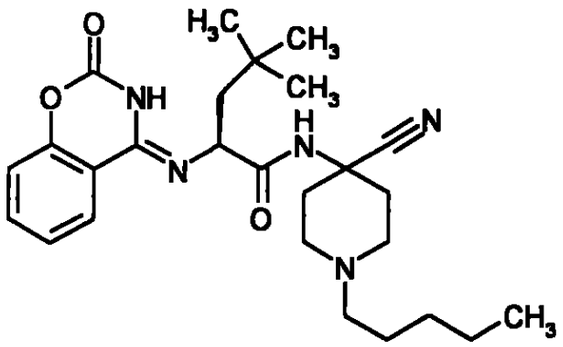
(4-ciano-1-fenetil-piperidin-4-il)-amida de ácido 4,4-dimetil-2-(2-oxo-2H-benzo[e][1,3]oxazin-4-ilamino)-pentanoico; MS: 502 (M+1)



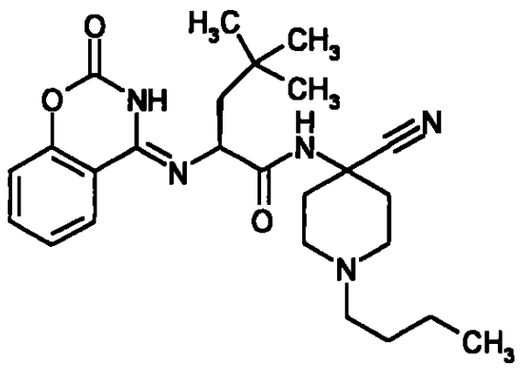
[4-ciano-1-(2,2-dimetil-propil)-piperidin-4-il]-amida de ácido 4,4-dimetil-2-(2-oxo-2H-benzo[e][1,3]oxazin-4-ilamino)-pentanoico; MS: 466 (M+1)



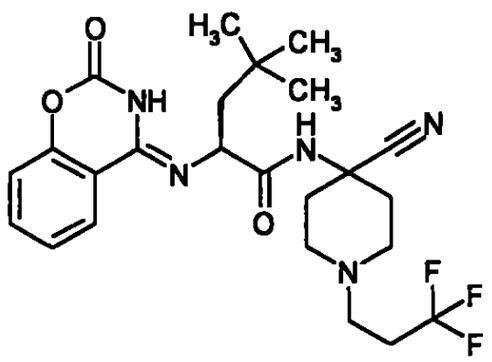
[4-ciano-1-(3,3-dimetil-butil)-piperidin-4-il]-amida de ácido 4,4-dimetil-2-(2-oxo-2H-benzo[e][1,3]oxazin-4-ilamino)-pentanoico; MS: 482 (M+1)



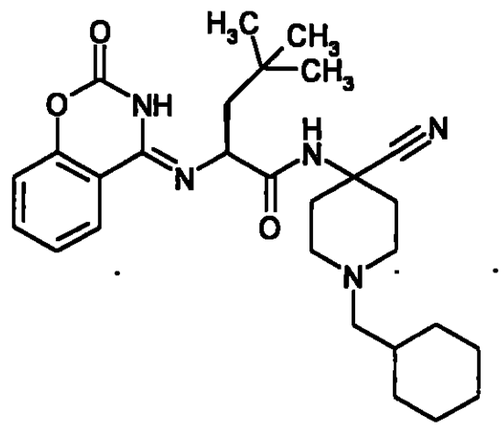
(4-ciano-1-pentil-piperidin-4-il)-amida de ácido 4,4-dimetil-2-(2-oxo-2H-benzo[e][1,3]oxazin-4-ilamino)-pentanoico; MS: 468 (M+1)



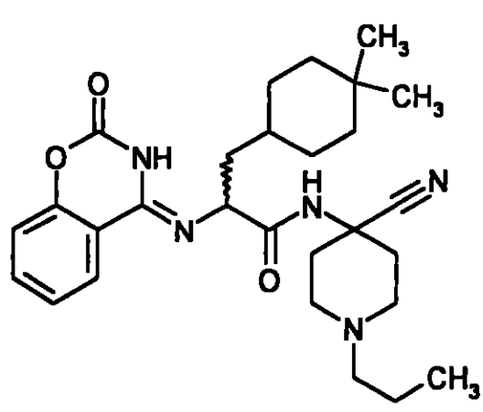
(1-butil-4-ciano-piperidin-4-il]-amida de ácido 4,4-dimetil-2-(2-oxo-2H-benzo[e][1,3]oxazin-4-ilamino)-pentanoico; MS: 454 (M+1)



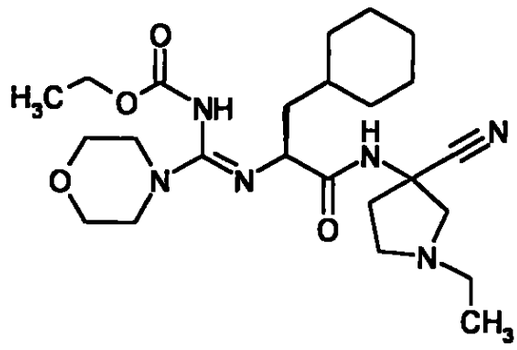
[4-ciano-1-(3,3,3-trifluoro-propil)-piperidin-4-il]-amida de ácido 4,4-dimetil-2-(2-oxo-2H-benzo[e][1,3]oxazin-4-ilamino)-pentanoico; MS: 494 (M+1)



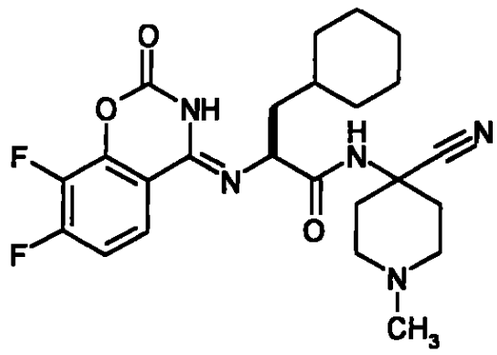
(4-ciano-1-ciclohexilmetil-piperidin-4-il)-amida de ácido 4,4-dimetil-2-(2-oxo-2H-benzo[e][1,3]oxazin-4-ilamino)-pentanoico; MS: 494 (M+1)



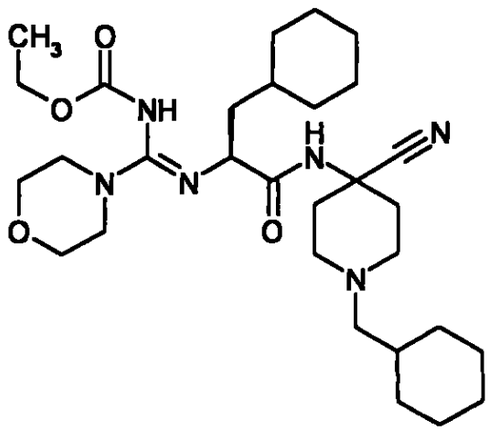
N-(4-ciano-1-propil-piperidin-4-il)-3-(4,4-dimetil-ciclohexil)-2-(2-oxo-2H-benzo[e][1,3]oxazin-4-ilamino)-propionamida; MS: 494 (M+1)



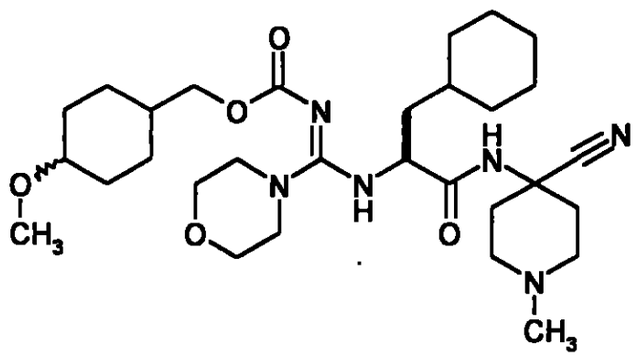
Éster etílico de ácido {[1-(3-ciano-1-etil-pirrolidin-3-il-carbamoil)-2-ciclohexil-etilamino]-morfolin-4-il-metileno}-carbámico: MS: 477 (M+1)



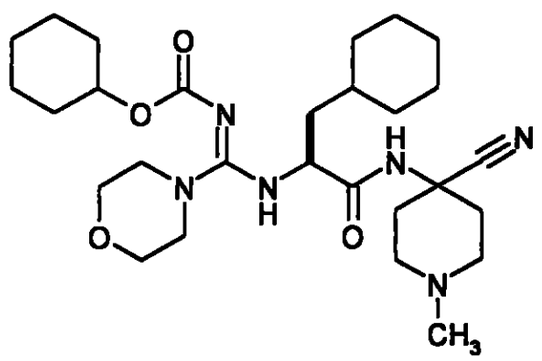
N-(4-ciano-1-metil-piperidin-4-il)-3-ciclohexil-2-(7,8-difluoro-2-oxo-2H-benzo[e][1,3]oxazin-4-ilamino)-propionamida; MS: 474 (M+1)



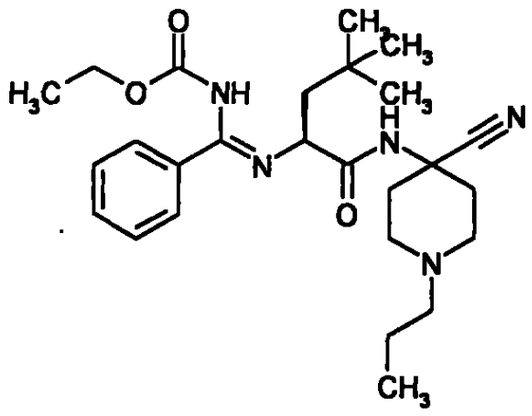
Éster etílico de ácido {[1-(4-ciano-1-ciclohexilmetil-piperidin-4-ilcarbamoil)-2-ciclohexil-etilamino]-morfolin-4-il-metileno}-carbámico: MS: 559 (M+1)



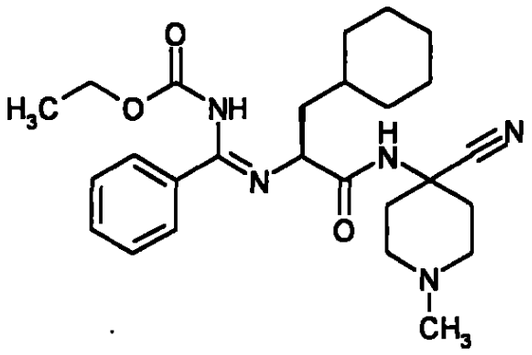
Éster 4-metoxi-ciclohexilmetílico de ácido {[1-(4-ciano-1-metil-piperidin-4-ilcarbamoil)-2-ciclohexil-etilamino]-morfolin-4-il-metileno}-carbámico: MS: 575 (M+1)



Éster ciclohexílico de ácido {[1-(4-ciano-1-metil-piperidin-4-ilcarbamoil)-2-ciclohexil-etilamino]-morfolin-4-il-metileno}-carbámico: MS: 531 (M+1)

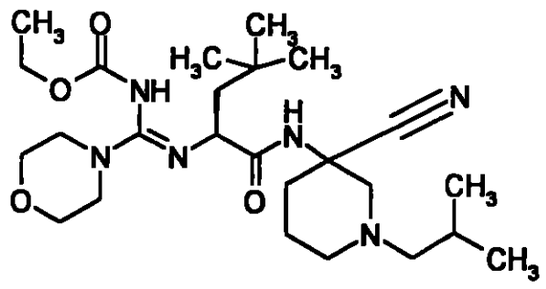


Éster etílico de ácido {[1-(4-ciano-1-propil-piperidin-4-ilcarbamoil)-3,3-dimetil-butilamino]-fenil-metileno}-carbámico: MS: 470 (M+1)

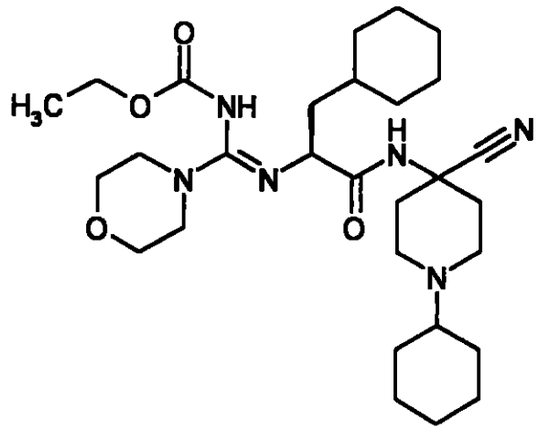


Éster etílico de ácido {[1-(4-ciano-1-metil-piperidin-4-ilcarbamoil)-2-ciclohexil-etilamino]-fenil-metileno}-carbámico: MS: 468 (M+1)

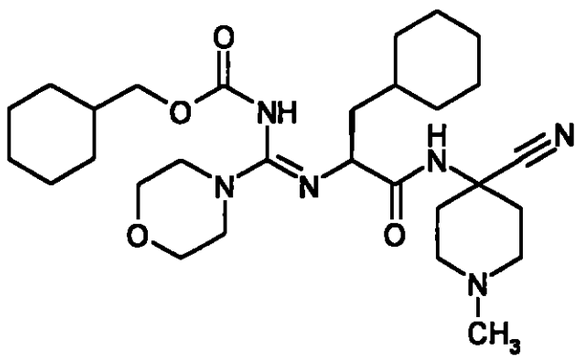
Compuestos de las fórmula (Ia) y (Ib) más preferidos son los elegidos de los siguientes:



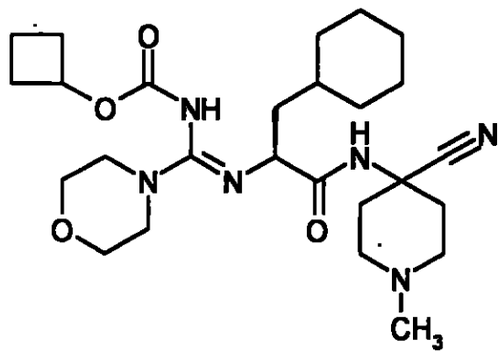
Éster etílico de ácido {[1-(3-ciano-1-isobutil-piperidin-3-ilcarbamoil)-3,3-dimetil-butilamino]-morfolin-4-il-metileno}-carbámico: MS: 493 (M+1)



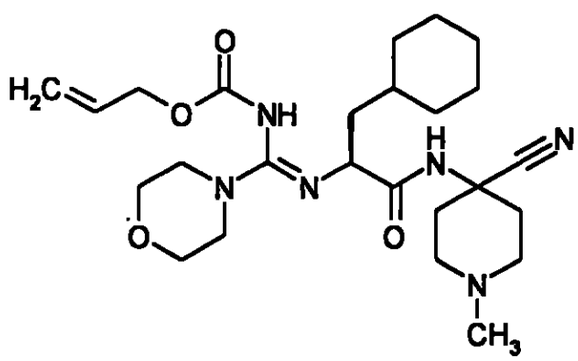
Éster etílico de ácido {[1-(4-ciano-1-ciclohexil-piperidin-4-ilcarbamoil)-2-ciclohexil-etilamino]-morfolin-4-il-metileno}-carbámico: MS: 545 (M+1)



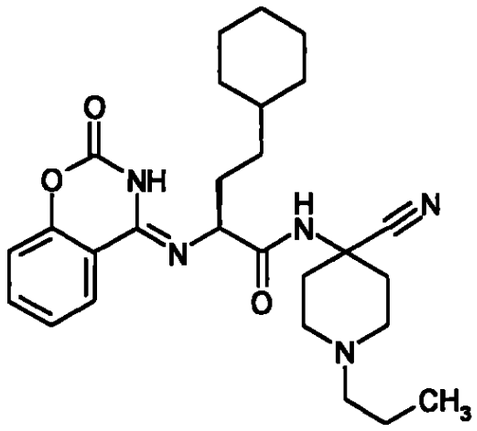
Éster ciclohexilmetílico de ácido {[1-(4-ciano-1-metil-piperidin-4-ilcarbamoil)-2-ciclohexil-etilamino]-morfolin-4-il-metileno}-carbámicc: MS: 545 (M+1)



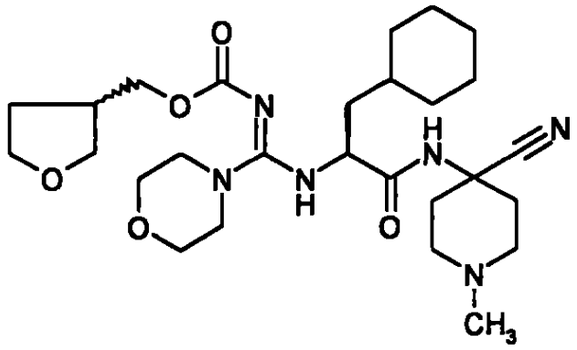
Éster ciclobutílicc de ácido {[1-(4-cianc-1-metil-piperidin-4-ilcarbamoil)-2-ciclohexil-etilamino]-morfolin-4-il-metileno}-carbámico: MS: 503 (M+1)



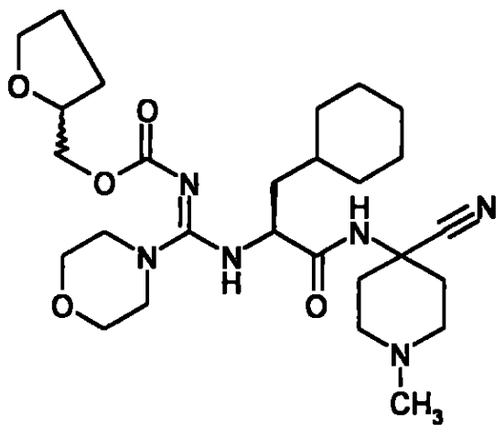
Éster alílico de ácido {[1-(4-ciano-1-metil-piperidin-4-ilcarbamoil)-2-ciclohexil-etilamino]-morfolin-4-il-metileno}-carbámico: MS: 489 (M+1)



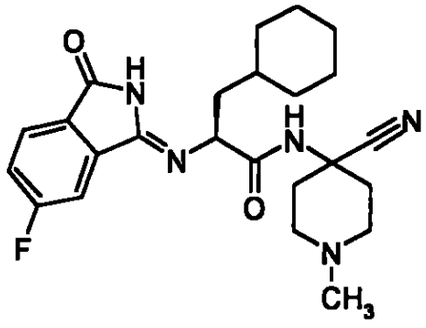
N-(4-ciano-1-propil-piperidin-4-il)-4-ciclohexil-2-(2-oxo-2,3-dihidro-benzo[e][1,3]oxazin-4-ilidenamino)-butiramida; MS: 480 (M+1)



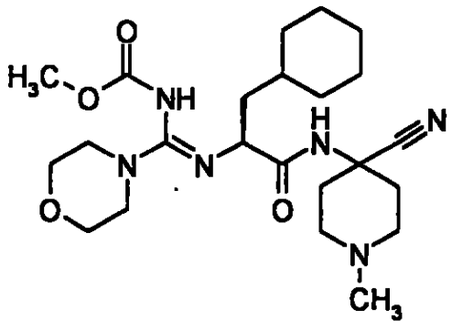
Éster tetrahidro-furan-3-ilmetílico de ácido {[1-(4-ciano-1-metil-piperidin-4-ilcarbamoil)-2-ciclohexil-etilamino]-morfolin-4-il-metileno}-carbámico: MS: 533 (M+1)



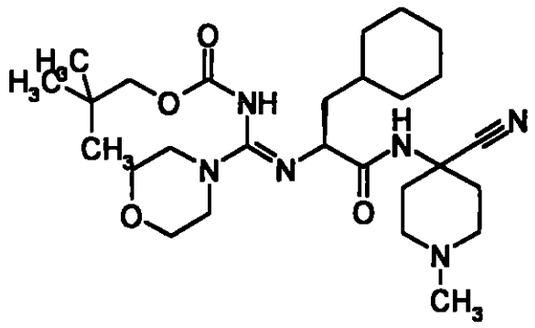
Éster tetrahidro-furan-2-ilmetílico de ácido {[1-(4-ciano-1-metil-piperidin-4-ilcarbamoil)-2-ciclohexil-etilamino]-morfolin-4-il-metileno}-carbámico: MS: 533 (M+1)



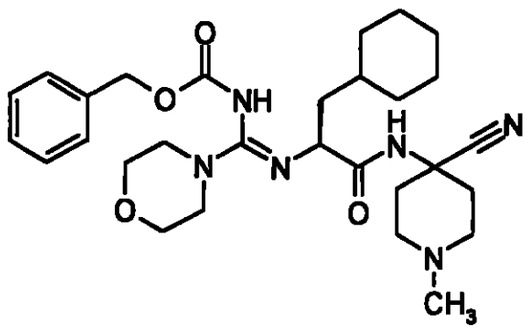
N-(4-ciano-1-metil-piperidin-4-il)-3-ciclohexil-2-(6-fluoro-3-oxo-2,3-dihidro-isoindol-1-ilidenamino)-propionamida; MS: 440 (M+1)



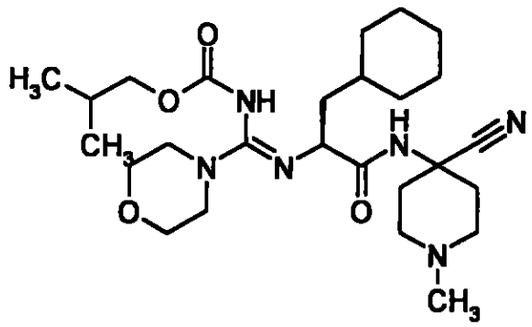
Éster metílico de ácido {[1-(4-ciano-1-metil-piperidin-4-ilcarbamoil)-2-ciclohexil-etilimino]-morfolin-4-il-metileno}-carbámico: MS: 463 (M+1)



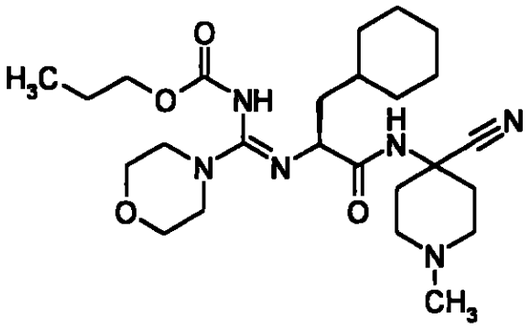
Éster 2,2-dimetil-propílico de ácido {[1-(4-ciano-1-metil-piperidin-4-ilcarbamoil)-2-ciclohexil-etilimino]-morfolin-4-il-metil}-carbámico: MS: 519 (M+1)



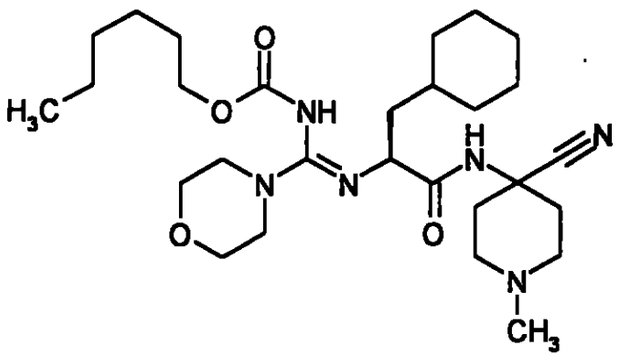
Éster bencílico de ácido {[1-(4-ciano-1-metil-piperidin-4-ilcarbamoil)-2-ciclohexil-etilimino]-morfolin-4-il-metil}-carbámico: MS: 539 (M+1)



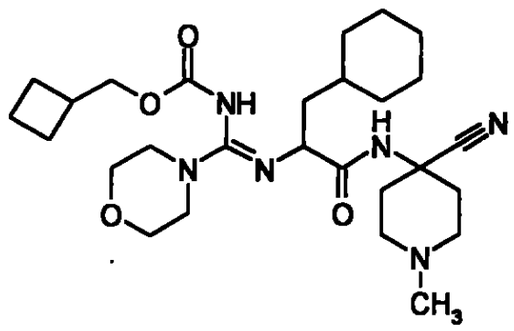
Éster isobutílico de ácido {[1-(4-ciano-1-metil-piperidin-4-ilcarbamoil)-2-ciclohexil-etilimino]-morfolin-4-il-metil}-carbámico: MS: 505 (M+1)



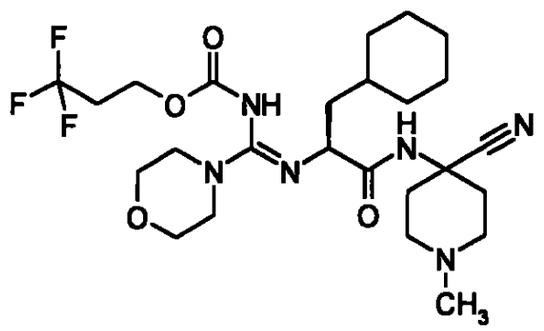
Éster propílico de ácido {[1-(4-ciano-1-metil-piperidin-4-ilcarbamoil)-2-ciclohexil-etilimino]-morfolin-4-il-metil}-carbámico: MS: 491 (M+1)



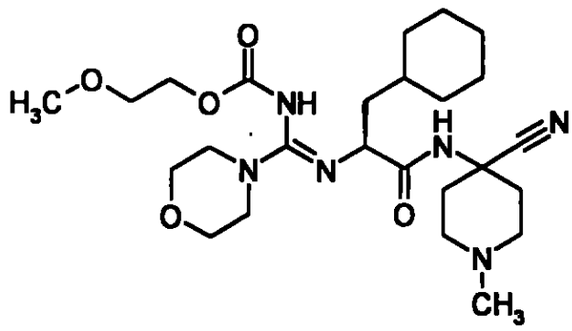
Éster hexílico de ácido {[1-(4-ciano-1-metil-piperidin-4-ilcarbamoil)-2-ciclohexil-etilimino]-morfolin-4-il-metil}-carbámico: MS: 533 (M+1)



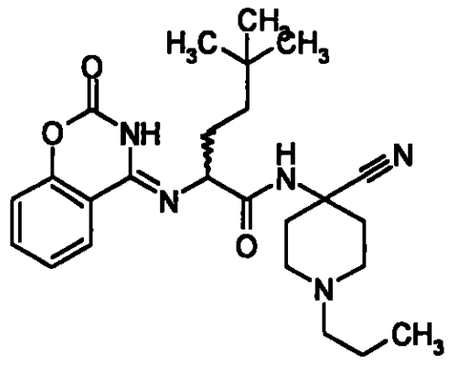
Éster ciclobutilmetílico de ácido {[1-(4-ciano-1-metil-piperidin-4-ilcarbamoil)-2-ciclohexil-etilimino]-morfolin-4-il-metil}-carbámico: MS: 517 (M+1)



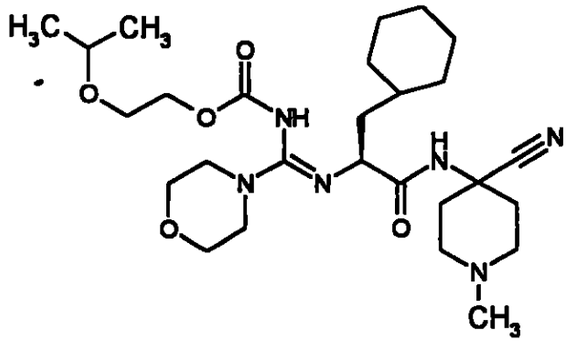
Éster 3,3,3-trifluoro-propílico de ácido {[1-(4-ciano-1-metil-piperidin-4-ilcarbamoil)-2-ciclohexil-etilimino]-morfolin-4-il-metil}-carbámico: MS: 545 (M+1)



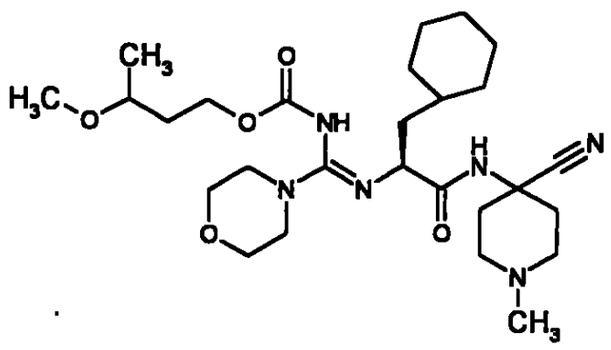
Éster 2-metoxi-etílico de ácido {[1-(4-ciano-1-metil-piperidin-4-ilcarbamoil)-2-ciclohexil-etilimino]-morfolin-4-il-metil}-carbámico: MS: 507 (M+1)



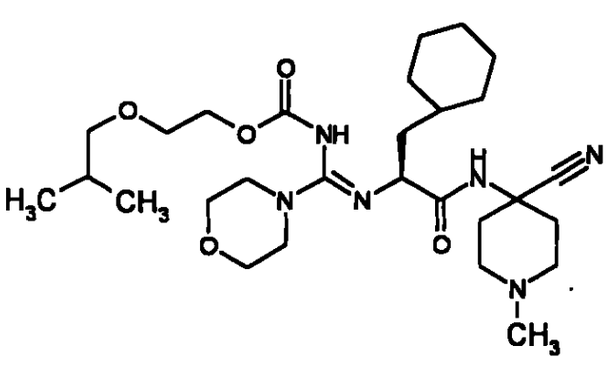
(4-ciano-1-propil-piperidin-4-il)-amida de ácido 5,5-dimetil-2-(2-oxo-2,3-dihidro-benzo[e][1,3]oxazin-4-ilidenamino)-hexanoico; MS: 454 (M+1)



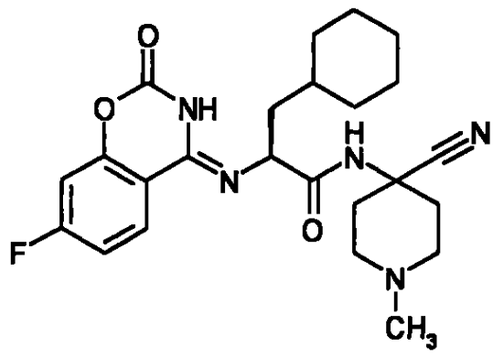
Éster 2-isopropoxi-etílico de ácido {[1-(4-ciano-1-metil-piperidin-4-ilcarbamoil)-2-ciclohexil-etilimino]-morfolin-4-il-metil}-carbámico: MS: 534 (M+1)



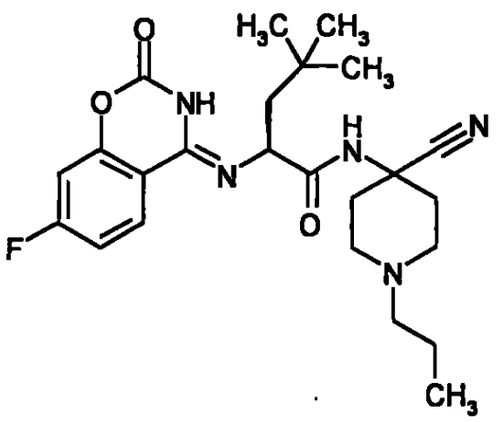
Éster 3-metoxi-butílico de ácido {[1-(4-ciano-1-metil-piperidin-4-ilcarbamoil)-2-ciclohexil-etilimino]-morfolin-4-il-metil}-carbámico: MS: 534 (M+1)



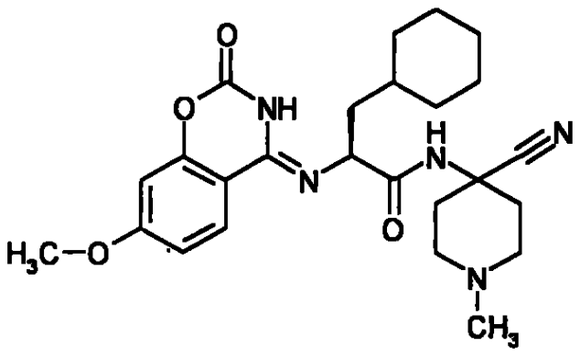
Éster 2-isobutoxi-etílico de ácido {[1-(4-ciano-1-metil-piperidin-4-ilcarbamoil)-2-ciclohexil-etilimino]-morfolin-4-il-metil}-carbámico: MS: 549 (M+1)



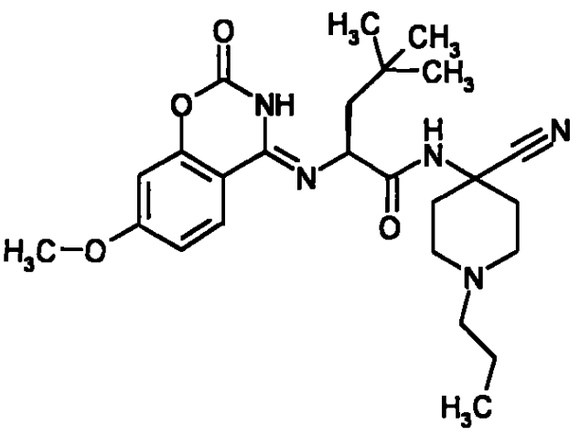
N-(4-ciano-1-metil-piperidin-4-il)-4-ciclohexil-2-(7-fluoro-2-oxo-2,3-dihidro-benzo[e][1,3]oxazin-4-ilidenamino)-butiramida; MS: 456 (M+1)



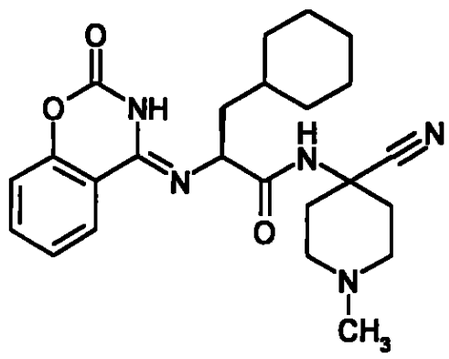
(4-ciano-1-propil-piperidin-4-il)-amida de ácido 2-(7-fluoro-2-oxo-2,3-dihidro-benzo[e][1,3]oxazin-4-ilidenamino)-5,5-dimetil-hexanoico; MS: 458 (M+1)



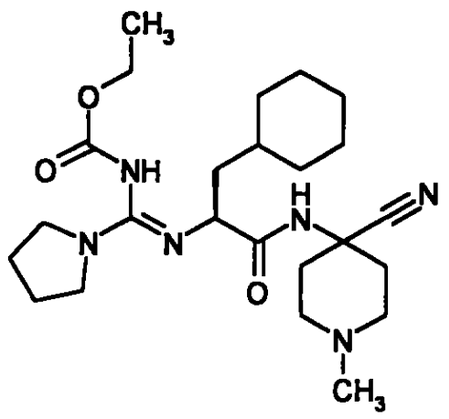
N-(4-ciano-1-metil-piperidin-4-il)-4-ciclohexil-2-(7-metoxi-2-oxo-2,3-dihidro-benzo[e][1,3]oxazin-4-ilidenamino)-butiramida; MS: 468 (M+1)



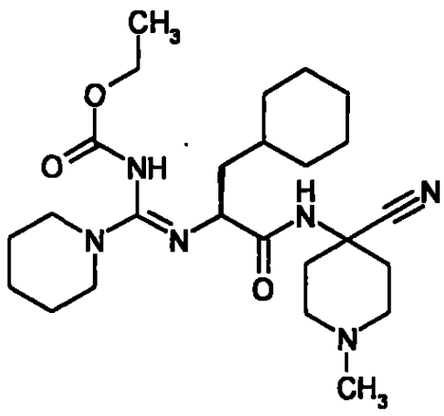
(4-ciano-1-propil-piperidin-4-il)-amida de ácido 2-(7-metoxi-2-oxo-2,3-dihidro-benzo[e][1,3]oxazin-4-ilidenamino)-5,5-dimetil-hexanoico; MS: 470 (M+1)



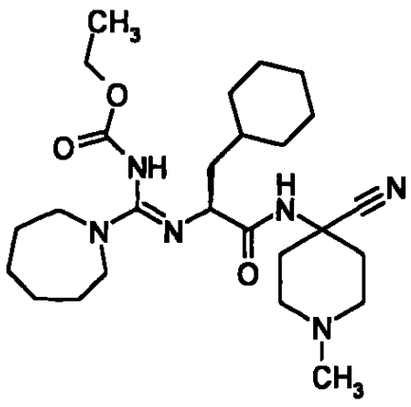
N-(4-ciano-1-metil-piperidin-4-il)-3-ciclohexil-2-(2-oxo-2,3-dihidro-benzo[e][1,3]oxazin-4-ilidenamino)-propionamida; MS: 438 (M+1)



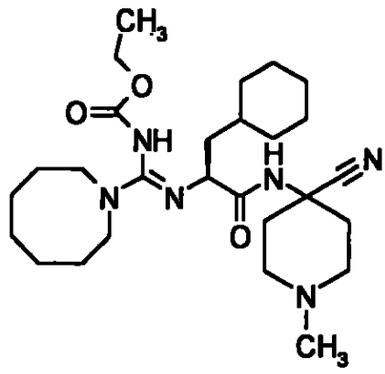
Éster etílico de ácido {[1-(4-ciano-1-metil-piperidin-4-ilcarbamoil)-2-ciclohexil-etilimino]-pirrolidin-1-il-metil}-carbámico: MS: 461 (M+1)



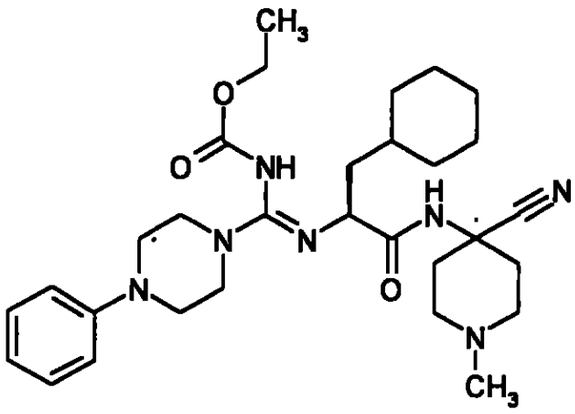
Éster etílico de ácido {[1-(4-ciano-1-metil-piperidin-4-ilcarbamoil)-2-ciclohexil-etilimino]-piperidin-1-il-metil}-carbámico: MS: 475 (M+1)



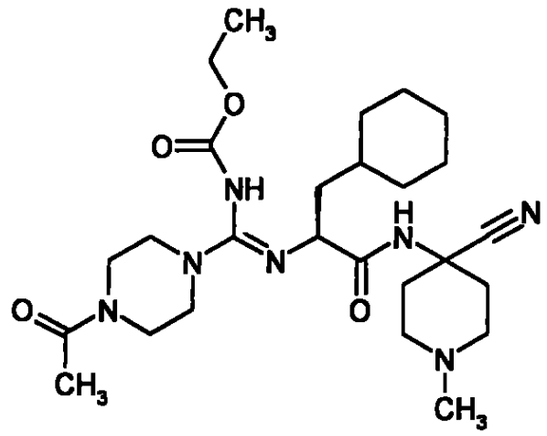
Éster etílico de ácido {azepan-1-il-[1-(4-ciano-1-metil-piperidin-4-ilcarbamoil)-2-ciclohexil-etilimino]-metil}-carbámico: MS: 489 (M+1)



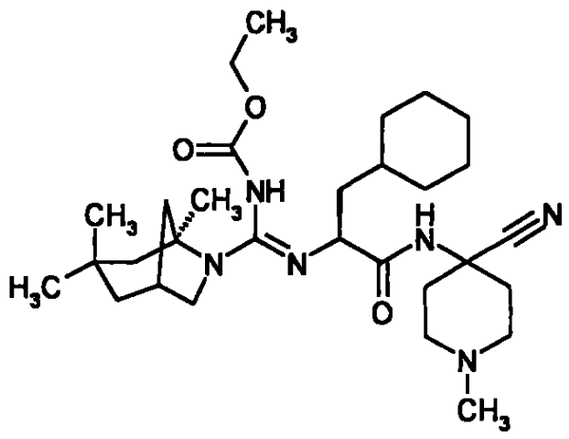
Éster etílico de ácido {azocan-1-il-[1-(4-ciano-1-metil-piperidin-4-ilcarbamoil)-2-ciclohexil-etilimino]-metil}-carbámico: MS: 503 (M+1)



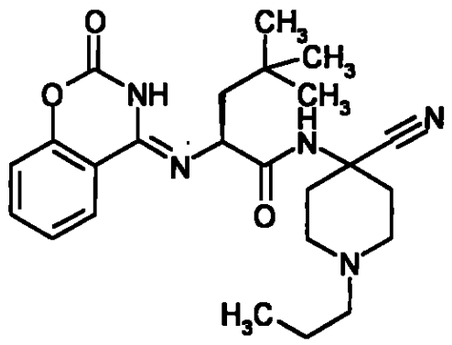
Éster etílico de ácido [[1-(4-ciano-1-metil-piperidin-4-ilcarbamoil)-2-ciclohexil-etilimino]-(4-fenil-piperazin-1-il)-metil]-carbámico: MS: 552 (M+1)



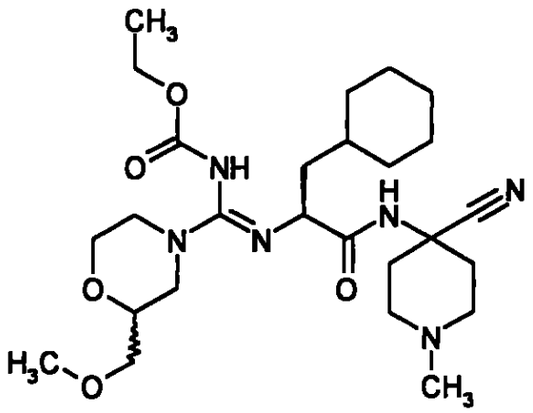
Éster etílico de ácido {(4-acetil-piperazin-1-il)-[1-(4-ciano-1-metil-piperidin-4-ilcarbamoil)-2-ciclohexil-etilimino]-metil}-carbámico: MS: 518 (M+1)



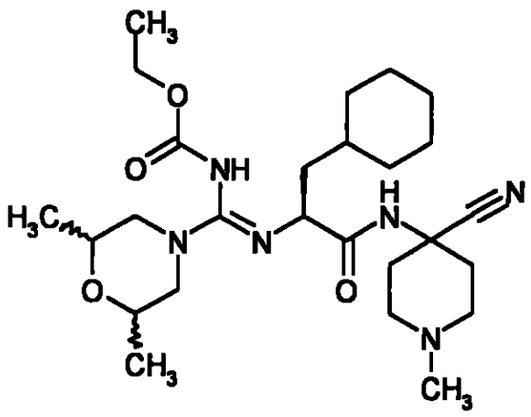
Éster etílico de ácido [[1-(4-ciano-1-metil-piperidin-4-ilcarbamoil)-2-ciclohexil-etilimino]-(3,3,5-trimetil-6-aza-biciclo[3.2.1]oct-6-il)-metil]-carbámico: MS: 543 (M+1)



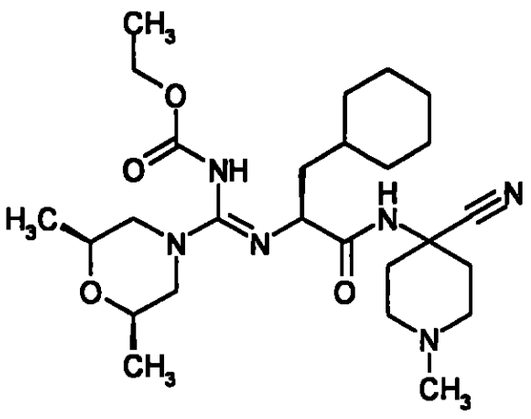
(4-ciano-1-propil-piperidin-4-il)-amida de ácido 4,4-dimetil-2-(2-oxo-2,3-dihidro-benzo[e][1,3]oxazin-4-ilidenamino)-pentanoico; MS: 440 (M+1)



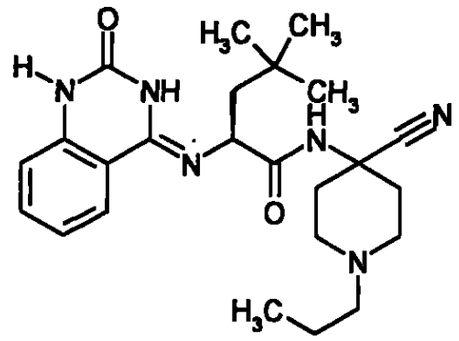
Éster etílico de ácido [[1-(4-ciano-1-metil-piperidin-4-ilcarbamoil)-2-ciclohexil-etilimino]-(2-metoximetil-morfolin-4-il)-metil]-carbámico: MS: 521 (M+1)



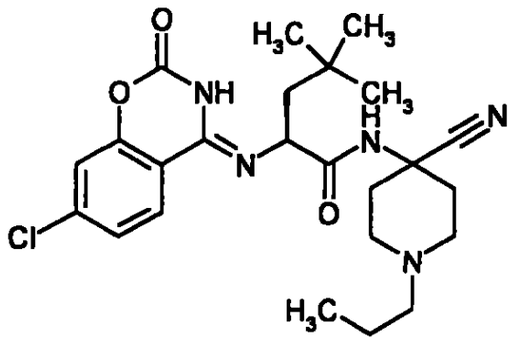
Éster etílico de ácido [[1-(4-ciano-1-metil-piperidin-4-ilcarbamoil)-2-ciclohexil-etilimino]-(2,6-dimetil-morfolin-4-il)-metil]-carbámico: MS: 505 (M+1)



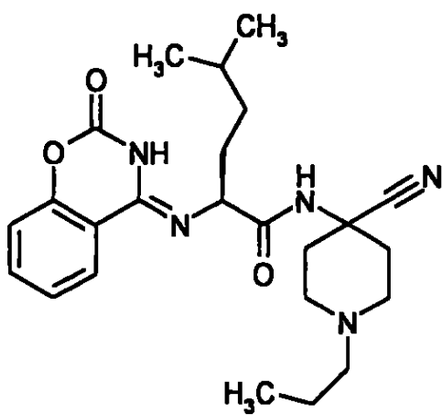
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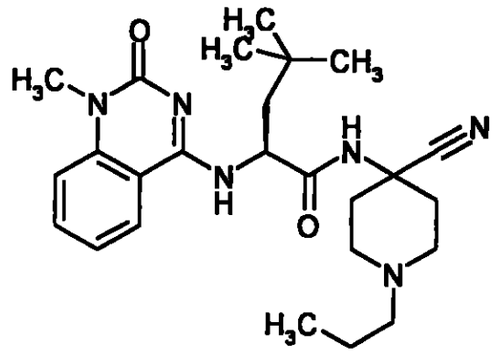
(4-ciano-1-propil-piperidin-4-il)-amida de ácido 4,4-dimetil-2-(2-oxo-2,3-dihidro-1*H*-quinazolin-4-ilidenamino)-pentanoico; MS: 439 (M+1)



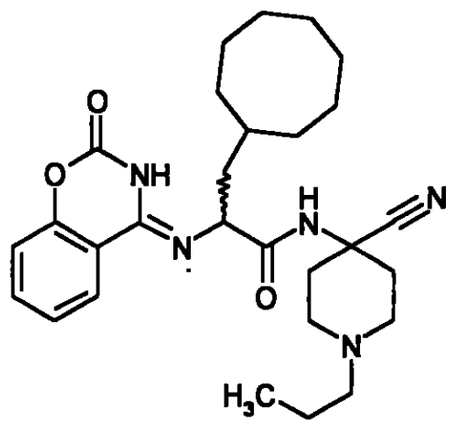
(4-ciano-1-propil-piperidin-4-il)-amida de ácido 2-(7-cloro-2-oxo-2,3-dihidro-benzo[e][1,3]oxazin-4-ilidenamino)-4,4-dimetil-pentanoico; MS: 475 (M+1)



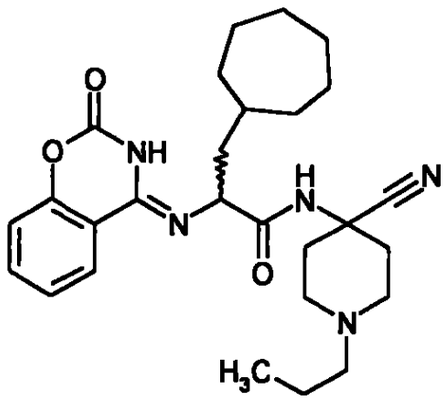
(4-ciano-1-propil-piperidin-4-il)-amida de ácido 5-metil-2-(2-oxo-2,3-dihidro-benzo[e][1,3]oxazin-4-ilidenamino)-hexanoico; MS: 440 (M+1)



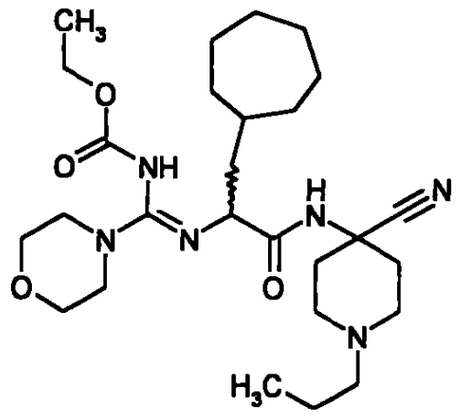
(4-ciano-1-propil-piperidin-4-il)-amida de ácido 4,4-dimetil-2-(1-metil-2-oxo-1,2-dihidro-quinazolin-4-ilamino)-pentanoico; MS: 453 (M+1)



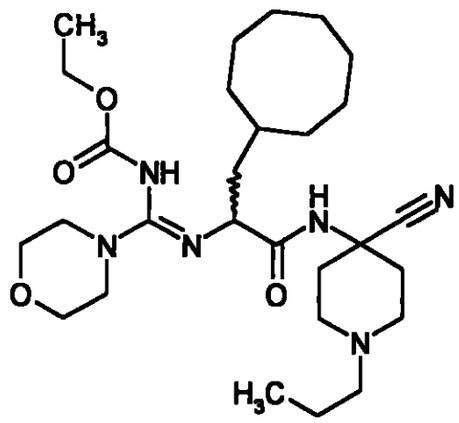
N-(4-ciano-1-propil-piperidin-4-il)-3-ciclooctil-2-(2-oxo-2,3-dihidro-benzo[e][1,3]oxazin-4-ilidenamino)-propionamida; MS: 494 (M+1)



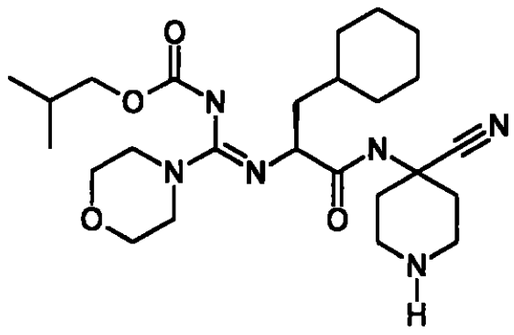
N-(4-ciano-1-propil-piperidin-4-il)-3-cicloheptil-2-(2-oxo-2,3-dihidro-benzo[e][1,3]oxazin-4-ilidenamino)-propionamida; MS: 480 (M+1)



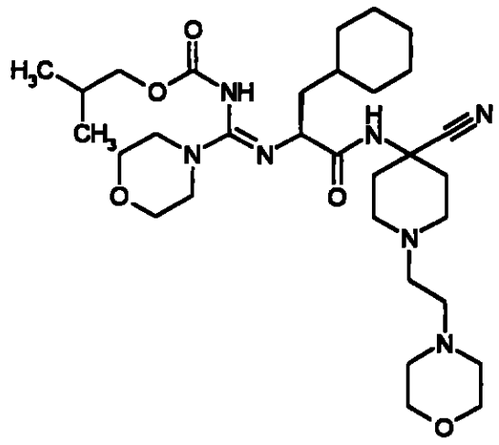
Éster etilico de ácido {[1-(4-ciano-1-propil-piperidin-4-ilcarbamoil)-2-cicloheptil-etilimino]-morfolin-4-il-metil}-carbámico; MS: 519 (M+1)



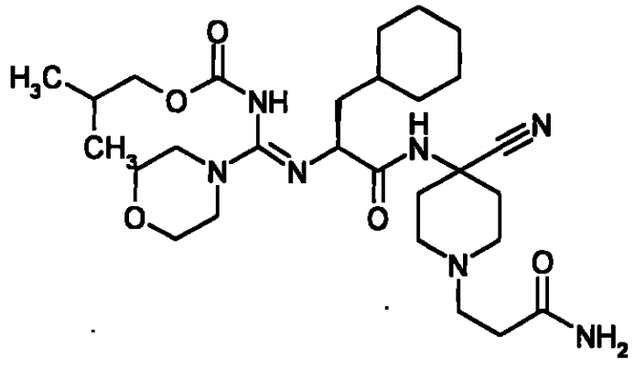
Éster etílico de ácido {[1-(4-ciano-1-propil-piperidin-4-ilcarbamoil)-2-ciclooctil-etilimino]-morfolin-4-il-metil}-carbámico; MS: 533 (M+1)



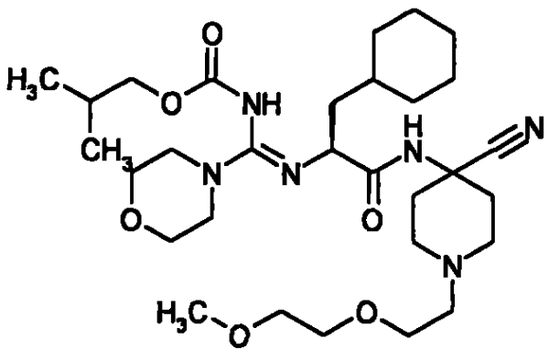
Éster isobutílico de ácido {[1-(4-ciano-piperidin-4-ilcarbamoil)-2-ciclohexil-etilamino]-morfolin-4-il-metileno}-carbámico; MS: 491 (M+1)



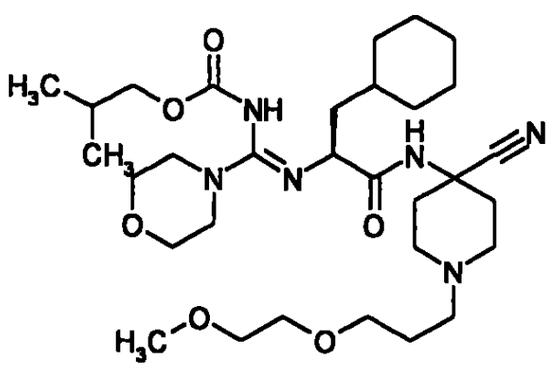
Éster isobutílico de ácido ({1-[4-ciano-1-(2-morfolin-4-il-etil)-piperidin-4-ilcarbamoil]-2-ciclohexil-etilamino}-morfolin-4-il-metileno)-carbámico; MS: 604 (M+1)



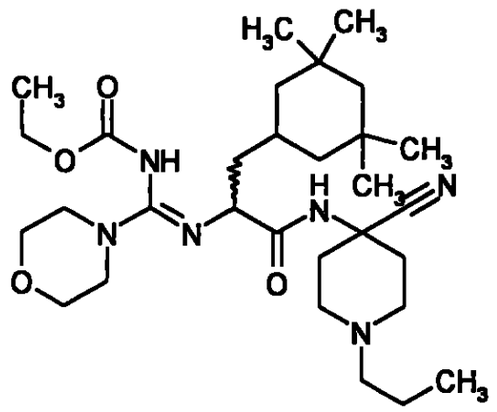
Éster isobutílico de ácido ({1-[1-(2-carbamoil-etil)-4-ciano-piperidin-4-ilcarbamoil]-2-ciclohexil-etilamino}-morfolin-4-il-metileno)-carbámico; MS: 562 (M+1)



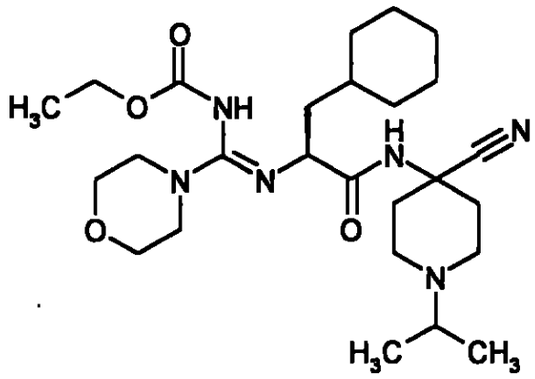
Éster isobutílico de ácido [(1-{4-ciano-1-[2-(2-metoxil-etoxi)-etil]-piperidin-4-ilcarbamoil}-2-ciclohexil-etilamino)-morfolin-4-il-metileno]-carbámico; MS: 593 (M+1)



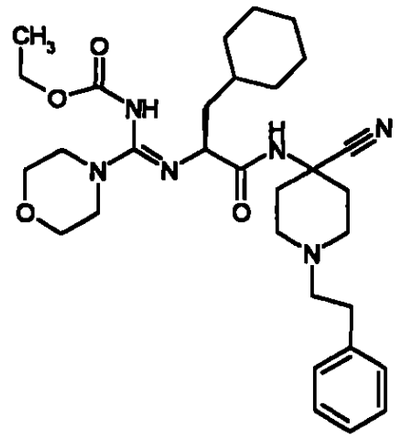
Éster isobutílico de ácido [(1-{4-ciano-1-[3-(2-metoxil-etoxi)-propil]-piperidin-4-ilcarbamoil}-2-ciclohexil-etilamino)-morfolin-4-il-metileno]-carbámico; MS: 607 (M+1)



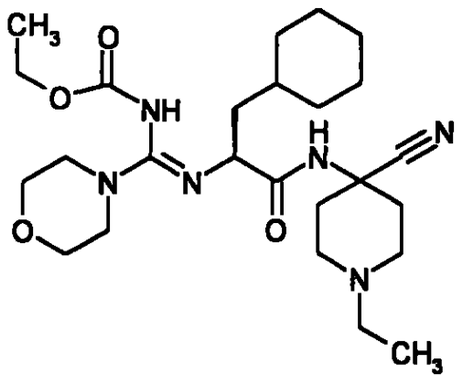
Éster etílico de ácido {[1-(4-ciano-1-propil-piperidin-4-ilcarbamoil)-2-(3,3,5,5-tetrametil-ciclohexil)-etilamino]-morfolin-4-il-metileno}-carbámico; MS: 561 (M+1)



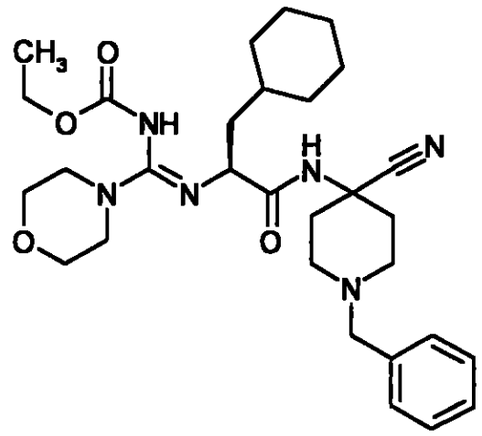
Éster etílico de ácido {[1-(4-ciano-1-isopropil-piperidin-4-ilcarbamoil)-2-ciclohexil-etilamino]-morfolin-4-il-metileno}-carbámico; MS: 505 (M+1)



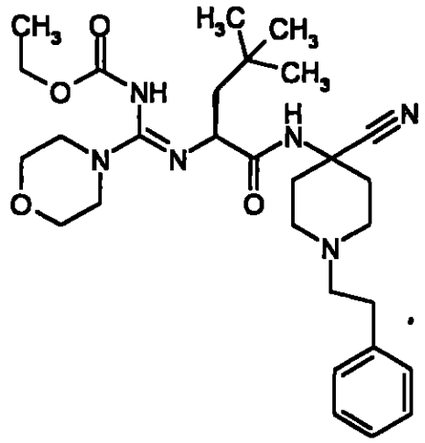
Éster etílico de ácido {[1-(4-ciano-1-fenetil-piperidin-4-ilcarbamoil)-2-ciclohexil-etilamino]-morfolin-4-il-metileno}-carbámico; MS: 567 (M+1)



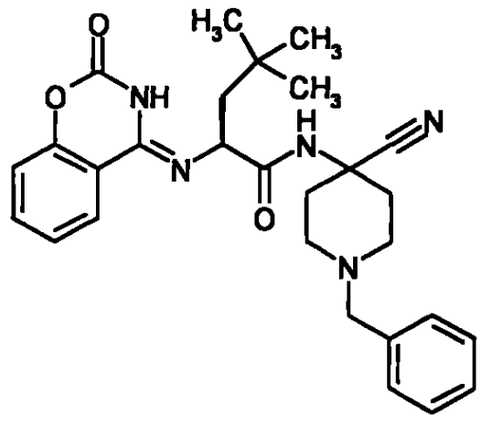
Éster etílico de ácido {[1-(4-ciano-1-etil-piperidin-4-ilcarbamoil)-2-ciclohexil-etilamino]-morfolin-4-il-metileno}-carbámico; MS: 491 (M+1)



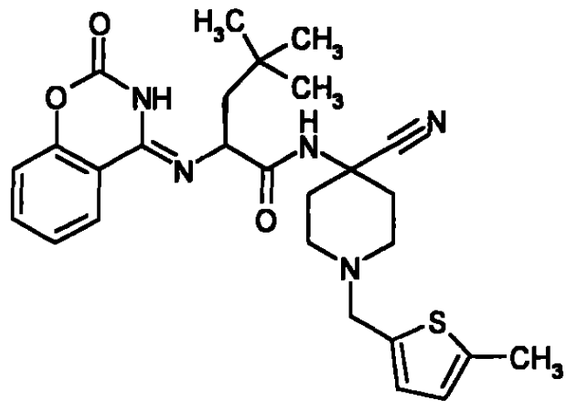
Éster etílico de ácido {[1-(1-bencil-4-ciano-piperidin-4-ilcarbamoil)-2-ciclohexil-etilamino]-morfolin-4-il-metileno}-carbámico; MS: 553 (M+1)



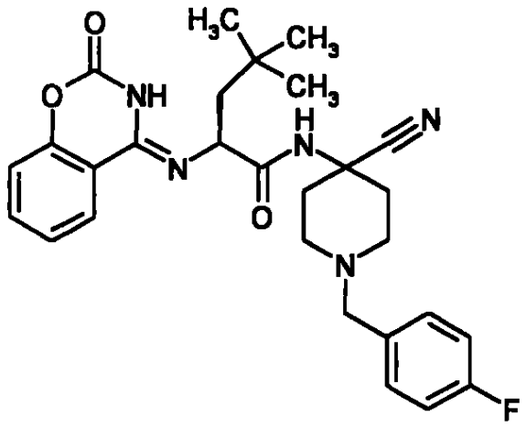
Éster etílico de ácido {[1-(4-ciano-1-fenetil-piperidin-4-ilcarbamoil)-3,3-dimetil-butilamino]-morfolin-4-il-metileno}-carbámico; MS: 541 (M+1)



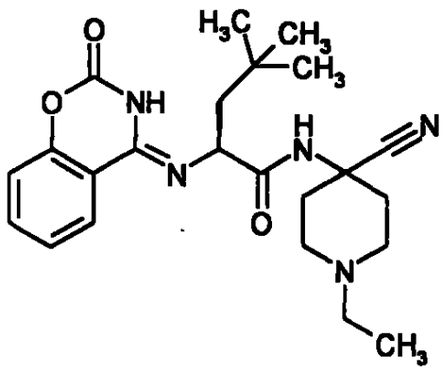
(1-bencil-4-ciano-piperidin-4-il)-amida de ácido 4,4-dimetil-2-(2-oxo-2H-benzo[e][1,3]oxazin-4-ilamino)-pentanoico; MS: 488 (M+1)



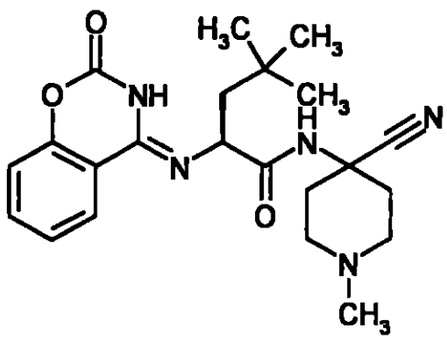
[4-ciano-1-(5-metil-tiofen-2-ilmetil)-piperidin-4-il]-amida de ácido 4,4-dimetil-2-(2-oxo-2H-benzo[e][1,3]oxazin-4-ilamino)-pentanoico; MS: 508 (M+1)



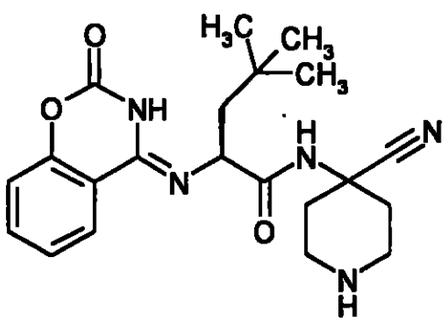
[4-ciano-1-(4-fluoro-bencil)-piperidin-4-il]-amida de ácido 4,4-dimetil-2-(2-oxo-2H-benzo[e][1,3]oxazin-4-ilamino)-pentanoico; MS: 506 (M+1)



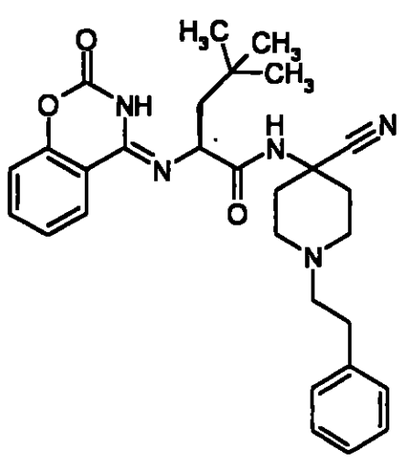
(4-ciano-1-etil-piperidin-4-il)-amida de ácido 4,4-dimetil-2-(2-oxo-2H-benzo[e][1,3]oxazin-4-ilamino)-pentanoico; MS: 426 (M+1)



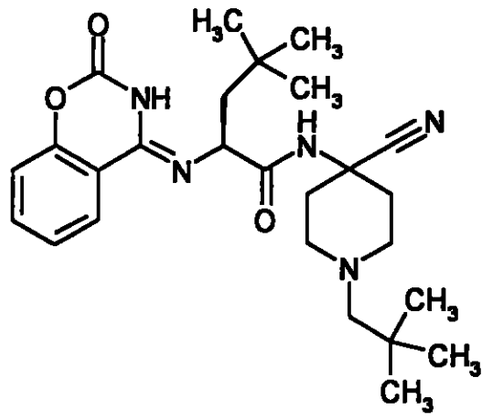
(4-ciano-1-metil-piperidin-4-il)-amida de ácido 4,4-dimetil-2-(2-oxo-2H-benzo[e][1,3]oxazin-4-ilamino)-pentanoico; MS: 412 (M+1)



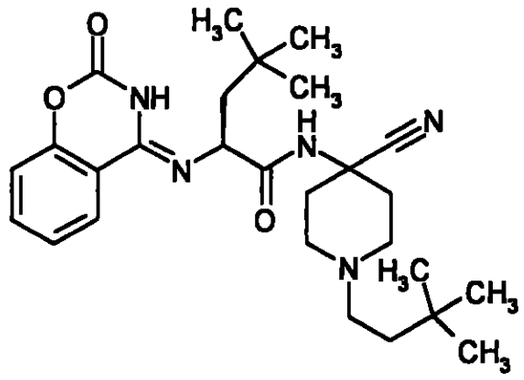
(4-ciano-piperidin-4-il)-amida de ácido 4,4-dimetil-2-(2-oxo-2H-benzo[e][1,3]oxazin-4-ilamino)-pentanoico; MS: 398 (M+1)



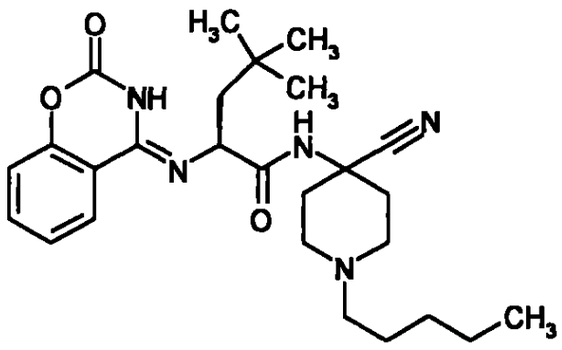
(4-ciano-1-fenetil-piperidin-4-il)-amida de ácido 4,4-dimetil-2-(2-oxo-2H-benzo[e][1,3]oxazin-4-ilamino)-pentanoico; MS: 502 (M+1)



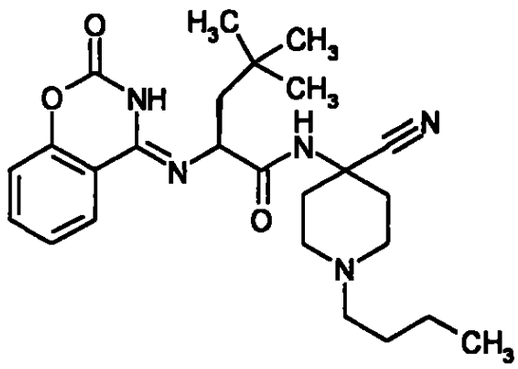
[4-ciano-1-(2,2-dimetil-propil)-piperidin-4-il]-amida de ácido 4,4-dimetil-2-(2-oxo-2H-benzo[e][1,3]oxazin-4-ilamino)-pentanoico; MS: 468 (M+1)



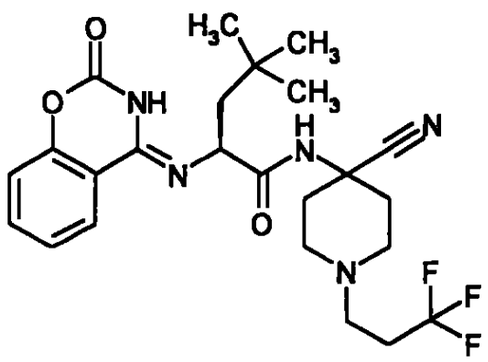
[4-ciano-1-(3,3-dimetil-butil)-piperidin-4-il]-amida de ácido 4,4-dimetil-2-(2-oxo-2H-benzo[e][1,3]oxazin-4-ilamino)-pentanoico; MS: 482 (M+1)



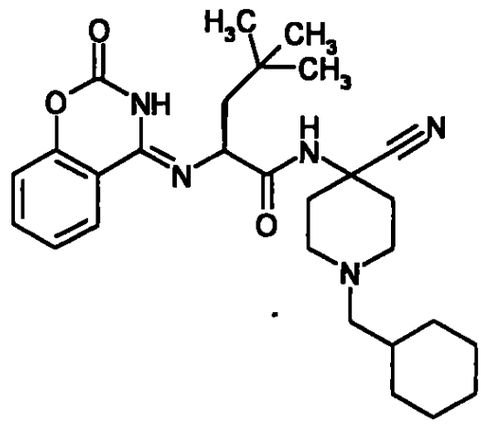
(4-ciano-1-pentil-piperidin-4-il)-amida de ácido 4,4-dimetil-2-(2-oxo-2H-benzo[e][1,3]oxazin-4-ilamino)-pentanoico; MS: 468 (M+1)



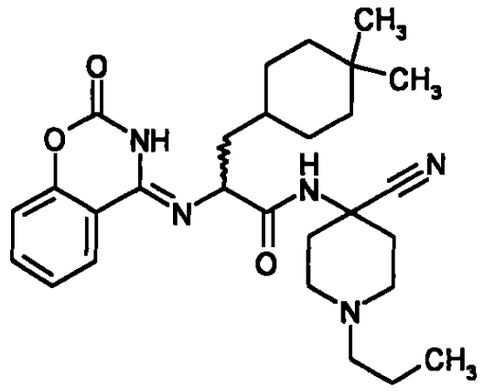
(1-butil-4-ciano-piperidin-4-il)-amida de ácido 4,4-dimetil-2-(2-oxo-2H-benzo[e][1,3]oxazin-4-ilamino)-pentanoico; MS: 454 (M+1)



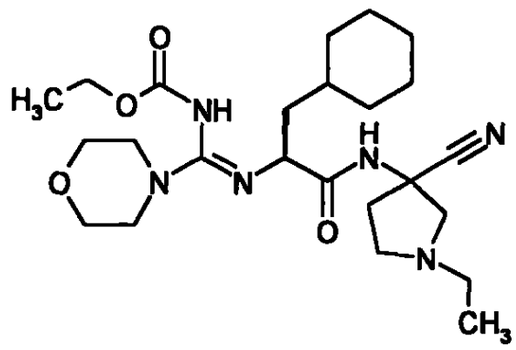
[4-ciano-1-(3,3,3-trifluoro-propil)-piperidin-4-il]-amida de ácido 4,4-dimetil-2-(2-oxo-2H-benzo[e][1,3]oxazin-4-ilamino)-pentanoico; MS: 494 (M+1)



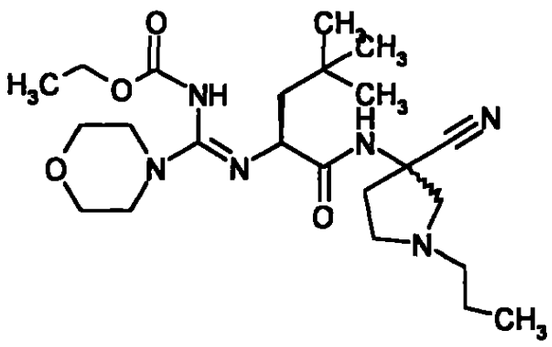
(4-ciano-1-ciclohexilmetil-piperidin-4-il)-amida de ácido 4,4-dimetil-2-(2-oxo-2H-benzo[e][1,3]oxazin-4-ilamino)-pentanoico; MS: 494 (M+1)



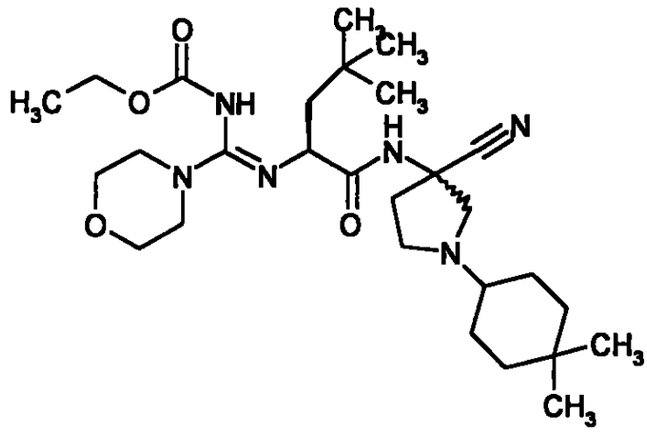
N-(4-ciano-1-propil-piperidin-4-il)-3-(4,4-dimetil-ciclohexil)-2-(2-oxo-2H-benzo[e][1,3]oxazin-4-ilamino)-propionamida; MS: 494 (M+1)



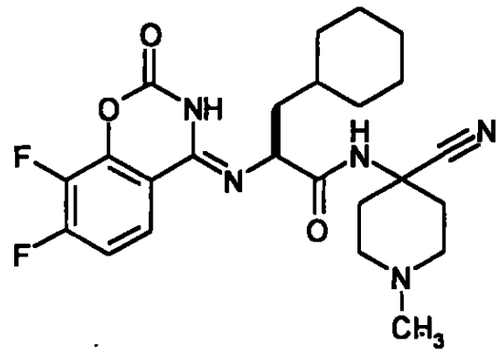
Éster etílico de ácido {[1-(3-ciano-1-etil-pirrolidin-3-ilcarbamoil)-2-ciclohexil-etilamino]-morfolin-4-il-metileno}-carbámico: MS: 477 (M+1)



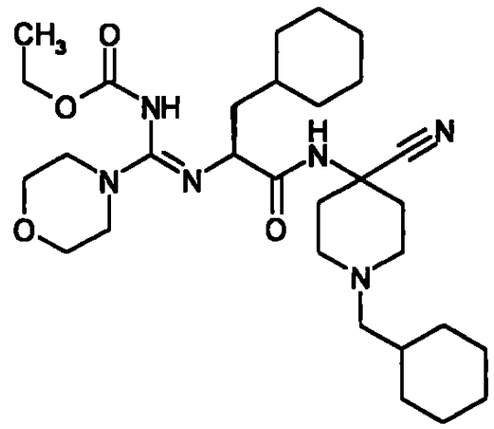
Éster etílico de ácido {[1-(3-ciano-1-propil-pirrolidin-3-ilcarbamoil)-3,3-dimetil-butilamino]-morfolin-4-il-metileno}-carbámico: MS: 465 (M+1)



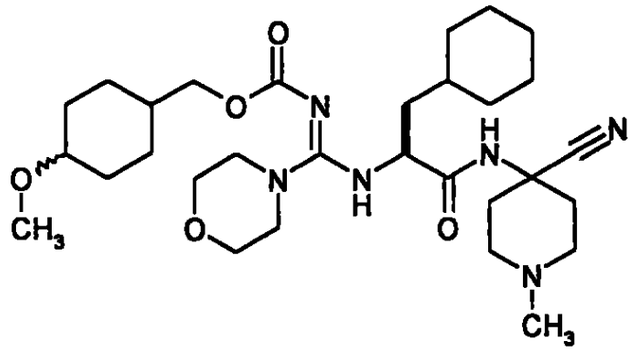
Éster etílico de ácido ({1-[3-ciano-1-(4,4-dimetil-ciclohexil)-pirrolidin-3-ilcarbamoil]-3,3-dimetil-butilamino}-morfolin-4-il-metileno)-carbámico: MS: 533 (M+1)



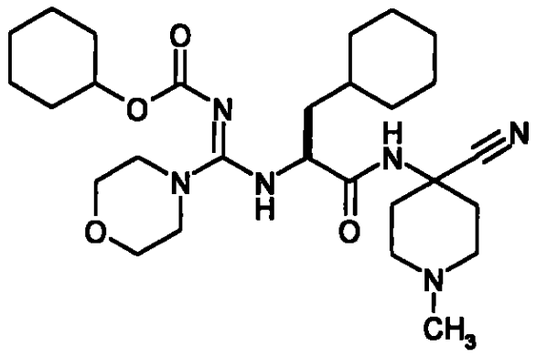
N-(4-ciano-1-metil-piperidin-4-il)-3-ciclohexil-2-(7,8-difluoro-2-oxo-2H-benzo[e][1,3]oxazin-4-ilamino)-propionamida; MS: 474 (M+1)



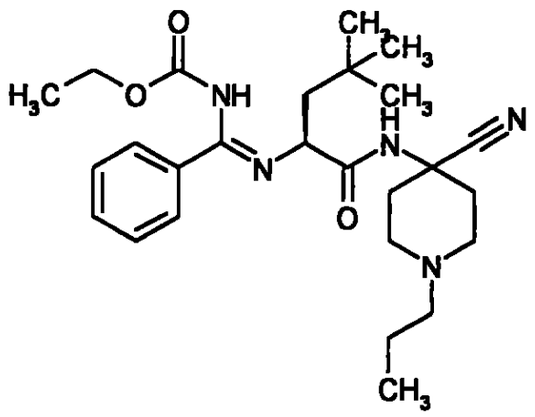
Éster etílico de ácido {[1-(4-ciano-1-ciclohexilmetil-piperidin-4-ilcarbamoil)-2-ciclohexil-etilamino]-morfolin-4-il-metileno}-carbámico: MS: 559 (M+1)



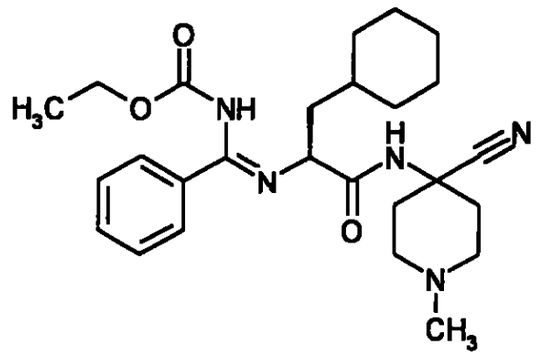
Éster 4-metoxi-ciclohexilmetílico de ácido {[1-(4-ciano-1-metil-piperidin-4-ilcarbamoil)-2-ciclohexil-etilamino]-morfolin-4-il-metileno}-carbámico: MS: 575 (M+1)



Éster ciclohexílico de ácido {[1-(4-ciano-1-metil-piperidin-4-ilcarbamoil)-2-ciclohexil-etilamino]-morfolin-4-il-metileno}-carbámicc: MS: 531 (M+1)



Éster etílico de ácido {[1-(4-ciano-1-propil-piperidin-4-ilcarbamoil)-3,3-dimetil-butilamino]-fenil-metileno}-carbámico: MS: 470 (M+1)



Éster etílico de ácido {[1-(4-ciano-1-metil-piperidin-4-ilcarbamoil)-2-ciclohexil-etilamino]-fenil-metileno}-carbámico: MS: 468 (M+1).

Cualesquiera compuestos de esta invención que contengan uno o más átomos de carbono asimétricos pueden manifestarse en forma de racematos y mezclas racémicas, enantiómeros sencillos, mezclas diastereoisómeras y diastereoisómeros individuales. La totalidad de tales formas isómeras de estos compuestos están expresamente incluidas en la presente invención. Cada carbono estereogénico puede estar en la configuración R o S, a menos que se especifique de otro modo, o en una combinación de configuraciones.

Alguno de los compuestos de fórmulas (Ia) y (Ib) puede existir en más de una forma tautómera. La invención incluye la totalidad de tales tautómeros.

Se entenderá por parte de un experto ordinario en la técnica que todos los compuestos de la invención son aquellos que sean químicamente estables.

La invención incluye derivados farmacéuticamente aceptables de compuestos de fórmulas (Ia) y (Ib). Un "derivado farmacéuticamente aceptable" se refiere a cualquier ácido, sal o éster de un compuesto de esta invención farmacéuticamente aceptable, o a cualquier otro compuesto que, tras la administración a un paciente, es capaz de proporcionar (directa o indirectamente) un compuesto de esta invención, un

metabolito farmacológicamente activo o un residuo farmacológicamente activo del mismo.

Además, los compuestos de esta invención incluyen profármacos de compuestos de las fórmulas (Ia) y (Ib). Los profármacos incluyen los compuestos que, tras una simple transformación, se modifican para producir los compuestos de la invención. Transformaciones químicas sencillas incluyen hidrólisis, oxidación y reducción que se manifiestan de modo enzimático, metabólico o de otra manera. Específicamente, cuando un profármaco de esta invención se administra a un paciente, el profármaco se puede transformar en un compuesto de fórmulas (Ia) y (Ib), impartiendo con ello el efecto farmacológico deseado.

Con el fin de que pueda entenderse más ampliamente la invención descrita en esta memoria, se recoge la siguiente descripción detallada. Tal como se utiliza en esta memoria, se utilizan las siguientes abreviaturas:

BOC o t-BOC es butoxicarbonilo terciario;

t-Bu es butilo terciario;

DMF es dimetilformamida;

EtOAc es acetato de etilo;

THF es tetrahidrofurano;

Ar es argón;

EDC es hidrocloruro de 1-(3-dimetilaminopropil)-3-etilcarbodiimida y

HOBT es 1-hidroxibenzotriazol.

También, tal como se utiliza en esta memoria, cada uno de los siguientes términos, ya sea utilizado solo o en unión con otros términos se define como sigue (excepto en los casos en los que se señale lo contrario).

El término "alquilo" se refiere a un radical alifático saturado que contiene de uno a diez átomos de carbono, o un radical hidrocarbonado alifático monosaturado o poliinsaturado que contiene de dos a doce átomos de carbono. El radical hidrocarburo alifático monosaturado o polinsaturado contiene

al menos un doble o triple enlace, respectivamente. "Alquilo" se refiere tanto a grupos alquilo ramificados como no ramificados. Ejemplos de "alquilo" incluyen grupos alquilo que son grupos alquilo de cadena lineal que contienen de uno a ocho átomos de carbono y grupos alquilo ramificados que contienen de tres a ocho átomos de carbono. Otros ejemplos incluyen grupos alquilo inferior que son grupos alquilo de cadena lineal que contienen de uno a seis átomos de carbono y grupos alquilo ramificados que contienen de tres a seis átomos de carbono. Debe entenderse que cualquier término de combinación que utilice un prefijo "alq" o "alquil" se refiere a análogos de acuerdo con la definición anterior de "alquilo". Por ejemplo, términos tales como "alcoxi", "alquiltio" se refieren a grupos alquilo enlazados a un segundo grupo a través de un átomo de oxígeno o azufre. "Alcanoílo" se refiere a un grupo alquilo enlazado a un grupo carbonilo (C=O). Cada alquilo o análogo de alquilo descrito en esta memoria ha de entenderse que está opcionalmente total o parcialmente halogenado.

El término "cicloalquilo" se refiere al análogo cíclico del grupo alquilo, según se define antes. Ejemplos de grupos cicloalquilo son grupos cicloalquilo no aromáticos saturados o insaturados que contienen de tres a ocho átomos de carbono, y otros ejemplos incluyen grupos cicloalquilo que tienen tres a seis átomos de carbono. Cada cicloalquilo descrito en esta memoria ha de entenderse que está opcionalmente, total o parcialmente halogenado.

El término "arilo" se refiere a fenilo y naftilo.

El término "halo" se refiere a un radical halógeno seleccionado de fluoro, cloro, bromo o yodo. Grupos halo representativos de esta invención son fluoro, cloro y bromo.

El término "heteroarilo" se refiere a un radical heterociclo aromático de 5-8 miembros (pero preferiblemente de 5 ó 6 miembros) monocíclico o de 8-11 miembros bicíclico, estable. Cada heterociclo consiste en átomos de carbono y en

1 a 4 heteroátomos elegidos de nitrógeno, oxígeno y azufre. El heterociclo puede estar fijado por cualquier átomo del ciclo, lo que resulta en la creación de una estructura estable. Ejemplos de "heteroarilo" incluyen radicales tales como furanilo, tienilo, pirrolilo, oxazolilo, tiazolilo, imidazolilo, pirazolilo, isoxazolilo, isotiazolilo, oxadiazolilo, triazolilo, tetrazolilo, tiadiazolilo, piridinilo, piridazinilo, pirmidinilo, pirazinilo, indolizinilo, indolilo, isoindolilo, benzofuranilo, benzotienilo, indazolilo, bencimidazolilo, benzotiazolilo, benzoxazolilo, purinilo, quinolizinilo, quinolinilo, isoquinolinilo, cinolinilo, ftalazinilo, quinazolinilo, quinoxalinilo, naftiridinilo, pteridinilo, carbazolilo, acridinilo, fenazinilo, fenotiazinilo y fenoxazinilo.

El término "heterociclo" se refiere a un radical heterociclo de 4-8 miembros (pero preferiblemente de 5 ó 6 miembros) monocíclico o de 8-11 miembros bicíclico, estable, que puede estar saturado o insaturado y que es no aromático. Cada heterociclo consiste en átomos de carbono y en 1 a 4 heteroátomos elegidos de nitrógeno, oxígeno y azufre. El heterociclo puede estar fijado por cualquier átomo del ciclo, lo que resulta en la creación de una estructura estable. Ejemplos de "heterociclo" incluyen radicales tales como pirrolinilo, pirrolidinilo, pirazolinilo, pirazolidinilo, piperidinilo, morfolinilo, tiomorfolinilo, piranilo, tiopiranilo, piperazinilo, indolinilo, azetidinilo, tetrahidropiranilo, tetrahidrotiopiranilo, tetrahidrofuranilo, hexahidropirimidinilo, hexahidropiridazinilo, 1,4,5,6-tetrahidropirimidin-2-ilamina, dihidro-oxoazolilo, 1,2-tiazinanil-1,1-dióxido, 1,2,6-tiadiazinanil-1,1-dióxido, isotiazolidinil-1,1-dióxido e imidazolidinil-2,4-diona.

Los términos "heterociclo", "heteroarilo" o "arilo", cuando se asocian con otro resto, a menos que se especifique de otro modo, han de tener el mismo significado que el dado anteriormente. Por ejemplo, "aroílo" se refiere a fenilo o

naftilo enlazado a un grupo carbonilo (C=O).

Cada arilo o heteroarilo, a menos que se especifique de otro modo, incluye su derivado parcial o totalmente hidrogenado. Por ejemplo, quinolinilo puede incluir decahidroquinolinilo y tetrahidroquinolinilo, naftilo puede incluir sus derivados hidrogenados tales como tetrahidronaftilo. Otros derivados parcial o totalmente hidrogenados de los compuestos de arilo y heteroarilo descritos en esta memoria resultarán evidentes para un experto ordinario en la técnica.

El término heterociclo, según pertenece a "Het", ha de entenderse que significa un radical espiroheterociclo no aromático estable, un radical heterociclo de 4-8 miembros (pero preferiblemente de 5 ó 6 miembros) monocíclico, de 8-11 miembros bicíclico que puede estar saturado o insaturado, o un biciclo C6-C10 puenteado, en donde uno o más átomos de carbono están opcionalmente reemplazados por un heteroátomo. Cada heterociclo consiste en átomos de carbono y en 1 a 4 heteroátomos elegidos de nitrógeno, oxígeno y azufre. El heterociclo puede estar fijado a cualquier átomo del ciclo, lo que resulta en la creación de una estructura estable. Ejemplos de "Het" incluyen los siguientes heterociclos: azepanilo, piperidinilo, pirrolidinilo, azetidinilo, oxepanilo, tetrahidropiranilo, tetrahidrotiopiranilo, tetrahidrofuranilo, oxetanilo, azocanilo, oxocanilo, 1,3-diazocanilo, 1,4-diazocanilo, 1,5-diazocanilo, 1,3-dioxocanilo, 1,4-dioxocanilo, 1,5-dioxocanilo, 1,3-oxazocanilo, 1,4-oxazocanilo, 1,5-oxazocanilo, 1,3-diazepanilo, 1,4-diazepanilo, 1,3-dioxepanilo, 1,4-dioxepanilo, 1,3-oxazepanilo, 1,4-oxazepanilo, 1,2-tiazocanil-1,1-dióxido, 1,2,8-tiadiazocanil-1,1-dióxido, 1,2-tiazepanil-1,1-dióxido, 1,2,7-tiadiazepanil-1,1-dióxido, tetrahidrotiofenilo, hexahidropirimidinilo, hexahidropiridazinilo, piperazinilo, 1,4,5,6-tetrahidropirimidinilo, pirazolidinilo, dihidro-oxazolilo, dihidrotiazolilo, dihidroimidazolilo, isoxazolinilo, oxazolidinilo, 1,2-tiazinanil-1,1-dióxido, 1,2,6-tiadiazinanil-1,1-dióxido,

isotiazolidinil-1,1-dióxido, imidazolidinil-2,4-diona, imidazolidinilo, morfolinilo, dioxanilo, tetrahidropiridinilo, tiomorfolinilo, tiazolidinilo, dihidropiranilo, ditianilo, decahidro-quinolinilo, decahidro-isoquinolinilo, 1,2,3,4-tetrahidro-quinolinilo, indolinilo, ocatahidro-quinolizinilo, dihidro-indolizinilo, octahidro-indolizinilo, octahidro-indolilo, decahidroquinazolinilo, decahidroquinoxalinilo, 1,2,3,4-tetrahidroquinazolinilo ó 1,2,3,4-tetrahidroquinoxalinilo, aza-biciclo[3.2.1]octano, aza-biciclo[2.2.1]heptano, aza-biciclo[2.2.2]octano, aza-biciclo[3.2.2]nonano, aza-biciclo[2.1.1]hexano, aza-biciclo[3.1.1]heptano, aza-biciclo[3.3.2]decano y 2-oxa- o 2-tia-5-aza-biciclo[2.2.1]heptano; estando cada anillo heterocíclico sustituido con uno o más $R_5$. El sustituyente $R_5$ es como se define anteriormente.

Tal como se utiliza antes y a lo largo de esta solicitud, "nitrógeno" y "azufre" incluyen cualquier forma oxidada de nitrógeno y azufre y la forma cuaternizada de cualquier nitrógeno básico.

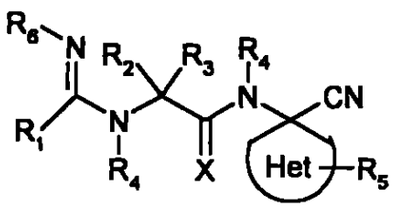
Con el fin de entender más completamente esta invención, se recogen los siguientes ejemplos. Estos ejemplos son con el fin de ilustrar realizaciones preferidas de esta invención, y no han de considerarse limitantes del alcance de la invención de modo alguno.

Los ejemplos que siguen son ilustrativos y, según se reconoce por un experto en la técnica, reactivos o condiciones particulares podrían modificarse según fuese necesario para los compuestos individuales. Materiales de partida utilizados en el esquema que figura más abajo son comercialmente disponibles o se pueden preparar fácilmente a partir de materiales comercialmente disponibles por parte de los expertos en la técnica.

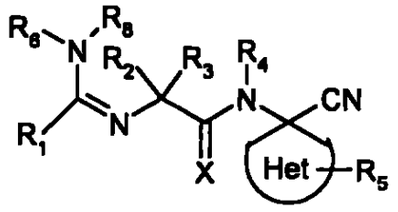
## MÉTODOS DE SÍNTESIS GENERALES

La invención proporciona también procedimientos para

preparar los presentes nuevos compuestos de fórmulas (Ia) y (Ib). Compuestos de la invención se pueden preparar por métodos descritos a continuación, los encontrados en la solicitud de EE.UU. n° de serie 09/655.351, incorporada en esta memoria como referencia en su totalidad, y por métodos conocidos por los de experiencia ordinaria en la técnica.

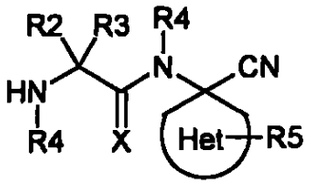



(Ia)




(Ib)

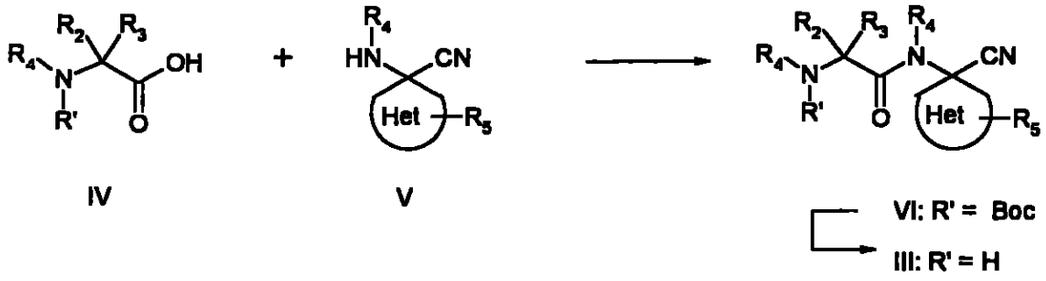
Un compuesto intermedio clave en la preparación de compuestos de fórmulas (Ia) y (Ib) es el compuesto intermedio dipéptido-nitrilo (III).




(III)

La síntesis de los compuestos intermedios de fórmula (III) se describe en la solicitud de patente provisional de EE.UU. 60/222.900 y está esbozada más abajo en los Esquemas I y II.

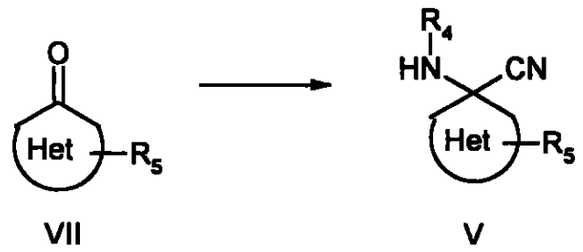
**Esquema I**




Tal como se ilustra en el Esquema I, un aminoácido que porta un grupo protector R' (IV) adecuado se hace reaccionar con un aminonitrilo (V) en condiciones de acoplamiento adecuadas. Un ejemplo de un grupo protector adecuado es el grupo t-butoxicarbonilo (BOC). Un ejemplo de condiciones de acoplamiento convencionales sería combinar los materiales de partida en presencia de un reactivo de acoplamiento tal como 1-(3-dimetilaminopropil)-3-etilcarbodiimida (EDC) con 1-hidroxibenzotriazol (HOBT) en un disolvente adecuado tal como DMF o cloruro de metileno. Se puede añadir una base tal como N-metilmorfolina. Esto es seguido de la desprotección para dar el aminoácido-nitrilo III.

El aminonitrilo (V) intermedio utilizado en el Esquema I anterior se puede preparar según se esboza en el Esquema II.

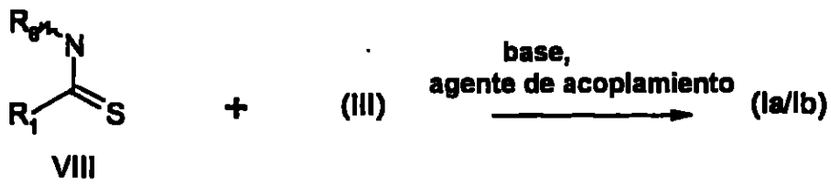
**Esquema II**



hace reaccionar con una amina primaria o una sal de amonio tal como cloruro de amonio, y una sal de cianuro tal como cianuro de potasio o cianuro de sodio, en un disolvente adecuado tal como agua o una solución de amoníaco en metanol a aproximadamente la temperatura ambiente hasta la temperatura de reflujo.

Compuestos con las fórmulas (Ia/Ib) se pueden preparar por los métodos A-D según se ilustra en los Esquemas III-VI.

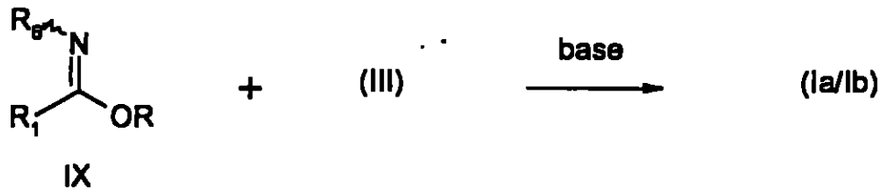
**Esquema III (Método A)**




De acuerdo con el Método A, un dipéptido-nitrilo intermedio (III) o una sal de carácter básico del mismo se permite que reaccione con (VIII) en presencia de un agente de acoplamiento adecuado para proporcionar el producto (Ia/Ib) deseado. Condiciones de reacción adecuadas son conocidas por los expertos en la técnica, y algunos ejemplos de agentes de acoplamiento adecuados incluyen yoduro de 2-cloro-1-metil-piridinio (Yong, Y.F. et al., J. Org. Chem. 1997, 62, 1540), fosgeno o trifosgeno (Barton, D.H. et al., J. Chem. Soc. Perkin Trans. I, 1982, 2085), haluros de alquilo (Brand, E. y Brand, F.C., Org. Synth., 1955, 3, 440), carbodiimidas (Poss, M.A. et al., Tetrahedron Lett., 1992, 40, 5933) y sales de mercurio (Su, W., Synthetic Comm., 1996, 26, 407 y Wiggall, K.J. y Richardson, S.K.J., Heterocyclic Chem., 1995, 32, 867).

Compuestos con las fórmulas (Ia) y (Ib) también se pueden preparar por el Método B según se ilustra en el Esquema IV, en que R es un grupo alquilo o arilo.

**Esquema IV (Método B)**

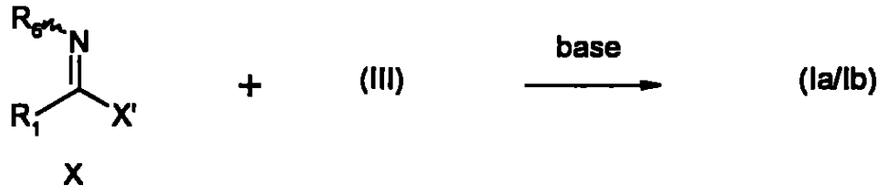



De acuerdo con el Método B un dipéptido-nitrilo intermedio (III) o una sal de carácter básico del mismo, se permite que reaccione con IX, con o sin una base añadida tal como trietilamina, para proporcionar el producto deseado (Ia/Ib). Condiciones de reacción adecuadas son conocidas por los expertos en la técnica, y ejemplos de tales adiciones de amina se pueden encontrar en la bibliografía química, por ejemplo Haake, M. y Schummelfeder, B., Synthesis, 1991, 9, 753; Dauwe, C. y Buddrus, J., Synthesis 1995, 2, 171; Ried, W. y Piechaczek, D., Justus Liebigs Ann. Chem. 1966, 97, 696 y Dean, W.D. y Papadopoulos, E.P., J. Heterocyclic Chem., 1982, 19, 1117.

El compuesto intermedio IX está comercialmente disponible o se puede sintetizar por métodos conocidos por los expertos en la técnica y descritos en la bibliografía, por ejemplo Francesconi, I. et. al., J.Med. Chem. 1999, 42, 2260; Kurzer, F., Lawson, A., Org. Synth. 1963, 645, y Gutman, A.D. documento US 3984410, 1976.

En una reacción similar, el compuesto intermedio X con un halógeno u otro grupo lábil adecuado (X') se puede utilizar en lugar del compuesto intermedio IX, según se ilustra en el Método C, Esquema V.

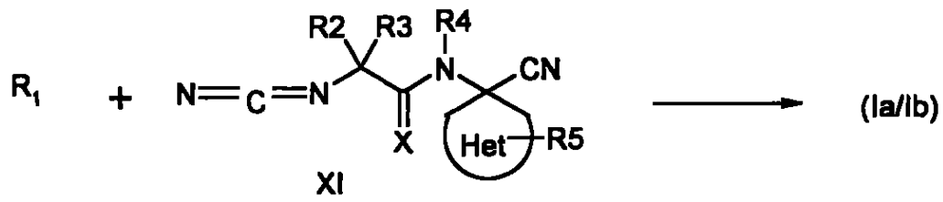
**Esquema V (Método C)**




De acuerdo con el Método C, un dipéptido-nitrilo intermedio o una sal de carácter básico del mismo, se permite que reaccione con X, con o sin una base añadida tal como trietilamina, para proporcionar el producto deseado (Ia/Ib). Procedimientos para lograr esta reacción adecuadas son conocidas por los expertos en la técnica, y están descritos en la bibliografía química (por ejemplo, Dunn, A.D., Org. Prep. Proceed. Int., 1998, 30, 709; Lindstroem, S. et al., Heterocycles, 1994, 38, 529; Katritzky, A.R. y Saczewski, F., Synthesis, 1990, 561; Hontz, A.C. y Wagner, E.C., Org Synth., 1963, IV, 383; Stephen, E. y Stephen, H., J. Chem. Soc., 1957, 490).

Compuestos con la fórmula (Ia/Ib), en la que $R_1$ es una amina también se pueden preparar por el Método D según se ilustra en el Esquema VI.

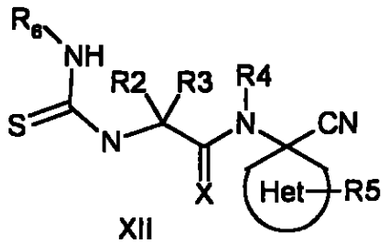
**Esquema VI (Método D)**




De acuerdo con el Método D, una carbodiimida (XI) derivada de (III) se deja que reaccione con una amina ($R_1$)

para proporcionar el producto de guanidina (Ia/Ib) deseado. La conversión de aminas en carbodiimidas es conocida por los expertos en la técnica y está descrita en la bibliografía (por ejemplo, Pri-Bar, I. y Schwartz, J., J. Chem. Soc. Chem. Commun., 1997, 347; Hirao, T. y Saegusa, T., J. Org. Chem., 1975, 40, 298). La reacción de carbodiimidas con nucleófilos de aminas se describe también en la bibliografía (por ejemplo, Yoshiizumi, K. et al., Chem. Pharm. Bull., 1997, 45, 2005; Thomas, E. W. et al., J. Med. Chem., 1989, 32, 228; Lawson, A. y Tinkler, R.B., J. Chem. Soc. C, 1971, 1429.

En una modificación del método D, se puede comenzar con la tiourea XII (formada por la reacción de la correspondiente amina con un isotiocianato $R_5N=C=S$) y luego formar la correspondiente carbodiimida (XI) in situ mediante la reacción con un agente desulfurante adecuado tal como $HgCl_2$ en un disolvente adecuado tal como DMF o acetonitrilo.

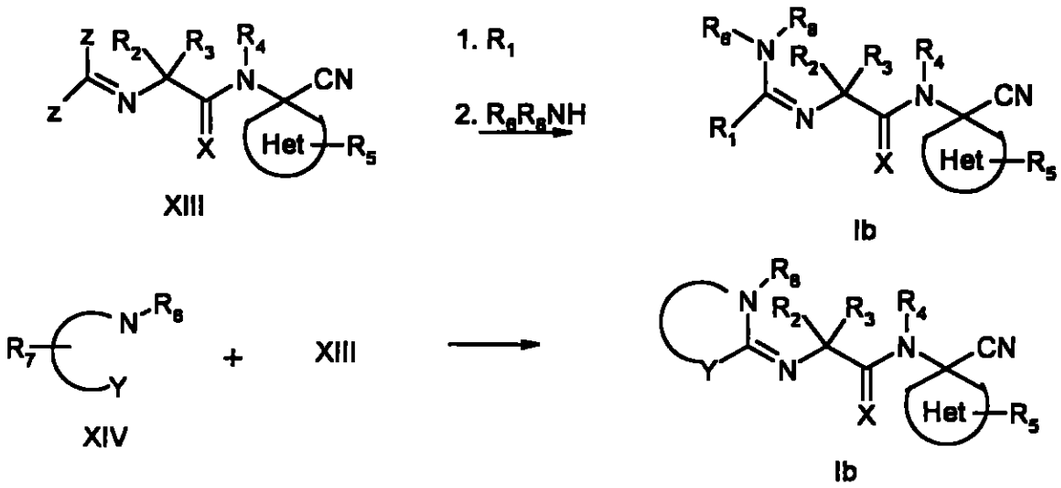



XII

Compuestos de fórmula (Ib), en que $R_i$ es una amina, se pueden preparar utilizando un proceso general descrito por M. Haake y B. Schummfelder (Synthesis, 1991, 753). De acuerdo con este procedimiento (Método E, Esquema VII), el compuesto intermedio XIII que porta dos grupos lábiles Z adecuados, tales como grupos fenoxi, se hace reaccionar secuencialmente con aminas $R_i$ y $R_6R_8NH$ en un disolvente adecuado tal como metanol o isopropanol, para proporcionar el producto deseado. La reacción de la primera amina se puede llevar a cabo a aproximadamente la temperatura ambiente, y la reacción de la segunda amina se lleva a cabo preferentemente con calentamiento a la temperatura de reflujo del disolvente. Si se deja

que XIII reaccione con un compuesto intermedio nucleófilo bifuncional XIV, en donde Y es un heteroátomo nucleófilo tal como N, O o S, se puede obtener el producto de fórmula (Ib), en que $R_1$ y $R_2$ forman un anillo heterocíclico. El compuesto intermedio XIII se puede preparar por reacción de III ($R_4$ = H) con diclorodifenoximetano que, a su vez, se puede preparar por calentamiento de difenilcarbonato con $PCl_5$ (R. L. Webb y C.S. Labow, J. Het. Chem., 1982, 1205).

**Esquema VII (Método E)**



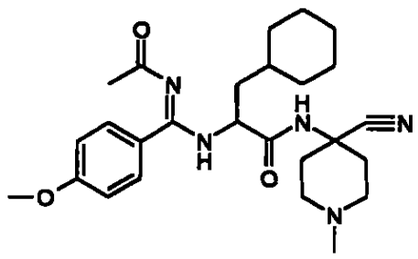

Con el fin de entender más ampliamente esta invención, se recogen los siguientes ejemplos. Estos ejemplos son con el fin de ilustrar realizaciones de esta invención, y no han de considerarse limitantes de modo alguno del alcance de la invención.

Los ejemplos que siguen son ilustrativos y, según se reconoce por un experto en la técnica, reactivos o condiciones particulares podrían ser modificados según fuese necesario para los compuestos individuales sin una experimentación excesiva. Materiales de partida utilizados en el esquema que figura a continuación están comercialmente disponibles o se

preparan fácilmente a partir de materiales comercialmente disponibles por los expertos en la técnica.

## EJEMPLOS DE SÍNTESIS

### EJEMPLO 1



2-{[acetilimino-(4-metoxi-fenil)-metil]-amino}-N-(4-ciano-1-metil-piperidin-4-il)-3-ciclohexil-propionamida (Método A)

(a) N-(4-metoxi-tiobenzoil)acetamida.

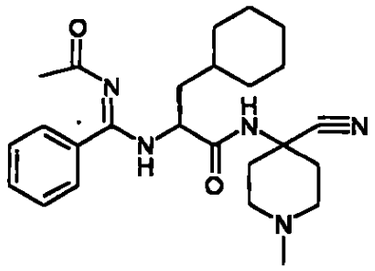
Una solución de cloruro de acetilo (4,69 g, 59,8 mmol) en acetona (20 ml) se añadió gota a gota a una solución de 4-metoxitiobenzamida (5,00 g, 29,9 mmol) y piridina (4,76 g, 60,1 mmol) en acetona (30 ml). La mezcla de reacción se calentó a reflujo durante 30 min y luego se vertió sobre agua helada. El precipitado resultante se aisló a través de filtración y se secó en vacío durante una noche para proporcionar un sólido amarillo pálido/naranja (4,52 g, 72%). $^1$H-RMN (400 MHz, $CDCl_3$) δ 2,56 (s, 3H), 3,87 (s, 3H), 6,89 (dd, J=6,9, 2,0 Hz, 2H), 7,77 (dd, J=6,9, 2,0 Hz, 2H).

(b) 2-{[acetilimino-(4-metoxi-fenil)-metil]-amino}-N-(4-ciano-1-metil-piperidin-4-il)-3-ciclohexil-propionamida

Yoduro de 2-cloro-N-metilpiridinio (660 mg, 2,58 mmol)

se añadió a una solución de N-(4-metoxi-tiobenzoil)acetamida (420 mg, 2,01 mmol), sal bis-hidrocloruro de 2-amino-N-(4--ciano-1-metil-piperidin-4-il)-3-ciclohexil-propionamida (730 mg, 2,00 mmol) y N,N-diisopropiletilamina (1,05 ml, 6,02 mmol) en diclorometano (8,0 ml). La mezcla de reacción se agitó a la temperatura ambiente durante 2 h, luego se diluyó con diclorometano (100 ml) y se lavó con 2 x 150 ml de bicarbonato de sodio saturado. La fase orgánica se secó ($MgSO_4$) y concentró. El residuo resultante se cromatografió sobre 100 g de sílice de resolución rápida utilizando primero EtOAc y luego diclorometano/metanol 9:1 en calidad de eluyente para proporcionar el producto deseado en forma de un sólido blancuzco (377 mg, 40%). $^1$H-RMN (400 MHz, DMSO-$d_6$) δ 0,70-0,90 (m, 2H), 1,00-1,30 (m, 4H), 1,35-1,65 (m, 8H), 1,72 (s, 3H), 1,85-2,20 (m, 6H), 2,48-2,60 (m, 1H), 3,78 (s, 3H), 4,20-4,35 (m, 1H), 6,95-6,99 (m, 2H), 7,33 (d, J=8,4 Hz, 1H), 7,72 (d, J=8,4 Hz, 1H). MS, m/z 468 = M+1.

**EJEMPLO 2**



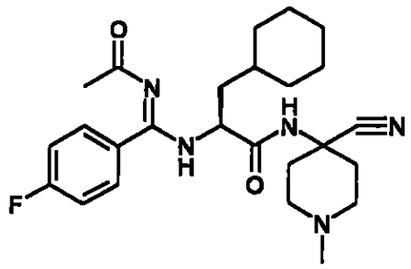
2-[(acetilimino-fenil-metil)-amino]-N-(4-ciano-1-metil--piperidin-4-il)-3-ciclohexil-propionamida

(a) Tiobenzoil-acetamida se preparó de acuerdo con el proceso del Ejemplo 1, etapa a, partiendo con tiobenzamida.

(b) El compuesto del título se preparó partiendo de tiobenzoil-acetamida y sal bis-hidrocloruro de 2-amino-N-(4-ciano-

-1-metil-piperidin-4-il)-3-ciclohexil-propionamida de acuerdo con el proceso del Ejemplo 1, etapa b. MS, m/z 438 = M+1.

**EJEMPLO 3**

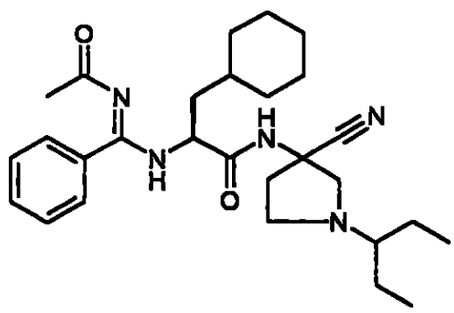


2-{[acetilimino-(4-fluoro-fenil-metil)-metil]-amino}-N-(4--ciano-1-metil-piperidin-4-il)-3-ciclohexil-propionamida.

(a) N-(4-fluoro-tiobenzoil)acetamida se preparó de acuerdo con el proceso del Ejemplo 1, etapa a, partiendo con 4--fluorotiobenzamida.

(b) El compuesto del título se preparó partiendo de N-(4--fluoro-tiobenzoil)acetamida y sal bis-hidrocloruro de 2--amino-N-(4-ciano-1-metil-piperidin-4-il)-3-ciclohexil-propionamida de acuerdo con el proceso del Ejemplo 1, etapa b. MS, m/z 456 = M+1.

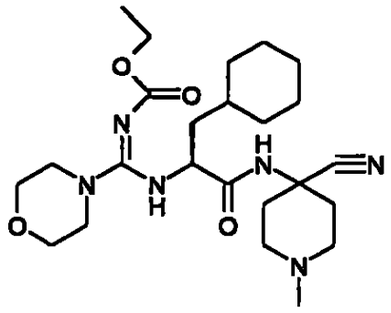
**EJEMPLO 4**



2-[(acetilimino-fenil-metil)]-amino}-N-[3-ciano-1-(1-etil-propil)-pirrolidin-3-il]-3-ciclohexil-propionamida.

(a) El compuesto del título se preparó partiendo de tiobenzoil-acetamida y sal bis-hidrocloruro de 2-amino-N-[3-ciano-1-(1-etil-propil)-pirrolidin-3-il]-3-ciclohexil-propionamida de acuerdo con el proceso del Ejemplo 1, etapa b., excepto que el compuesto se purificó por HPLC utilizando una columna de fase inversa C18 de 20 x 250 mm, siendo el método acetonitrilo al 20% en agua a acetonitrilo al 90% en agua. MS, m/z 480 = M+1.

**EJEMPLO 5**



Éster etílico de ácido {[1-(4-ciano-1-metil-piperidin-4-ilcarbamoil)-2-ciclohexil-etilamino]-morfolin-4-il-metilen}--carbámico (Método A)

(a) Éster etílico de ácido (morfolina-4-carbotioil)-carbámico

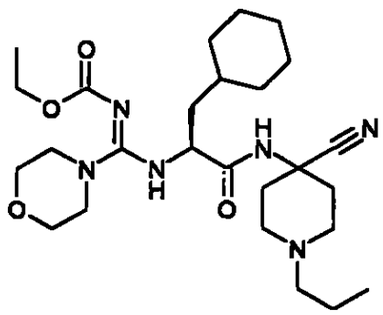
Morfolina (7,5 ml, 86,0 mmol) se añadió gota a gota a una solución de isotiocianato-formiato de etilo (10,0 ml, 84,8 mmol) en tetrahidrofurano (200 ml). La mezcla de reacción se agitó a temperatura ambiente durante 2,5 h, luego se concentró y se secó en vacío para proporcionar el producto deseado en forma de un sólido blanco (16,5 g, 89%). Este

material se utilizó sin purificación adicional. $^1$H-RMN (400 MHz, $CDCl_3$) δ 1,28 (t, J=7,1 Hz, 3H), 3,61-3,97 (m, 8H), 4,16 (q, 7,1 Hz, 2H), 7,44 (s ancho, 1H).

(b) Éster etílico de ácido {[1-(4-ciano-1-metil-piperidin-4-ilcarbamoil)-2-ciclohexil-etilamino]-morfolin-4-il-metilen}-carbámico.

Yoduro de 2-cloro-N-metilpiridinio (680 mg, 2,66 mmol) se añadió a una solución de éster etílico de ácido (morfolina-4-carbotioil)-carbámico (450 mg, 2,06 mmol), sal bis-hidrocloruro de 2-amino-N-(4-ciano-1-metil-piperidin-4-il)-3-ciclohexil-propionamida (745 mg, 2,04 mmol) y N,N-diisopropiletilamina (1,10 ml, 6,3 mmol) en diclorometano (8,0 ml). La reacción se agitó a la temperatura ambiente durante 2,5 h, luego se recogió en solución al 10% de ácido cítrico y se lavó con EtOAc. La fase acuosa se basificó después con carbonato de sodio saturado y se extrajo con EtOAc. El extracto orgánico se secó ($MgSO_4$) y se concentró para proporcionar el producto deseado en forma de un sólido blanco (250 mg, 26%). Este material se purificó adicionalmente mediante HPLC utilizando una columna de fase inversa C18 de 20 x 250 mm, siendo el método acetonitrilo al 20% en agua a acetonitrilo al 90% en agua. MS, m/z 477 = M+1.

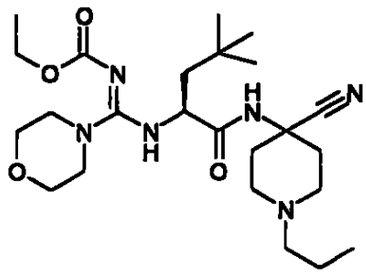
**EJEMPLO 6**



Éster etílico de ácido {[1-(4-ciano-1-propil-piperidin-4-ilcarbamoil)-2-ciclohexil-etilimino]-morfolin-4-il-metil}-carbámico

El compuesto del título se preparó partiendo de éster etílico de ácido (morfolina-4-carbotioil)-carbámico y sal bis-hidrocloruro de 2-amino-N-(4-ciano-1-propil-piperidin-4-il)-3-ciclohexil-propionamida de acuerdo con el proceso del Ejemplo 5, etapa b, excepto que el compuesto se purificó primero por cromatografía sobre gel de sílice utilizando 9:1 cloruro de metileno:metanol como eluyente antes de la purificación por HPLC de fase inversa. MS, m/z 505 = M+1.

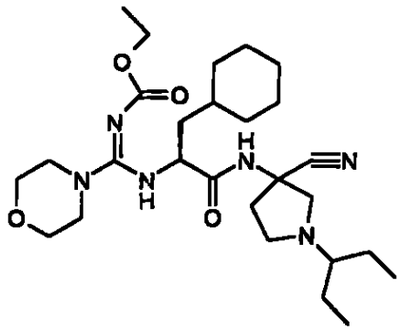
**EJEMPLO 7**



Éster etílico de ácido {[1-(4-ciano-1-propil-piperidin-4-ilcarbamoil)-3,3-dimetil-butilimino]-morfolin-4-il-metil}-carbámico

El compuesto del título se preparó partiendo de éster etílico de ácido (morfolina-4-carbotioil)-carbámico y sal bis-hidrocloruro de (4-ciano-1-propil-piperidin-4-il)-amida de ácido 2-amino-4,4-dimetil-pentanoico de acuerdo con el proceso del Ejemplo 5. MS, m/z 460 = M+1.

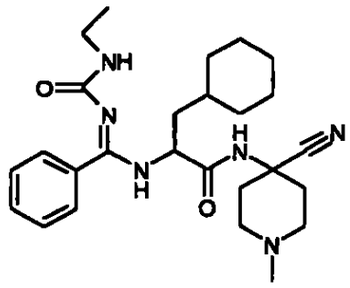
**EJEMPLO 8**



Éster etilico de ácido ({1-[3-ciano-1-(1-etil-propil)--pirrolidin-3-ilcarbamoil)-2-ciclohexil-etilamino]-morfolin--4-il-metileno}-carbámico

El compuesto del título se preparó partiendo de éster etílico de ácido (morfolina-4-carbotioil)-carbámico y sal bis-hidrocloruro de 2-amino-N-[3-ciano-1-(1-etil-propil)--pirrolidin-3-il]-3-ciclohexil-propionamida de acuerdo con el proceso del Ejemplo 5, etapa b. MS, m/z 519 = M+1.

**EJEMPLO 9**



N-(4-ciano-1-metil-piperidin-4-il)-3-ciclohexil-2-[(etilcarbamoilimino-fenil-metil)-amino]-propionamida (Método B)

(a) Éster metílico de ácido bencimídico

Hidrocloruro de éster metílico de ácido bencimídico (5

g, 29,1 mmol) se repartió entre solución saturada de carbonato de sodio (200 ml) y dietil-éter (100 ml). La capa orgánica se secó ($MgSO_4$) y se concentró para proporcionar el producto deseado en forma de un líquido incoloro (3,20 g, 81%). Este material se utilizó sin purificación adicional. $^1$H-RMN (400 MHz, $CDCl_3$) δ 3,93 (s, 3H), 7,39-7,46 (m, 3H), 7,75 (d, J = 1,1 Hz, 2H).

(a) 1-etil-3-(metoxi-fenil-metilen)-urea.

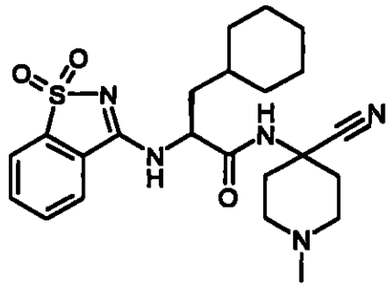
Una mezcla pura de éster metílico de ácido bencimídico (750 mg, 5,56 mmol) e isocianato de etilo (808 mg, 11,3 mmol) se agitó a 50°C durante 24 h. Isocianato en exceso se separó en vacío para proporcionar el producto deseado en forma de un aceite viscoso incoloro (1,09 g, 95%). Este material se utilizó sin purificación adicional. $^1$H-RMN (400 MHz, $CDCl_3$) δ 1,07 (t, J= 7,3 Hz, 3H), 3,25 (q, J = 7,3 Hz, 2H), 3,87 (s, 3H), 4,97 (s ancho, 1H), 7,26-7,40 (m, 2H), 7,45 (d, J = 7,4 Hz, 1H), 7,69-7,71 (m, 2H). MS, m/z 207 = M+1.

(a) N-(4-ciano-1-metil-piperidin-4-il)-3-ciclohexil-2-[(etilcarbamoilimino-fenil-metil)-amino]-propionamida

Una solución de 1-etil-3-(metoxi-fenil-metilen)-urea (350 mg, 1,70 mmol), sal bis-hidrocloruro de 2-amino-N-(4-ciano-1-metil-piperidin-4-il)-3-ciclohexil-propionamida (512 mg, 1,40 mmol) y N,N-diisopropiletilamina (352 mg, 27,3 mmol) en metanol seco (5,0 ml) se agitó a la temperatura ambiente durante 60 h. La mezcla de reacción se concentró y el residuo resultante se cromatografió sobre 50 g de gel de sílice de resolución rápida utilizando diclorometano a metanol al 5% en diclorometano como eluyente. Esto proporcionó el producto deseado en forma de un sólido amarillo claro (280 mg, 43%) que se purificó adicionalmente por HPLC utilizando una columna de fase inversa $C_{18}$ de 20 x 250 mm, siendo el método

acetonitrilo al 20' en agua a acetonitrilo al 90% en agua. MS, m/z 467 = M+1.

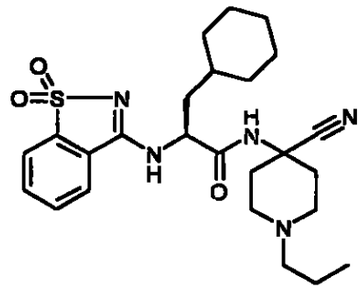
**EJEMPLO 10**



N-(4-ciano-1-metil-piperidin-4-il)-3-ciclohexil-2-(1,1-dioxo--1H-1λ⁶-benzo[d]isotiazol-3-ilamino)-propionamida (Método C)

Una suspensión de 3-cloro-benzo[d]isotiazol-1,1-dióxido (300 mg, 1,49 mmol) y sal bis-hidrocloruro de 2-amino-N-(4--ciano-1-metil-piperidin-4-il)-3-ciclohexilpropionamida (500 mg, 1,37 mmol) se preparó en 5,5 ml de acetonitrilo. Se añadió trietilamina (575 µl, 4,10 mmol) y la mezcla de reacción se agitó a la temperatura ambiente durante 1 día. La suspensión se filtró para separar hidrocloruro de trietilamina y el filtrado se concentró. El residuo resultante se cromatografió sobre 50 g de gel de sílice de resolución rápida utilizando diclorometano/metanol 9:1 como eluyente para proporcionar el producto deseado en forma de un sólido amarillo claro (310 mg, 49%). $^1$H-RMN (400 MHz, $CDCl_3$) δ 0,25--0,45 (m, 1H), 0,65-0,85 (m, 2H), 0,95-1,10 (m, 2H), 1,30--1,60 (m, 7H), 1,75-1,85 (m, 2H), 1,85-2,2 (m, 2H), 2,31 (s, 3H), 2,35-2,50 (m, 3H), 2,65-2,80 (m, 2H), 4,60-4,70 (m, 1H), 7,35-7,50 (m, 2H), 7,58 (t, J = 7,3, 1H), 7,78 (d, J = 7,7 Hz, 1H), 7,81 (s ancho, 1H), 8,91 (s ancho, 1H). MS, m/z 458 = M+1.

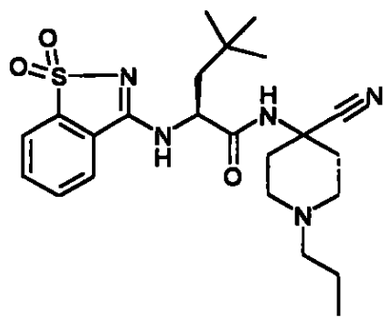
EJEMPLO 11



N-(4-ciano-1-propil-piperidin-4-il)-3-ciclohexil-2-(1,1-dioxo-1H-1λ⁶-benzo[d]isotiazol-3-ilamino)-propionamida.

Se preparó el compuesto del título partiendo de 3-cloro-benzo[d]isotiazol-1,1-dióxido y sal bis-hidrocloruro de 2-amino-N-(4-ciano-1-propil-piperidin-4-il)-3-ciclohexilpropionamida de acuerdo con el proceso del Ejemplo 10, excepto que el compuesto se purificó adicionalmente por HPLC utilizando una columna de fase inversa $C_{18}$ de 20 x 250 mm, siendo el método acetonitrilo al 20% en agua a acetonitrilo. MS, m/z 486 = M+1.

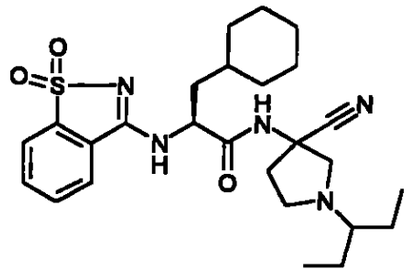
EJEMPLO 12



(4-ciano-1-propil-piperidin-4-il)-amida de ácido 2-(1,1-dioxo-1H-1λ⁶-benzo[d]isotiazol-3-ilamino)-4,4-dimetil-pentanoico

El compuesto del título se preparó partiendo de 3-cloro-benzo[d]isotiazol-1,1-dióxido y sal bis-hidrocloruro de (4-ciano-1-propil-piperidin-4-il)-amida de ácido 2-amino-4,4-dimetil-pentanoico de acuerdo con el proceso del Ejemplo 10, excepto que el compuesto se purificó adicionalmente por HPLC utilizando una columna de fase inversa $C_{18}$ de 20 x 250 mm, siendo el método acetonitrilo al 20% en agua a acetonitrilo. MS, m/z 460 = M+1.

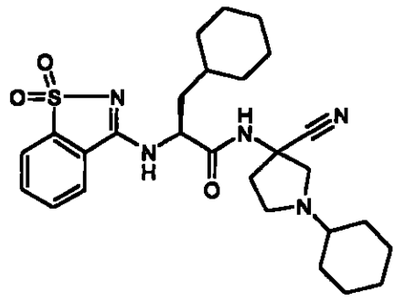
**EJEMPLO 13**



N-[3-ciano-1-(1-etil-propil)-pirrolidin-3-il]-3-ciclohexil-2-(1,1-dioxo-1H-1λ⁶-benzo[d]isotiazol-3-ilamino)-propionamida

Se preparó el compuesto del título partiendo de 3-cloro-benzo[d]isotiazol-1,1-dióxido y sal bis-hidrocloruro de 2-amino-N-[3-ciano-1-(1-etil-propil)-pirrolidin-3-il)-3-ciclohexil-propionamida de acuerdo con el proceso del Ejemplo 10, excepto que el compuesto se purificó adicionalmente por HPLC utilizando una columna de fase inversa $C_{18}$ de 20 x 250 mm, siendo el método acetonitrilo al 40% en agua a acetonitrilo. MS, m/z 500 = M+1.

**EJEMPLO 14**



N-(3-ciano-1-ciclohexil-pirrolidin-3-il)-3-ciclohexil-2-(1,1-dioxo-1H-1λ⁶-benzo[d]isotiazol-3-ilamino)-propionamida

Se preparó el compuesto del título partiendo de 3-cloro-benzo[d]isotiazol-1,1-dióxido y sal bis-hidrocloruro de 2-amino-N-(3-ciano-1-ciclohexil-pirrolidin-3-il)-3-ciclohexil-propionamida de acuerdo con el proceso del Ejemplo 10, excepto que el compuesto se purificó adicionalmente por HPLC utilizando una columna de fase inversa $C_{18}$ de 20 x 250 mm, siendo el método acetonitrilo al 40% en agua a acetonitrilo. MS, m/z 512 = M+1.

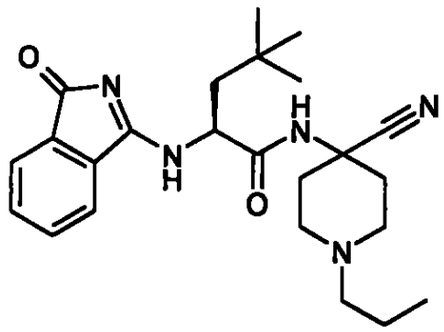
## EJEMPLO 15

N-(4-ciano-metil-piperidin-4-il)-3-ciclohexil-2-(3-oxo-3H-isoindol-1-ilamino)-propionamida.

Se preparó el compuesto del título partiendo de 3-imino-2,3-dihidro-isoindol-1-ona y sal bis-hidrocloruro de 2-amino-N-(4-ciano-metil-piperidin-4-il)-3-ciclohexil-propionamida de acuerdo con el proceso del Ejemplo 10, excepto que como disolvente se utilizó THF a reflujo. El compuesto se purificó adicionalmente por HPLC utilizando una columna de fase inversa $C_{18}$ de 20 x 250 mm, siendo el método acetonitrilo al 20% en agua a acetonitrilo. MS, m/z 422,5 = M+1.

660

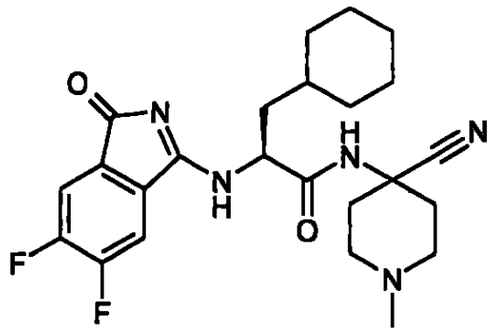
EJEMPLO 16



(4-ciano-1-propil-piperidin-4-il)-amida de ácido 4,4-dimetil-2-(3-oxo-3H-isoindol-1-ilamino)-pentanoico

Se preparó el compuesto del título partiendo de 3-imino-2,3-dihidro-isoindol-1-ona y sal bis-hidrocloruro de (4-ciano-1-propil-piperidin-4-il)amida de ácido 2-amino-4,4-dimetil-pentanoico de acuerdo con el proceso del Ejemplo 15. MS, m/z 424,5 = M+1.

EJEMPLO 17



N-(4-ciano-1-metil-piperidin-4-il)-3-ciclohexil-2-(5,6-difluoro-3-oxo-3H-isoindol-1-ilamino) propionamida

(a) Éster metílico de ácido 2-cloro-4,5-difluorobenzoico

Ácido 2-cloro-4,5-difluorobenzoico (1,93 g, 10 mmol) se disolvió en 20 ml de acetona. Se añadió carbonato de cesio (5,29 g, 15 mmol), seguido de yodometano (1,0 ml, 15 mmol). Esta mezcla de reacción se calentó a reflujo durante 1 h y luego se enfrió hasta la temperatura ambiente. A continuación, esta suspensión se diluyó con 40 ml de etil-éter. El solido se separó por filtración y se lavó con etil-éter. El filtrado se evaporó en vacio para dar el compuesto del título con un rendimiento cuantitativo en forma de un aceite transparente.

(b) Éster metílico de ácido 2-ciano-4,5-difluorobenzoico

El aceite anterior (2,06 g, 10 mmol) se disolvió en 10 ml de N-metil-pirrolidinona. Se añadió cianuro de cobre(I) (1,79 g, 20 mmol). Esta mezcla se calentó a 195°C bajo nitrógeno durante 1 h. Después de enfriar hasta la tempeatura ambiente, esta solución se diluyó con 100 ml de agua. El sólido resultante se recogió por filtración. A continuación, este sólido se suspendió en una solución, rápidamente agitada, de cianuro de potasio (0,5 g) en 30 ml de agua durante 1 h. Se añadió EtOAc (30 ml). La mezcla se filtró a través de tierra de diatomeas. La fase orgánica se separó y la fase acuosa se extrajo con EtOAc (20 ml x 2). La fase orgánica reunida se lavó con salmuera y se secó sobre sulfato de magnesio. El disolvente se separó en vacío. El residuo se cristalizó en etil-éter y éter de petróleo para dar el compuesto del título en forma de un sólido amarillo (1,26 g, 64%).

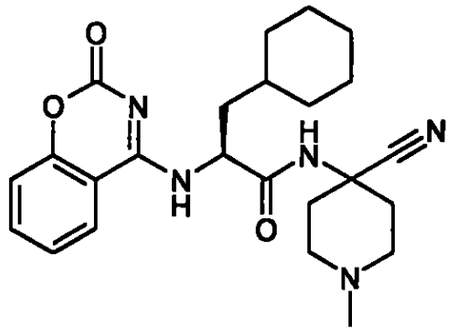
(c) 5,6-difluoro-2,3-dihidro-3-imino-1H-isoindol-1-ona

El sólido anterior (0,493 g, 2,5 mmol) se disolvió en 20 ml de MeOH. Esta solución se saturó con amoníaco a 0°C y luego se agitó en un tubo a presión a temperatura ambiente

durante 3 días. El sólido se recogió por filtración y se lavó con etil-éter para dar el compuesto del título en forma de un sólido amarillo (0,363 g, 80%).

El compuesto del título se preparó a partir de 5,6-difluoro-2,3-dihidro-3-imino-1H-isoindol-1-ona y sal bis-hidrocloruro de 2-amino-N-(4-ciano-1-metil-piperidin-4-il)-3-ciclohexil-propionamida de acuerdo con el proceso del Ejemplo 15. MS, m/z 458,3 = M+1.

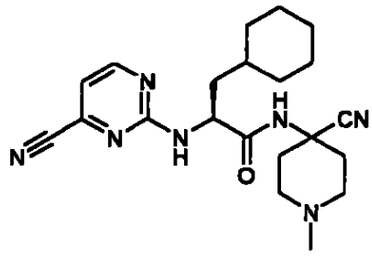
**EJEMPLO 18**



N-(4-ciano-1-metil-piperidin-4-il)-3-ciclohexil-2-(2-oxo-2H-benzo[e][1,3]oxazin-4-ilamino)-propionamida

El compuesto del título se preparó a partir de 4-cloro-benzo[e][1,3]oxazina-2-ona (preparada a partir de benzo-[e][1,3]oxazin-2,4-diona y $PCl_5$ en tolueno a reflujo) y sal bis-hidrocloruro de 2-amino-N-(4-ciano-1-metil-piperidin-4-il)-3-ciclohexil-propionamida de acuerdo con el proceso del Ejemplo 10. MS, m/z 438 = M+1.

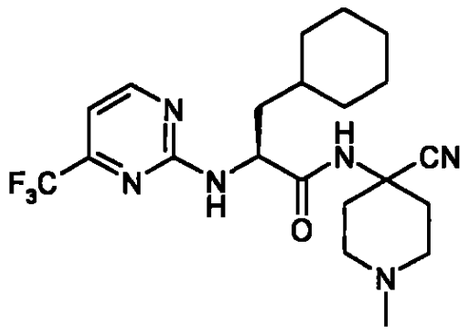
**EJEMPLO 19**



N-(4-ciano-1-metil-piperidin-4-il)-2-(4-ciano-pirimidin-2-ilamino)-3-ciclohexil-propionamida (Método C)

2-cloro-4-pirimidincarbonitrilo (0,3 mmol, Daves, G.D. Jr., O'Brien, D.E., Cheng, C. C. J. Het. Chem, 1964, 1, 130) y 2-amino-N-(4-ciano-1-metil-piperidin-4-il)-3-ciclohexil-propionamida (0,7 mmol) se disolvieron en acetonitrilo (10 ml) que contenía N,N-diisopropiletilamina (0,6 mmol). La solución se calentó a reflujo suavemente durante 17 h. Los componentes volátiles se evaporaron y el residuo se sometió a cromatografía (gel de sílice, eluyente = EtOAc, luego MeOH). La fracción metanólica se concentró hasta un sólido incoloro que se recromatografió (MeOH al 10%/EtOAc) para proporcionar el compuesto del título en forma de un sólido incoloro (52%). El material se recristalizó en diclorometano/éter de petróleo.

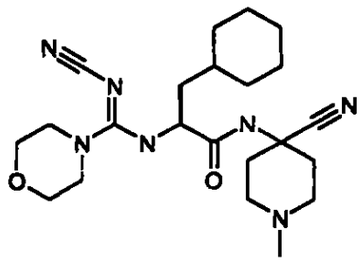
EJEMPLO 20



N-(4-ciano-1-metil-piperidin-4-il)-2-(4-trifluorometil-pirimidin-2-ilamino)-3-ciclohexil-propionamida

El compuesto del título se preparó a partir de 2-cloro-4-trifluorometil-pirimidina y 2-amino-N-(4-ciano-1-metil-1--piperidin-4-il)-3-ciclohexil-propionamida de acuerdo con el proceso del Ejemplo 19. MS, m/z 439,5 = M+1.

**EJEMPLO 21**



N-(4-ciano-1-metil-piperidina-4-il)-3-ciclohexil-2[N-ciano-morfolina-4-carboximidoil)-amino]-propionamida (Método D)

(a) 2-(N-ciano-iminometilen-amino)-N-(4-ciano-1-metil-piperidin-4-il)-3-ciclohexil-propionamida

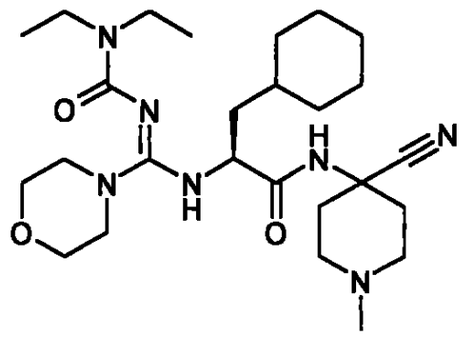
Una solución de cianocarbonimidato de difenilo (455 mg, 1,91 mmol), sal bis-hidrocloruro de 2-amino-N-(4-ciano-1-metil-piperidin-4-il)-3-ciclohexil-propionamida (680 mg, 1,86 mmol) y N,N-diisopropiletilamina (482 mg, 3,73 mmol) en isopropanol (5,0 ml) se agitó durante una noche a la temperatura ambiente. A continuación la mezcla de reacción se filtró para proporcionar la carbodiimida deseada en forma de un polvo blanco (140 mg, 22%). Este material se utilizó sin purificación adicional. $^1$H-RMN (400 MHz, $CDCl_3$) δ 0,80-1,00 (m, 2H), 1,05-1,20 (m, 1H), 1,20-1,40 (2H), 1,50-1,85 (m, 8H), 2,32 (s, 3H), 2,40-2,50 (m, 2H), 2,55-2,70 (m, 4H), 2,85-2,95 (m, 2H), 4,10-4,20 (m, 1H), 8,77 (s ancho, 1H). MS,

m/z 343 = M+1.

(b) 2-(N-ciano-bencimidoil-amino)-N-(4-ciano-1-metil-piperidina-4-il)-3-ciclohexil-propionamida

Una suspensión de 2-(N-ciano-iminometilen-amino)-N-(4-ciano-1-metil-piperidina-4-il)-3-ciclohexil-propionamida (120 mg, 0,35 mmol) en tetrahidrofurano (1 ml) se trató con morfolina (4 ml, 45,9 mmol). La mezcla de reacción se agitó a temperatura ambiente durante 3 días y luego se concentró hasta sequedad. El residuo se purificó por HPLC utilizando una columna de fase inversa $C_{18}$ de 20 x 250 mm, siendo el método acetonitrilo al 20% en agua a acetonitrilo al 90% en agua. MS, m/z 430 = M+1.

**EJEMPLO 22**



N-(4-ciano-1-metil-piperidin-4-il)-3-ciclohexil-2-{[(dietil-carbamoilimino)-morfolin-4-il-metil]-amino}-propionamida (Método D)

(a) Tiocianato de N,N-dietilcarbamoílo

Una suspensión de tiocianato de sodio (3,30 g, 40,7 mmol) en acetonitrilo seco (25 ml) a 80°C se trató gota a gota con una solución de cloruro de N,N-dietil-carbamoílo

(5,0 g, 36,9 mmol) en acetonitrilo seco (15 ml). La mezcla de reacción se agitó a 80°C durante 50 min, se enfrió hasta la temperatura ambiente y luego se filtró a través de una fina frita de vidrio. El filtrado resultante se utilizó en forma de una solución 0,9 M de tiocianato de N,N-dietil-carbamoílo en acetonitrilo.

(b) N-(4-ciano-1-metil-piperidin-4-il)-3-ciclohexil-2-(3-dietilamino-carbonil-tioureido)-propionamida

Una solución de sal bis-hidrocloruro de 2-amino-N-(4-ciano-1-propil-piperidin-4-il)-3-ciclohexil propionamida (560 mg, 1,53 mmol) y trietilamina (500 µl, 3,59 mmol) en acetonitrilo (4 ml) se trató con una solución de tiocianato de N,N-dietil-carbamoílo en acetonitrilo (3,0 ml, 2,7 mmol). La mezcla de reacción se agitó durante una noche a la temperatura ambiente y se concentró en un evaporador rotatorio. El residuo resultante se cromatografió (acetato de etilo:hexanos 1:1, luego acetato de etilo y, finalmente, metanol: cloruro de metileno 1:9 como eluyente) para proporcionar el producto deseado en forma de un sólido amarillo claro (340 mg, 49%). MS, m/z 451,3 = M+1.

El compuesto del título se preparó tratando una solución de la tiourea resultante (340 mg, 0,75 mmol) y trietilamina (230 µl, 1,65 mmol) en acetonitrilo seco (4 ml) con cloruro de mercurio(II) (225 mg, 0,83 mmol) y morfolina (200 µl, 2,23 mmol). La mezcla de reacción se agitó a la temperatura ambiente durante 4 h y luego se filtró a través de un disco de filtro de 0,45 µm. El filtrado resultante se filtró a través de una columna de sílice (metanol al 5%/cloruro de metileno como eluyente) y el producto bruto resultante se purificó adicionalmente por HPLC utilizando una columna de fase inversa $C_{18}$ de 20 x 250 mm, siendo el método acetonitrilo al 20% en agua a acetonitrilo. MS, m/z 504,6 = M+1.

Los siguientes ejemplos se prepararon de una manera parelela por el Método D:

**EJEMPLO 23**

Éster etílico de ácido {[1-(4-ciano-1-metil-piperidin-4-ilcarbamoil)-2-ciclohexil-etilamino]-pirrolidin-1-il-metil}-carbámico. MS, m/z 461 = M+1.

**EJEMPLO 24**

Éster etílico de ácido {[1-(4-ciano-1-metil-piperidin-4-ilcarbamoil)-2-ciclohexil-etilamino]-piperidin-1-il-metil}-carbámico. MS, m/z 477 = M+1.

**EJEMPLO 25**

Éster etílico de ácido {azepan-1-il-[1-(4-ciano-1-metil-piperidin-4-ilcarbamoil)-2-ciclohexil-etilamino]-metileno}-carbámico. MS, m/z 490 = M+1.

**EJEMPLO 26**

Éster etílico de ácido {azocan-1-il-[1-(4-ciano-1-metil-piperidin-4-ilcarbamoil)-2-ciclohexil-etilamino]-metileno}-carbámico. MS, m/z 504 = M+1.

**EJEMPLO 27**

Éster etílico de ácido 1-{[1-(4-ciano-1-metil-piperidin-4-ilcarbamoil)-2-ciclohexil-etilamino]-etoxicarbonilimino-metil}-piperidina-4-carboxílico. MS, m/z 548 = M+1.

**EJEMPLO 28**

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Éster etílico de ácido 1-{[1-(4-ciano-1-metil-piperidin-4-ilcarbamoil)-2-ciclohexil-etilamino]-etoxicarbonilimino-metil}-piperidina-3-carboxílico. MS, m/z 548 = M+1.

**EJEMPLO 29**

Éster etílico de ácido [[1-(4-ciano-1-metil-piperidin-4-ilcarbamoil)-2-ciclohexil-etilamino]-(4-pirrolidin-1-il-piperidin-1-il)-metileno]-carbámico. MS, m/z 545 = M+1.

**EJEMPLO 30**

Éster etílico de ácido {[1,4']bipiperidinil-1'-il-[1-(4-ciano-1-metil-piperidin-4-ilcarbamoil)-2-ciclohexil-etilamino]-metileno}-carbámico. MS, m/z 559 = M+1.

**EJEMPLO 31**

Éster etílico de ácido [[1-(4-ciano-1-metil-piperidin-4-ilcarbamoil)-2-ciclohexil-etilamino]-(4-fenil-piperazin-1-il)-metileno]-carbámico. MS, m/z 553 = M+1.

**EJEMPLO 32**

Éster etílico de ácido [[1-(4-ciano-1-metil-piperidin-4-ilcarbamoil)-2-ciclohexil-etilamino]-(4-etil-piperazin-1-il)-metileno]-carbámico. MS, m/z 505 = M+1.

**EJEMPLO 33**

Éster etílico de ácido {(4-acetil-piperazin-1-il)-[1-(4-ciano-1-metil-piperidin-4-ilcarbamoil)-2-ciclohexil-etilamino]-metileno}-carbámico. MS, m/z 519 = M+1.

**EJEMPLO 34**

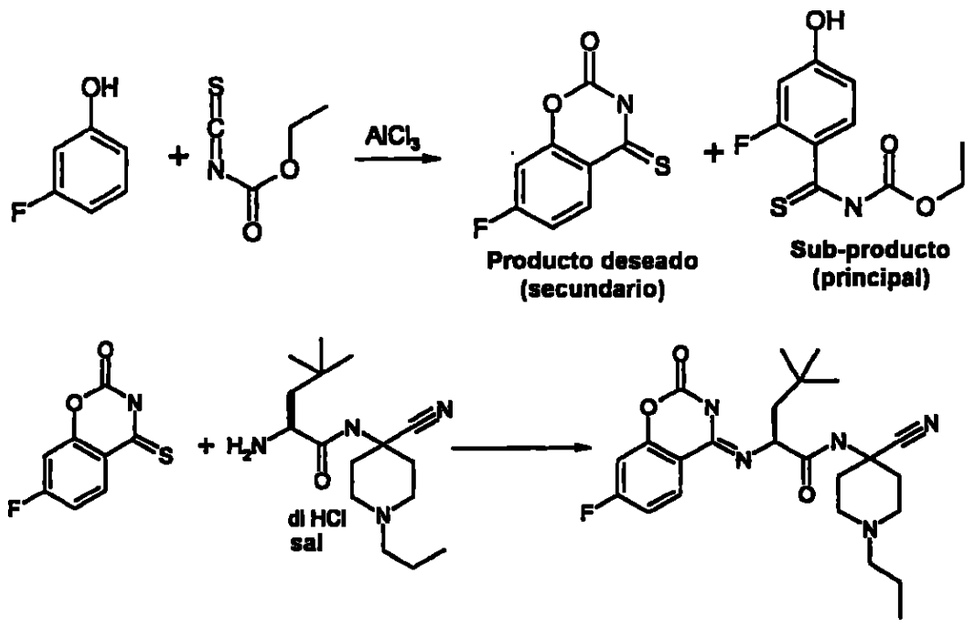
Éster etílico de ácido 4-{[1-(4-ciano-1-metil-piperidin-4-ilcarbamoil)-2-ciclohexil-etilamino]-etoxicarbonilimino-metil}-piperazina-1-carboxílico. MS, m/z 549 = M+1.

## EJEMPLO 35

Éster etílico de ácido [[1-(4-ciano-1-metil-piperidin-4-ilcarbamoil)-2-ciclohexil-etilamino]-(3,3,5-trimetil-6-aza-biciclo[3.2.1]oct-6-il)-metileno]-carbámico. MS, m/z 544 = M+1.

## EJEMPLO 36

(4-ciano-1-propil-piperidin-4-il) amida de ácido 2-(7-fluoro-2-oxo-2,3-dihidro-benzo[e][1,3]oxazin-4-ildenamino)-5,5-dimetil-hexanoico

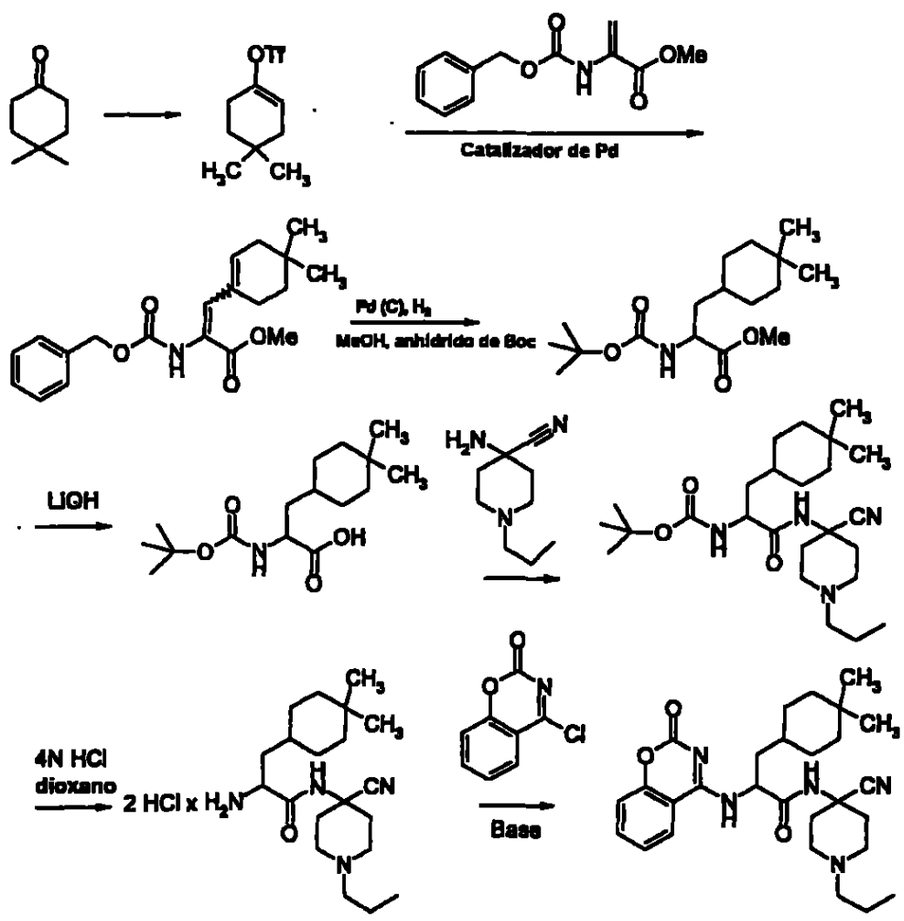


A una solución agitada de cloruro de aluminio (7,13 g, 53,5 mmol) en nitrometano (40 ml) a 0°C se añadió isotiocianato-formiato de etilo (3,5 g, 26,8 mmol). La reacción se agitó a 0°C durante 1 h y luego a la temperatura ambiente durante 48 h. La mezcla de reacción se vertió luego sobre hielo machacado y se filtró para dar 2,0 g de un sólido naranja. El sólido se disolvió en piridina (20 ml) y se calentó a reflujo durante 4 h. La reacción se diluyó con cloruro de metileno y se lavó con agua. La fracción orgánica se secó sobre sulfato de sodio anhidro y se evaporó en un evaporador rotatorio. El producto bruto se purificó por cromatografía en columna de resolución rápida sobre gel de sílice utilizando EtOAc al 25% y hexano para dar 0,27 g de 7-fluoro-4-tioxo-3,4-dihidro-benzo[e][1,3]oxazin-2-ona (5,1%).

Al compuesto intermedio anterior (0,125 g, 0,685 mmol) y (4-ciano-1-propil-piperidin-4-il)-amida de ácido 2-amino-5,5-dimetil-hexanoico (0,251 g, 0,685 mmol) en THF seco (10 ml) se añadió diisopropiletilamina (0,36 ml, 2,06 mmol) y yoduro de 2-cloro-1-metilpiridinio (0,288 g, 0,89 mmol). La reacción se agitó a la temperatura ambiente durante 48 h. El disolvente se evaporó y el residuo se disolvió en cloruro de metileno, se lavó con agua, se secó sobre sulfato de sodio anhidro y se evaporó. El producto bruto se purificó inicialmente por cromatografía en columna de resolución rápida sobre gel de sílice utilizando MeOH al 10%/cloruro de metileno (0,25 g, 79,8%). La purificación final por HPLC proporcionó el compuesto del título, $^1$H-RMN y MS eran consistentes con el producto deseado; MS: 458 (M+1).

## EJEMPLO 37

N-(4-ciano-1-propil-piperidin-4-il)-3-(4,4-dimetil-ciclohexil)-2-(2-oxo-2H-benzo[e][1,3]oxazin-4-ilamino)propionamida.




A una solución de 4,4-dimetil-ciclohexanona (4,60 g, 36,5 mmol) en THF seco (82 ml), enfriada en un baño de hielo seco/acetona, se añadió bis(trimetilsilil)amiduro de sodio (38 ml de una de solución 1,0 M en THF, 38 mmol). La mezcla de reacción se agitó bajo una atmósfera de argón a -78°C durante 30 min. Una solución de 2-(N,N-bis-trifluorometano-sulfonil)amino-5-cloropiridina (15 g, 37,7 mmol) en THF seco (20 ml) se introdujo a través de una jeringa, y la solución resultante se calentó moderadamente hasta temperatura ambiente y se agitó durante una noche. La mezcla de reacción se lavó con salmuera semisaturada (60 ml), y la fase acuosa

se extrajo con dietil-éter. Los extractos orgánicos reunidos se secaron ($MgSO_4$) y concentraron para proporcionar un aceite pardo oscuro (23 g). La cromatografía sobre gel de sílice utilizando éter de petróleo como eluyente proporcionó éster 4,4-dimetil-ciclohexil-1-enílico de ácido trifluorometano-sulfónico en forma de un líquido incoloro (5,2 g, 56%) $^1$H-RMN (400 MHz, $CDCl_3$) δ 0,98 (s, 6H), 1,53 (t, J = 6,5 Hz, 2H), 1,95-1,99 (m, 2H), 2,30-2,40 (m, 2H), 5,65-5,70 (m, 1H).

Una mezcla del éster-triflato anterior (2,26 g, 8,75 mmol), Cbz-deshidroalanina-éster metílico (2,10 g, 8,93 mmol), $Pd(OAc)_2$ (160 mg, 0,71 mmol) y KOAc (3,42 g, 34,8 mmol) en DMF seca se agitó a la temperatura ambiente durante 24 h. La mezcla de reacción se diluyó con agua (400 ml) y se extrajo con EtOAc (2 x 150 ml). Los extractos orgánicos reunidos se secaron ($MgSO_4$) y concentraron. La cromatografía del residuo resultante sobre gel de sílice utilizando 1:20 EtOAc/hexanos y 3:17 EtOAc/hexanos proporcionó éster metílico de ácido 2-benciloxicarbonilamino-3-(4,4-dimetil-ciclohex-1-enil)-acrílico en forma de un aceite amarillo (1,38 g, 46%). $^1$H-RMN (400 MHz, $CDCl_3$) δ 0,88 (s, 6H), 1,34 (t, J = 6,4 Hz, 2H), 1,95-2,00 (m, 2H), 2,23-2,30 (m, 2H), 3,74 (s, 3H), 5,15 (s, 2H), 5,90-6,10 (m, 1H), 6,10-6,15 (m, 1H), 7,0 (s, 1H), 7,25-7,36 (m, 5H). m/z 382,4 ($MK^+$).

Una suspensión del éster de ácido acrílico anterior (2,18 g, 6,35 mmol), anhídrido de Boc (1,52 g, 6,96 mmol) y Pd al 10%/C (300 mg) en MeOH se sacudieron en un aparato Parr bajo 2,8 kg/cm$^2$ de gas hidrógeno durante 17 h. La mezcla de reacción se filtró a través de una almohadilla de tierra de diatomeas y se concentró para proporcionar éster metílico de ácido 2-terc.-butoxicarbonilamino-3-(4,4-dimetil-ciclohexil)-propiónico en forma de un aceite amarillo (1,87 g, 94%). $^1$H-RMN (400 MHz, $CDCl_3$) δ 0,85 (s, 3H), 0,88 (s, 3H), 1.05-1,20 (m, 5H), 1,21-1,40 (m, 2H), 1,44 (s, 9H), 1,45-1,59 (m, 2H), 1,60-1,78 (m, 2H), 3,72 (s ancho, 3H), 4,27-4,40 (m, 1H), 4,82-4,96 (m, 1H).

Una suspensión del éster metílico anterior (1,87, 5,97 mmol) e hidróxido de litio monohidrato (1,76 g, 41,9 mmol) en THF (18 ml), MeOH (6 ml) y agua (6 ml) se agitó a la temperatura ambiente durante 4 h. La mezcla de reacción se acidificó con ácido cítrico al 10% (acuoso) y se extrajo con dietiléter (3 x 100 ml). Las capas orgánicas reunidas se secaron ($MgSO_4$) y concentraron para proporcionar el correspondiente ácido carboxílico en forma de una espuma blanca (1,21 g, 68%). $^1$H-RMN (400 MHz, $DMSOd_6$) δ 0,83 (s, 3H), 0,85 (s, 3H), 0,87-1,10 (m, 4H), 1,10-1,46 (m, 3H), 1,35 (s, 9H), 1,46-1,60 (m, 4H), 3,88-3,94 (m, 1H), 7,0 (d, 8,2 Hz, 1H), 11,7-12,9 (s ancho, 1H).

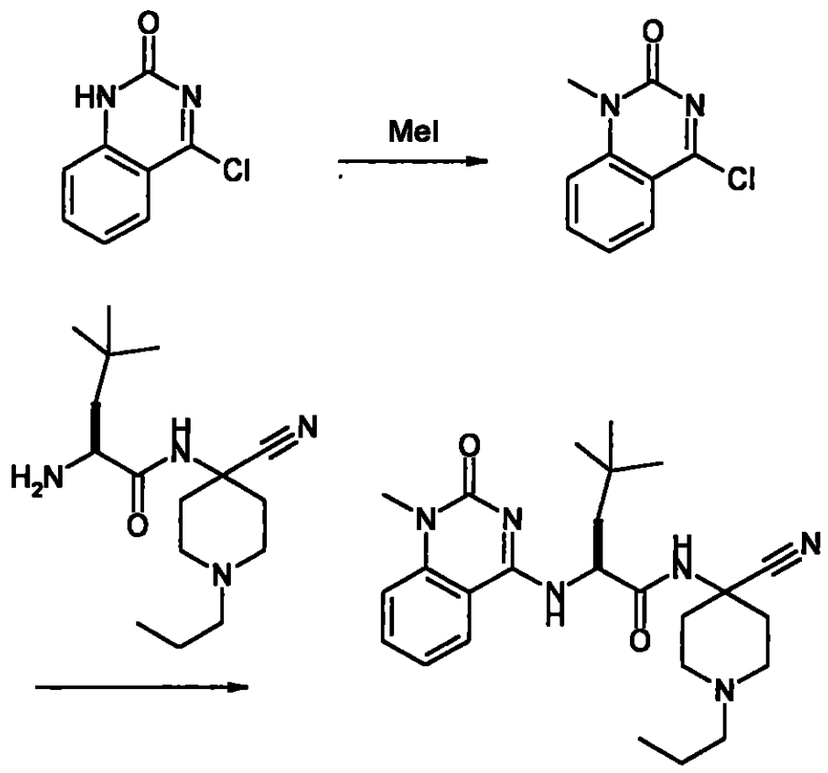
Cloroformiato de isobutilo (0,55 ml, 4,24 mmol) se añadió gota a gota a una solución del ácido carboxílico anterior (1,21 g, 4,04 mmol) y N-metil-morfolina (0,89 ml, 8,10 mmol) en THF seco enfriado hasta 0°C. La mezcla de reacción se agitó a 0°C durante 1 h. Se añadió una solución de 4-amino-1-propil-piperidina-4-carbonitrilo (780 mg, 4,65 mmol) en THF seco (5 ml) y la mezcla de reacción se dejó calentar hasta la temperatura ambiente y se agitó durante una noche. Los componentes volátiles se separaron en un evaporador rotatorio, y el residuo resultante se disolvió en EtOAc (50 ml) y se lavó con $Na_2CO_3$ saturado (50 ml). La fase orgánica se secó ($MgSO_4$) y se concentró. La cromatografía de este material bruto sobre gel de sílice utilizando un gradiente de diclorometano a MeOH al 5% en diclorometano proporcionó éster terc.-butílico de ácido [1-(4-ciano-1-propil-piperidin-4-il-ilcarbamoil)-2-(4,4-dimetil-ciclohexil)-etil]-carbámico en forma de una espuma blanca (1,17 g, 65%). $^1$H-RMN (400 MHz, $CDCl_3$) δ 0,85 (s, 3H), 0,88 (s, 3H), 0,89 (t, J = 7,3 Hz, 3H), 1,05-1,30 (m, 6H), 1,30-1,40 (m, 2H), 1,45 (s, 9H), 1,40-1,60 (m, 5H), 1,70-1,83 (m, 1H), 1,87-2,02 (m, 2H), 2,32-2,54 (m, 6H), 2,68-2,90 (m, 2H), 4,00-4,10 (m, 1H), 4,80-5,00 (m, 1H), 6,70-6,90 (m, 1H); m/z 449,5 $(M+H)^+$, 447,4 $(M-H)^-$.

El éster terc.-butílico anterior (1,17 g, 2,6 mmol) se disolvió en una solución de HCl en 1,4-dioxano (10,0 ml de una solución 4,0 M, 40 mmol) y se agitó bajo un barrido activo de gas argón durante 10 min. La solución se concentró en un evaporador rotatorio y luego se recogió en $CHCl_3$ (50 ml) y se concentró de nuevo para proporcionar el dihidrocloruro de amina en forma de un polvo blanco (1,05 g, 95%). m/z = 349,5 $(M+H)^+$.

Una suspensión de 4-cloro-benzoxazin-2-ona (500 mg, 2,69 mmol), la sal de amina anterior (400 mg, 0,95 mmol) y diisopropilamina soportada con poliestireno (2,40 g, 8,40 mmol) en acetonitrilo seco se calentó a 50°C durante 5 h. La mezcla de reacción se filtró a través de una almohadilla de tierra de diatomeas y el filtrado se concentró. El residuo resultante se cromatografió sobre gel de sílice utilizando cloruro de metileno y luego MeOH al 2,5% en cloruro de metileno y, finalmente, MeOH al 10% en cloruro de metileno como eluyente para proporcionar el compuesto del título en forma de un sólido blanco (45 mg, 10%). $^1$H-RMN (400 MHz, DMSOd..) δ 0,82 (t, J = 7,5 Hz, 3H), 0,83 (s, 3H), 0,84 (s, 3H), 1,00-1,20 (m, 5H), 1,25-1,42 (m, 5H), 1,48-1,58 (m, 2H), 1,60-1,70 (m, 1H), 1,80-1,92 (m, 2H), 2,10-2,30 (m, 6H), 2,55-2,68 (m, 2H), 4,83-4,92 (m, 1H), 7,29 (d, J = 8,3 Hz, 1H), 7,36 (t, J = 7,7 Hz, 1H), 7,73 (t, J = 7,3 Hz, 1H), 8,36 (d, J = 8,1 Hz, 1H), 8,73 (s, 1H), 8,98-9,10 (m, 1H); m/z = 494,5 $(M+H)^+$, 492,4 $(M-H)^-$.

## EJEMPLO 38

(4-ciano-1-propil-piperidin-4-il) amida de ácido 4,4-dimetil-2-(1-metil-2-oxo-1,2-dihidro-quinazolin-4-ilamino)-pentanoico



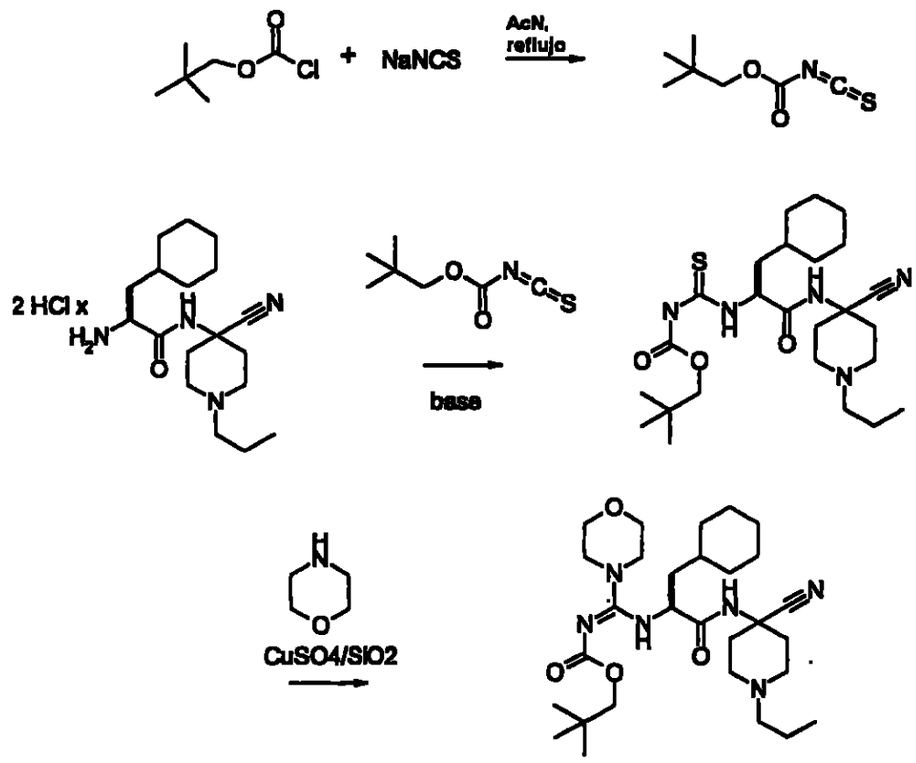

Una mezcla de 4-cloro-1,2-dihidro-2-oxo-quinazolina (1,0 g, 5,5 mmol), yodometano (0,86 ml, 2,5 equiv.) y carbonato de potasio (1,91 g, 2,5 equiv.) en DMF (15 ml) se calentó a 80°C durante 90 min antes de separar el disolvente a presión reducida a 80°C. El residuo se recogió en diclorometano y se filtró. El filtrado se concentró y la cromatografía en columna sobre gel de sílice (eluyente: EtOAc) dio el análogo de N-metilo (0,21 g, 19,5%).

Una mezcla del compuesto intermedio anterior (100 mg, 0,5 mmol), (4-ciano-1-propil-piperidin-4-il)amida de ácido 2-amino-4,4-dimetilpentanoico (151 mg, 0,5 mmol), Cu (polvo, 66 mg, 1 mmol) y carbonato de potasio (285 mg, 2 mmol) en NMP (3 ml) se calentó a 150°C durante 16 h. Después de enfriar hasta la temperatura ambiente, se filtró. El filtrado se diluyó con agua y se extrajo con diclorometano. La fase orgánica se lavó con salmuera, se secó (sulfato de sodio), concentró y cromatografió sobre gel de sílice, proporcionando el compues-

to del título (101 mg, 44,6%); MS: 453 (M+1).

## EJEMPLO 39

Éster 2,2-dimetil-propílico de ácido {[1-(4-ciano-1-metil-piperidin-4-ilcarbamoil)-2-ciclohexil-etilimino]-morfolin-4-il-metil}-carbámico




A una solución de tiocianato de sodio (4,46 g, 55 mmol) en 50 ml de acetonitrilo se añadió cloroformiato de neopentilo (6,15 ml, 50 mmol). Esta mezcla se calentó a 80°C durante 2 h. Después de enfriar hasta la temperatura ambiente, el sólido se separó por filtración y el filtrado se utilizó en

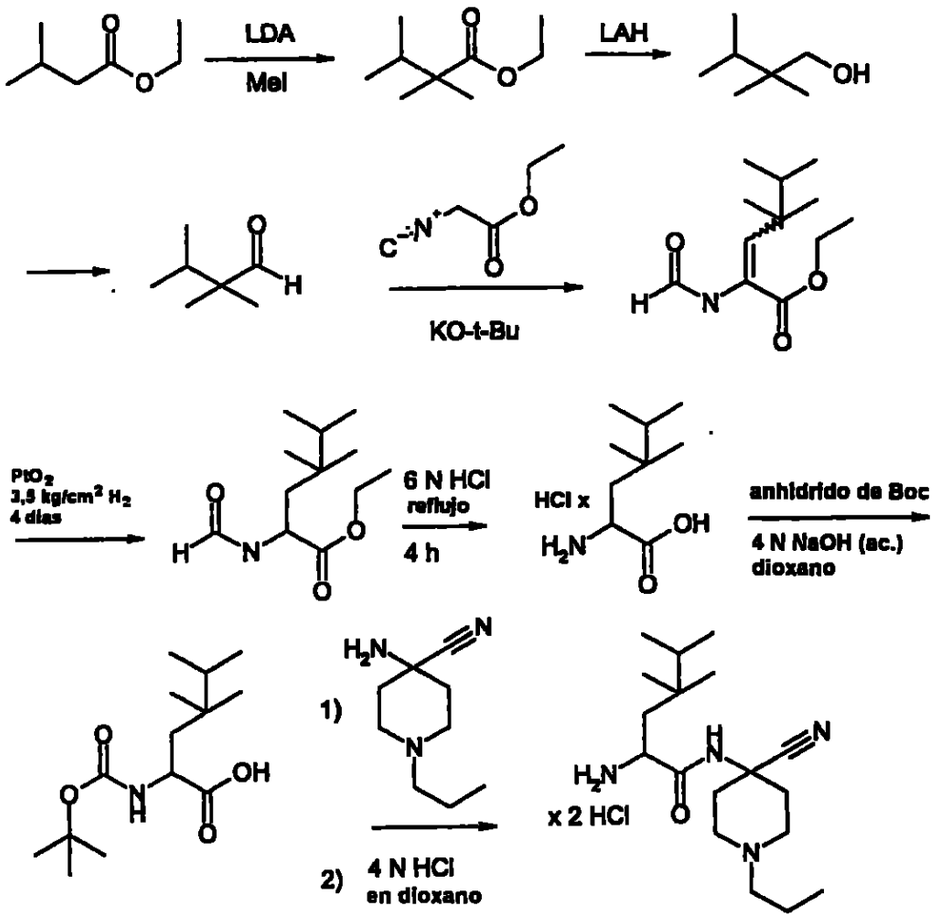
forma de una solución original 1 M de isotiocianato-formiato de neopentilo.

Sal dihidrocloruro de 2-amino-N-(4-ciano-1-metil-piperidin-4-il)-3-ciclohexil-propionamida (6,33 g, 17,32 mmol) se suspendió en 50 ml de cloruro de metileno. Se añadió trietilamina (5,00 ml, 35,9 ml). A esta solución se añadió a 0°C la solución anterior (20 ml, 20 mmol). Esta mezcla se agitó a 0°C durante 1 h. El disolvente se separó en vacío. El residuo se purificó por cromatografía de resolución rápida sobre gel de sílice eluyendo con MeOH al 5% en etil-éter (Rf = 0,2) para dar la tiourea (4,76 g, 59%) en forma de un aceite amarillo; MS: M+1 = 466.

La tiourea (4,67 g, 10,0 mmol) se disolvió en 30 ml de THF. Se añadió sulfato de cobre sobre gel de sílice (4,00 g, 10,0 mmol), seguido de 1 ml de trietilamina. Esta mezcla se agitó a la temperatura ambiente durante 30 min. Se añadió morfolina (1,25 ml, 20 mmol). La mezcla de reacción se calentó a reflujo durante 2 h. Se añadieron otros 4 g de sulfato de cobre sobre gel de sílice y 1,25 ml de morfolina. La mezcla de reacción se calentó durante 2 h adicionales. Después de enfriar hasta la temperatura ambiente, los sólidos se separaron por filtración y se lavaron con acetonitrilo. El filtrado se concentró a presión reducida y luego se purificó por cromatografía de resolución rápida sobre gel de sílice, eluyendo con una mezcla de etil-éter, cloruro de metileno y MeOH (2:1:0,1) para dar un aceite amarillo. Este aceite se cristalizó en etil-éter y hexano para dar el compuesto del título (1,81 g, 35%) en forma de un sólido blanco; M+1 = 519.

## EJEMPLO 40

Bis-hidrocloruro de (4-ciano-1-propil-piperidin-4-il)-amida de ácido 2-amino-4,4,5-trimetil-hexanoico




Diisopropilamiduro de litio (solución 1,5 M en ciclohexano/THF/etilbenceno) (113 ml, 169 mmol, 1,1 equiv.) se incorporó con una jeringa en un matraz de fondo redondo de 1000 ml bajo una manta de Ar. Se añadió THF seco (150 ml), y la mezcla se enfrió hasta -78°C con un baño de hielo seco/acetona. Éster etílico de ácido 3-metil-butanoico (20 g, 23 ml, 154 mmol, 1,0 equiv.) se añadió gota a gota a partir de una jeringa a lo largo de un período de 10 min, seguido de agitación a -78°C durante 1 h. Yoduro de metilo (10,5 ml, 169 mmol, 1,1 equiv.) se añadió gota a gota a partir de una jeringa a lo largo de un peródo de 10 min, y la mezcla

cremosa se agitó durante 1 h a -78°C, dando como resultado una mezcla muy espesa. El baño de hielo seco se separó y se reemplazó por un baño de hielo a 0°C. Se añadieron otros 150 ml de THF seco, seguido de otra adición de LDA (113 ml, 169 mmol, 1,1 equiv.). La mezcla resultante se agitó durante 10 min y luego el matraz se volvió a sumergir en un baño de hielo seco/acetona. La agitación se continuó durante otros 50 min y luego se añadió gota a gota yoduro de metilo (10,5 ml, 169 mmol, 1,1 equiv.) y el baño de hielo seco/acetona se retiró y la mezcla resultante se agitó a la temperatura ambiente durante 14 h. La mezcla de reacción se enfrió bruscamente con 3 ml de HCl concentrado y se añadió HCl 2 N hasta que el pH se ajustó a < 1. La mezcla se diluyó adicionalmente con 150 ml de agua y 500 ml de $Et_2O$. Las capas se separaron, y la capa orgánica se lavó con 1 x 100 ml de HCl 2 N, 1 x 100 ml de $NaHCO_3$ saturado y 1 x 200 ml de salmuera. La capa orgánica se secó sobre $Na_2SO_4$ y luego se concentró en vacío para proporcionar éster etílico de ácido 2,2,3-trimetilbutanoico en forma de un aceite naranja mezclado con etilbenceno (36,4 g, de los que 22,1 g era producto por RMN). La mezcla se utilizó sin purificación adicional.

Un matraz de fondo redondo de 500 ml, equipado con una varilla de agitación, se barrió con Ar y se cargó con 50 ml de THF seco y una solución 1 M de LAH en $Et_2O$ (87,5 ml, 87,5 mmol, 0,625 equiv.). La solución se enfrió hasta 0°C con un baño de hielo y el éster etílico anterior (22,1 g, 140 mmol, 1,0 equiv.) (aproximadamente una solución al 50% en etilbenceno) se añadió gota a gota a una velocidad tal que la solución no refluía (requería 50 min). Después de la adición del éster, la reacción se agitó a 0°C durante 2 h y luego a la temperatura ambiente durante 14 h. La solución de reacción se volvió a enfriar a 0°C y se enfrió bruscamente con cuidado mediante la adición de EtOAc. Se añadió NaOH 1 N hasta que se formó un precipitado granular (7,5 ml). La mezcla se filtró sobre una almohadilla de tierra de diatomeas que luego se

lavó 3 veces con 100 ml de $Et_2O$. Los componentes orgánicos se reunieron y se secaron sobre $Na_2SO_4$. La solución se decantó y se concentró en vacío para proporcionar 2,2,3-trimetil--butanol en forma de un aceite casi incoloro (11,7 g de alcohol en 15,4 g de una mezcla con etilbenceno). El producto bruto se utilizó sin purificación adicional.

Un matraz de fondo redondo de 1000 ml se equipó con una varilla de agitación, se barrió con Ar y se cargó con 300 ml de $CH_2Cl_2$ seco y cloruro de oxalilo (13,2 ml, 151 mmol, 1,5 equiv.). La solución se enfrió hasta -78°C con un baño de hielo seco/acetona. DMSO seco (21,5 ml, 302 mmol, 3,0 equiv.) se añadió gota a gota a lo largo de un período de 30 min (vigoroso desprendimiento de gas). El alcohol anterior (11,7 g, 100 mmol, 1,0 equiv.) se añadió (con etilbenceno residual) a lo largo de un período de 10 min. La solución resultante se agitó durante 90 min. Trietilamina (56 ml, 403 mmol, 4,0 equiv.) se añadió a lo largo de 5 min y el baño frío se retiró. La mezcla blanca cremosa resultante se agitó a la temperatura ambiente a lo largo de 1,5 h. La mezcla de reacción se diluyó cuidadosamente con 200 ml de agua (más desprendimiento de gas). Las capas se separaron y la fase orgánica se lavó con 1 x 100 ml de HCl 2 N y 1 x 100 ml de salmuera. La capa orgánica se secó sobre $Na_2SO_4$, se decantó y concentró en vacío. El aldehído bruto se destiló fraccionadamente a través de una columna Vigreux de 101,6 centímetros a 57-67°C a 15 mm de Hg para proporcionar 2,2,3-trimetilbutanal (9,1 g) en forma de un aceite incoloro.

Un matraz de fondo redondo de 250 ml, limpio y seco, se equipó con una varilla de agitación y se barrió con Ar. Se añadió THF seco (40 ml), seguido de la adición de una solución 1,0 M de KO-t-Bu (32,2 ml, 32,2 mmol, 1,05 equiv.). La solución se enfrió hasta -78°C en un baño de hielo seco/acetona. Isocianoacetato de etilo (3,35 ml, 30,7 mmol, 1,0 equiv.) se añadió gota a gota a lo largo de un período de 10 min. La mezcla resultante se agitó durante 5 min adiciona-

les, seguido de la adición, a través de jeringa, de 2,2,3-trimetil-butanal (3,5 g, 30,7 mmol, 1,0 equiv.). El baño frio se retiró y la mezcla resultante se agitó a temperatura ambiente durante 1 h. La mezcla de reacción se diluyó mediante la adición de una mezcla de 125 ml de $Et_2O$, 20 g de hielo, 2 ml de AcOH. Una vez que se fundió el hielo, se añadieron 50 ml de agua, y las capas se mezclaron y separaron. La capa orgánica se lavó con 1 x 50 ml de $NaHCO_3$ saturado y se secó sobre $Na_2SO_4$. La capa orgánica se decantó y concentró. La enamida bruta se purificó mediante cromatografía de resolución rápida sobre gel de sílice utilizando $CH_2Cl_2$ a MeOH al 4% en $CH_2Cl_2$ para proporcionar éster etílico de ácido 2-formilamino-4,4,5-trimetil-hex-2-enoico en forma de un aceite espeso (4,54 g); MS: 228 (M+1).

El éster etílico anterior (4,54 g, 20 mmol, 1,0 equiv.) se disolvió en 35 ml de MeOH en un frasco Parr, seguido de la adición de $PtO_2$ (1 g, 4,4 mmol, 0,22 equiv.). La mezcla se sacudió en un aparato de hidrogenación Parr durante 4 días, momento en el que la MS mostró un consumo del material de partida; MS: 230 (M+1), 216 (M+1 de éster metílico). El líquido se decantó cuidadosamente y el Pt se lavó 3 veces con 20 ml de MeOH, seguido en cada caso de decantación, teniendo cuidado de no permitir que se secara el Pt (si se deja secar, el Pt puede incendiarse). Las soluciones de MeOH se reunieron y concentraron hasta un aceite espeso que se suspendió en 25 ml de HCl 6 N, y la mezcla se sometió a reflujo durante 4 h, tiempo durante el cual se añadieron 5 ml de HCl concentrado al final de cada una de las 3 primeras horas. La mezcla se enfrió y el agua y el HCl en exceso se separaron en un evaporador rotatorio a una temperatura del baño de 70°C. Después de una concentración de aproximadamente 50%, se formó un sólido cristalino escamoso. La mezcla se enfrió hasta 0°C y el precipitado se recogió por filtración. El filtrado se concentró de nuevo en aproximadamente el 50% y se enfrió de nuevo hasta 0°C para proporcionar una segunda cosecha de

cristales. Los cristales se reunieron y se secaron en alto vacío para proporcionar hidrocloruro de ácido 2-amino-4,4,5-trimetil-hexanoico en forma de un sólido cristalino blancuzco (2,32 g); MS: 174 (M-Cl+1).

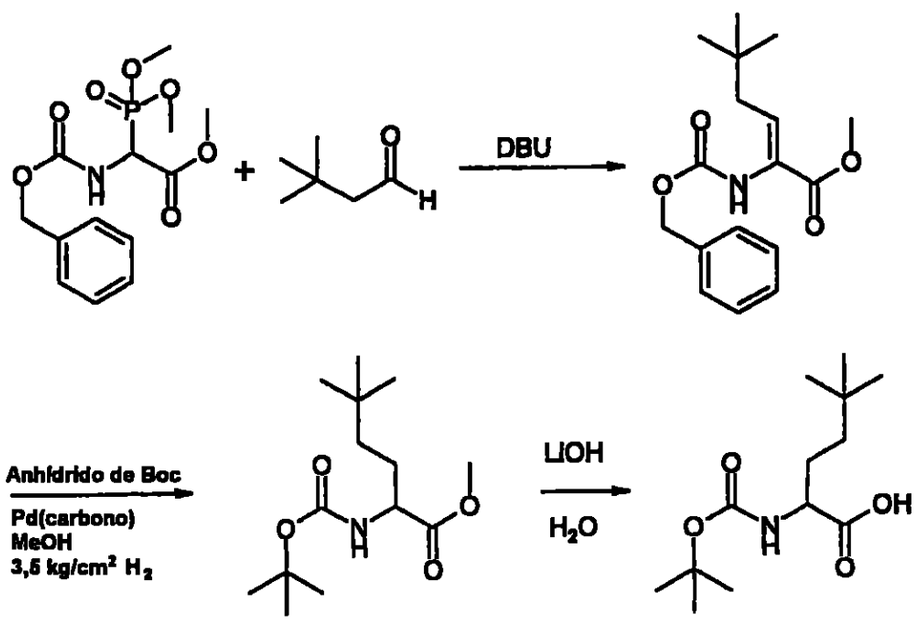
La sal de aminoácido anterior (2,32 g, 11,1 mmol, 1,0 equiv.) se disolvió en 100 ml de 50/50 dioxano/NaOH 4 N. La solución se enfrió hasta 0°C y se añadió anhidrido de Boc (3,6 g, 16,6 mmol, 1,5 equiv.). El baño frío se retiró y la reacción se agitó a la temperatura ambiente durante 16 h. El pH se ajustó cuidadosamente a 2 con HCl concentrado y el producto se extrajo con 3 x 100 ml de $CH_2Cl_2$. Las capas orgánicas se reunieron y secaron sobre $Na_2SO_4$. La solución se decantó y concentró utilizando 100 ml de hexano en calidad de un trazador para proporcionar un vidrio grueso que se trituró con 100 ml de hexano. Después de agitar vigorosamente durante 4 h, resultó un sólido céreo que se filtro y se secó al aire para proporcionar ácido 2-terc.-butoxicarbonilamino-4,4,4-trimetil-hexanoico (1,42 g).

El ácido carboxílico anterior (0,400 g, 1,46 mmol, 1,0 equiv.) se disolvió en 15 ml de THF y se enfrió hasta 0°C. Se añadió N-metilmorfolina (0,338 ml, 3,07 mmol, 2,1 equiv.), seguido de la adición gota a gota, a lo largo de 1 min, de cloroformiato de isobutilo (0,19 ml, 1,0 equiv.). Inmediatamente se formó un precipitado blanco. La mezcla se agitó durante 30 min, momento en el que se añadió una solución de 4-amino-4-ciano-1-propil-piperidina (0,257 g, 1,54 mmol, 1,05 equiv.) en 5 ml de THF. La mezcla resultante se agitó durante 16 h a la temperatura ambiente. Los componentes volátiles se separaron en un evaporador rotatorio, y la pasta resultante se trituró con 100 ml de agua con agitación vigorosa para dar un sólido blanco esponjoso que se recogió por filtración. El sólido se lavó con 100 ml de agua y se secó en vacío para proporcionar el producto deseado en forma de un polvo blancuzco (0,521 g); MS: 423 (M+1). El grupo protector de Boc se separó por tratamiento del sólido bajo Ar con 20 ml de HCl

4 N en dioxano durante 1 h. La pasta resultante se diluyó con 40 ml de $Et_2O$ y el sólido se filtró bajo Ar. La pasta resultante se lavó 1 x 25 ml de $Et_2O$ y se secó en vacío para proporcionar el compuesto del título en forma de la sal dihidrocloruro; MS: 323 (M+1).

## EJEMPLO 41

Ácido 2-terc.-butoxicarbonilamino-5,5-dimetil-hexanoico




Éster trimetílico de N-(benciloxicarbonil)-α-fosfonoglicina (2 g, 6,0 mmol, 1,0 equiv.) se disolvió en THF seco (20 ml). Se añadieron terc.-butilacetaldehído (0,758 ml, 6,0 mmol, 1,0 equiv.) y DBU (0,903 ml, 6,0 mmol, 1,0 equiv.), y la mezcla de reacción se agitó durante 16 h. La solución se diluyó con 100 ml de $CH_2Cl_2$ y se lavó con 1 x 50 ml de agua y 1 x 50 ml de salmuera. La capa orgánica se secó sobre $Na_2SO_4$, decantó y concentró en vacío para proporcionar éster metílico

de ácido 2-benciloxicarbonilamino-5,5-dimetil-hex-2-enoico en forma de un aceite espeso (1,73 g, 94%) que se utilizó sin purificación adicional; MS: 306 (M+1).

El éster anterior (1,73 g, 5,67 mmol, 1,0 equiv.) se disolvió en un frasco Parr con anhídrido de Boc (1,36 g, 6,23 mmol, 1,0 equiv.) y MeOH (35 ml). Se añadió Pd sobre carbono (tipo Degussa) (0,5 g). La mezcla se sacudió bajo 3,5 kg/cm$^2$ de $H_2$ durante 16 h. La mezcla se filtró sobre tierra de diatomeas, seguido del lavado de la tierra de diatomeas con 3 x 50 ml de MeOH. Los componentes orgánicos se reunieron y concentraron para proporcionar éster metílico de ácido 2-terc.-butoxicarbonilamino-5,5-dimetil-hexanoico en forma de un aceite muy espeso que se utilizó sin purificación adicional.

El éster anterior (1,31 g, 4,79 mmol, 1,0 equiv.) se disolvió en 50 ml de MeOH. Se añadió LiOH 1 N (50 ml), y la mezcla se agitó durante 16 h. Se añadió cuidadosamente HCl concentrado hasta que el pH se aproximó a 2, momento en el cual precipitó un sólido blanco brillante. El sólido se recogió por filtración y se lavó 2 x 20 ml de agua y secó en vacío para proporcionar el compuesto del título (1,05 g, 85%); MS: 256 (M-1).

## MÉTODOS DE USO TERAPÉUTICO

Los compuestos de la invención son útiles para inhibir la actividad de catepsinas S, K, F, L y B. Al hacerlo así, estos compuestos son útiles para bloquear los procesos patológicos mediados por estas cisteína-proteasas.

Compuestos de esta invención bloquean eficazmente la degradación de la cadena invariable a CLIP mediante catepsina S y, así, inhiben la presentación del antígeno y respuestas inmunitarias específicas para el antígeno. El control de las respuestas inmunitarias específicas para el antígeno constituye medios atractivos para tratar enfermedades autoinmunes y

otras respuestas inmunitarias mediadas por células T indeseables. Así, se proporcionan métodos de tratamiento utilizando los compuestos de esta invención para estados de este tipo. Estos abarcan enfermedades autoinmunes y otras enfermedades que implican respuestas inmunitarias específicas para antígenos inapropiadas que incluyen, pero no se limitan a artritis reumatoide, lupus eritematoso sistémico, enfermedad de Crohn, colitis ulcerosa, esclerosis múltiple, síndrome de Guillain-Barre, psoriasis, enfermedad de Grave, miastenia grave, escleroderma, glomerulonefritis, dermatitis incluida dermatitis por contacto y atópica, diabetes mellitus dependiente de insulina, y asma, incluido asma alérgico. Los compuestos de la invención también se pueden utilizar para tratar otros trastornos asociados con la proteolisis extracelular tal como enfermedad de Alzheimer y aterosclerosis. Los compuestos de la invención también se pueden utilizar para tratar otros trastornos asociados con respuestas autoinmunitarias inapropiadas, respuestas inmunitarias mediadas por células T, o proteolisis extracelular mediada por catepsina S, no relacionadas con las listadas anteriormente o comentadas en los antecedentes de la invención. Por lo tanto, la invención proporciona también métodos para modular una enfermedad autoinmune, que comprende administrar a un paciente que necesita de un tratamiento de este tipo una cantidad farmacéuticamente eficaz de un compuesto de acuerdo con la invención.

Compuestos de la invención inhiben también catepsina K. Al hacerlo así, éstos pueden bloquear la degradación inapropiada del colágeno de los huesos y otras proteasas de la matriz ósea. Así, se proporciona un método para tratar enfermedades en las que estos procesos juegan un papel tal como la osteoporosis. La inhibición de catepsinas F, L y B se encuentra también dentro del alcance de la invención debido a la similitud de los sitios activos en las cisteína-proteasas según se describe anteriormente.

Para uso terapéutico, los compuestos de la invención se pueden administrar en cualquier forma de dosificación convencional y de cualquier manera convencional. Vías de administración incluyen, pero no se limitan a intravenosa, intramuscular, subcutánea, intrasinovial, por infusión, sublingual, transdermal, oral, tópica o por inhalación. Los modos de administración preferidos son oral e intravenoso.

Los compuestos de esta invención se pueden administrar solos o en combinación con adyuvantes que refuerzan la estabilidad de los inhibidores facilitando la administración de composiciones farmacéuticas que los contienen en determinadas realizaciones, proporcionan una disolución o dispersión incrementada, aumentan la actividad inhibidora, proporcionan una terapia auxiliar y similares, incluidos otros ingredientes activos. Ventajosamente, terapias de combinación de este tipo utilizan dosificaciones menores de los agentes terapéuticos convencionales, evitando así una posible toxicidad y efectos secundarios adversos en los que se incurre cuando esos agentes se utilizan en calidad de monoterapias. Compuestos de la invención pueden combinarse físicamente con componentes terapéuticos convencionales u otros adyuvantes formando una composición farmacéutica sencilla. Ventajosamente, los compuestos se pueden entonces administrar juntos en una forma de dosificación sencilla. En algunas realizaciones, las composiciones farmacéuticas que comprenden combinaciones de compuestos de este tipo contienen al menos aproximadamente 15%, pero más preferiblemente al menos aproximadamente 20% de un compuesto de la invención (p/p) o una combinación de los mismos. Alternativamente, los compuestos se pueden administrar por separado (ya sea en serie o en paralelo). La dosificación separada permite una mayor flexibilidad en el régimen de dosificación.

Tal como se ha mencionado antes, las formas de dosificación de los compuestos de esta invención incluyen vehículos y adyuvantes farmacéuticamente aceptables conocidos

por los expertos ordinarios en la técnica. Estos vehículos y adyuvantes incluyen, por ejemplo, intercambiadores de iones, alúmina, estearato de aluminio, lecitina, proteínas del suero, sustancias tampón, agua, sales o electrólitos y sustancias basadas en celulosa. Formas de dosificación preferidas incluyen comprimidos, cápsulas, caplet, líquido, solución, suspensión, emulsión, pastillas, jarabe, polvo reconstituible, gránulo, supositorio y parche transdermal. Métodos para preparar formas de dosificación de este tipo son conocidos (véase, por ejemplo, H. C. Ansel y N.G. Popovish, *Pharmaceutical Dosage Forms and Drug Delivery Systems,* 5ª edición, Lea y Febiger (1990)). Niveles de dosificación y requisitos son bien reconocidos en la técnica y se pueden seleccionar por parte de los expertos ordinarios en la técnica a partir de métodos y técnicas disponibles, adecuados para un paciente particular. En algunas realizaciones, niveles de dosificación oscilan desde aproximadamente 10-1000 mg/dosis para un paciente de 70 kg. A pesar de que puede ser suficiente una dosis al día, se pueden administrar hasta 5 dosis al día. Para dosis orales, se pueden requerir hasta 2000 mg/día. Como apreciará el experto, se pueden requerir dosis menores o mayores en función de factores particulares. Por ejemplo, regímenes de dosificación y tratamiento específicos dependerán de factores tales como el perfil de salud general del paciente, la gravedad y el curso de trastorno del paciente o la disposición al mismo y el juicio del médico que le esté tratando.

## VERIFICACIÓN DE PROPIEDADES BIOLÓGICAS

Expresión y purificación de catepsina S humana recombinante

Clonación de catepsina S humana:

ARN de U937 se sometió a transcriptasa inversa/reacción en cadena de polimerasa con el cebador A (5'-

cacaatgaaacggctggtttg 3') y el cebador B (5' ctagatttctgggtaagaggg 3') diseñado para amplificar específicamente ADNc de catepsina S. El fragmento de ADN de 900 pb resultante se subclonó en pGEM-T (Promega) y se secuenció para confirmar su identidad. Esta contrucción se utilizó para todas las manipulaciones subsiguientes. Este proceso es típico para la clonación de genes conocidos y está establecido en su campo.

Pre-Pro-Cat S humana se separó del vector pGem-T (Promega, 2800 Woods Hollow Rd, Madison, WI 53711) mediante digestión con enzima de restricción SacII, seguido de tratamiento con T4 ADN polimerasa para generar un extremo romo, y una segunda digestión con enzima de restricción con SalI. Ésta se subclonó en el plásmido donante pFastBac1 (GibcoBRL, 8717 Grovemont Cr., Gaithersburg, MD 20884) que había sido cortado con la enzima de restricción BamHI y había sido provista de extremos romos, y luego había sido cortada con enzima de restricción SalI. La mezcla de ligamientos se utilizó para transformar células competentes DH5a (Gibco BRL) y se extendió en placas LB que contenían 100 µg/ml de ampicilina. Las colonias se desarrollaron en cultivos de una noche de medios LB que contenían 50 µg/ml de ampicilina, se aisló el ADN del plásmido y se confirmó la inserción correcta mediante digestión con enzimas de restricción. El plásmido donante pFastBac recombinante se transformó en células competentes DH10Bac (Gibco BRL). Grandes colonias blancas se recogieron de las placas LB que contenían 50 µg/ml de canamicina, 7 µg/ml de gentamicina, 10 µg/ml de tetraciclina, 100 µg/ml de Bluo-gal y 40 µg/ml de IPTG. El ADN se aisló y se utilizó para transfectar células de insectos Sf9 utilizando reactivo CellFECTIN (Gibco BRL). Las células y el sobrenadante se recolectaron después de 72 horas. El sobrenadante viral se hizo pasar dos veces y la presencia de Cat S se confirmó mediante PCR del sobrenadante.

Células SF9 se infectaron con baculovirus recombinante

a una MDI de 5 durante 48-72 h. El sedimento de células se lisó y se incubó en tampón a pH 4,5 a 37°C durante 2 horas para activar Cat S a partir de la pro-forma para activar la forma madura (Bromme, D y McGrath, M., Protein Science, 1996, 5:789-791). La presencia de Cat S se confirmó mediante SDS-PAGE y transferencia Western utilizando proCat S anti-humana de conejo.

Inhibición de catepsina S

Catepsina S recombinante humana expresada en baculovirus se utiliza a una concentración final de 10 nM en tampón. El tampón es acetato de Na 50 mM, pH 6,5, EDTA 2,5 mM, TCEP 2,5 mM. La enzima se incuba con el compuesto o DMSO durante 10 min a 37°C. El sustrato 7-amino-4-metilcumarina, CBZ-L-valil-L-valil-L-argininamida (síntesis habitual por Molecular Probes) se diluye hasta 20 µM en agua (concentración final de 5 M), se añade al ensayo y se incuba durante 10 minutos adicionales a 37°C. Se mide la actividad del compuesto mediante la fluorescencia disminuida en comparación con el control de DMSO cuando se lee a una excitación de 360 nm y una emisión de 460 nm.

Los ejemplos listados anteriormente se evaluaron en cuanto a la inhibición de la catepsina S en el ensayo anterior. Todos tenían valores de $CI_{50}$ de 100 micromolar o inferiores.

Inhibición de catepsinas K, F, L y B:

La inhibición de estas enzimas por parte de compuestos particulares de la invención se puede determinar sin una experimentación excesiva utilizando métodos reconocidos en la técnica según se proporcionan aquí en lo que sigue, cada uno de los cuales se incorpora en esta memoria como referencia:

Ensayos de catepsina B y L se encuentran en las siguientes referencias:

1. Methods in Enzymology, Vol. 244. Proteolytic Enzymes: Serine and Cysteine Peptidases, Alan J. Barret, comp.

El ensayo de catepsina K se encuentra en la siguiente referencia:

2. Bromme, D., Okamoto, K., Wang, B.B., y Biroc, S. (1996) J. Biol. Chem. 271, 2126-2132.

Los ensayos de catepsina F se encuentran en las siguientes referencias:

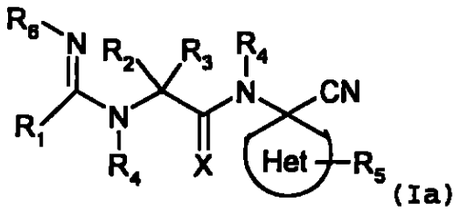
3. Wang, B., Shi, G.P., Yao, P,M., Li, Z., Chapman, H.A., y Bromme, D. (1998) J. Biol Chem. 273, 32000-32008.

4. Santamaria, I., Velasco, G., Pendas, A.M., Paz, A., y Lopez-Otin, C (1999) J. Biol. Chem. 274, 13800-13809.

Compuestos preferidos a evaluar para la inhibición de catepsinas K, F, L y B en los ensayos anteriores tienen deseablemente valores $CI_{50}$ de 100 micromolar o inferiores.

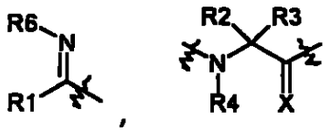
## REIVINDICACIONES

1.- Un compuesto de la fórmula (Ia):

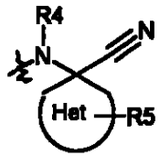


(Ia)

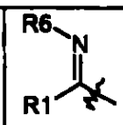
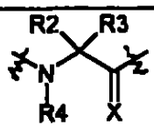
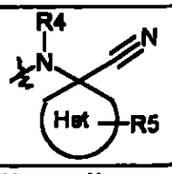
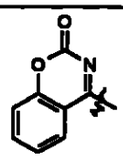
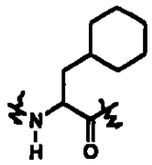
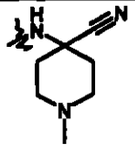
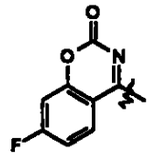
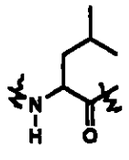
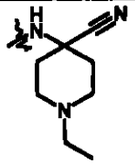
en donde para la fórmula (Ia), los componentes

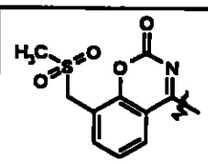
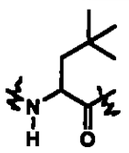
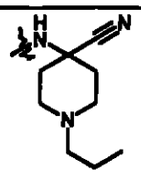
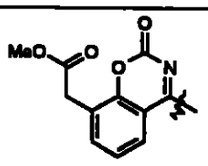
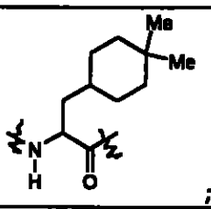
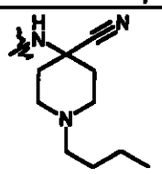
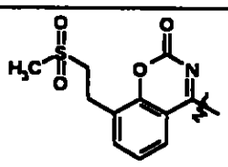
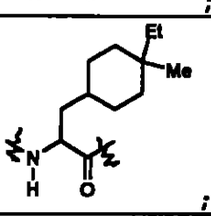
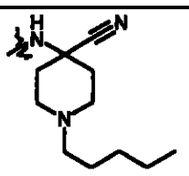
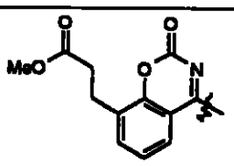
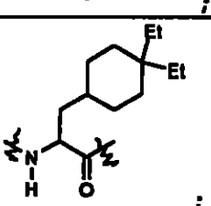
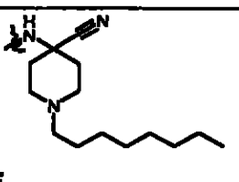
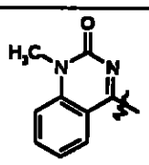
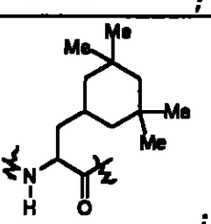
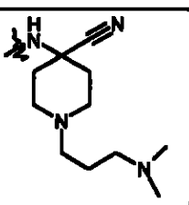
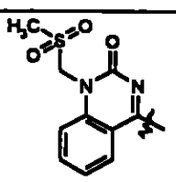
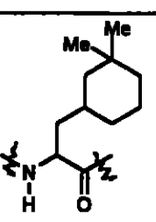
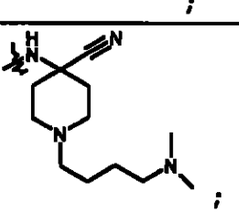
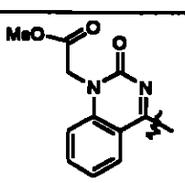
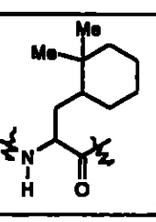
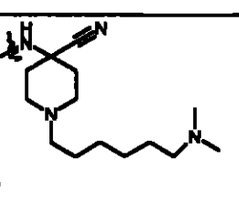


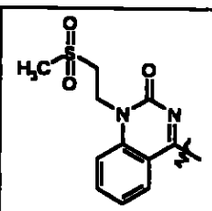
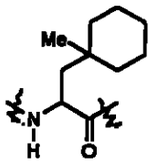
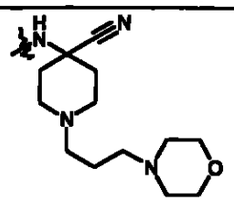
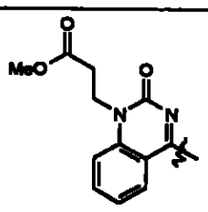
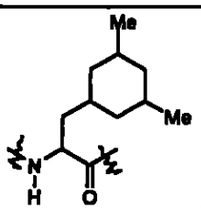
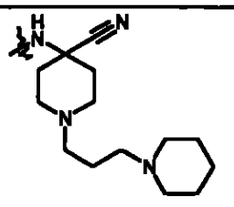
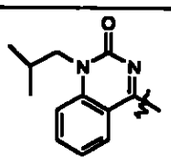
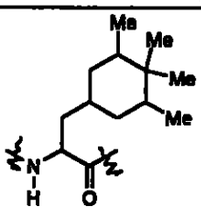
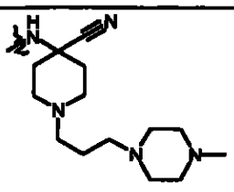
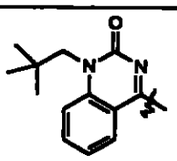
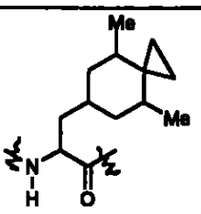
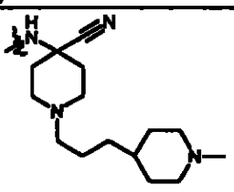
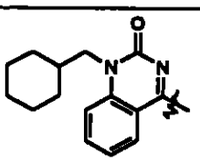
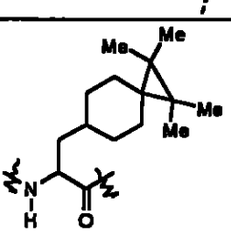
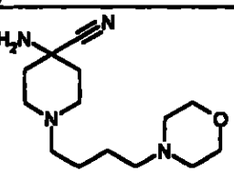
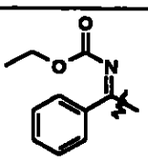
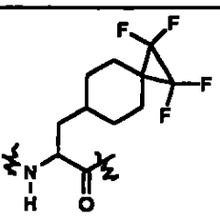
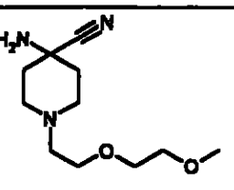
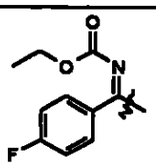
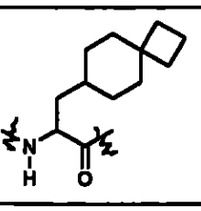
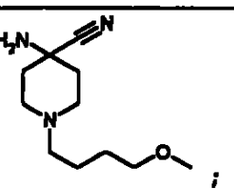
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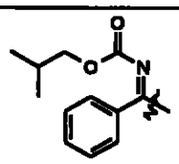
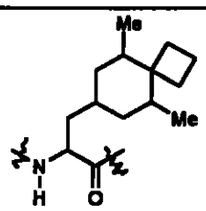
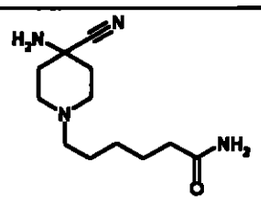
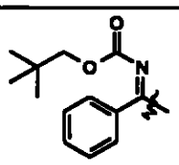
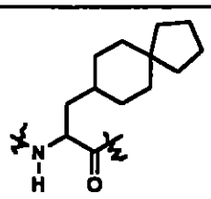
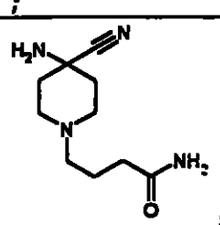
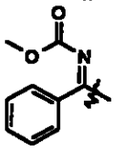
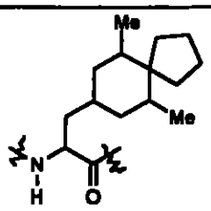
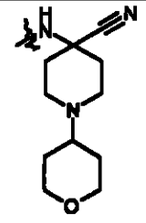
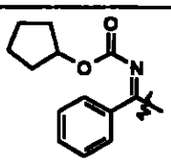
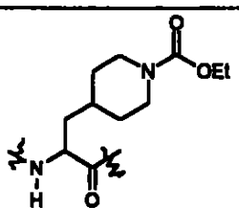
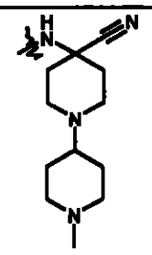
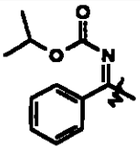
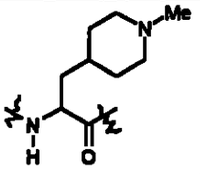
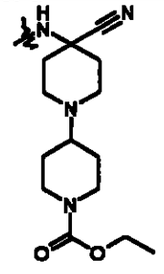
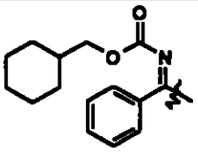
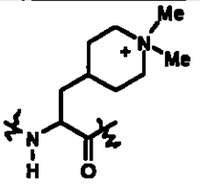
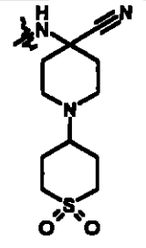


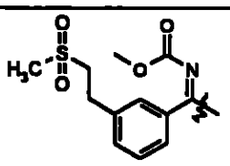
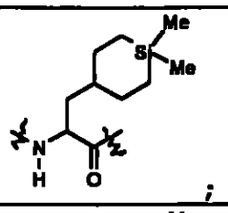
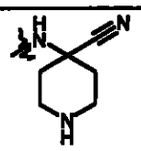
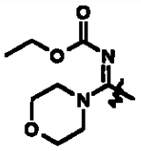
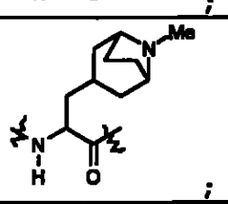
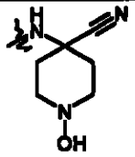
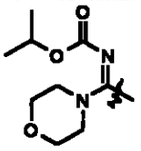
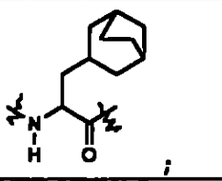
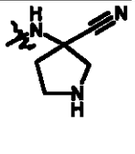
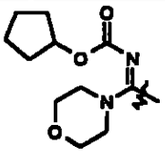
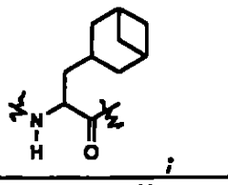
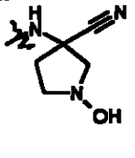
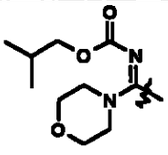
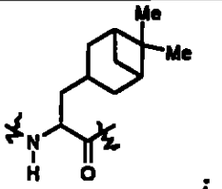
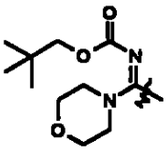
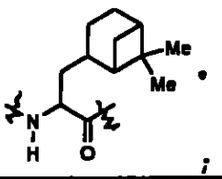
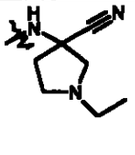
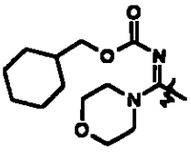
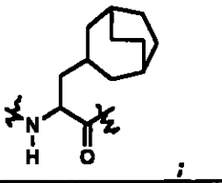
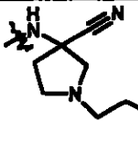
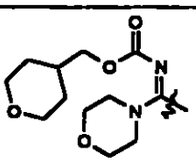
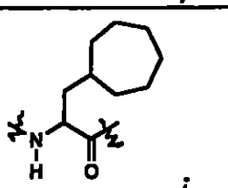
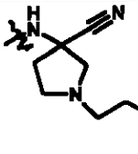
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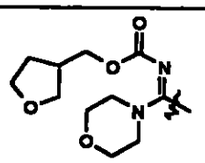
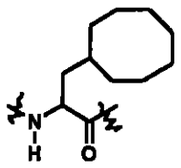
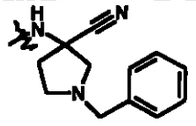
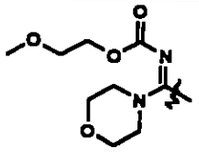
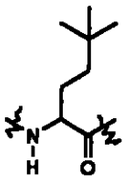
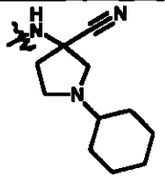
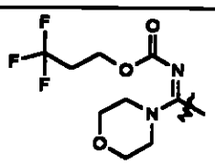
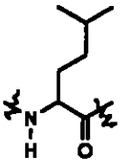
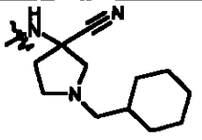
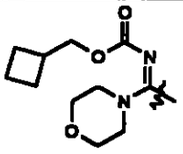
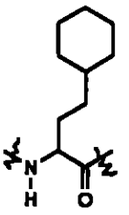
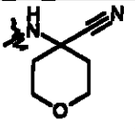
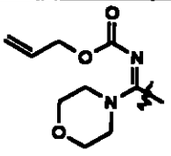
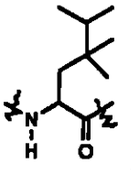
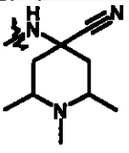
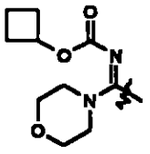
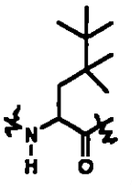
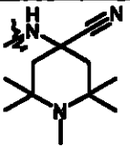
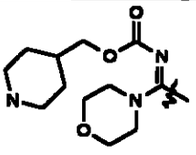
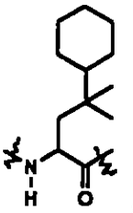
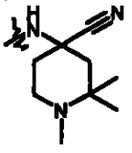
| | | | | | |
|---|---|---|---|---|---|
| A |  | B |  | C |  |
| A1 |  ; | B1 |  ; | C1 |  ; |
| A2 |  ; | B2 |  ; | C2 |  ; |

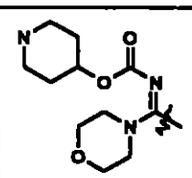
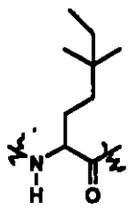
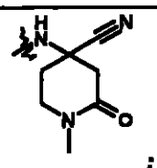
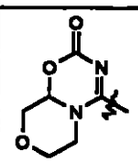
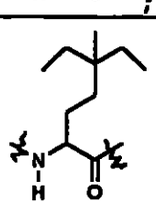
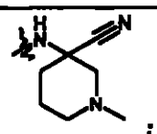
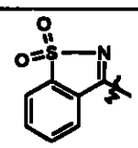
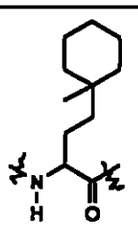
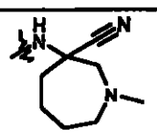
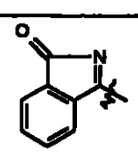
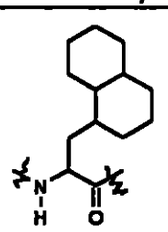
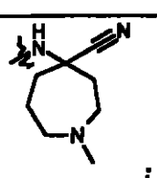
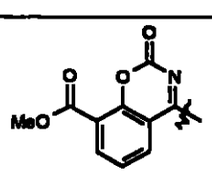
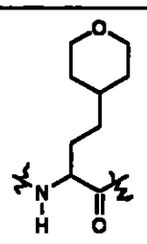
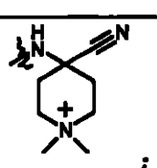
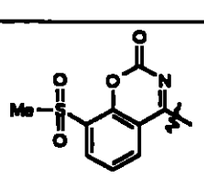
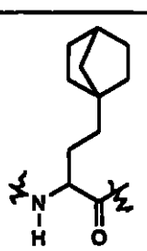
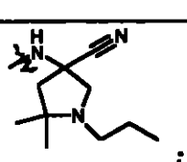
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| A5 |  ; | B5 |  ; | C5 |  ; |
| A6 |  ; | B6 |  ; | C6 |  ; |
| A7 |  ; | B7 |  ; | C7 |  ; |
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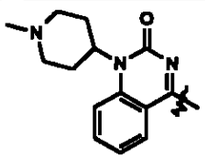
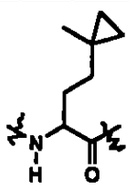
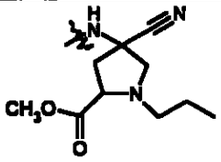
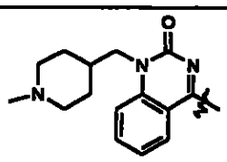
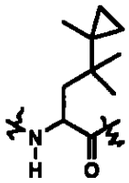
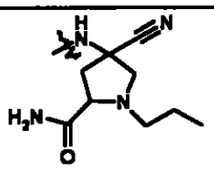
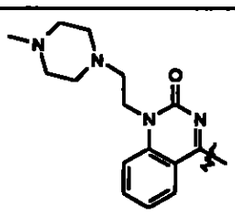
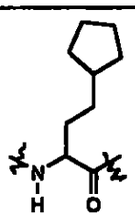
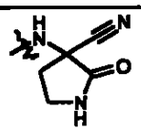
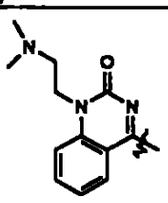
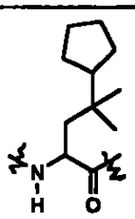
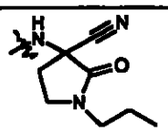
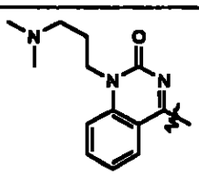
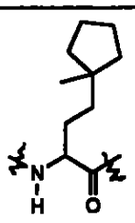
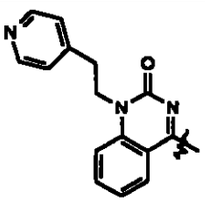
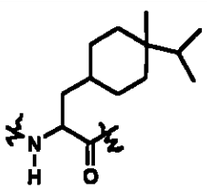
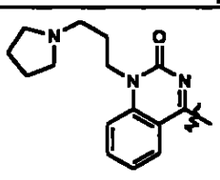
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| A11 |  ; | B11 |  ; | C11 |  ; |
| A12 |  ; | B12 |  ; | C12 |  ; |
| A13 |  ; | B13 |  ; | C13 |  ; |
| A14 |  ; | B14 |  ; | C14 |  ; |
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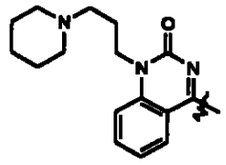
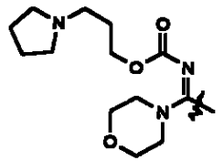
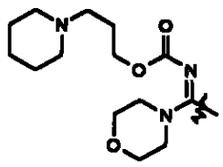
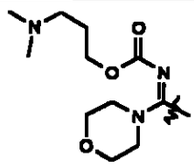
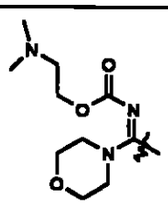
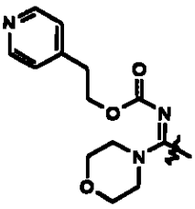
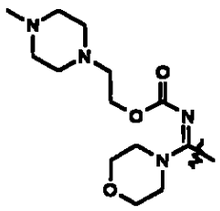
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| A18 |  ; | B18 |  ; | C18 |  ; |
| A19 |  ; | B19 |  ; | C19 |  ; |
| A20 |  ; | B20 |  ; | C20 |  ; |
| A21 |  ; | B21 |  ; | C21 |  ; |
| A22 |  ; | B22 |  ; | C22 |  ; |

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|---|---|---|---|---|---|
| A23 |  ; | B23 |  ; | C23 |  ; |
| A24 |  ; | B24 |  ; | C24 |  ; |
| A25 |  ; | B25 |  ; | C25 |  ; |
| A26 |  ; | B26 |  ; | C26 |  ; |
| A27 |  ; | B27 |  ; | C27 |  ; |
| A28 |  ; | B28 |  ; | C28 |  ; |
| A29 |  ; | B29 |  ; | C29 |  ; |
| A30 |  ; | B30 |  ; | C30 |  ; |

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|---|---|---|---|---|---|
| A31 |  ; | B31 |  ; | C31 |  ; |
| A32 |  ; | B32 |  ; | C32 |  ; |
| A33 |  ; | B33 |  ; | C33 |  ; |
| A34 |  ; | B34 |  ; | C34 |  ; |
| A35 |  ; | B35 |  ; | C35 |  ; |
| A36 |  ; | B35 |  ; | C36 |  ; |
| A37 |  ; | B37 |  ; | C37 |  ; |

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|---|---|---|---|---|---|
| A38 |  ; | B38 |  ; | C38 |  ; |
| A39 |  ; | B39 |  ; | C39 |  ; |
| A40 |  ; | B40 |  ; | C40 |  ; |
| A41 |  ; | B41 |  ; | C41 |  ; |
| A42 |  ; | B42 |  ; | C42 |  ; |
| A43 |  ; | B43 |  ; | C43 |  ; |

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|---|---|---|---|---|---|
| A44 |  ; | B44 |  ; | C44 |  ; |
| A45 |  ; | B45 |  ; | C45 |  ; |
| A46 |  ; | B46 |  ; | C46 |  ; |
| A47 |  ; | B47 |  ; | C47 |  ; |
| A48 |  ; | B48 |  ; | C48 |  ; |
| A49 |  ; | B49 |  ; | | |
| A50 |  ; | | | | |

| | | | | | |
|---|---|---|---|---|---|
| A51 |  ; | | | | |
| A52 |  ; | | | | |
| A53 |  ; | | | | |
| A54 |  ; | | | | |
| A55 |  ; | | | | |
| A56 |  ; | | | | |
| A57 |  | | | | |

y los derivados farmacéuticamente aceptables de los mismos.

2.- Un compuesto elegido de:

éster etílico de ácido {[1-3-ciano-1-isobutil-piperidin-3-il-carbamoil)-3,3-dimetil-butilamino]-morfolin-4-il-metileno}-carbámico;

N-(2-ciano-octahidro-quinolizin-2-il)-3-ciclohexil-2-(1,1-dioxo-1H-1λ-benzo-3-ilamino)-propionamida;

éster etílico de ácido {[1-3-ciano-1-metil-piperidin-3-il-carbamoil)-3,3-dimetil-butilamino]-morfolin-4-il-metileno}-carbámico;

éster etílico de ácido {[1-(2-ciano-octahidro-quinolizin-2-ilcarbamoil)-3,3-dimetil-butilamino]-morfolin-4-il-metileno}-carbámico;

éster etílico de ácido {[1-(4-ciano-1-propil-piperidin-4-ilcarbamoil)-3-metil-butilamino]-morfolin-4-il-metileno}-carbámico;

éster etílico de ácido {[1-(4-ciano-1-ciclohexil-piperidin-4-ilcarbamoil)-2-ciclohexil-etilamino]-morfolin-4-il-metileno}-carbámico;

éster ciclohexilmetílico de ácido {[1-(4-ciano-1-metil-piperidin-4-ilcarbamoil)-2-ciclohexil-etilamino]-morfolin-4-il-metileno}-carbámico;

éster ciclobutílico de ácido {[1-(4-ciano-1-metil-piperidin-4-ilcarbamoil)-2-ciclohexil-etilamino]-morfolin-4-il-metileno}-carbámico;

éster alílico de ácido {[1-(4-ciano-1-metil-piperidin-4-il-carbamoil)-2-ciclohexil-etilamino]-morfolin-4-il-metileno}--carbámico;

N-(4-ciano-1-propil-piperidin-4-il)-4-ciclohexil-2-(2-oxo-2,3-dihidro-benzo[e][1,3]oxazin-4-ilidenamino)-butiramida;

éster de ácido {[1-(4-ciano-1-propil-piperidin-4-ilcarbamoil)-3-ciclohexil-propilamino]-morfolin-4-il-metileno}-carbámico;

éster tetrahidro-furan-3-ilmetílico de ácido {[1-(4-ciano-1-metil-piperidin-4-ilcarbamoil)-2-ciclohexil-etilamino]-morfolin-4-il-metileno}-carbámico;

éster tetrahidro-furan-2-ilmetílico de ácido {[1-(4-ciano-1-metil-piperidin-4-ilcarbamoil)-2-ciclohexil-etilamino]-morfolin-4-il-metileno}-carbámico;

N-(4-ciano-1-metil-piperidin-4-il)-3-ciclohexil-2-(5,6-difluoro-3-oxo-2,3-dihidro-isoindol-1-ilidenamino)-propionamida;

(4-ciano-1-propil-piperidin-4-il)-amida de ácido 2-(5,6-difluoro-3-oxo-2,3-dihidro-isoindol-1-ilidenamino)-4,4-dimetil-pentanoico;

(4-ciano-1-propil-piperidin-4-il)-amida de ácido 2-(6-fluoro-3-oxo-2,3-dihidro-isoindol-1-ilidenamino)-4,4-dimetil-pentanoico;

N-(4-ciano-1-metil-piperidin-4-il)-3-ciclohexil-2-(6-fluoro-3-oxo-2,3-dihidro-isoindol-1-ilideneamino)-propionamida;

éster metílico de ácido {[1-(4-ciano-1-propil-piperidin-4-ilcarbamoil)-3,3-dimetil-butilamino]-morfolin-4-il-metil}-carbámico;

éster metílico de ácido {[1-(4-ciano-1-metil-piperidin-4-il-

carbamoil)-2-ciclohexil-etilimino]-morfolin-4-il-metil}-carbámico;

éster 2,2-dimetil-propílico de ácido {[1-(4-ciano-1-metil-piperidin-4-ilcarbamoil)-2-ciclohexil-etilimino]-morfolin-4-il-metil}-carbámico;

éster metílico de ácido {[1-(4-ciano-1-metil-piperidin-4-il-carbamoil)-3,3-dimetil-butilimino]-morfolin-4-il-metil}-carbámico;

éster bencílico de ácido {[1-(4-ciano-1-metil-piperidin-4-il-carbamoil)-2-ciclohexil-etilimino]-morfolin-4-il-metil}-carbámico;

éster isobutílico de ácido {[1-(4-ciano-1-metil-piperidin-4-ilcarbamoil)-2-ciclohexil-etilimino]-morfolin-4-il-metil}-carbámico;

éster propílico de ácido {[1-(4-ciano-1-metil-piperidin-4-il-carbamoil)-2-ciclohexil-etilimino]-morfolin-4-il-metil}-carbámico;

éster hexílico de ácido {[1-(4-ciano-1-metil-piperidin-4-il-carbamoil)-2-ciclohexil-etilimino]-morfolin-4-il-metil}-carbámico;

éster ciclobutilmetílico de ácido {[1-(4-ciano-1-metil-piperidin-4-ilcarbamoil)-2-ciclohexil-etilimino]-morfolin-4-il-metil}-carbámico;

éster 3,3,3-trifluoro-propílico de ácido {[1-(4-ciano-1-metil-piperidin-4-ilcarbamoil)-2-ciclohexil-etilimino]-morfolin-4-il-metil}-carbámico;

éster 2-metoxi-etílico de ácido {[1-(4-ciano-1-metil-piperidin-4-ilcarbamoil)-2-ciclohexil-etilimino]-morfolin-4-il-metil}-carbámico;

(4-ciano-1-propil-piperidin-4-il)-amida de ácido 5,5-dimetil-2-(2-oxo-2,3-dihidro-benzo[e][1,3]oxazin-4-ilidenamino)-hexanoico;

éster etílico de ácido {[1-(4-ciano-1-propil-piperidin-4-ilcarbamoil)-4,4-dimetil-pentilimino]-morfolin-4-il-metil}-carbámico;

éster 2-isopropoxi-etílico de ácido {[1-(4-ciano-1-metil-piperidin-4-ilcarbamoil)-2-ciclohexil-etilimino]-morfolin-4-il-metil}-carbámico;

éster 3-metoxi-butílico de ácido {[1-(4-ciano-1-metil-piperidin-4-ilcarbamoil)-2-ciclohexil-etilimino]-morfolin-4-il-metil}-carbámico;

éster 2-isobutoxi-etílico de ácido {[1-(4-ciano-1-metil-piperidin-4-ilcarbamoil)-2-ciclohexil-etilimino]-morfolin-4-il-metil}-carbámico;

éster 2-metoxi-etílico de ácido {[1-(4-ciano-1-propil-piperidin-4-ilcarbamoil)-3,3-dimetil-butilimino]-morfolin-4-il-metil}-carbámico;

N-(4-ciano-1-metil-piperidin-4-il)-4-ciclohexil-2-(6-metoxi-2-oxo-2,3-dihidro-benzo[e][1,3]oxazin-4-ilidenamino)-butiramida;

N-(4-ciano-1-metil-piperidin-4-il)-4-ciclohexil-2-(6-fluoro-2-oxo-2,3-dihidro-benzo[e][1,3]oxazin-4-ilidenamino)-butiramida;

N-(4-ciano-1-metil-piperidin-4-il)-4-ciclohexil-2-(7-fluoro-2-oxo-2,3-dihidro-benzo[e][1,3]oxazin-4-ilidenamino)-butiramida;

(4-ciano-1-propil-piperidin-4-il)-amida de ácido 2-(7-fluoro-2-oxo-2,3-dihidro-benzo[e][1,3]oxazin-4-ilidenamino)-5,5-dimetil-hexanoico;

N-(4-ciano-1-metil-piperidin-4-il)-4-ciclohexil-2-(7-metoxi-2-oxo-2,3-dihidro-benzo[e][1,3]oxazin-4-ilidenamino)-butiramida;

(4-ciano-1-propil-piperidin-4-il)-amida de ácido 2-(7-metoxi-2-oxo-2,3-dihidro-benzo[e][1,3]oxazin-4-ilidenamino)-5,5-dimetil-hexanoico;

éster etílico de ácido {[1-(4-ciano-1-propil-piperidin-4-il-carbamoil)-5-metil-hexilimino]-morfolin-4-il-metil}-carbámico;

2-[(N-bencil-morfolin-4-carboximidoil)-amino]-N-(4-ciano-1-metil-piperidin-4-il)-3-ciclohexil-propionamida;

N-(4-ciano-1-metil-piperidin-4-il)-3-ciclohexil-2-(2-oxo-2,3-dihidro-benzo[e][1,3]oxazin-4-ilidenamino)-propionamida;

éster etílico de ácido {[1-(4-ciano-1-metil-piperidin-4-il-carbamoil)-2-ciclohexil-etilimino]-pirrolidin-1-il-metil}-carbámico;

éster etílico de ácido {[1-(4-ciano-1-metil-piperidin-4-il-carbamoil)-2-ciclohexil-etilimino]-piperidin-1-il-metil}-carbámico;

éster etílico de ácido {azepan-1-il-[1-(4-ciano-1-metil-pipe-

ridin-4-ilcarbamoil)-2-ciclohexil-etilimino]-metil}-carbámico;

éster etílico de ácido {azocan-1-il-[1-(4-ciano-1-metil-piperidin-4-ilcarbamoil)-2-ciclohexil-etilimino]-metil}-carbámico;

éster etílico de ácido 1-{[1-(4-ciano-1-metil-piperidin-4-ilcarbamoil)-2-ciclohexil-etilimino]-etoxicarbonilamino-metil}-piperidina-4-carboxílico;

éster etílico de ácido 1-{[1-(4-ciano-1-metil-piperidin-4-ilcarbamoil)-2-ciclohexil-etilimino]-etoxicarbonilamino-metil}-piperidina-3-carboxílico;

éster etílico de ácido [[1-(4-ciano-1-metil-piperidin-4-ilcarbamoil)-2-ciclohexil-etilimino]-(4-pirrolidin-1-il-piperidin-1-il)-metil]-carbámico;

éster etílico de ácido {[1,4']bipiperidinil-1'-il-[1-(4-ciano-1-metil-piperidin-4-ilcarbamoil)-2-ciclohexil-etilimino]-metil}-carbámico;

éster etílico de ácido [[1-(4-ciano-1-metil-piperidin-4-ilcarbamoil)-2-ciclohexil-etilimino]-(4-fenilpiperazin-1-il)-metil]-carbámico;

éster etílico de ácido [[1-(4-ciano-1-metil-piperidin-4-ilcarbamoil)-2-ciclohexil-etilimino]-(4-etilpiperazin-1-il)-metil]-carbámico;

éster etílico de ácido {(4-acetil-piperazin-1-il)-[1-(4-ciano-1-metil-piperidin-4-ilcarbamoil)-2-ciclohexil-etilimino]-metil}-carbámico;

éster etílico de ácido 4-{[1-(4-ciano-1-metil-piperidin-4-il-carbamoil)-2-ciclohexil-etilimino]-etoxicarbonilamino-metil}-piperazina-1-carboxílico;

éster etílico de ácido [[1-(4-ciano-1-metil-piperidin-4-il-carbamoil)-2-ciclohexil-etilimino]-(3,3,5-trimetil-6-aza-biciclo[3.2.1]oct-6-il)-metil]-carbámico;

éster etílico de ácido {(3-acetilamino-pirrolidin-1-il)-[1-(4-ciano-1-metil-piperidin-4-ilcarbamoil)-2-ciclohexil-etilimino]-metil}-carbámico;

éster etílico de ácido {(3-acetilamino-pirrolidin-1-il)-[1-(4-ciano-1-metil-piperidin-4-ilcarbamoil)-2-ciclohexil-etilimino]-metil}-carbámico;

éster etílico de ácido {(3-azapent-3-il)-[1-(4-ciano-1-metil-piperidin-4-ilcarbamoil)-2-ciclohexil-etilimino]-metil}-carbámico;

éster etílico de ácido {(1-metoxi-3-azapent-3-il)-[1-(4-ciano-1-metil-piperidin-4-ilcarbamoil)-2-ciclohexil-etilimino]-metil}-carbámico;

éster etílico de ácido [[1-(4-ciano-1-metil-piperidin-4-il-carbamoil)-2-ciclohexil-etilimino]-(3-oxo-piperazin-1-il)-metil]-carbámico;

éster etílico de ácido {(1,5-dimetoxi-3-azapent-3-il)-[1-(4-ciano-1-metil-piperidin-4-ilcarbamoil)-2-ciclohexil-etilimino]-metil}-carbámico;

(4-ciano-1-propil-piperidin-4-il)-amida de ácido 4,4-dimetil-2-(2-oxo-2,3-dihidro-benzo[e][1,3]oxazin-4-ilidenamino)-pentanoico;

éster etílico de ácido {(4-carbamoil-piperidin-1-il)-[1-(4-ciano-1-metil-piperidin-4-ilcarbamoil)-2-ciclohexil-etilimino]-metil}-carbámico;

éster etílico de ácido [[1-(4-ciano-1-metil-piperidin-4-ilcarbamoil)-2-ciclohexil-etilimino]-(2-metoximetil-morfolin-4-il)-metil]-carbámico;

éster etílico de ácido (4-{[1-(4-ciano-1-metil-piperidin-4-ilcarbamoil)-2-ciclohexil-etilimino]-etoxicarbonilamino-metil}-piperazin-1-il)-acético;

éster etílico de ácido [[1-(4-ciano-1-metil-piperidin-4-ilcarbamoil)-2-ciclohexil-etilimino]-(2,6-dimetil-morfolin-4-il)-metil]-carbámico;

éster etílico de ácido [[1-(4-ciano-1-metil-piperidin-4-ilcarbamoil)-2-ciclohexil-etilimino]-(2,6-dimetil-morfolin-4-il)-metil]-carbámico;

éster etílico de ácido {[1-(4-ciano-1-metil-piperidin-4-ilcarbamoil)-2-ciclohexil-etilimino]-tiomorfolin-4-il-metil}-carbámico;

(4-ciano-1-propil-piperidin-4-il)-amida de ácido 4,4-dimetil-2-(6-metil-2-oxo-2,3-dihidro-benzo[e][1,3]oxazin-4-ilidenamino)-pentanoico;

(4-ciano-1-propil-piperidin-4-il)-amida de ácido 2-(6-cloro-2-oxo-2,3-dihidro-benzo[e][1,3]oxazin-4-ilidenamino)-4,4-dimetil-pentanoico;

(4-ciano-1-propil-piperidin-4-il)-amida de ácido 4,4-dimetil-2-(2-oxo-2,3-dihidro-1*H*-quinazolin-4-ilidenamino)-pentanoico;

(4-ciano-1-propil-piperidin-4-il)-amida de ácido 2-(7-cloro-2-oxo-2,3-dihidro-benzo[e][1,3]oxazin-4-ilidenamino)-4,4-dimetil-pentanoico;

(4-ciano-1-propil-piperidin-4-il)-amida de ácido 5-metil-2-(2-oxo-2,3-dihidro-benzo[e][1,3]oxazin-4-ilidenamino)-hexanoico;

(4-ciano-1-propil-piperidin-4-il)-amida de ácido 4,4-dimetil-2-(1-metil-2-oxo-1,2-dihidro-quinazolin-4-ilamino)-pentanoico;

3-terc.-butilsulfanil-N-(4-ciano-1-propil-piperidin-4-il)-2-(2-oxo-2,3-dihidro-benzo[e][1,3]oxazin-4-ilidenamino)-propionamida;

éster etílico de ácido {[2-terc.-butilsulfanil-1-(4-ciano-1-propil-piperidin-4-ilcarbamoil)-etilimino]-morfolin-4-il-metil}-carbámico;

3-bencilsulfanil-N-(4-ciano-1-propil-piperidin-4-il)-2-(2-oxo-2,3-dihidro-benzo[e][1,3]oxazin-4-ilidenamino)-propionamida;

éster etílico de ácido {[2-bencilsulfanil-1-(4-ciano-1-propil-piperidin-4-ilcarbamoil)-etilimino]-morfolin-4-il-metil}-carbámico;

N-(4-ciano-1-propil-piperidin-4-il)-3-ciclooctil-(2-oxo-2,3-dihidro-benzo[e][1,3]oxazin-4-ilidenamino)-propionamida;

N-(4-ciano-1-propil-piperidin-4-il)-3-cicloheptil-2-(2-oxo-2,3-dihidro-benzo[e][1,3]oxazin-4-ilidenamino)-propionamida;

éster etílico de ácido {[1-(4-ciano-1-propil-piperidin-4-il-

carbamoil)-2-cicloheptil-etilimino]-morfolin-4-il-metil}-carbámico;

éster etílico de ácido {[1-(4-ciano-1-propil-piperidin-4-il-carbamoil)-2-ciclooctil-etilimino]-morfolin-4-il-metil}-carbámico;

éster isobutílico de ácido {[1-(4-ciano-piperidin-4-ilcarbamoil)-2-ciclohexil-etilamino]-morfolin-4-il-metileno}-carbámico;

éster isobutílico de ácido {[1-[4-ciano-1-(2-morfolin-4-il-etil)-piperidin-4-ilcarbamoil]-2-ciclohexil-etilamino}-morfolin-4-il-metileno}-carbámico;

éster isobutílico de ácido ({1-[1-(2-carbamoil)-etil)-4-ciano-piperidin-4-ilcarbamoil]-2-ciclohexil-etilamino}-morfolin-4-il-metileno}-carbámico;

éster isobutílico de ácido ([1-(4-ciano-1-[2-(2-metoxil-etoxi)-etil]-piperidin-4-ilcarbamoil}-2-ciclohexil-etilamino)-morfolin-4-il-metileno]-carbámico;

éster isobutílico de ácido [(1-{4-ciano-1-[3-(2-metoxil-etoxi)-propil]-piperidin-4-ilcarbamoil}-2-ciclohexil-etilamino)-morfolin-4-il-metileno]-carbámico;

éster etílico de ácido {[2-terc.-butoxi-1-(4-ciano-1-propil]-piperidin-4-ilcarbamoil)-etilamino]-morfolin-4-il-metileno]-carbámico;

N-(4-ciano-1-metil-piperidin-4-il)-3-ciclohexil-2-{[dietil-carbamoilimino)-morfolin-4-il-metil]-amino}-propionamida;

éster etílico de ácido {[1-(4-ciano-1-propil-piperidin-4-

ilcarbamoil)-2-(3,3,5,5-tetrametil-ciclohexil)-etilamino]-morfolin-4-il-metileno}-carbámico;

éster etílico de ácido {[1-(4-ciano-1-propil-piperidin-4-ilcarbamoil)-2-(4,4-dipropil-ciclohexil)-etilamino]-morfolin-4-il-metileno}-carbámico;

éster etílico de ácido {[1-(4-ciano-1-isopropil-piperidin-4-ilcarbamoil)-2-ciclohexil-etilamino]-morfolin-4-il-metileno}-carbámico;

éster etílico de ácido {[1-(4-ciano-1-fenetil-piperidin-4-il-carbamoil)-2-ciclohexil-etilamino]-morfolin-4-il-metileno}-carbámico;

éster etílico de ácido {[1-(4-ciano-1-etil-piperidin-4-ilcarbamoil)-2-ciclohexil-etilamino]-morfolin-4-il-metileno}-carbámico;

éster etílico de ácido {[1-(1-bencil-4-ciano-piperidin-4-il-carbamoil)-2-ciclohexil-etilamino]-morfolin-4-il-metileno}-carbámico;

éster bencílico de ácido 4-ciano-4-(3-ciclohexil-2-[(etoxicarbonilimino-morfolin-4-il-metil)-amino]-propionilamino}-piperidina-1-carboxílico;

éster etílico de ácido {[1-(1-bencil-4-ciano-piperidin-4-il-carbamoil)-3,3-dimetil-butilamino]-morfolin-4-il-metileno}-carbámico;

éster etílico de ácido {[1-(4-ciano-1-fenetil-piperidin-4-il-carbamoil)-3,3-dimetil-butilamino]-morfolin-4-il-metileno}-carbámico;

(1-bencil-4-ciano-piperidin-4-il)-amida de ácido 4,4-dimetil-2-(2-oxo-2H-benzo[e][1,3]oxazin-4-ilamino)-pentanoico;

[4-ciano-1-(5-metil-tiofen-2-ilmetil)-piperidin-4-il]-amida de ácido 4,4-dimetil-2-(2-oxo-2H-benzo[e][1,3]oxazin-4-ilamino)-pentanoico;

[4-ciano-1-(4-fluoro-bencil)-piperidin-4-il]-amida de ácido 4,4-dimetil-2-(2-oxo-2H-benzo[e][1,3]oxazin-4-ilamino)-pentanoico;

(4-ciano-1-etil-piperidin-4-il)-amida de ácido 4,4-dimetil-2-(2-oxo-2H-benzo[e][1,3]oxazin-4-ilamino)-pentanoico;

(4-ciano-1-metil-piperidin-4-il)-amida de ácido 4,4-dimetil-2-(2-oxo-2H-benzo[e][1,3]oxazin-4-ilamino)-pentanoico;

(4-ciano-piperidin-4-il)-amida de ácido 4,4-dimetil-2-(2-oxo-2H-benzo[e][1,3]oxazin-4-ilamino)-pentanoico;

(4-ciano-1-fenetil-piperidin-4-il)-amida de ácido 4,4-dimetil-2-(2-oxo-2H-benzo[e][1,3]oxazin-4-ilamino)-pentanoico;

[4-ciano-1-(2,2-dimetil-propil)-piperidin-4-il]-amida de ácido 4,4-dimetil-2-(2-oxo-2H-benzo[e][1,3]oxazin-4-ilamino)-pentanoico;

[4-ciano-1-(3,3-dimetil-butil)-piperidin-4-il]-amida de ácido 4,4-dimetil-2-(2-oxo-2H-benzo[e][1,3]oxazin-4-ilamino)-pentanoico;

(4-ciano-1-pentil-piperidin-4-il)-amida de ácido 4,4-dimetil-2-(2-oxo-2H-benzo[e][1,3]oxazin-4-ilamino)-pentanoico;

(1-butil-4-ciano-piperidin-4-il)-amida de ácido 4,4-dimetil-

2-(2-oxo-2H-benzo[e][1,3]oxazin-4-ilamino)-pentanoico;

[4-ciano-1-(3,3,3-trifluoro-propil)-piperidin-4-il]-amida de ácido 4,4-dimetil-2-(2-oxo-2H-benzo[e][1,3]oxazin-4-ilamino)-pentanoico;

(4-ciano-1-ciclohexilmetil-piperidin-4-il)-amida de ácido 4,4-dimetil-2-(2-oxo-2H-benzo[e][1,3]oxazin-4-ilamino)-pentanoico;

N-(4-ciano-1-propil-piperidin-4-il)-3-(4,4-dimetil-ciclohexil)-2-(2-oxo-2H-benzo[e][1,3]oxazin-4-ilamino)-propionamida;

N-(4-ciano-1-propil-piperidin-4-il)-3-(4,4-dipropil-ciclohexil)-2-(2-oxo-2H-benzo[e][1,3]oxazin-4-ilamino)-propionamida;

N-(4-ciano-1-propil-piperidin-4-il)-3-(4-terc.-butil-ciclohexil)-2-(2-oxo-2H-benzo[e][1,3]oxazin-4-ilamino)-propionamida;

N-(4-ciano-1-propil-piperidin-4-il)-3-(3,3,5,5-tetrametil-ciclohexil)-2-(2-oxo-2H-benzo[e][1,3]oxazin-4-ilamino)-propionamida;

éster etílico de ácido {[1-(3-ciano-1-etil-pirrolidin-3-il-carbamoil)-2-ciclohexil-etilamino]-morfolin-4-il-metileno}-carbámico;

(4-ciano-1-propil-piperidin-4-il)-amida de ácido 2-[(metano-sulfonilimino-morfolin-4-il-metil)-amino]-4,4-dimetil-pentanoico;

éster etílico de ácido {[1-(3-ciano-1-propil-pirrolidin-3-ilcarbamoil)-3,3-dimetil-butilamino]-morfolin-4-il-metileno}-carbámico;

éster etílico de ácido ({1-[3-ciano-1-(4,4-dimetil-ciclohexil)-pirrolidin-3-ilcarbamoil]-3,3-dimetil-butilamino}-morfolin-4-il-metileno)-carbámico;

éster etílico de ácido {[1-(3-ciano-1-etil-5,5-dimetil-pirrolidin-3-ilcarbamoil)-3,3-dimetil-butilamino]-morfolin-4-il-metileno}-carbámico;

N-(4-ciano-1-metil-piperidin-4-il)-3-ciclohexil-2-(7,8-difluoro-2-oxo-2H-benzo[e][1,3]oxazin-4-ilamino)-propionamida;

éster etílico de ácido {[1-(4-ciano-1-ciclohexilmetil-piperidin-4-ilcarbamoil)-2-ciclohexil-etilamino]-morfolin-4-il-metileno}-carbámico;

éster bencílico de ácido 3-ciano-3-[4,4-dimetil-2-(2-oxo-2*H*-benzo[e][1,3]oxazin-4-ilamino)-pentanoilamino]-azepan-1-carboxílico;

(3-ciano-1-propil-azepan-3-il)-amida de ácido 4,4-dimetil-2-(2-oxo-2*H*-benzo[e][1,3]oxazin-4-ilamino)-pentanoico;

(4-ciano-1-propil-azepan-4-il)-amida de ácido 4,4-dimetil-2-(2-oxo-2*H*-benzo[e][1,3]oxazin-4-ilamino)-pentanoico;

éster 4-metoxi-ciclohexilmetílico de ácido {[1-(4-ciano-1-metil-piperidin-4-ilcarbamoil)-2-ciclohexil-etilamino]-morfolin-4-il-metileno}-carbámico;

éster ciclohexílico de ácido {[1-(4-ciano-1-metil-piperidin-4-ilcarbamoil)-2-ciclohexil-etilamino]-morfolin-4-il-metileno}-carbámico;

éster etílico de ácido {[1-(4-ciano-1-propil-piperidin-4-

ilcarbamoil)-3,3-dimetil-butilamino]-fenil-metileno}-carbámico;

éster etílico de ácido {[1-(4-ciano-1-metil-piperidin-4-ilcarbamoil)-2-ciclohexil-etilamino]-fenil-metileno}-carbámico;

(4-ciano-1-propil-piperidin-4-il)-amida de ácido 2-{[N-(4-ciano-fenil)-morfolina-4-carboximidoil]-amino}-4,4-dimetil-pentanoico;

(4-ciano-1-propil-piperidin-4-il)-amida de ácido 4,4-dimetil-2-{[N-(4-trifluorometil-fenil)-morfolina-4-carboximidoil]-amino}-pentanoico;

y los derivados farmacéuticamente aceptables del mismo.

3.- El compuesto de acuerdo con la reivindicación 2, en donde le compuesto se elige de

éster etílico de ácido {[1-(3-ciano-1-isobutil-piperidin-3-il-carbamoil)-3,3-dimetil-butilamino]-morfolin-4-il-metileno}-carbámico;

éster etílico de ácido {[1-(4-ciano-1-ciclohexil-piperidin-4-ilcarbamoil)-2-ciclohexil-etilamino]-morfolin-4-il-metileno}-carbámico;

éster ciclohexilmetílico de ácido {[1-(4-ciano-1-metil-piperidin-4-ilcarbamoil)-2-ciclohexil-etilamino]-morfolin-4-il-metileno}-carbámico;

éster ciclobutílico de ácido {[1-(4-ciano-1-metil-piperidin-4-ilcarbamoil)-2-ciclohexil-etilamino]-morfolin-4-il-metileno}-carbámico;

éster alílico de ácido {[1-(4-ciano-1-metil-piperidin-4-il-

carbamoil)-2-ciclohexil-etilamino]-morfolin-4-il-metileno}-carbámico;

N-(4-ciano-1-propil-piperidin-4-il)-4-ciclohexil-2-(2-oxo-2,3-dihidro-benzo[e][1,3]oxazin-4-ilidenamino)-butiramida;

éster tetrahidro-furan-3-ilmetílico de ácido {[1-(4-ciano-1-metil-piperidin-4-ilcarbamoil)-2-ciclohexil-etilamino]-morfolin-4-il-metileno}-carbámico;

éster tetrahidro-furan-2-ilmetílico de ácido {[1-(4-ciano-1-metil-piperidin-4-ilcarbamoil)-2-ciclohexil-etilamino]-morfolin-4-il-metileno}-carbámico;

N-(4-ciano-1-metil-piperidin-4-il)-3-ciclohexil-2-(5,6-difluoro-3-oxo-2,3-dihidro-isoindol-1-ilidenamino)-propionamida;

(4-ciano-1-propil-piperidin-4-il)-amida de ácido 2-(5,6-difluoro-3-oxo-2,3-dihidro-isoindol-1-ilidenamino)-4,4-dimetil-pentanoico;

(4-ciano-1-propil-piperidin-4-il)-amida de ácido 2-(6-fluoro-3-oxo-2,3-dihidro-isoindol-1-ilidenamino)-4,4-dimetil-pentanoico;

N-(4-ciano-1-metil-piperidin-4-il)-3-ciclohexil-2-(6-fluoro-3-oxo-2,3-dihidro-isoindol-1-ilidenamino)-propionamida;

éster metílico de ácido {[1-(4-ciano-1-propil-piperidin-4-ilcarbamoil)-3,3-dimetil-butilimino]-morfolin-4-il-metil}-carbámico;

éster metílico de ácido {[1-(4-ciano-1-metil-piperidin-4-ilcarbamoil)-2-ciclohexil-etilimino]-morfolin-4-il-metil}-

carbámico;

éster 2,2-dimetil-propílico de ácido {[1-(4-ciano-1-metil-piperidin-4-ilcarbamoil)-2-ciclohexil-etilimino]-morfolin-4-il-metil}-carbámico;

éster metílico de ácido {[1-(4-ciano-1-metil-piperidin-4-ilcarbamoil)-3,3-dimetil-butilimino]-morfolin-4-il-metil}-carbámico;

éster bencílico de ácido {[1-(4-ciano-1-metil-piperidin-4-ilcarbamoil)-2-ciclohexil-etilimino]-morfolin-4-il-metil}-carbámico;

éster isobutílico de ácido {[1-(4-ciano-1-metil-piperidin-4-ilcarbamoil)-2-ciclohexil-etilimino]-morfolin-4-il-metil}-carbámico;

éster propílico de ácido {[1-(4-ciano-1-metil-piperidin-4-ilcarbamoil)-2-ciclohexil-etilimino]-morfolin-4-il-metil}-carbámico;

éster hexílico de ácido {[1-(4-ciano-1-metil-piperidin-4-ilcarbamoil)-2-ciclohexil-etilimino]-morfolin-4-il-metil}-carbámico;

éster ciclobutilmetílico de ácido {[1-(4-ciano-1-metil-piperidin-4-ilcarbamoil)-2-ciclohexil-etilimino]-morfolin-4-il-metil}-carbámico;

éster 3,3,3-trifluoro-propílico de ácido {[1-(4-ciano-1-metil-piperidin-4-ilcarbamoil)-2-ciclohexil-etilimino]-morfolin-4-il-metil}-carbámico;

éster 2-metoxi-etílico de ácido {[1-(4-ciano-1-metil-piperi-

din-4-ilcarbamoil)-2-ciclohexil-etilimino]-morfolin-4-il-metil}-carbámico;

(4-ciano-1-propil-piperidin-4-il)-amida de ácido 5,5-dimetil-2-(2-oxo-2,3-dihidro-benzo[e][1,3]oxazin-4-ilidenamino)-hexanoico;

éster 2-isopropoxi-etílico de ácido {[1-(4-ciano-1-metil-piperidin-4-ilcarbamoil)-2-ciclohexil-etilimino]-morfolin-4-il-metil}-carbámico;

éster 3-metoxi-butílico de ácido {[1-(4-ciano-1-metil-piperidin-4-ilcarbamoil)-2-ciclohexil-etilimino]-morfolin-4-il-metil}-carbámico;

éster 2-isobutoxi-etílico de ácido {[1-(4-ciano-1-metil-piperidin-4-ilcarbamoil)-2-ciclohexil-etilimino]-morfolin-4-il-metil}-carbámico;

éster 2-metoxi-etílico de ácido {[1-(4-ciano-1-propil-piperidin-4-ilcarbamoil)-3,3-dimetil-butilimino]-morfolin-4-il-metil}-carbámico;

N-(4-ciano-1-metil-piperidin-4-il)-4-ciclohexil-2-(6-metoxi-2-oxo-2,3-dihidro-benzo[e][1,3]oxazin-4-ilidenamino)-butiramida;

N-(4-ciano-1-metil-piperidin-4-il)-4-cicloexil-2-(6-fluoro-2-oxo-2,3-dihidro-benzo[e][1,3]oxazin-4-ilidenamino)-butiramida;

N-(4-ciano-1-metil-piperidin-4-il)-4-ciclohexil-2-(7-fluoro-2-oxo-2,3-dihidro-benzo[e][1,3]oxazin-4-ilidenamino)-butiramida;

(4-ciano-1-propil-piperidin-4-il)-amida de ácido 2-(7-fluoro-2-oxo-2,3-dihidro-benzo[e][1,3]oxazin-4-ilidenamino)-5,5-dimetil-hexanoico;

N-(4-ciano-1-metil-piperidin-4-il)-4-ciclohexil-2-(7-metoxi-2-oxo-2,3-dihidro-benzo[e][1,3]oxazin-4-ilideneamino)-butiramida;

(4-ciano-1-propil-piperidin-4-il)-amida de ácido 2-(7-metoxi-2-oxo-2,3-dihidro-benzo[e][1,3]oxazin-4-ilidenamino)-5,5-dimetil-hexanoico;

N-(4-ciano-1-metil-piperidin-4-il)-3-ciclohexil-2-(2-oxo-2,3-dihidro-benzo[e][1,3]oxazin-4-ilidenamino)-propionamida;

éster etílico de ácido {[1-(4-ciano-1-metil-piperidin-4-il-carbamoil)-2-ciclohexil-etilimino]-pirrolidin-1-il-metil}-carbámico;

éster etílico de ácido {[1-(4-ciano-1-metil-piperidin-4-il-carbamoil)-2-ciclohexil-etilimino]-piperidin-1-il-metil}-carbámico;

éster etílico de ácido {azepan-1-il-[1-(4-ciano-1-metil-piperidin-4-ilcarbamoil)-2-ciclohexil-etilimino]-metil}-carbámico;

éster etílico de ácido {azocan-1-il-[1-(4-ciano-1-metil-piperidin-4-ilcarbamoil)-2-ciclohexil-etilimino]-metil}-carbámico;

éster etílico de ácido 1-{[1-(4-ciano-1-metil-piperidin-4-ilcarbamoil)-2-ciclohexil-etilimino]-etoxicarbonilamino-metil}-piperidina-4-carboxílico;

éster etílico de ácido 1-{[1-(4-ciano-1-metil-piperidin-4-ilcarbamoil)-2-ciclohexil-etilimino]-etoxicarbonilamino-metil}-piperidina-3-carboxílico;

éster etílico de ácido [[1-(4-ciano-1-metil-piperidin-4-ilcarbamoil)-2-ciclohexil-etilimino]-(4-fenil-piperazin-1-il-metil]-carbámico;

éster etílico de ácido [[1-(4-ciano-1-metil-piperidin-4-ilcarbamoil)-2-ciclohexil-etilimino]-(4-etil-piperazin-1-il)-metil]-carbámico;

éster etílico de ácido {(4-acetil-piperazin-1-il)-[1-(4-ciano-1-metil-piperidin-4-ilcarbamoil)-2-ciclohexil-etilimino]-metil}-carbámico;

éster etílico de ácido 4-{[1-(4-ciano-1-metil-piperidin-4-ilcarbamoil)-2-ciclohexil-etilimino]-etoxicarbonilamino-metil}-piperazina-1-carboxílico;

éster etílico de ácido [[1-(4-ciano-1-metil-piperidin-4-ilcarbamoil)-2-ciclohexil-etilimino]-(3,3,5-trimetil-6-aza-biciclo[3.2.1]oct-6-il]-metil]-carbámico;

éster etílico de ácido {(3-acetilamino-pirrolidin-1-il)-[1-(4-ciano-1-metil-piperidin-4-ilcarbamoil)-2-ciclohexil-etilimino]-metil}-carbámico;

éster etílico de ácido {(3-acetilamino-pirrolidin-1-il)-[1-(4-ciano-1-metil-piperidin-4-ilcarbamoil)-2-ciclohexil-etilimino]-metil}-carbámico;

éster etílico de ácido {(3-azapent-3-il)-[1-(4-ciano-1-metil-piperidin-4-ilcarbamoil)-2-ciclohexil-etilimino]-metil}-carbámico;

éster etílico de ácido {(1-metoxi-3-azapent-3-il)-[1-(4-ciano-1-metil-piperidin-4-ilcarbamoil)-2-ciclohexil-etilimino]-metil}-carbámico;

éster etílico de ácido [[1-(4-ciano-1-metil-piperidin-4-ilcarbamoil)-2-ciclohexil-etilimino]-(3-oxo-piperazin-1-il)-metil]-carbámico;

éster etílico de ácido {(1,5-dimetoxi-3-azapent-3-il)-[1-(4-ciano-1-metil-piperidin-4-ilcarbamoil)-2-ciclohexil-etilimino]-metil}-carbámico;

(4-ciano-1-propil-piperidin-4-il)-amida de ácido 4,4-dimetil-2-(2-oxo-2,3-dihidro-benzo[e][1,3]oxazin-4-ilidenamino)-pentanoico;

éster etílico de ácido {(4-carbamoil-piperidin-1-il)-[1-(4-ciano-1-metil-piperidin-4-ilcarbamoil)-2-ciclohexil-etilimino]-metil}-carbámico;

éster etílico de ácido [[1-(4-ciano-1-metil-piperidin-4-ilcarbamoil)-2-ciclohexil-etilimino]-(2-metoximetil-morfolin-4-il)-metil]-carbámico;

éster etílico de ácido (4-{[1-(4-ciano-1-metil-piperidin-4-ilcarbamoil)-2-ciclohexil-etilimino]-etoxicarbonilamino-metil}-piperazin-1-il)-metil]-acético;

éster etílico de ácido [[1-(4-ciano-1-metil-piperidin-4-ilcarbamoil)-2-ciclohexil-etilimino]-(2,6-dimetil-morfolin-4-il)-metil]-carbámico;

éster etílico de ácido [[1-(4-ciano-1-metil-piperidin-4-ilcarbamoil)-2-ciclohexil-etilimino]-(2,6-dimetil-morfolin-4-il)-metil]-carbámico;

éster etílico de ácido {[1-(4-ciano-1-metil-piperidin-4-il-carbamoil)-2-ciclohexil-etilimino]-tiomorfolin-4-il-metil}-carbámico;

(4-ciano-1-propil-piperidin-4-il)-amida de ácido 4,4-dimetil-2-(6-metil-2-oxo-2,3-dihidro-benzo[e][1,3]oxazin-4-ilidenamino)-pentanoico;

(4-ciano-1-propil-piperidin-4-il)-amida de ácido 2-(6-cloro-2-oxo-2,3-dihidro-benzo[e][1,3]oxazin-4-ilidenamino)-4,4-dimetil-pentanoico;

(4-ciano-1-propil-piperidin-4-il)-amida de ácido 4,4-dimetil-2-(2-oxo-2,3-dihidro-1*H*-quinazolin-4-ilidenamino)-pentanoico;

(4-ciano-1-propil-piperidin-4-il)-amida de ácido 2-(7-cloro-2-oxo-2,3-dihidro-benzo[e][1,3]oxazin-4-ilidenamino)-4,4-dimetil-pentanoico;

(4-ciano-1-propil-piperidin-4-il)-amida de ácido 5-metil-2-(2-oxo-2,3-dihidro-benzo[e][1,3]oxazin-4-ilidenamino)-hexanoico;

(4-ciano-1-propil-piperidin-4-il)-amida de ácido 4,4-dimetil-2-(1-metil-2-oxo-1,2-dihidro-quinazolin-4-ilamino)-pentanoico;

3-terc.-butilsulfanil-N-(4-ciano-1-propil-piperidin-4-il)-2-(2-oxo-2,3-dihidro-benzo[e][1,3]oxazin-4-ilidenamino)-propionamida;

3-bencilsulfanil-N-(4-ciano-1-propil-piperidin-4-il)-2-(2-oxo-2,3-dihidro-benzo[e][1,3]oxazin-4-ilidenamino)-propionamida;

éster etílico de ácido {[2-bencilsulfanil-1-(4-ciano-1-propil-piperidin-4-ilcarbamoil)-etilimino]-morfolin-4-il-metil}-carbámico;

N-(4-ciano-1-propil-piperidin-4-il)-3-ciclooctil-2-(2-oxo-2,3-dihidro-benzo[e][1,3]oxazin-4-ilidenamino)-propionamida;

N-(4-ciano-1-propil-piperidin-4-il)-3-cicloheptil-2-(2-oxo-2,3-dihidro-benzo[e][1,3]oxazin-4-ilidenamino)-propionamida;

éster etílico de ácido {[1-(4-ciano-1-propil-piperidin-4-ilcarbamoil)-2-cicloheptil-etilimino]-morfolin-4-il-metil}-carbámico;

éster etílico de ácido {[1-(4-ciano-1-propil-piperidin-4-ilcarbamoil)-2-ciclooctil-etilimino]-morfolin-4-il-metil}-carbámico;

éster isobutílico de ácido {[1-(4-ciano-piperidin-4-il-carbamoil)-2-ciclohexil-etilamino]-morfolin-4-il-metileno}-carbámico;

éster isobutílico de ácido ({1-[4-ciano-1-(2-morfolin-4-il-etil)-piperidin-4-ilcarbamoil]-2-ciclohexil-etilamino}-morfolin-4-il-metileno}-carbámico;

éster isobutílico de ácido ({1-[1-(2-carbamoil-etil)-4-ciano-piperidin-4-ilcarbamoil]-2-ciclohexil-etilamino}-morfolin-4-il-metileno)-carbámico;

éster isobutílico de ácido [(1-{4-ciano-1-[2-(2-metoxil-etoxi)-etil]-piperidin-4-ilcarbamoil}-2-ciclohexil-etilamino)-morfolin-4-il-metileno]-carbámico;

éster isobutílico de ácido [(1-{4-ciano-1-[3-(2-metoxil-

etoxi)-propil]-piperidin-4-ilcarbamoil}-2-ciclohexil-etilamino]-morfolin-4-il-metileno}-carbámico;

éster etílico de ácido {[2-terc.-butoxi-1-(4-ciano-1-propil-piperidin-4-ilcarbamoil)-etilamino]-morfolin-4-il-metileno}-carbámico;

N-(4-ciano-1-metil-piperidin-4-il)-3-ciclohexil-2-{[dietil-carbamoilimino)-morfolin-4-il-metil]-amino}-propionamida;

éster etílico de ácido {[1-(4-ciano-1-propil-piperidin-4-ilcarbamoil)-2-(3,3,5,5-tetrametil-ciclohexil)-etilamino]-morfolin-4-il-metileno}-carbámico;

éster etílico de ácido {[1-(4-ciano-1-propil-piperidin-4-ilcarbamoil)-2-(4,4-dipropil-ciclohexil)-etilamino]-morfolin-4-il-metileno}-carbámico;

éster etílico de ácido {[1-(4-ciano-1-isopropil-piperidin-4-ilcarbamoil)-2-ciclohexil-etilamino]-morfolin-4-il-metileno}-carbámico;

éster etílico de ácido {[1-(4-ciano-1-fenetil-piperidin-4-ilcarbamoil)-2-ciclohexil-etilamino]-morfolin-4-il-metileno}-carbámico;

éster etílico de ácido {[1-(4-ciano-1-etil-piperidin-4-ilcarbamoil)-2-ciclohexil-etilamino]-morfolin-4-il-metileno}-carbámico;

éster etílico de ácido {[1-(1-bencil-4-ciano-piperidin-4-ilcarbamoil)-2-ciclohexil-etilamino]-morfolin-4-il-metileno}-carbámico;

éster bencílico de ácido 4-ciano-4-(3-ciclohexil-2-[(etoxi-

carbonilimino-morfolin-4-il-metil)-amino]-propionilamino}-piperidina-1-carboxílico;

éster etílico de ácido {[1-(1-bencil-4-ciano-piperidin-4-ilcarbamoil)-3,3-dimetil-butilamino]-morfolin-4-il-metileno}-carbámico;

éster etílico de ácido {[1-(4-ciano-1-fenetil-piperidin-4-ilcarbamoil)-3,3-dimetil-butilamino]-morfolin-4-il-metileno}-carbámico;

(1-bencil-4-ciano-piperidin-4-il)-amida de ácido 4,4-dimetil-2-(2-oxo-2H-benzo[e][1,3]oxazin-4-ilamino)-pentanoico;

[4-ciano-1-(5-metil-tiofen-2-ilmetil)-piperidin-4-il]-amida de ácido 4,4-dimetil-2-(2-oxo-2H-benzo[e][1,3]oxazin-4-il-amino)-pentanoico;

[4-ciano-1-(4-fluoro-bencil)-piperidin-4-il]-amida de ácido 4,4-dimetil-2-(2-oxo-2H-benzo[e][1,3]oxazin-4-ilamino)-pentanoico;

(4-ciano-1-etil-piperidin-4-il)-amida de ácido 4,4-dimetil-2-(2-oxo-2H-benzo[e][1,3]oxazin-4-ilamino)-pentanoico;

(4-ciano-1-metil-piperidin-4-il)-amida de ácido 4,4-dimetil-2-(2-oxo-2H-benzo[e][1,3]oxazin-4-ilamino)-pentanoico;

(4-ciano-piperidin-4-il)-amida de ácido 4,4-dimetil-2-(2-oxo-2H-benzo[e][1,3]oxazin-4-ilamino)-pentanoico;

(4-ciano-1-fenetil-piperidin-4-il)-amida de ácido 4,4-dimetil-2-(2-oxo-2H-benzo[e][1,3]oxazin-4-ilamino)-pentanoico;

[4-ciano-1-(2,2-dimetil-propil)-piperidin-4-il]-amida de ácido 4,4-dimetil-2-(2-oxo-2H-benzo[e][1,3]oxazin-4-ilamino)-pentanoico;

[4-ciano-1-(3,3-dimetil-butil)-piperidin-4-il]-amida de ácido 4,4-dimetil-2-(2-oxo-2H-benzo[e][1,3]oxazin-4-ilamino)-pentanoico;

(4-ciano-1-pentil-piperidin-4-il)-amida de ácido 4,4-dimetil-2-(2-oxo-2H-benzo[e][1,3]oxazin-4-ilamino)-pentanoico;

(1-butil-4-ciano-piperidin-4-il)-amida de ácido 4,4-dimetil-2-(2-oxo-2H-benzo[e][1,3]oxazin-4-ilamino)-pentanoico;

[4-ciano-1-(3,3,3-trifluoro-propil)-piperidin-4-il]-amida de ácido 4,4-dimetil-2-(2-oxo-2H-benzo[e][1,3]oxazin-4-ilamino)-pentanoico;

(4-ciano-1-ciclohexilmetil-piperidin-4-il)-amida de ácido 4,4-dimetil-2-(2-oxo-2H-benzo[e][1,3]oxazin-4-ilamino)-pentanoico;

N-(4-ciano-1-propil-piperidin-4-il)-3-(4,4-dimetil-ciclohexil)-2-(2-oxo-2H-benzo[e][1,3]oxazin-4-ilamino)-propionamida;

N-(4-ciano-1-propil-piperidin-4-il)-3-(4,4-dipropil-ciclohexil)-2-(2-oxo-2H-benzo[e][1,3]oxazin-4-ilamino)-propionamida;

N-(4-ciano-1-propil-piperidin-4-il)-3-(4-terc.-butil-ciclohexil)-2-(2-oxo-2H-benzo[e][1,3]oxazin-4-ilamino)-propionamida;

N-(4-ciano-1-propil-piperidin-4-il)-3-(3,3,5,5-tetrametil-ciclohexil)-2-(2-oxo-2H-benzo[e][1,3]oxazin-4-ilamino)-propionamida;

éster etílico de ácido {[1-(3-ciano-1-etil-pirrolidin-3-ilcarbamoil)-2-ciclohexil-etilamino]-morfolin-4-il-metileno}-carbámico;

éster etílico de ácido {[1-(3-ciano-1-propil-pirrolidin-3-ilcarbamoil)-3,3-dimetil-butilamino]-morfolin-4-il-metileno}-carbámico;

éster etílico de ácido ({1-[3-ciano-1-(4,4-dimetil-ciclohexil)-pirrolidin-3-ilcarbamoil]-3,3-dimetil-butilamino}-morfolin-4-il-metileno)-carbámico;

N-(4-ciano-1-metil-piperidin-4-il)-3-ciclohexil-2-(7,8-difluoro-2-oxo-2H-benzo[e][1,3]oxazin-4-ilamino)-propionamida;

éster etílico de ácido {[1-(4-ciano-1-ciclohexilmetil-piperidin-4-ilcarbamoil)-2-ciclohexil-etilamino]-morfolin-4-il-metileno}-carbámico;

éster bencílico de ácido 3-ciano-3-[4,4-dimetil-2-(2-oxo-2*H*-benzo[e][1,3]oxazin-4-ilamino)-pentanoilamino]-azepan-1-carboxílico;

(3-ciano-1-propil-azepan-3-il)-amida de ácido 4,4-dimetil-2-(2-oxo-2H-benzo[e][1,3]oxazin-4-ilamino)-pentanoico;

(4-ciano-1-propil-azepan-4-il)-amida de ácido 4,4-dimetil-2-(2-oxo-2H-benzo[e][1,3]oxazin-4-ilamino)-pentanoico;

éster 4-metoxi-ciclohexilmetílico de ácido {[1-(4-ciano-1-metil-piperidin-4-ilcarbamoil)-2-ciclohexil-etilamino]-morfolin-4-il-metileno}-carbámico;

éster ciclohexílico de ácido {[1-(4-ciano-1-metil-piperidin-4-ilcarbamoil)-2-ciclohexil-etilamino]-morfolin-4-il-metile-

no}-carbámico;

éster etílico de ácido {[1-(4-ciano-1-propil-piperidin-4-ilcarbamoil)-3,3-dimetil-butilamino]-fenil-metileno}-carbámico;

y

éster etílico de ácido {[1-(4-ciano-1-metil-piperidin-4-ilcarbamoil)-2-ciclohexil-etilamino]-fenil-metileno}-carbámico.

4.- El compuesto de acuerdo con la reivindicación 3, en donde el compuesto se elige de:

éster etílico de ácido {[1-(4-ciano-1-ciclohexil-piperidin-4-ilcarbamoil)-2-ciclohexil-etilamino]-morfolin-4-il-metileno}-carbámico;

éster ciclohexilmetílico de ácido {[1-(4-ciano-1-metil-piperidin-4-ilcarbamoil)-2-ciclohexil-etilamino]-morfolin-4-il-metileno}-carbámico;

éster ciclobutílico de ácido {[1-(4-ciano-1-metil-piperidin-4-ilcarbamoil)-2-ciclohexil-etilamino]-morfolin-4-il-metileno}-carbámico;

éster alílico de ácido {[1-(4-ciano-1-metil-piperidin-4-ilcarbamoil)-2-ciclohexil-etilamino]-morfolin-4-il-metileno}-carbámico;

éster tetrahidro-furan-3-ilmetílico de ácido {[1-(4-ciano-1-metil-piperidin-4-ilcarbamoil)-2-ciclohexil-etilamino]-morfolin-4-il-metileno}-carbámico;

éster tetrahidro-furan-2-ilmetílico de ácido {[1-(4-ciano-1-metil-piperidin-4-ilcarbamoil)-2-ciclohexil-etilamino]-morfo-

lin-4-il-metileno}-carbámico;

éster metílico de ácido {[1-(4-ciano-1-metil-piperidin-4-il-carbamoil)-2-ciclohexil-etilimino]-morfolin-4-il-metil}-carbámico;

éster 2,2-dimetil-propílico de ácido {[1-(4-ciano-1-metil-piperidin-4-ilcarbamoil)-2-ciclohexil-etilimino]-morfolin-4-il-metil}-carbámico;

éster bencílico de ácido {[1-(4-ciano-1-metil-piperidin-4-il-carbamoil)-2-ciclohexil-etilimino]-morfolin-4-il-metil}-carbámico;

éster isobutílico de ácido {[1-(4-ciano-1-metil-piperidin-4-ilcarbamoil)-2-ciclohexil-etilimino]-morfolin-4-il-metil}-carbámico;

éster propílico de ácido {[1-(4-ciano-1-metil-piperidin-4-il-carbamoil)-2-ciclohexil-etilimino]-morfolin-4-il-metil}-carbámico;

éster hexílico de ácido {[1-(4-ciano-1-metil-piperidin-4-il-carbamoil)-2-ciclohexil-etilimino]-morfolin-4-il-metil}-carbámico;

éster ciclobutilmetílico de ácido {[1-(4-ciano-1-metil-piperidin-4-ilcarbamoil)-2-ciclohexil-etilimino]-morfolin-4-il-metil}-carbámico;

éster 3,3,3-trifluoro-propílico de ácido {[1-(4-ciano-1-metil-piperidin-4-ilcarbamoil)-2-ciclohexil-etilimino]-morfolin-4-il-metil}-carbámico;

éster 2-metoxi-etílico de ácido {[1-(4-ciano-1-metil-piperi-

din-4-ilcarbamoil)-2-ciclohexil-etilimino]-morfolin-4-il-metil)-carbámico;

(4-ciano-1-propil-piperidin-4-il)-amida de ácido 5,5-dimetil-2-(2-oxo-2,3-dihidro-benzo[e][1,3]oxazin-4-ilideneamino)-hexanoico;

éster 2-isopropoxi-etílico de ácido {[1-(4-ciano-1-metil-piperidin-4-ilcarbamoil)-2-ciclohexil-etilimino]-morfolin-4-il-metil}-carbámico;

éster 3-metoxi-butílico de ácido {[1-(4-ciano-1-metil-piperidin-4-ilcarbamoil)-2-ciclohexil-etilimino]-morfolin-4-il-metil}-carbámico;

éster 2-isobutoxi-etílico de ácido {[1-(4-ciano-1-metil-piperidin-4-ilcarbamoil)-2-ciclohexil-etilimino]-morfolin-4-il-metil}-carbámico;

N-(4-ciano-1-metil-piperidin-4-il)-4-ciclohexil-2-(7-fluoro-2-oxo-2,3-dihidro-benzo[e][1,3]oxazin-4-ilidenamino)-butiramida;

(4-ciano-1-propil-piperidin-4-il)-amida de ácido 2-(7-fluoro-2-oxo-2,3-dihidro-benzo[e][1,3]oxazin-4-ilidenamino)-5,5-dimetil-hexanoico;

N-(4-ciano-1-metil-piperidin-4-il)-4-ciclohexil-2-(7-metoxi-2-oxo-2,3-dihidro-benzo[e][1,3]oxazin-4-ilidenamino)-butiramida;

(4-ciano-1-propil-piperidin-4-il)-amida de ácido 2-(7-metoxi-2-oxo-2,3-dihidro-benzo[e][1,3]oxazin-4-ilidenamino)-5,5-dimetil-hexanoico;

N-(4-ciano-1-metil-piperidin-4-il)-3-ciclohexil-2-(2-oxo-2,3-dihidro-benzo[e][1,3]oxazin-4-ilidenamino)-propionamida;

(4-ciano-1-propil-piperidin-4-il)-amida de ácido 4,4-dimetil-2-(2-oxo-2,3-dihidro-benzo[e][1,3]oxazin-4-ilidenamino)-pentanoico;

(4-ciano-1-propil-piperidin-4-il)-amida de ácido 4,4-dimetil-2-(2-oxo-2,3-dihidro-1*H*-quinazolin-4-ilidenamino)-pentanoico;

(4-ciano-1-propil-piperidin-4-il)-amida de ácido 2-(7-cloro-2-oxo-2,3-dihidro-benzo[e][1,3]oxazin-4-ilidenamino)-4,4-dimetil-pentanoico;

(4-ciano-1-propil-piperidin-4-il)-amida de ácido 4,4-dimetil-2-(1-metil-2-oxo-1,2-dihidro-quinazolin-4-ilidenamino)-pentanoico;

N-(4-ciano-1-propil-piperidin-4-il)-3-ciclooctil-2-(2-oxo-2,3-dihidro-benzo[e][1,3]oxazin-4-ilidenamino)-propionamida;

N-(4-ciano-1-propil-piperidin-4-il)-3-cicloheptil-2-(2-oxo-2,3-dihidro-benzo[e][1,3]oxazin-4-ilidenamino)-propionamida;

éster etílico de ácido {[1-(4-ciano-1-propil-piperidin-4-ilcarbamoil)-2-cicloheptil-etilimino]-morfolin-4-il-metil}-carbámico;

éster etílico de ácido {[1-(4-ciano-1-propil-piperidin-4-ilcarbamoil)-2-ciclooctil-etilimino]-morfolin-4-il-metil}-carbámico;

éster isobutílico de ácido ({1-[1-(2-carbamoil-etil)-4-ciano-piperidin-4-ilcarbamoil)-2-ciclohexil-etilamino]-morfolin-4-il-metileno)-carbámico;

éster isobutílico de ácido [(1-{4-ciano-1-[2-(2-metoxil-etoxi)-etil]-piperidin-4-ilcarbamoil}-2-ciclohexil-etilamino)-morfolin-4-il-metileno]-carbámico;

éster isobutílico de ácido [(1-{4-ciano-1-[3-(2-metoxil-etoxi)-propil]-piperidin-4-ilcarbamoil}-2-ciclohexil-etilamino)-morfolin-4-il-metileno]-carbámico;

éster etílico de ácido {[1-(4-ciano-1-isopropil-piperidin-4-ilcarbamoil)-2-ciclohexil-etilamino]-morfolin-4-il-metileno}-carbámico;

éster etílicc de ácido {[1-(4-ciano-1-fenetil-piperidin-4-ilcarbamoil)-2-ciclohexil-etilamino]-morfolin-4-il-metileno}-carbámico;

éster etílico de ácido {[1-(4-ciano-1-etil-piperidin-4-ilcarbamoil)-2-ciclohexil-etilamino]-morfolin-4-il-metileno}-carbámico;

éster etílico de ácido {[1-(1-bencil-4-ciano-piperidin-4-ilcarbamoil)-2-ciclohexil-etilamino]-morfolin-4-il-metileno}-carbámico;

(1-bencil-4-ciano-piperidin-4-il)-amida de ácido 4,4-dimetil-2-(2-oxo-2H-benzo[e][1,3]oxazin-4-ilamino)-pentanoico;

[4-ciano-1-(5-metil-tiofen-2-ilmetil)-piperidin-4-il]-amida de ácido 4,4-dimetil-2-(2-oxo-2H-benzo[e][1,3]oxazin-4-ilamino)-pentanoico;

[4-ciano-1-(4-fluoro-bencil)-piperidin-4-il]-amida de ácido 4,4-dimetil-2-(2-oxo-2H-benzo[e][1,3]oxazin-4-ilamino)-pentanoico;

(4-ciano-1-etil-piperidin-4-il)-amida de ácido 4,4-dimetil-2-(2-oxo-2H-benzo[e][1,3]oxazin-4-ilamino)-pentanoico;

(4-ciano-1-metil-piperidin-4-il)-amida de ácido 4,4-dimetil-2-(2-oxo-2H-benzo[e][1,3]oxazin-4-ilamino)-pentanoico;

(4-ciano-1-fenetil-piperidin-4-il)-amida de ácido 4,4-dimetil-2-(2-oxo-2H-benzo[e][1,3]oxazin-4-ilamino)-pentanoico;

[4-ciano-1-(2,2-dimetil-propil)-piperidin-4-il]-amida de ácido 4,4-dimetil-2-(2-oxo-2H-benzo[e][1,3]oxazin-4-ilamino)-pentanoico;

[4-ciano-1-(3,3-dimetil-butil)-piperidin-4-il]-amida de ácido 4,4-dimetil-2-(2-oxo-2H-benzo[e][1,3]oxazin-4-ilamino)-pentanoico;

(4-ciano-1-pentil-piperidin-4-il)-amida de ácido 4,4-dimetil-2-(2-oxo-2H-benzo[e][1,3]oxazin-4-ilamino)-pentanoico;

(1-butil-4-ciano-piperidin-4-il)-amida de ácido 4,4-dimetil-2-(2-oxo-2H-benzo[e][1,3]oxazin-4-ilamino)-pentanoico;

[4-ciano-1-(3,3,3-trifluoro-propil)-piperidin-4-il]-amida de ácido 4,4-dimetil-2-(2-oxo-2H-benzo[e][1,3]oxazin-4-ilamino)-pentanoico;

(4-ciano-1-ciclohexilmetil-piperidin-4-il)-amida de ácido 4,4-dimetil-2-(2-oxo-2H-benzo[e][1,3]oxazin-4-ilamino)-pentanoico;

N-(4-ciano-1-propil-piperidin-4-il)-3-(4,4-dimetil-ciclohexil)-2-(2-oxo-2H-benzo[e][1,3]oxazin-4-ilamino)-propionamida;

éster etílico de ácido {[1-(3-ciano-1-etil-pirrolidin-3-il-

carbamoil)-2-ciclohexil-etilamino]-morfolin-4-il-metileno}-carbámico;

N-(4-ciano-1-metil-piperidin-4-il)-3-ciclohexil-2-(7,8-difluoro-2-oxo-2H-benzo[e][1,3]oxazin-4-ilamino)-propionamida;

éster etílico de ácido {[1-(4-ciano-1-ciclohexilmetil-piperidin-4-ilcarbamoil)-2-ciclohexil-etilamino]-morfolin-4-il-metileno}-carbámico;

éster 4-metoxi-ciclohexilmetílico de ácido {[1-(4-ciano-1-metil-piperidin-4-ilcarbamoil)-2-ciclohexil-etilamino]-morfolin-4-il-metileno}-carbámico;

éster ciclohexílico de ácido {[1-(4-ciano-1-metil-piperidin-4-ilcarbamoil)-2-ciclohexil-etilamino]-morfolin-4-il-metileno}-carbámico;

éster etílico de ácido {[1-(4-ciano-1-propil-piperidin-4-ilcarbamoil)-3,3-dimetil-butilamino]-fenil-metileno}-carbámico;

y

éster etílico de ácido {[1-(4-ciano-1-metil-piperidin-4-il-carbamoil)-2-ciclohexil-etilamino]-fenil-metileno}-carbámico.

5.- Una composición farmacéutica que comprende una cantidad farmacéuticamente eficaz de un compuesto de acuerdo con las reivindicaciones 1 ó 2.

6.- Un método para modular una enfermedad autoinmunitaria, comprendiendo dicho método administrar a un paciente que necesita de un tratamiento de este tipo una cantidad farmacéuticamente eficaz de un compuesto de acuerdo con las reivindicaciones 1 ó 2.

7.- El método de acuerdo con la reivindicación 6, en el que la enfermedad autoinmunitaria es artritis reumatoide, lupus eritematoso sistémico, enfermedad de Crohn, colitis ulcerosa, esclerosis múltiple, síndrome de Guillain-Barre, psoriasis, enfermedad de Grave, mistenia grave, escleroderma, glomerulonefritis, dermatitis, endometriosis o diabetes mellitus dependiente de insulina.

8.- Un método para tratar la enfermedad de Alzheimer, que comprende administrar a un paciente que necesita de un tratamiento de este tipo una cantidad farmacéuticamente eficaz de un compuesto de acuerdo con las reivindicaciones 1 ó 2.

9.- Un método para tratar aterosclerosis, que comprende administrar a un paciente que necesita de un tratamiento de este tipo una cantidad farmacéuticamente eficaz de un compuesto de acuerdo con las reivindicaciones 1 ó 2.

10.- Un método para tratar osteoporosis, que comprende administrar a un paciente que necesita de un tratamiento de este tipo una cantidad farmacéuticamente eficaz de un compuesto de acuerdo con las reivindicaciones 1 ó 2.

11.- Un método para tratar asma, que comprende administrar a un paciente que necesita de un tratamiento de este tipo una cantidad farmacéuticamente eficaz de un compuesto de acuerdo con las reivindicaciones 1 ó 2.

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**Industria y Com rcio**

SUPERINTENDENCIA Y COMERCIO NCIA

Radicacion : 03019100 00000000 Folios: 735

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Tramite : 011 PCT-PATENT 379 FASE NACI 411 PRESENTAC

Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 03 - 13,521
FECHA : FEBRERO 24 DE 2003

***** C O N S I G N A C I O N *****

| DEPOSITANTE | TIPO PAGO | BANCO | CUENTA | No. PAGO | FECHA PGO | Vr. PAGO |
|---|---|---|---|---|---|---|
| CAVELIER ABOGADOS | CONSIGNACION | BANCO POPULAR | 050-00110-6 | 3136963 | 24/02/2003 | 25,600,000.00 |

***** C O N C E P T O *****

| CANT. | RENTISTICO | CONCEPTO | TOTAL CONCEPTO |
|---|---|---|---|
| 1 | 50005-01-01 SOLICITUDES | 1 TRAMITES DE SOL. DE PATENTE DE IN | 400,000.00 |
| | | TOTAL : $ | 400,000.00 |

SON: CUATROCIENTOS MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No._____

Carrera 13 No. 27-00 Pisos 5, 7 y 10
Conmutador 382 0840
Fax 350 5220
E-mail: info@sic.gov.co
www.sic.gov.co
Bogotá, D.C., Colombia

C66 07612 - 841 - 001 - 6

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SUPERINDUSTRIA Y COMERCIO
Radicacion : 03019100 00000000 Folios: 75
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Tramite 011 PCT-PATENT 379 FASE NACI 411 PRESENTAC
Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

# REQUISITOS NECESARIOS PARA PRESENTACION Y AGILIZACION DEL TRAMITE

| | USUARIO | RADICADOR |
|---|---|---|
| **PATENTE DE INVENCIÓN MODELO DE UTILIDAD** | ( ) | ( ) |
| Indicación de que se solicita la concesión de una patente. | | ( ) |
| Datos de identificación del solicitante o de la persona que se presenta la solicitud | | ( ) |
| Descripción de la invención. | | ( ) |
| Dibujos de ser estos pertinentes | | ( ) |
| Comprobante de Pago de las tasas establecidas | | |
| **COMPLETA ( ) INCOMPLETA** | ( ) | ( ) |
| **DISEÑO INDUSTRIAL ( )** | | |
| Indicación de que se solicita el registro de Diseño Industrial | ( ) | ( ) |
| Datos de identificación del solicitante o de la persona que presenta la solicitud | ( ) | ( ) |
| Representación gráfica y fotográfica del Diseño Industrial o muestra del Material que incorpora el diseño | ( ) | ( ) |
| Comprobante de pago de las tasas establecidas | ( ) | ( ) |
| **COMPLETA ( ) INCOMPLETA** | ( ) | ( ) |
| **ESQUEMA DE TRAZADO ( )** | | |
| Indicación de que solicita el registro de un Esquema de trazado | ( ) | ( ) |
| Datos de identificación del solicitante o de la persona que presenta La solicitud | ( ) | ( ) |
| Representación gráfica del esquema de trazado | ( ) | ( ) |
| Comprobante de pago de las tasas establecidas | ( ) | ( ) |
| **COMPLETA ( ) INCOMPLETA** | ( ) | ( ) |

**Firma Responsable:** ANDRES POSSE

**Fecha**

Industria y Comercio
SUPERINTENDENCIA

737

Folio 737

2020
Bogotá DC

Doctor(a)
EMILIO FERRERO
Apoderado(a)
BOEHRINGER INGELHEIM PHARMACEUTICAL, INC

| | | |
|---|---|---|
| **REFERENCIA.** | Radicación No. | 03-19100 |
| | Solicitud Internacional | PCT/US2001/08084 |
| | Fecha inicio fase nacional | 08/04/2003 |
| | Trámite | 011 |
| | Evento | 379 |
| | Actuación | 416 |
| | Oficio No. | 1125 |
| | Folios | 001 |

Teniendo en cuenta que la solicitud de privilegio de patente que se tramita bajo el expediente indicado en la referencia, reúne los requisitos de forma establecidos en la Decisión 486 de la Comisión de la Comunidad Andina el Tratado de Cooperación en Materia de Patentes (PCT) el Reglamento y la Circular Unica de la Superintendencia de Industria y Comercio se envía el extracto de la solicitud a la Oficina de Comunicaciones para efecto de su publicación en la Gaceta de Propiedad Industrial

**Cúmplase** 02 OCT 2020
Dado en Bogotá DC

**ALIX CARMENZA CÉSPEDES DE VERGEL**
Jefe de la División de Nuevas Creaciones

202047