SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

**DELEGATURA PROPIEDAD INDUSTRIAL**

**División de Nuevas Creaciones**

PCT

SOLICITUD

# PATENTE DE INVENCION

ENTRADA EN FASE NACIONAL

21 **EXPEDIENTE No** 06-75897

54 **TITULO** NOVEDOSOS COMPJESTOS DE PIRIDIN-2-ONA UTILES COMO INHIBIDORES DE TROMBINA

51 **CLASIFICACION INTERNACIONAL** A61K31/4412 // A61P7/02

71 **SOLICITANTE** ASTRA'ENECA AB

**DOMICILIO** SODERTALJE SUECIA

74 **APODERADO** JUAN PABLO CADENA SARMIENTO

22 **SANTAFE DE BOGOTA, D C** 02/08/2006

(FORMA P 10)

Oficina de Comunicaciones

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1

AS: 101.650

Industria y Comercio
SUPERINTENDENCIA

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## FORMULARIO ÚNICO DE SOLICITUD DE PATENTE

## PCT

## ENTRADA EN FASE NACIONAL 06-09-06

**1 SOLICITUD DE:**

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

☒ Capítulo I. ☐ Capítulo II.

| | | |
|---|---|---|
| **2 SOLICITANTE (71)** | Nombre: **ASTRAZENECA AB**<br>Dirección: S-1-51 85 Sodertalje, Suecia<br>Nacionalidad o Domicilio: Suecia<br>Lugar de Constitución: Suecia<br>Teléfono: Fax:<br>E-mail | **IDENTIFICACION**<br>C.C. ☐ NIT ☐<br>C.E. ☐ Otro ☐<br>Cual_____<br>Número _____ |
| **3 REPRESENTANTE O APODERADO** | Nombre: **JUAN PABLO CADENA SARMIENTO**<br>Dirección: Cra. 7 No. 16-56 Piso 9<br>Teléfono: 380-2200 Fax: 380-2700<br>E-mail: | **IDENTIFICACION**<br>C.C. ☒ NIT ☐<br>C.E. ☐ Otro ☐<br>Cual_____<br>Número 80.410.337 TP 57492 |
| **4 INVENTOR (ES) (72)** | Nombre: Malkan BAYRAKDARIAN, Kristina BERGGREN, Öjvind DAVIDSSON, Ola FJELLSTRÖM, David GUSTAFSSON, Stephen HANESSIAN, Tord INGHARDT, Ingemar NILSSON, Mats NÄGÅRD, Daniel SIMARD, Eric THERRIEN<br>Dirección: AstraZeneca R & D Montreal, 7171 Frederick-Banting, St. Laurent, Montreal, Quebec H4S IZ9, CA; AstraZeneca R & D Mölndal, S-431 83 Mölndal, SE; AstraZeneca R & D Mölndal, S-431 83 Mölndal, SE; AstraZeneca R & D Mölndal, S-431 83 Mölndal, SE; AstraZeneca R & D Mölndal, S-431 83 Mölndal, SE; University of Montreal, Dep of Chemistry, C.P. 6128, Succursale Centre-Ville, Montreal, Québec H3C 1J7, CA; AstraZeneca R & D Mölndal, S-431 83 Mölndal, SE; AstraZeneca R & D Mölndal, S-431 83 Mölndal, SE; AstraZeneca R & D Mölndal, S-431 83 Mölndal, SE; University of Montreal, Dep of Chemistry, C.P. 6128, Succursale Centre-Ville, Montreal, Québec H3C IJ7, CA; 969 Marc-Aurele Fortin Laval, Québec H7L 6H9, CA (Respectivamente)<br>Nacionalidad o Domicilio: Canadá y Suecia (Respectivamente) | |

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**Título (54):** NOVEDOSOS COMPUESTOS DE PIRIDIN-2-ONA ÚTILES COMO INHIBIDORES DE TROMBINA

**7 Clasificación Internacional (51)** A61K31/4412 // A61P7/02

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

**10** **ANEXOS**

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

**12** Solicito la concesión de la patente,

**NOMBRE:** JUAN PABLO CADENA SARMIENTO

**FIRMA:**

C.C. 80.410.337 de Usaquén T.P. 57492 del C.S.J.

Instrucciones para la presentación de los anexos, ver reverso de esta página.

3

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
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| DEPOSITANTE | TIPO PAGO | BANCO | CUENTA | No. PAGO | FECHA PGO | Vr. PAGO |
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| 1 | 50005-01-01 SOLICITUDES | 1 TRAMITES DE SOL. DE PATENTE DE IN | 463,000.00 |
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(71) Applicant *(for all designated States except US)*: ASTRAZENECA AB [SE/SE]; S-151 85 Södertälje (SE).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: BAYRAKDARIAN, Maiken [CA/CA]; AstraZeneca R & D Montreal, 7171 Frederick-Banting, St. Laurent, Montreal, Québec H4S 1Z9 (CA). BERGGREN, Kristina [SE/SE]; AstraZeneca R & D Mölndal, S-431 83 Mölndal (SE). DAVIDSSON, Öjvind [SE/SE]; AstraZeneca R & D Mölndal, S-431 83 Mölndal (SE). FJELLSTRÖM, Ola [SE/SE]; AstraZeneca R & D Mölndal, S-431 83 Mölndal (SE). GUSTAFSSON, David [SE/SE]; AstraZeneca R & D Mölndal, S-431 83 Mölndal (SE). HANESSIAN, Stephen [CA/CA]; University of Montreal, Dep of Chemistry, C.P. 6128, Succursale Centre-Ville, Montreal, Québec H3C 1J7 (CA). INGHARDT, Tord [SE/SE]; AstraZeneca R & D Mölndal, S-431 83 Mölndal (SE). NILSSON, Ingemar [SE/SE]; AstraZeneca R & D Mölndal, S-431 83 Mölndal (SE). NÅGÅRD, Mats [SE/SE]; AstraZeneca R & D Mölndal, S-431 83 Mölndal (SE). SIMARD, Daniel [CA/CA]; University of Montreal, Dep of Chemistry, C.P. 6128, Succursale Centre-Ville, Montreal, Québec H3C 1J7 (CA). THERRIEN, Eric [CA/CA]; University of Montreal, Dep of Chemistry, C.P. 6128, Succursale Centre-Ville, Montreal, Québec H3C 1J7 (CA).

(74) Agent: ASTRAZENECA; Global Intellectual Property, S-151 85 Södertälje (SE).

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WO 2005/075424 A1

(54) Title: NEW PYRIDIN-2-ONE COMPOUNDS USEFUL AS INHIBITORS OF THROMBIN

(57) Abstract: There is provided a compound of formula I, wherein the dashed line, $R^1$, $R^2$, $R^{3a}$, $R^{3b}$, A, D, E, G and L have meanings given in the description, which compounds are useful as, or are useful as prodrugs of, competitive inhibitors of trypsin-like proteases, such as thrombin, and thus, in particular, in the treatment of conditions where inhibition of thrombin is beneficial (e.g. conditions, such as thrombo-embolisms, where inhibition of thrombin is required or desired, and/or conditions where anticoagulant therapy is indicated).

# NEW PYRIDIN-2-ONE COMPOUNDS USEFUL AS INHIBITORS OF THROMBIN

## Field of the Invention

This invention relates to novel pharmaceutically useful compounds, in particular compounds that are, and/or compounds that are metabolised to compounds which are, competitive inhibitors of trypsin-like serine proteases, especially thrombin, their use as medicaments, pharmaceutical compositions containing them and synthetic routes to their production.

## Background

Blood coagulation is the key process involved in both haemostasis (i.e. the prevention of blood loss from a damaged vessel) and thrombosis (i.e. the formation of a blood clot in a blood vessel, sometimes leading to vessel obstruction).

Coagulation is the result of a complex series of enzymatic reactions. One of the ultimate steps in this series of reactions is the conversion of the proenzyme prothrombin to the active enzyme thrombin.

Thrombin is known to play a central role in coagulation. It activates platelets, leading to platelet aggregation, converts fibrinogen into fibrin monomers, which polymerise spontaneously into fibrin polymers, and activates factor XIII, which in turn crosslinks the polymers to form insoluble fibrin. Furthermore, thrombin activates factor V, factor VIII and FXI leading to a "positive feedback" generation of thrombin from prothrombin.

By inhibiting the aggregation of platelets and the formation and crosslinking of fibrin, effective inhibitors of thrombin would be expected to exhibit antithrombotic activity. In addition, antithrombotic activity would be expected to be enhanced by effective inhibition of the positive feedback mechanism. Indeed, the convincing antithrombotic effects of a thrombin inhibitor in man has recently been described by S. Schulman *et al.* in *N. Engl. J. Med.* 349, 1713-1721 (2003).

**Prior Art**

The early development of low molecular weight inhibitors of thrombin has been described by Claesson in *Blood Coagul. Fibrinol.* 5, 411 (1994).

Blombäck *et al.* (in *J. Clin. Lab. Invest.* 24, suppl. 107, 59 (1969)) reported thrombin inhibitors based on the amino acid sequence situated around the cleavage site for the fibrinogen Aα chain. Of the amino acid sequences discussed, these authors suggested the tripeptide sequence Phe-Val-Arg (P9-P2-P1, hereinafter referred to as the P3-P2-P1 sequence) would be the most effective inhibitor.

Thrombin inhibitors based on peptidyl derivatives, having cyclic or acyclic basic groups at the P1-position (e.g. groups containing amino, amidino or guanidino functions), are disclosed in, for example, International Patent Application numbers WO 93/11152, WO 93/18060, WO 94/29336, WO 95/23609, WO 95/35309, WO 96/03374, WO 96/25426, WO 96/31504, WO 96/32110, WO 97/02284, WO 97/23499, WO 97/46577, WO 97/49404, WO 98/06740, WO 98/57932, WO 99/29664, WO 00/35869, WO 00/42059, WO 01/87879, WO 02/14270, WO 02/44145 and WO 03/018551, European Patent Application numbers 185 390, 468 231, 526

877, 542 525, 559 046 and 641 779, 648 780, 669 317 and US Patent number 4,346,078.

Inhibitors of serine proteases (e.g. thrombin) based on electrophilic ketones in the P1-position are also known, such as the compounds disclosed in European Patent Application numbers 195 212, 362 002, 364 344 and 530 167.

Inhibitors of trypsin-like serine proteases based on C-terminal boronic acid derivatives of arginine (and isothiouronium analogues thereof) are known from European Patent Application number 293 881.

Achiral thrombin inhibitors having, at the P2-position of the molecule, a phenyl group, and a cyclic or acyclic basic group at the P3-position, are disclosed in International Patent Application numbers WO 94/20467, WO 96/06832, WO 96/06849, WO 97/11693, WO 97/24135, WO 98/01422 and WO 01/68605, as well as in *Bioorg. Med. Chem. Lett.* 7, 1283 (1997).

International Patent Application numbers WO 99/26920 and WO 01/79155 disclose thrombin inhibitors having groups at the P2-position based, respectively, upon 2-aminophenols and 1,4-benzoquinones. Similar, phenol-based compounds are also disclosed in International Patent Application numbers WO 01/68605 and WO 02/28825.

Further known inhibitors of thrombin and other trypsin-like serine proteases are based (at the P2-position of the molecule) on the 3-amino-2-pyridone structural unit. For example, compounds based upon 3-amino-2-pyridone, 3-amino-2-pyrazinone, 5-amino-6-pyrimidone, 5-amino-2,6-pyrimidione and 5-amino-1,3,4-triazin-6-one are disclosed in International Patent Application numbers WO 96/18644, WO 97/01338, WO 97/30708, WO

98/16547, WO 99/26926, WO 00/73302, WO 00/75134, WO 01/38323,WO 01/04117, WO 01/70229, WO 01/79262, WO 02/057225, WO 02/064140 and WO 03/29224, US patent numbers 5,668,289 and 5,792,779, as well as in *Bioorg. Med. Chem. Lett.* 8, 817 (1998) and *J. Med. Chem.* 41, 4466 (1998).

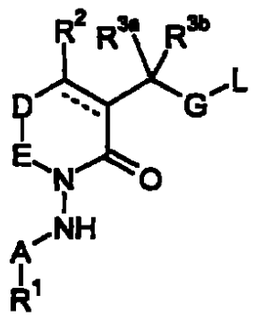
Thrombin inhibitors based upon 2-oxo-3-amino-substituted saturated azaheterocycles are disclosed in International Patent Application number WO 95/35313. More recently, thrombin inhibitors have been disclosed that are based upon 4-amino-3-morpholinone (see *J. Med. Chem.* 46, 1165 (2003)).

None of the above-mentioned documents disclose or suggest compounds based (at the P2-position) on the 1-amino-2-pyridone or 1-amino-2-piperidone structural unit.

Moreover, there remains a need for effective inhibitors of trypsin-like serine proteases, such as thrombin. There is also a need for compounds that have a favourable pharmacokinetic profile. Such compounds would be expected to be useful as anticoagulants and therefore in the therapeutic treatment of thrombosis and related disorders.

**Disclosure of the Invention**

According to the invention there is provided a compound of formula I



I

wherein

the dashed line is absent or represents a bond;

A represents C(O), $S(O)_2$, C(O)O (in which latter group the O moiety is attached to $R^1$), C(O)NH, $S(O)_2NH$ (in which latter two groups the NH moiety is attached to $R^1$) or $C_{1-6}$ alkylene;

$R^1$ represents

(a) $C_{1-10}$ alkyl, $C_{2-10}$ alkenyl, $C_{2-10}$ alkynyl (which latter three groups are optionally substituted by one or more substituents selected from halo, CN, $C_{3-10}$ cycloalkyl (optionally substituted by one or more substituents selected from halo, OH, =O, $C_{1-6}$ alkyl, $C_{1-6}$ alkoxy and aryl), $OR^{4a}$, $S(O)_nR^{4b}$, $S(O)_2N(R^{4c})(R^{4d})$, $N(R^{4e})S(O)_2R^{4f}$, $N(R^{4g})(R^{4h})$, $B^1$-C(O)-$B^2$-$R^{4i}$, aryl and $Het^1$),

(b) $C_{3-10}$ cycloalkyl or $C_{4-10}$ cycloalkenyl, which latter two groups are optionally substituted by one or more substituents selected from halo, =O, CN, $C_{1-10}$ alkyl, $C_{3-10}$ cycloalkyl (optionally substituted by one or more substituents selected from halo, OH, =O, $C_{1-6}$ alkyl, $C_{1-6}$ alkoxy and aryl), $OR^{4a}$, $S(O)_nR^{4b}$, $S(O)_2N(R^{4c})(R^{4d})$, $N(R^{4e})S(O)_2R^{4f}$, $N(R^{4g})(R^{4h})$, $B^3$-C(O)-$B^4$-$R^{4i}$, aryl and $Het^2$,

(c) aryl, or

(d) $Het^3$;

$R^{4a}$ to $R^{4i}$ independently represent, at each occurrence,

(a) H,

(b) $C_{1-10}$ alkyl, $C_{2-10}$ alkenyl, $C_{2-10}$ alkynyl (which latter three groups are optionally substituted by one or more substituents selected from halo, OH, $C_{1-6}$ alkoxy, aryl and $Het^4$),

(c) $C_{3-10}$ cycloalkyl, $C_{4-10}$ cycloalkenyl (which latter two groups are optionally substituted by one or more substituents selected from halo, OH, =O, $C_{1-6}$ alkyl, $C_{1-6}$ alkoxy, aryl and $Het^5$),

(d) aryl or

(e) $Het^6$,

provided that $R^{4b}$ does not represent H when n is 1 or 2;

the group -D-E-

(a) when the dashed line represents a bond, represents $-C(R^{5a})=C(R^{5b})-$, or

(b) when the dashed line is absent, represents $-C(R^{6a})(R^{6b})-C(R^{7a})(R^{7b})-$;

$R^{5a}$ and $R^{5b}$ independently represent H, halo, OH, $C_{1-4}$ alkyl, $(CH_2)_{0-4}O(C_{1-3}$ alkyl) (which latter two groups are optionally substituted by one OH group or one or more F atoms);

$R^{6a}$, $R^{6b}$, $R^{7a}$ and $R^{7b}$ independently represent H, F or methyl;

or $R^{5a}$ and $R^{5b}$ together represent $C_{2-4}$ *n*-alkylene;

or one of $R^{6a}$ and $R^{6b}$, together with one of $R^{7a}$ and $R^{7b}$, represents $C_{1-4}$ *n*-alkylene;

$R^2$ represents

(a) H,

(b) halo;

(c) $C_{1-6}$ alkyl, $C_{2-6}$ alkenyl, $C_{2-6}$ alkynyl, $C_{1-6}$ alkoxy (which latter four groups are optionally substituted by one or more substituents selected from halo, OH, CN, $C_{1-4}$ alkoxy, C(O)OH, C(O)O-$C_{1-4}$ alkyl and OC(O)-$C_{1-4}$ alkyl) or

(d) together with $R^{3a}$, $R^2$ represents $C_{2-3}$ *n*-alkylene, $T^1$-($C_{1-2}$ *n*-alkylene) or ($C_{1-2}$ *n*-alkylene)-$T^1$, which latter three groups are optionally substituted by halo, or

(e) together with $R^{3a}$ and $R^{3b}$, $R^2$ represents $T^2$-[C(H)=], wherein $T^2$ is bonded to the C-atom to which the group $R^2$ is attached;

$R^{3a}$ and $R^{3b}$ independently represent H, F or methyl (which latter group is optionally substituted by one or more F atoms), or

(a) together with $R^2$, $R^{3a}$ represents $C_{2-3}$ *n*-alkylene, $T^1$-($C_{1-2}$ *n*-alkylene) or ($C_{1-2}$ *n*-alkylene)-$T^1$, which latter three groups are optionally substituted by halo, or

(b) together with $R^2$, $R^{3a}$ and $R^{3b}$ represent $T^2$-[C(H)=], wherein $T^2$ is bonded to the C-atom to which the group $R^2$ is attached;

$T^1$ and $T^2$ independently represent O, S, N(H) or N($C_{1-4}$ alkyl);

G represents

(a) -C(O)N($R^{8a}$)-[CH(C(O)$R^9$)]$_{0-1}$-$C_{0-3}$ alkylene-($Q^1$)$_n$-,

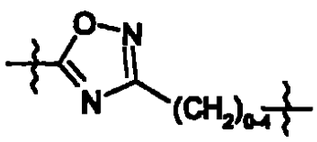
(b) -C(O)N($R^{8b}$)-$C_{2-3}$ alkenylene-($Q^1$)$_n$-,

(c)



, or

(d)



;

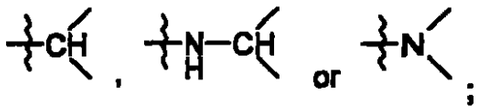
$R^9$ represents H or a 5- to 10-membered aromatic heterocyclic group comprising one or two rings and containing, as heteroatom(s), one sulfur or oxygen atom and/or one or more nitrogen atoms, which heterocyclic group

is optionally substituted by one or more substituents selected from halo and $C_{1-6}$ alkyl;

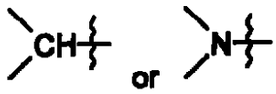
$Q^1$ represents O, $NR^{10a}$, $[N(H)]_{0-1}C(O)$-$C_{0-2}$ alkylene, C(O)NHNHC(O), or -N=C($R^{10b}$)-;

a represents 0 or 1;

$Q^{2a}$ represents



$Q^{2b}$ represents



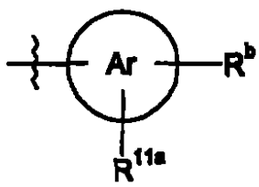
L represents

(a) $C_{0-6}$ alkylene-$R^a$,

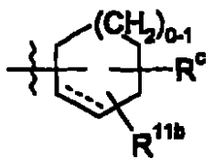
(b) $C_{0-2}$ alkylene-CH=CH-$C_{0-2}$ alkylene-$R^a$,

(c) $C_{0-2}$ alkylene-C≡C-$C_{0-2}$ alkylene-$R^a$,

(d)

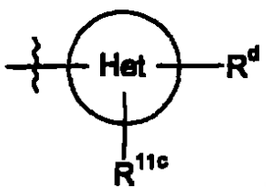


(e)



wherein the dashed line represents an optional double bond, or

(f)




;

Ar represents phenyl or naphthyl;

Het represents a 5- to 10-membered heterocyclic group comprising one or two rings and containing, as heteroatom(s), one sulfur or oxygen atom and/or one or more nitrogen atoms;

$R^{11a}$ represents H or one or more substituents selected from halo, OH, CN, $C_{1-6}$ alkyl, $C_{1-6}$ alkoxy (which latter two groups are optionally substituted by one or more substituents selected from halo, OH, $C_{1-4}$ alkoxy, $C(O)OR^{12a}$ and $C(O)N(R^{12b})R^{12c}$) and $S(O)_{0-2}R^{12d}$;

$R^{11b}$ and $R^{11c}$ independently represent H or one or more substituents selected from halo, OH, CN, $C_{1-6}$ alkyl, $C_{1-6}$ alkoxy (which latter two groups are optionally substituted by one or more substituents selected from halo, OH, $C_{1-4}$ alkoxy, $C(O)OR^{12a}$ and $C(O)N(R^{12b})R^{12c}$), $S(O)_{0-2}R^{12d}$, =O, =NH, =NOH and =N-CN;

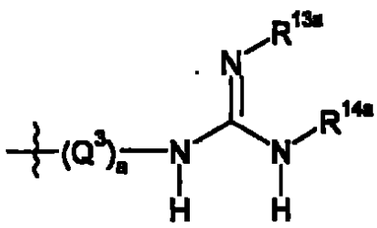
$R^{12a}$ to $R^{12c}$ independently represent H, $C_{1-6}$ alkyl or $C_{3-7}$ cycloalkyl (which latter two groups are optionally substituted by one OH or $N(R^{12e})R^{12f}$ group or by one or more halo atoms);

$R^{12d}$ represents, independently at each occurrence, $C_{1-6}$ alkyl optionally substituted by one OH or $N(R^{12e})R^{12f}$ group or by one or more halo atoms;

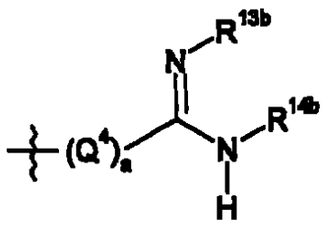
$R^{12e}$ and $R^{12f}$ represent, independently at each occurrence, H or $C_{1-4}$ alkyl optionally substituted by one or more halo atoms;

$R^a$ to $R^d$ independently represent

(a)



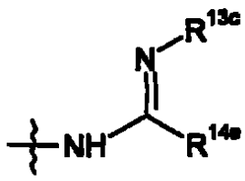
(b)



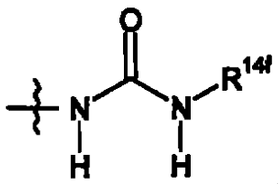
(c)



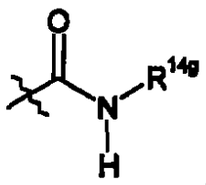
(d)



(e)



(f)



(g) $Het^x$

or $R^b$ to $R^d$ may also represent H;

$Q^3$ represents O, $N(R^{10a})$, $S(O)_2$, $S(O)_2NH$, C(O) or -CH=N-;

$Q^4$ represents O, S or $CH_2$;

a represents 0 or 1;

$Het^x$ represents a 5- or 6-membered heterocyclic group containing one to four heteroatoms selected from oxygen, nitrogen and/or sulfur, which heterocyclic group may be substituted by one or more substituents selected from halo, =O, $C_{1-6}$ alkyl and $C_{1-6}$ alkoxy (which latter two groups are optionally substituted by one or more halo atoms);

$R^{13a}$ to $R^{13e}$ independently represent

(a) H,

(b) CN,

(c) $NH_2$,

(d) $OR^{15}$ or

(e) $C(O)OR^{16}$;

$R^{15}$ represents

(a) H,

(b) $C_{1-10}$ alkyl, $C_{3-10}$ alkenyl, $C_{3-10}$ alkynyl,

(c) $C_{3-10}$ cycloalkyl, $C_{4-10}$ cycloalkenyl, which latter two groups are optionally substituted by one or more substituents selected from halo and $C_{1-6}$ alkyl, or

(d) $C_{1-3}$ alkyl, which latter group is optionally interrupted by oxygen and is substituted by aryl or -O-aryl;

$R^{16}$ represents

(a) $C_{1-10}$ alkyl, $C_{3-10}$ alkenyl, $C_{3-10}$ alkynyl, which latter three groups are optionally interrupted by one or more oxygen atoms, or

(b) $C_{3-10}$ cycloalkyl, $C_{4-10}$ cycloalkenyl, which latter two groups are optionally substituted by one or more substituents selected from halo and $C_{1-6}$ alkyl, or

(c) $C_{1-3}$ alkyl, which latter group is optionally interrupted by oxygen and is substituted by aryl or -O-aryl;

$R^{8a}$ to $R^{8c}$, $R^{10a}$ to $R^{10e}$ and $R^{14a}$ to $R^{14g}$ independently represent

(a) H or

(b) $C_{1-4}$ alkyl (which latter group is optionally substituted by one or more substituents selected from halo and OH),

or $R^{14a}$ and $R^{14b}$ independently represent $C(O)O-C_{1-6}$ alkyl (the alkyl part of which latter group is optionally substituted by aryl and/or one or more halo atoms),

or $R^{14c}$ represents

(a) $C_{1-4}$ alkyl substituted by $C_{3-7}$ cycloalkyl or aryl,

(b) $C_{3-7}$ cycloalkyl,

(c) $C(O)O-C_{1-6}$ alkyl (the alkyl part of which latter group is optionally substituted by aryl and/or one or more halo atoms),

(d) $C(O)C_{1-6}$ alkyl,

(e) $C(O)N(H)-C_{1-6}$ alkyl (the alkyl part of which latter group is optionally substituted by aryl and/or one or more halo atoms) or

(f) $S(O)_2-C_{1-6}$ alkyl (the alkyl part of which latter group is optionally substituted by aryl and/or one or more halo atoms),

or $R^{14c}$ and $R^{14d}$ together represent $C_{3-6}$ *n*-alkylene optionally interrupted by O, S, N(H) or $N(C_{1-4}$ alkyl) and/or substituted by one or more $C_{1-4}$ alkyl groups;

each aryl independently represents a $C_{6-10}$ carbocyclic aromatic group, which group may comprise either one or two rings and may be substituted by one or more substituents selected from

(a) halo,

(b) CN,

(c) $C_{1-10}$ alkyl, $C_{2-10}$ alkenyl, $C_{2-10}$ alkynyl (which latter three groups are optionally substituted by one or more substituents selected from halo, OH, $C_{1-6}$ alkoxy, C(O)OH, C(O)O-$C_{1-6}$ alkyl, phenyl (which latter group is optionally substituted by halo) and $Het^7$),

(d) $C_{3-10}$ cycloalkyl, $C_{4-10}$ cycloalkenyl (which latter two groups are optionally substituted by one or more substituents selected from halo, OH, =O, $C_{1-6}$ alkyl, $C_{1-6}$ alkoxy, phenyl (which latter group is optionally substituted by halo) and $Het^8$),

(e) $OR^{17a}$,

(f) $S(O)_pR^{17b}$,

(g) $S(O)_2N(R^{17c})(R^{17d})$,

(h) $N(R^{17e})S(O)_2R^{17f}$,

(i) $N(R^{17g})(R^{17h})$,

(j) $B^5$-C(O)-$B^6$-$R^{17i}$,

(k) phenyl (which latter group is optionally substituted by halo),

(l) $Het^9$ and

(m) $Si(R^{18a})(R^{18b})(R^{18c})$;

$R^{17a}$ to $R^{17i}$ independently represent, at each occurrence,

(a) H,

(b) $C_{1-10}$ alkyl, $C_{2-10}$ alkenyl, $C_{2-10}$ alkynyl (which latter three groups are optionally substituted by one or more substituents selected from halo, OH, $C_{1-6}$ alkoxy, phenyl (which latter group is optionally substituted by halo) and $Het^{10}$),

(c) $C_{3-10}$ cycloalkyl, $C_{4-10}$ cycloalkenyl (which latter two groups are optionally substituted by one or more substituents selected from halo, OH, =O, $C_{1-6}$ alkyl, $C_{1-6}$ alkoxy, phenyl (which latter group is optionally substituted by halo) and $Het^{11}$),

(d) phenyl (which latter group is optionally substituted by halo) or

(e) $Het^{12}$,

provided that $R^{17b}$ does not represent H when p is 1 or 2;

$Het^{1}$ to $Het^{12}$ independently represent 4- to 14-membered heterocyclic groups containing one or more heteroatoms selected from oxygen, nitrogen and/or sulfur, which heterocyclic groups may comprise one, two or three rings and may be substituted by one or more substituents selected from

(a) halo,

(b) CN,

(c) $C_{1-10}$ alkyl, $C_{2-10}$ alkenyl, $C_{2-10}$ alkynyl (which latter four groups are optionally substituted by one or more substituents selected from halo, OH, $C_{1-6}$ alkoxy, C(O)OH, C(O)O-$C_{1-6}$ alkyl, phenyl (which latter group is optionally substituted by halo) and $Het^{a}$),

(d) $C_{3-10}$ cycloalkyl, $C_{4-10}$ cycloalkenyl (which latter two groups are optionally substituted by one or more substituents selected from halo, OH, =O, $C_{1-6}$ alkyl, $C_{1-6}$ alkoxy, phenyl (which latter group is optionally substituted by halo) and $Het^{b}$),

(e) =O,

(f) $OR^{19a}$,

(g) $S(O)_qR^{19b}$,

(h) $S(O)_2N(R^{19c})(R^{19d})$,

(i) $N(R^{19e})S(O)_2R^{19f}$,

(j) $N(R^{19g})(R^{19h})$,

(k) $B^{7}$-C(O)-$B^{8}$-$R^{19i}$,

(l) phenyl (which latter group is optionally substituted by halo),

(m) $Het^e$ and

(n) $Si(R^{20a})(R^{20b})(R^{20c})$;

$R^{19a}$ to $R^{19i}$ independently represent, at each occurrence,

(a) H,

(b) $C_{1-10}$ alkyl, $C_{2-10}$ alkenyl, $C_{2-10}$ alkynyl (which latter three groups are optionally substituted by one or more substituents selected from halo, OH, $C_{1-6}$ alkoxy, phenyl (which latter group is optionally substituted by halo) and $Het^d$),

(c) $C_{3-10}$ cycloalkyl, $C_{4-10}$ cycloalkenyl (which latter two groups are optionally substituted by one or more substituents selected from halo, OH, =O, $C_{1-6}$ alkyl, $C_{1-6}$ alkoxy, phenyl (which latter group is optionally substituted by halo) and $Het^e$),

(d) phenyl (which latter group is optionally substituted by halo) or

(e) $Het^f$,

provided that $R^{19b}$ does not represent H when q is 1 or 2;

$Het^a$ to $Het^f$ independently represent 5- or 6-membered heterocyclic groups containing one to four heteroatoms selected from oxygen, nitrogen and/or sulfur, which heterocyclic groups may be substituted by one or more substituents selected from halo, =O and $C_{1-6}$ alkyl;

$B^1$ to $B^8$ independently represent a direct bond, O, S or NH;

n, p and q independently represent 0, 1 or 2;

$R^{18a}$, $R^{18b}$, $R^{18c}$, $R^{20a}$, $R^{20b}$ and $R^{20c}$ independently represent $C_{1-6}$ alkyl or phenyl (which latter group is optionally substituted by halo or $C_{1-4}$ alkyl);

unless otherwise specified

(i) alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, alkylene and alkenylene groups, as well as the alkyl part of alkoxy groups, may be substituted by one or more halo atoms, and

(ii) cycloalkyl and cycloalkenyl groups may comprise one or two rings and may additionally be ring-fused to one or two phenyl groups;

or a pharmaceutically-acceptable derivative thereof,

which compounds are referred to hereinafter as "the compounds of the invention".

The term "pharmaceutically-acceptable derivatives" includes pharmaceutically-acceptable salts (e.g. acid addition salts).

For the avoidance of doubt, the definitions of the terms aryl, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, alkylene, alkenylene and alkoxy groups provided above apply, unless otherwise stated, at each usage of such terms herein.

The term "halo", when used herein, includes fluoro, chloro, bromo and iodo.

Heterocyclic (Het, $Het^1$ to $Het^{12}$, $Het^a$ to $Het^f$ and $Het^x$) groups may be fully saturated, partly unsaturated, wholly aromatic or partly aromatic in character. Values of heterocyclic (Het, $Het^1$ to $Het^{12}$, $Het^a$ to $Het^f$ and $Het^x$) groups that may be mentioned include 1-azabicyclo[2.2.2]octanyl, benzimidazolyl, benzo[*c*]isoxazolidinyl, benzisoxazolyl, benzodioxanyl, benzodioxepanyl, benzodioxolyl, benzofuranyl, benzofurazanyl, benzomorpholinyl, 2,1,3-benzoxadiazolyl, benzoxazolidinyl, benzoxazolyl, benzopyrazolyl, benzo[*e*]pyrimidine, 2,1,3-benzothiadiazolyl, benzo-

thiazolyl, benzothienyl, benzotriazolyl, chromanyl, chromenyl, cinnolinyl, 2,3-dihydrobenzimidazolyl, 2,3-dihydrobenzo[*b*]furanyl, 1,3-dihydrobenzo-[*c*]furanyl, 1,3-dihydro-2,1-benzisoxazolyl 2,3-dihydropyrrolo[2,3-*b*]-pyridinyl, dioxanyl, furanyl, hexahydropyrimidinyl, hydantoinyl, imidazolyl, imidazo[1,2-*a*]pyridinyl, imidazo[2,3-*b*]thiazolyl, indolyl, isoquinolinyl, isoxazolidinyl, isoxazolyl, maleimido, morpholinyl, naphtho[1,2-*b*]furanyl, oxadiazolyl, 1,2- or 1,3-oxazinanyl, oxazolyl, phthalazinyl, piperazinyl, piperidinyl, purinyl, pyranyl, pyrazinyl, pyrazolyl, pyridinyl, pyridonyl, pyrimidinyl, pyrrolidinonyl, pyrrolidinyl, pyrrolinyl, pyrrolo[2,3-*b*]pyridinyl, pyrrolo[5,1-*b*]pyridinyl, pyrrolo[2,3-*c*]pyridinyl, pyrrolyl, quinazolinyl, quinolinyl, sulfolanyl, 3-sulfolenyl, 4,5,6,7-tetrahydrobenzimidazolyl, 4,5,6,7-tetrahydrobenzopyrazolyl, 5,6,7,8-tetrahydrobenzo[*e*]pyrimidine, tetrahydrofuranyl, tetrahydropyranyl, 3,4,5,6-tetrahydropyridinyl, 1,2,3,4-tetrahydropyrimidinyl, 3,4,5,6-tetrahydropyrimidinyl, thiadiazolyl, thiazolidinyl, thiazolyl, thienyl, thieno[5,1-*c*]-pyridinyl, thiochromanyl, triazolyl, 1,3,4-triazolo[2,3-*b*]pyrimidinyl, xanthenyl and the like.

Values of Het that may be mentioned include 1-azabicyclo[2.2.2]octanyl, benzimidazolyl, benzo[*c*]isoxazolidinyl, benzisoxazolyl, benzo[*b*]furanyl, benzopyrazolyl, benzo[*e*]pyrimidine, benzothiazolyl, benzo[*b*]thienyl, benzotriazolyl, 2-oxo-2,3-dihydrobenzimidazolyl, 1,3-dihydro-2,1-benzisoxazolyl, 2,3-dihydropyrrolo[2,3-*b*]pyridinyl, furanyl, 2-imino-hexahydropyrimidinyl, imidazolyl, imidazo[1,2-*a*]pyridinyl, indolyl, isoquinolinyl, isoxazolidinyl, isoxazolyl, 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2-oxazinanyl, 2-imino-1,3-oxazinanyl, piperazinyl, piperidinyl, 2-oxo-piperidinyl, pyrazinyl, pyridinyl, pyrimidinyl, 2-imino-pyrrolidinyl, 3-pyrrolinyl, pyrrolo[2,3-*b*]pyridinyl, pyrrolo[5,1-*b*]pyridinyl, pyrrolo[2,3-*c*]pyridinyl, pyrrolyl, quinolinyl, 4,5,6,7-tetrahydrobenzimidazolyl, 4,5,6,7-tetrahydrobenzopyrazolyl, 5,6,7,8-tetrahydrobenzo[*e*]-

pyrimidine, 3,4,5,6-tetrahydro-pyridinyl, 3,4,5,6-tetrahydropyrimidinyl, 2-imino-thiazolidinyl, thiazolyl, thienyl and thieno[5,1-*c*]pyridinyl.

Values of $Het^1$ that may be mentioned include benzodioxolyl, benzo[*b*]furanyl, 2,3-dihydrobenzo[*b*]furanyl, pyridinyl, pyrimidinyl and thienyl.

Values of $Het^3$ that may be mentioned include benzodioxanyl, benzo[*b*]dioxepanyl, benzodioxolyl, benzomorpholinyl, 2,1,3-benzoxadiazolyl, 2-oxo-benzoxazolidinyl, benzopyrazolyl, 2,1,3-benzothiadiazolyl, benzo[*b*]thienyl, 2-oxo-chromenyl, 2,3-dihydrobenzo[*b*]furanyl, 1-oxo-1,3-dihydrobenzo[*c*]furanyl, furanyl, imidazolyl, imidazo[2,3-*b*]thiazolyl, isoquinolinyl, isoxazolyl, naphtho[1,2-*b*]furanyl, pyrazinyl, pyrazolyl, pyridinyl, pyridonyl, pyrrolyl, quinolinyl, sulfolanyl, 3-sulfolenyl, 2,4-dioxo-1,2,3,4-tetrahydropyrimidinyl, thiazolyl, thienyl, 1,3,4-triazolo[2,3-*b*]pyrimidinyl and xanthenyl.

Values of $Het^9$ that may be mentioned include morpholinyl, 1,3,4-oxadiazolyl, oxazolyl and pyrazolyl.

Values of $Het^{10}$ that may be mentioned include isoxazolyl, oxazolyl and thiazolyl.

Values of $Het^o$ that may be mentioned include isoxazolyl, morpholinyl, oxazolyl, pyridinyl, thienyl and triazolyl (e.g. 1,3,4-triazolyl).

Values of $Het^x$ that may be mentioned include dihydrooxadiazolyl (e.g. 4,5-dihydro-1,2,4-oxadiazol-3-yl), oxadiazolyl (e.g. 1,2,4-oxadiazol-3-yl), tetrazolyl (e.g. triazol-1-yl) and triazolyl (e.g. 1,2,4-triazol-1-yl).

Substituents on heterocyclic (Het, Het[1] to Het[12], Het[a] to Het[f] and Het[x]) groups may, where appropriate, be located on any atom in the ring system including a heteroatom. The point of attachment of heterocyclic (Het, Het[1] to Het[12], Het[a] to Het[f] and Het[x]) groups may be *via* any atom in the ring system including (where appropriate) a heteroatom, or an atom on any fused carbocyclic ring that may be present as part of the ring system.

For the avoidance of doubt, cycloalkyl and cycloalkenyl groups may be monocyclic or, where the number of C-atoms allows, be bi- or tri-cyclic (although monocyclic cycloalkyl and cycloalkenyl are preferred). Further, when a cycloalkyl or cycloalkenyl group is fused to two phenyl groups, the phenyl groups may also be fused to each other (to form a fused tricyclic ring system).

Compounds of formula I may exhibit tautomerism. All tautomeric forms and mixtures thereof are included within the scope of the invention.

Compounds of formula I may also contain one or more asymmetric carbon atoms and may therefore exhibit optical and/or diastereoisomerism. Diastereoisomers may be separated using conventional techniques, e.g. chromatography or fractional crystallisation. The various stereoisomers may be isolated by separation of a racemic or other mixture of the compounds using conventional, e.g. fractional crystallisation or HPLC, techniques. Alternatively the desired optical isomers may be made by reaction of the appropriate optically active starting materials under conditions which will not cause racemisation or epimerisation, or by derivatisation, for example with a homochiral acid followed by separation of the diastereomeric esters by conventional means (e.g. HPLC, chromatography over silica). All stereoisomers are included within the scope of the invention.

Abbreviations are listed at the end of this specification. The wavy lines on the bonds in structural fragments signify the bond positions of those fragments.

Compounds of formula I that may be mentioned include those in which:

(1) $R^{5a}$ represents H, halo, OH, $C_{1-4}$ alkyl (which latter group is optionally substituted by $C_{1-3}$ alkoxy) or $C_{1-4}$ alkoxy;

(2) $R^{5b}$, $R^{6a}$, $R^{6b}$, $R^{7a}$ and $R^{7b}$ independently represent H, F or methyl;

(3) $R^2$ represents

(a) H,

(b) halo;

(c) $C_{1-6}$ alkyl, $C_{2-6}$ alkenyl, $C_{2-6}$ alkynyl, $C_{1-6}$ alkoxy (which latter four groups are optionally substituted by one or more substituents selected from halo, OH, CN, $C_{1-4}$ alkoxy, C(O)OH, C(O)O-$C_{1-4}$ alkyl and OC(O)-$C_{1-4}$ alkyl) or

(d) together with $R^{3a}$, $R^2$ represents $C_{2-3}$ *n*-alkylene or O-($C_{1-2}$ *n*-alkylene), which latter two groups are optionally substituted by halo and wherein the O-atom of the latter group is bonded to the C-atom to which the group $R^2$ is attached;

(4) $R^{3a}$ and $R^{3b}$ independently represent H, F or methyl, or $R^{3a}$, together with $R^2$, represents $C_{2-3}$ *n*-alkylene or O-($C_{1-2}$ *n*-alkylene), which latter two groups are optionally substituted by halo and wherein the O-atom of the latter group is bonded to the C-atom to which the group $R^2$ is attached;

(5) $R^{11a}$ represents H or one or more substituents selected from halo, OH, CN, $C_{1-6}$ alkyl and $C_{1-6}$ alkoxy (which latter two groups are optionally substituted by one or more substituents selected from halo, OH, $C_{1-4}$ alkoxy, C(O)O$R^{12a}$ and C(O)N($R^{12b}$)$R^{12c}$);

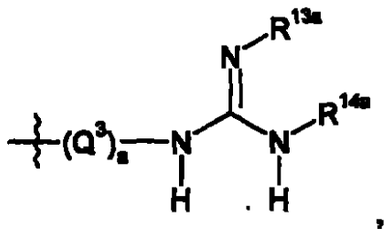
(6) $R^{11b}$ and $R^{11a}$ independently represent H or one or more substituents selected from halo, OH, CN, $C_{1-6}$ alkyl, $C_{1-6}$ alkoxy (which latter two groups are optionally substituted by one or more substituents selected

from halo, OH, $C_{1-4}$ alkoxy, $C(O)OR^{12a}$ and $C(O)N(R^{12b})R^{12c}$), =O, =NH, =NOH and =N-CN;

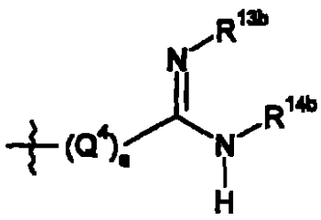
(7) $R^{12a}$ to $R^{12c}$ independently represent H, $C_{1-6}$ alkyl or $C_{3-7}$ cycloalkyl (which latter two groups are optionally substituted by one or more halo atoms);

(8) $R^a$ to $R^d$ independently represent

(a)



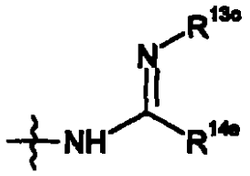
(b)



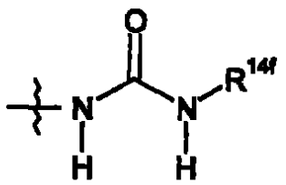
(c)



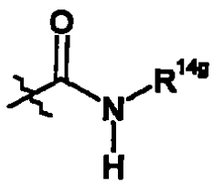
(d)



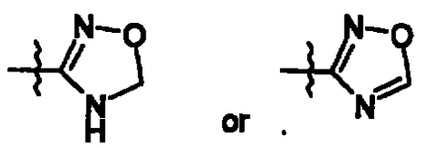
(e)



(f)



(g)



(h)



or $R^b$ to $R^d$ may also represent H.

Other compounds of formula I that may be mentioned include those in which:

$R^{8a}$ to $R^{8c}$, $R^{10a}$ to $R^{10c}$ and $R^{14a}$ to $R^{14g}$ independently represent

(a) H or

(b) $C_{1-4}$ alkyl (which latter group is optionally substituted by one or more substituents selected from halo and OH),

or $R^{14c}$ represents

(a) $C_{1-4}$ alkyl substituted by $C_{3-7}$ cycloalkyl or aryl,

(b) $C_{3-7}$ cycloalkyl,

(c) $C(O)O$-$C_{1-6}$ alkyl (the alkyl part of which latter group is optionally substituted by aryl and/or one or more halo atoms),

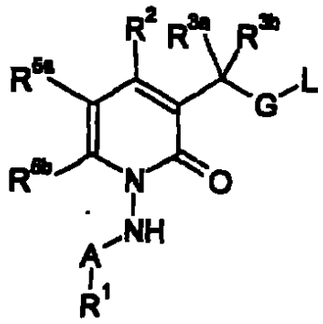
(d) $C(O)C_{1-6}$ alkyl,

(e) $C(O)N(H)$-$C_{1-6}$ alkyl (the alkyl part of which latter group is optionally substituted by aryl and/or one or more halo atoms) or

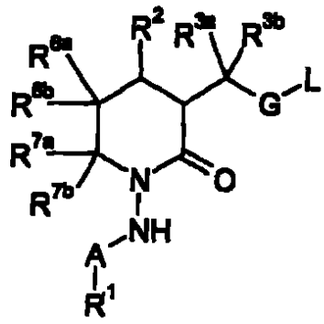
(f) $S(O)_2$-$C_{1-6}$ alkyl (the alkyl part of which latter group is optionally substituted by aryl and/or one or more halo atoms),

or $R^{14c}$ and $R^{14d}$ together represent $C_{3-6}$ *n*-alkylene optionally interrupted by O, S, N(H) or $N(C_{1-4}$ alkyl) and/or substituted by one or more $C_{1-4}$ alkyl groups.

Compounds of formula I may alternatively be represented as compounds of formulae Ia and Ib,



Ia



Ib

wherein $R^1$, $R^2$, $R^{3a}$, $R^{3b}$, $R^{5a}$, $R^{5b}$, $R^{6a}$, $R^{6b}$, $R^{7a}$, $R^{7b}$, A, G and L are as hereinbefore defined.

In this respect, the skilled person will understand that the preferences given below in respect of compounds of formula I apply equally (where appropriate) to compounds of formulae Ia and Ib (either together or separately).

Preferred values of G include:

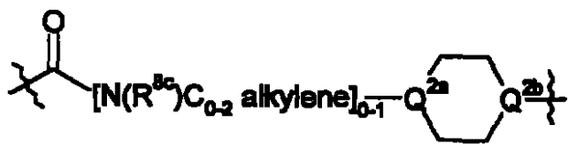
(a) $-C(O)N(R^{8a})$-$C_{0-3}$ alkylene-;

(b) $-C(O)N(R^{8a})$-$CH(C(O)R^9)$-$C_{0-3}$ alkylene-;

(c) $-C(O)N(R^{8a})-C_{1-3}$ alkylene-$Q^1$-;

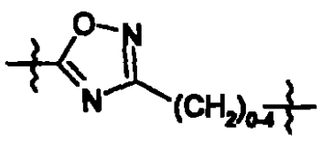
(d) $-C(O)N(R^{8b})-C_{2-3}$ alkenylene-;

(e)



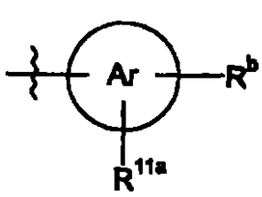

; and

(f)



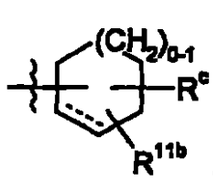

When G represents $-C(O)N(R^{8a})-C_{0-3}$ alkylene-$Q^1$-, preferred values of L include:

(a)



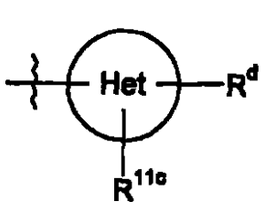

;

(b)




; and

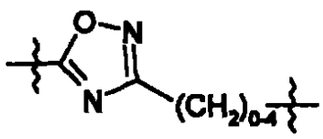
(c)



When G represents -C(O)N($R^{8b}$)-$C_{2-3}$ alkenylene-,



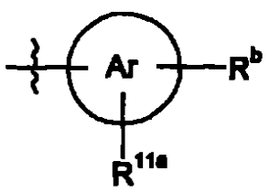

, or




,

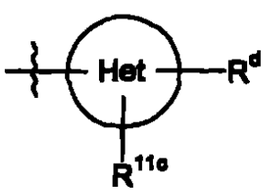
preferred values of L include:

(a)




; and

(b)




Compounds of formula I that are preferred include those in which:

(1) A represents C(O), $S(O)_2$, C(O)NH (in which latter group the NH moiety is attached to $R^1$) or $C_{1-4}$ alkylene;

(2) $R^1$ represents

(a) $C_{1-6}$ alkyl, $C_{2-6}$ alkenyl, $C_{2-6}$ alkynyl (which latter three groups are optionally substituted by one or more substituents selected from halo, CN, $C_{3-8}$ cycloalkyl (optionally substituted by one or more substituents selected from halo, OH, =O, $C_{1-6}$ alkyl, $C_{1-6}$ alkoxy and aryl), $OR^{4a}$, $SR^{4b}$, $S(O)_2R^{4b}$, $S(O)_2N(H)R^{4e}$, $N(H)S(O)_2R^{4f}$, $N(R^{4g})(R^{4h})$, $C(O)R^{4i}$, $OC(O)R^{4i}$, $C(O)OR^{4i}$, $N(H)C(O)R^{4i}$, $C(O)N(H)R^{4i}$, aryl and $Het^1$),

(b) $C_{3-8}$ cycloalkyl or $C_{4-8}$ cycloalkenyl, which latter two groups are optionally fused to one or two phenyl groups and are optionally substituted by one or more substituents selected from halo, =O, $C_{1-6}$ alkyl, $C_{4-6}$ cycloalkyl (optionally substituted by one or more substituents selected from halo, $C_{1-4}$ alkyl, $C_{1-4}$ alkoxy and phenyl), $OR^{4a}$, $SR^{4b}$, $S(O)_2R^{4b}$, $S(O)_2N(H)R^{4c}$, $N(H)S(O)_2R^{4f}$, $N(R^{4g})(R^{4h})$, $OC(O)R^{4i}$, $C(O)OR^{4i}$, $N(H)C(O)R^{4i}$, $C(O)N(H)R^{4i}$, aryl and $Het^2$,

(c) aryl, or

(d) $Het^3$;

(3) $R^{4a}$ to $R^{4i}$ independently represent, at each occurrence,

(a) H,

(b) $C_{1-6}$ alkyl, $C_{2-6}$ alkenyl, $C_{2-6}$ alkynyl (which latter three groups are optionally substituted by one or more substituents selected from halo, OH, $C_{1-4}$ alkoxy, aryl and $Het^4$),

(c) $C_{4-6}$ cycloalkyl, $C_{4-6}$ cycloalkenyl (which latter two groups are optionally substituted by one or more substituents selected from halo, =O and $C_{1-4}$ alkyl),

(d) aryl or

(e) $Het^6$,

provided that $R^{4b}$ does not represent H when n is 1 or 2;

(4) $R^{5a}$ represents H, F, methyl or methoxy;

(5) $R^{5b}$ represents H;

(6) $R^{6a}$ and $R^{6b}$ both represent H, both represent methyl or both represent F;

(7) $R^{7a}$ and $R^{7b}$ both represent H;

(8) $R^2$ represents H, halo, $C_{1-4}$ alkoxy or $C_{1-4}$ alkyl (which latter group is optionally substituted by one or more substituents selected from halo (e.g. F), OH or methoxy);

(9) $R^{3a}$ and $R^{3b}$ independently represent H or F;

(10) the group G-L takes any of the following definitions

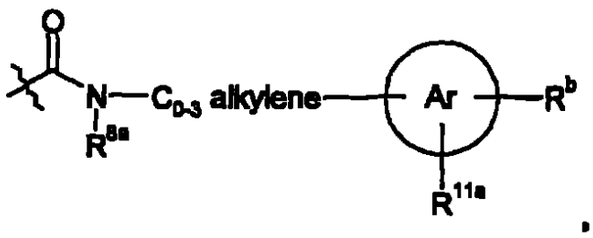
(a) $C(O)N(R^{8a})$-$C_{0-6}$ alkylene-$R^a$,

(b) $C(O)N(R^{8a})$-$CH(C(O)R^9)$-$C_{0-5}$ alkylene-$R^a$,

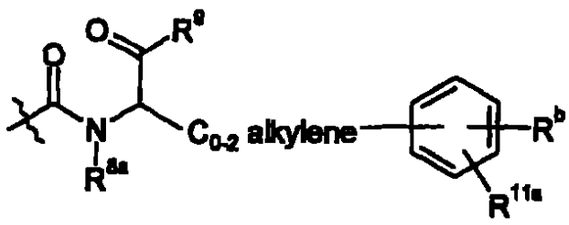
(c) $C(O)N(R^{8a})$-$C_{0-3}$ alkylene-CH=CH-$C_{0-2}$ alkylene-$R^a$,

(d) $C(O)N(R^{8a})$-$C_{0-3}$ alkylene-C≡C-$C_{0-2}$ alkylene-$R^a$,

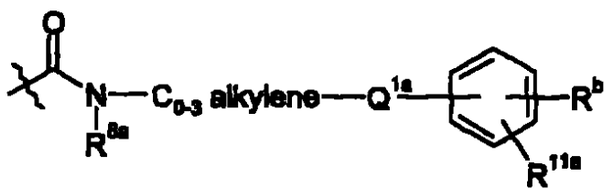
(e)



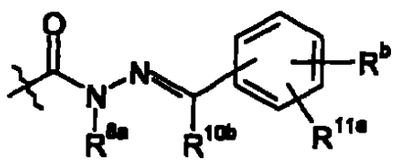

(f)



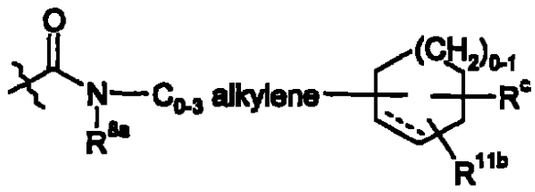

(g)



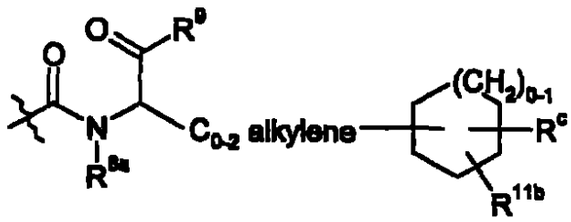

(h)



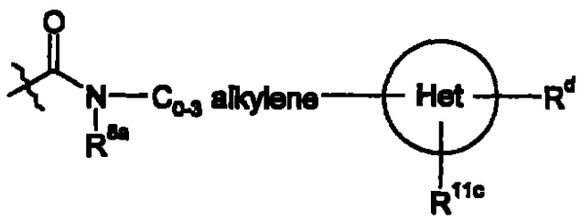
(i)



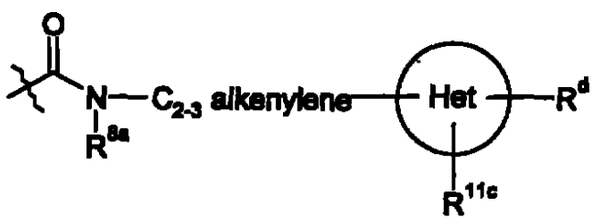
(j)



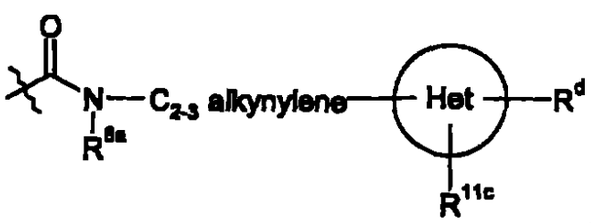
(k)



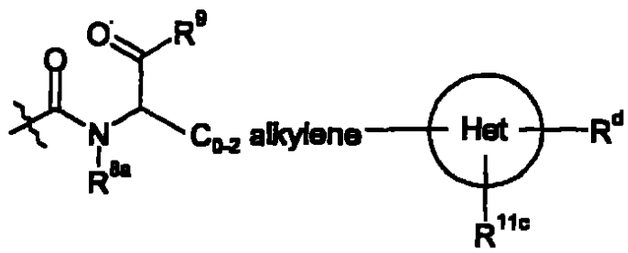
(l)



(m)



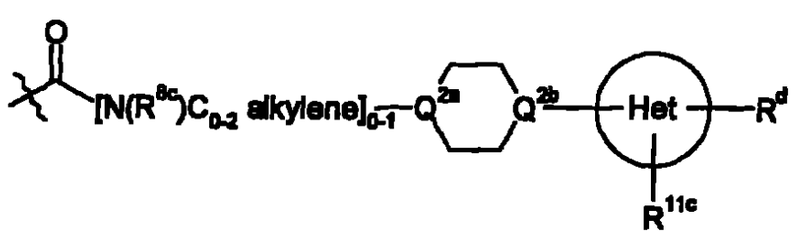
(n)



(o)



(p)



wherein $Q^{1a}$ represents O, $NR^{10a}$ or $[N(H)]_{0-1}C(O)$-$C_{0-2}$ alkylene;

(11) $R^9$ represents a 5- to 10-membered aromatic heterocyclic group comprising one or two rings and containing, as heteroatom(s), one sulfur or oxygen atom and/or one to three nitrogen atoms, which heterocyclic group is optionally substituted by one or more substituents selected from halo and $C_{1-4}$ alkyl;

(12) Het represents a 5- or 6-membered monocyclic, or a 8-, 9- or 10-membered bicyclic heterocyclic group containing, as heteroatom(s), one sulfur or oxygen atom and/or one to four nitrogen atoms;

(13) $R^{11a}$ represents H or one to three substituents selected from halo, OH, CN, $C_{1-4}$ alkyl and $C_{1-4}$ alkoxy (which latter two groups are optionally substituted by one or more substituents selected from OH,

halo, $C(O)OR^{12a}$ and $C(O)N(R^{12b})R^{12c}$ (e.g. one or more substituents selected from the latter three groups));

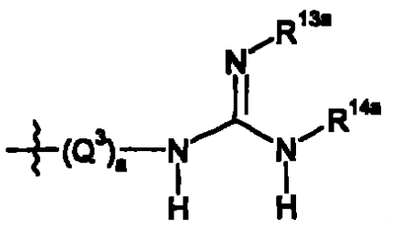
(14) $R^{11b}$ represents H or one to three substituents selected from halo, OH, $C_{1-4}$ alkyl, $C_{1-4}$ alkoxy and =O;

(15) $R^{11c}$ represents H or one to three substituents selected from halo, OH, CN, $C_{1-4}$ alkyl, $C_{1-4}$ alkoxy (which latter two groups are optionally substituted by one or more substituents selected from halo, OH and $C_{1-2}$ alkoxy), =O, =NH, =NOH and =N-CN;

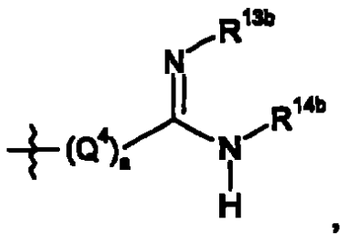
(16) $R^{12a}$ to $R^{12e}$ independently represent H, $C_{1-4}$ alkyl (optionally substituted by one $N(R^{12e})R^{12f}$ group) or $C_{3-6}$ cycloalkyl (e.g. H, $C_{1-4}$ alkyl or $C_{3-6}$ cycloalkyl);

(17) $R^8$ represents

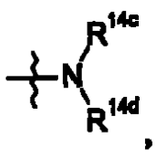
(a)



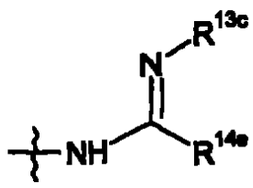
(b)



(c)

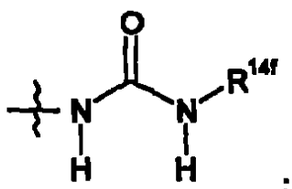


(d)



or

(e)

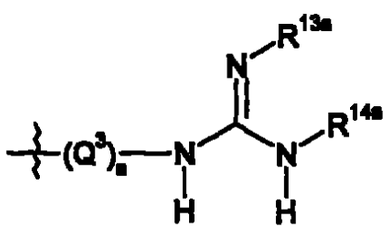


;

(18) $R^b$ represents

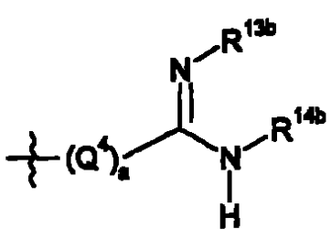
(a) H,

(b)



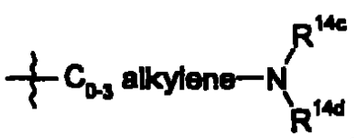
,

(c)



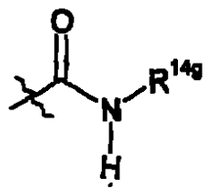
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(d)

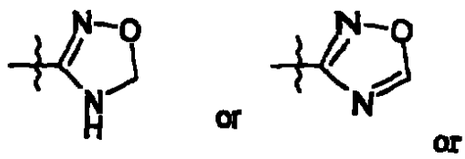


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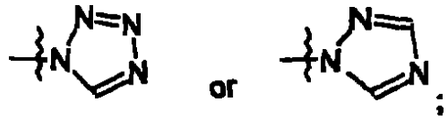
(e)



(f)

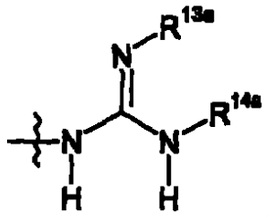


(g)

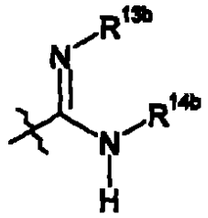


(19) $R^c$ and $R^d$ independently represent

(a)



(b)



(c)



(d) $R^d$ may also represent H;

(20) $Q^3$ represents O, $S(O)_2$, $S(O)_2NH$, C(O) or -CH=N-;

(21) $Q^4$ represents O or S;

(22) $R^{15}$ represents H, $C_{1-6}$ alkyl, $C_{3-6}$ alkenyl (which latter two groups are optionally interrupted by an oxygen atom), $C_{3-6}$ cycloalkyl or $C_{1-2}$ alkyl (which latter group is substituted by aryl);

(23) $R^{16}$ represents $C_{1-6}$ alkyl, $C_{3-6}$ alkenyl, $C_{3-6}$ cycloalkyl or $C_{1-2}$ alkyl substituted by aryl;

(24) $R^{8a}$ to $R^{8c}$ represent H or methyl;

(25) $R^{10a}$ to $R^{10e}$ independently represent H or $C_{1-3}$ alkyl (which latter group is optionally substituted by OH or one or more halo atoms);

(26) $R^{14a}$ represents $C_{1-2}$ alkyl, $C(O)O$-$C_{1-5}$ alkyl (the alkyl part of which latter group is optionally substituted by phenyl) or H (e.g. H or $C_{1-2}$ alkyl);

(27) $R^{14b}$ to $R^{14g}$ independently represents H or $C_{1-2}$ alkyl (which latter group is optionally substituted by one or more halo atoms, but is preferably unsubstituted), or $R^{14c}$ represents $C_{4-6}$ cycloalkyl or $C(O)O$-$C_{1-5}$ alkyl (the alkyl part of which latter group is optionally substituted by phenyl) or $R^{14c}$ and $R^{14d}$ together represent $C_{4-5}$ *n*-alkylene optionally interrupted by O;

(28) each aryl independently represents phenyl or naphthyl, each of which groups may be substituted by one or more substituents selected from

(a) halo,

(b) CN,

(c) $C_{1-8}$ alkyl, $C_{2-4}$ alkenyl, $C_{2-4}$ alkynyl (which latter three groups are optionally substituted by one or more substituents selected from halo, OH, $C_{1-2}$ alkoxy, C(O)OH, $C(O)O$-$C_{1-2}$ alkyl and phenyl),

(d) $C_{3-6}$ cycloalkyl optionally substituted by one or more substituents selected from halo, =O and $C_{1-4}$ alkyl,

(e) $OR^{17a}$,

(f) $SR^{17b}$, $S(O)_2R^{17b}$,

(g) $S(O)_2N(H)R^{17e}$,

(h) $N(H)S(O)_2R^{17f}$,

(i) $N(H)R^{17g}$,

(j) $C(O)R^{17i}$, $C(O)OR^{17i}$, $OC(O)R^{17i}$, $C(O)N(H)R^{17i}$, $N(H)C(O)R^{17i}$, $N(H)C(O)OR^{17i}$,

(k) phenyl (which latter group is optionally substituted by one or more halo atoms),

(l) $Het^9$ and

(m) $Si(CH_3)_3$;

(29) $R^{17a}$ to $R^{17i}$ independently represent, at each occurrence,

(a) H,

(b) $C_{1-8}$ alkyl optionally substituted by one or more substituents selected from halo, OH, $C_{1-2}$ alkoxy, phenyl (which latter group is optionally substituted by one or more halo atoms) and $Het^{10}$ (e.g. one or more substituents selected from halo, OH, $C_{1-2}$ alkoxy and phenyl (which latter group is optionally substituted by one or more halo atoms)),

(c) $C_{3-6}$ cycloalkyl optionally substituted by one or more substituents selected from halo, =O and $C_{1-4}$ alkyl,

(d) phenyl optionally substituted by one or more halo atoms or

(e) $Het^{12}$,

provided that $R^{17b}$ does not represent H;

(30) $Het^1$ to $Het^{12}$ independently represent 5- to 13-membered heterocyclic groups containing one to four heteroatoms selected from oxygen, nitrogen and/or sulfur, which heterocyclic groups may comprise one, two or three rings and may be substituted by one or more substituents selected from

(a) halo,

(b) CN,

(c) $C_{1-8}$ alkyl, $C_{2-4}$ alkenyl, $C_{2-4}$ alkynyl (which latter three groups are optionally substituted by one or more substituents selected from halo, OH and $C_{1-2}$ alkoxy),

(d) $C_{3-6}$ cycloalkyl optionally substituted by one or more substituents selected from halo, =O and $C_{1-4}$ alkyl,

(e) =O,

(f) $OR^{19a}$,

(g) $S(O)_2R^{19b}$,

(h) $S(O)_2N(H)R^{19c}$,

(i) $N(H)S(O)_2R^{19f}$,

(j) $N(H)R^{19g}$,

(j) $C(O)R^{19i}$, $C(O)OR^{19l}$, $C(O)N(H)R^{19i}$, $N(H)C(O)R^{19l}$, $N(H)C(O)OR^{19l}$,

(l) phenyl (which latter group is optionally substituted by halo) and

(m) $Het^a$;

(31) $R^{19a}$ to $R^{19l}$ independently represent, at each occurrence,

(a) H,

(b) $C_{1-6}$ alkyl optionally substituted by one or more substituents selected from halo, OH, $C_{1-2}$ alkoxy and phenyl,

(c) $C_{3-6}$ cycloalkyl optionally substituted by one or more substituents selected from halo, =O and $C_{1-4}$ alkyl,

(d) phenyl optionally substituted by halo or

(e) $Het^f$,

provided that $R^{19b}$ does not represent H;

(32) $Het^a$ to $Het^f$ independently represent 5- or 6-membered heterocyclic groups containing, as heteroatoms, one oxygen or sulfur atom and/or one to three nitrogen atoms, which heterocyclic groups may be substituted by one or more substituents selected from halo and $C_{1-4}$ alkyl;

(33) alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, alkylene and alkenylene groups, as well as the alkyl part of alkoxy groups, may be substituted by one or more Cl or, particularly, F atoms.

Also preferred are compounds of formula I in which $R^{3a}$ and $R^{3b}$ both take the same definition (i.e. compounds in which $R^5$ and $R^6$ both represent H, both represent F or both represent methyl, $CH_2F$, $CHF_2$ or $CF_3$).

When A represents C(O) or C(O)NH (in which latter group the NH moiety is attached to $R^1$), preferred compounds of formula I also include those in which $R^1$ represents:

(a) $C_{1-6}$ alkyl, $C_{2-6}$ alkenyl, $C_{2-6}$ alkynyl, which latter three groups are

(i) substituted by one substituent selected from $C_{3-8}$ cycloalkyl (optionally substituted by one or more substituents selected from halo, OH, =O, $C_{1-6}$ alkyl, $C_{1-6}$ alkoxy and aryl), aryl and $Het^1$, and

(ii) optionally substituted by one or more further substituents selected from halo, CN, $C_{4-6}$ cycloalkyl (optionally substituted by one or more substituents selected from halo and $C_{1-4}$ alkyl), $OR^{4a}$, $SR^{4b}$, $S(O)_2R^{4b}$, $S(O)_2N(H)R^{4e}$, $N(H)S(O)_2R^{4f}$, $N(R^{4g})(R^{4h})$, $OC(O)R^{4l}$, $C(O)OR^{4l}$, $N(H)C(O)R^{4l}$, $C(O)N(H)R^{4i}$, aryl and $Het^1$;

(b) $C_{3-8}$ cycloalkyl or $C_{4-8}$ cycloalkenyl, which latter two groups are

(i) fused to one or two phenyl groups and optionally substituted by one or more substituents selected from halo, $C_{1-4}$ alkyl and $C(O)OR^{4i}$, or

(ii) substituted by aryl and optionally further substituted by one or more substituents selected from halo and $C_{1-4}$ alkyl;

(c) aryl; or

(d) $Het^3$,

wherein $R^{4a}$ to $R^{4c}$, $R^{4f}$ to $R^{4i}$ aryl and $Het^1$ are as defined above or below.

When A represents $S(O)_2$, preferred compounds of formula I also include those in which $R^1$ represents:

(a) $C_{1-3}$ alkyl or $C_{2-3}$ alkenyl, which latter two groups are substituted by aryl and are optionally further substituted by one or more halo atoms;

(b) $C_{1-6}$ alkyl optionally substituted by one or more substituents selected from halo, $OR^{4a}$ and $S(O)_2R^{4b}$;

(c) $C_{3-6}$ monocyclic cycloalkyl optionally substituted by one or more substituents selected from halo and $C_{1-4}$ alkyl;

(d) $C_{6-8}$ bicyclic cycloalkyl optionally substituted by one or more substituents selected from halo, =O and $C_{1-6}$ alkyl;

(c) aryl; or

(d) $Het^3$,

wherein $R^{4a}$ and $R^{4b}$ are as defined above or below.

When A represents $C_{1-6}$ alkylene, preferred compounds of formula I also include those in which $R^1$ represents:

(a) $C_{1-6}$ alkyl or $C_{2-6}$ alkenyl, which latter two groups are optionally substituted by one or more substituents selected from halo and OH;

(b) $C_{3-8}$ cycloalkyl or $C_{4-8}$ (e.g. $C_{4-6}$) cycloalkenyl, which latter two groups are optionally substituted by one to four substituents selected from halo, =O, OH, $C_{1-4}$ alkyl, O-$C_{1-4}$ alkyl (which latter two groups are optionally substituted by one or more halo (e.g. F) atoms) and aryl, or, particularly,

(c) aryl (e.g. naphthyl or, particularly, phenyl), or

(d) $Het^3$,

(e.g. any one of the groups listed in (b) to (d) above).

Compounds of formula I that are more preferred include those in which the group G-L takes any of the preferred definitions provided at (10)(a), (c), (d), (e), (g), (h), (i), (k), (l), (m), (o) and (p) above.

More preferred compounds of formula I particularly include compounds in which:

(1) A represents C(O), $S(O)_2$, C(O)NH (in which latter group the NH moiety is attached to $R^1$) or $C_{1-3}$ alkylene;

(2) $R^1$ represents

(a) $C_{1-5}$ alkyl, $C_{2-4}$ alkenyl (which latter two groups are optionally substituted by one or more substituents selected from halo, $C_{6-8}$ bicyclic cycloalkyl, $C_{3-6}$ monocyclic cycloalkyl (which latter two groups are optionally substituted by one or more substituents selected from halo, =O, $C_{1-4}$ alkyl, $C_{1-4}$ alkoxy and phenyl (which latter group is optionally substituted by one or more substituents selected from halo, $C_{1-4}$ alkyl and $C_{1-4}$ alkoxy)), $OR^{4a}$, $SR^{4b}$, $S(O)_2R^{4b}$, $C(O)R^{4i}$, $OC(O)R^{4i}$, $C(O)OR^{4i}$, aryl and $Het^1$),

(b) $C_{3-6}$ cycloalkyl or $C_{4-8}$ (e.g. $C_{4-6}$) cycloalkenyl, which latter two groups are optionally fused to one or two phenyl groups and are optionally substituted by one or more substituents selected from halo, =O, $C_{1-4}$ alkyl, $OR^{4a}$, $C(O)OR^{4i}$ and phenyl (which latter group is optionally substituted by one or more substituents selected from halo, $C_{1-4}$ alkyl and $C_{1-4}$ alkoxy),

(c) aryl, or

(d) $Het^3$;

(3) $R^{4a}$ to $R^{4l}$ independently represent, at each occurrence,

(a) H,

(b) $C_{1-6}$ alkyl, $C_{2-4}$ alkenyl (which latter two groups are optionally substituted by one or more substituents selected from halo, OH, $C_{1-4}$ alkoxy and phenyl),

(c) $C_{4-6}$ cycloalkyl (which latter group is optionally substituted by one or more substituents selected from halo and $C_{1-2}$ alkyl) or

(d) phenyl (which latter group is optionally substituted by one or more substituents selected from halo, $C_{1-4}$ alkyl and $C_{1-4}$ alkoxy)

provided that $R^{4b}$ does not represent H;

(4) $R^2$ represents H, halo (such as Cl) or $C_{1-3}$ alkyl (which latter group is optionally substituted by F);

(5) $R^{3a}$ and $R^{3b}$ both represent H or both represent F;

(6) $R^{5a}$ represents H;

(7) $R^{6a}$ and $R^{6b}$ both represent H;

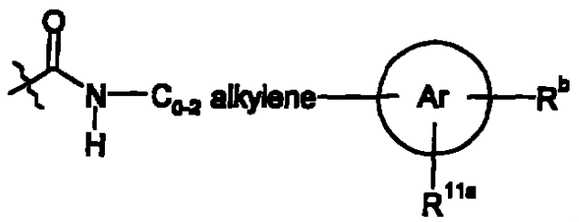
(8) the group G-L takes any of the following definitions

(i) $C(O)N(H)$-$C_{0-5}$ alkylene-$R^{a1}$,

(ii) $C(O)N(H)$-$C_{0-3}$ alkylene-CH=CH-$R^{a2}$,

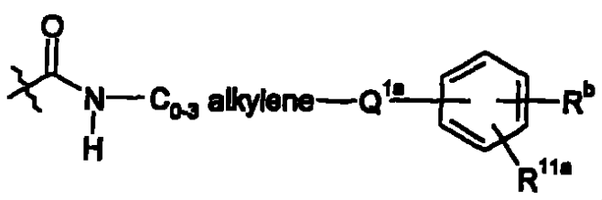
(iii) $C(O)N(H)$-$C_{1-3}$ alkylene-C≡C-$CH_2$-$R^{a3}$,

(iv)



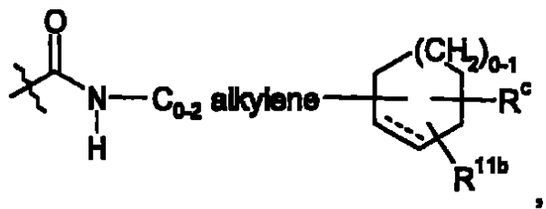

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(v)

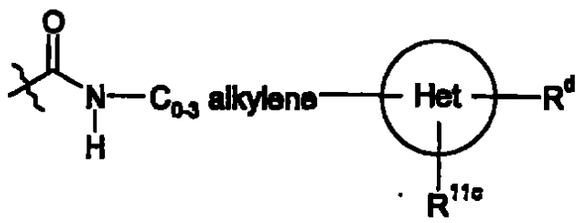



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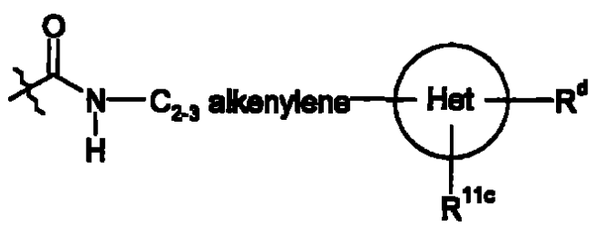
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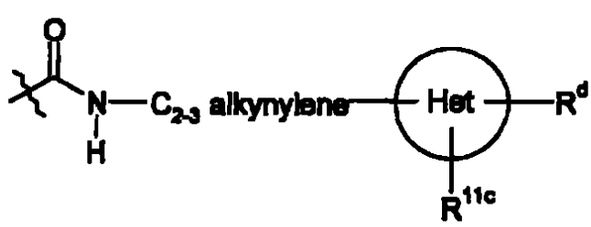

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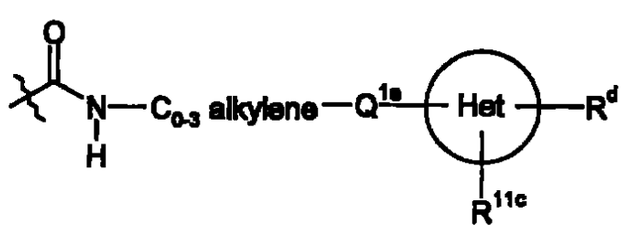

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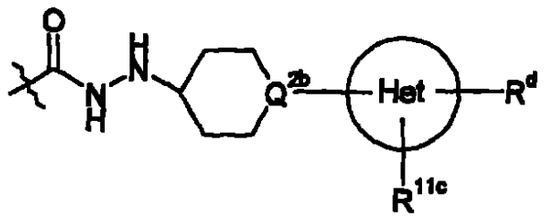

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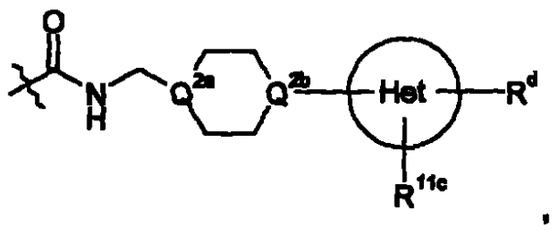

(x)



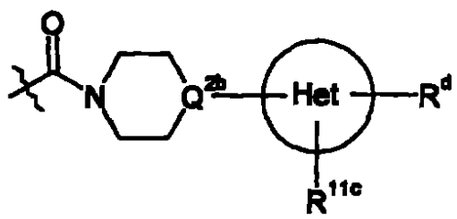
(xi)



(xii)



(xiii)



wherein $Q^{1a}$ is as defined above;

(9) Het represents a 5- or 6-membered monocyclic, an 8-membered bicyclic, or a 9- or 10-membered ring-fused bicyclic heterocyclic group containing, as heteroatom(s), one sulfur or oxygen atom and/or one to three nitrogen atoms, which heterocyclic group

(i) when 5- or 6-membered, is fully aromatic, fully saturated or mono-unsaturated,

(ii) when 8-membered, is fully aromatic or, preferably, fully saturated, or

(iii) when 9- or 10-membered, is fully aromatic or part-aromatic;

(10) $R^{11a}$ represents H or one to three substituents selected from halo, OH, CN, $C_{1-3}$ alkyl and $C_{1-3}$ alkoxy (which latter two groups are optionally substituted by one or more substituents selected from OH,

halo, $C(O)OR^{12a}$ and $C(O)N(R^{12b})R^{12c}$ (e.g. one or more substituents selected from the latter three groups));

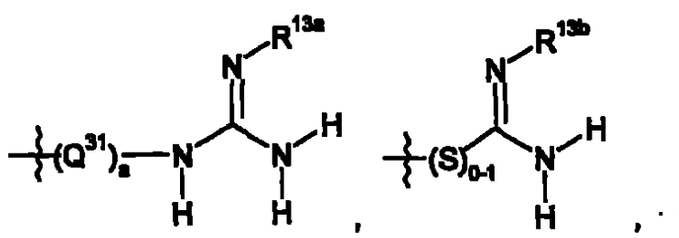
(11) $R^{11b}$ represents one or two substituents selected from halo and $C_{1-3}$ alkyl or, preferably, $R^{11b}$ represents H;

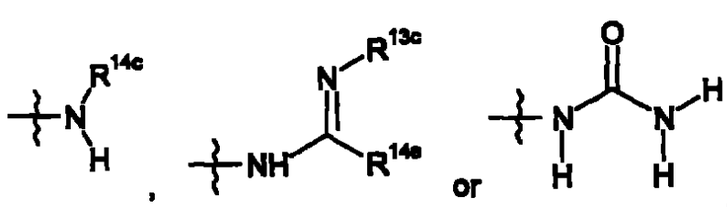
(12) $R^{11c}$ represents H or one to three substituents selected from halo, OH, CN, $C_{1-3}$ alkyl (which latter group is optionally substituted by one or more substituents selected from halo and OH), =O, =NH and =N-CN;

(13) $R^{12a}$ to $R^{12c}$ independently represent H, $C_{1-3}$ alkyl (optionally substituted by one $N(R^{12e})R^{12f}$ group) or $C_{3-5}$ cycloalkyl (e.g. H, $C_{1-3}$ alkyl or $C_{3-5}$ cycloalkyl);

(14) $R^{12e}$ and $R^{12f}$ independently represent H or $C_{1-2}$ alkyl;

(15) $R^{a1}$, $R^{a2}$ and $R^{a3}$ represent $R^a$ as defined above, but preferably independently represent



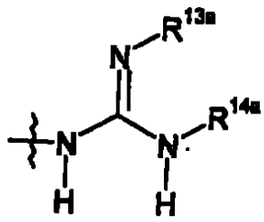


wherein $Q^{31}$ represents O, C(O) or -CH=N- and a represents 0 or, preferably, 1;

(16) $R^b$ represents

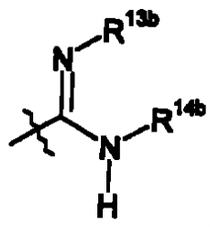
(a) H,

(b)



,

(c)



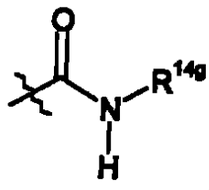
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(d)



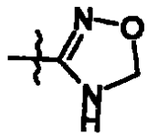
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(e)

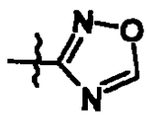


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(f)

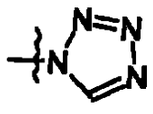


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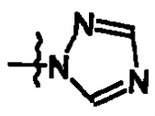


or

(g)

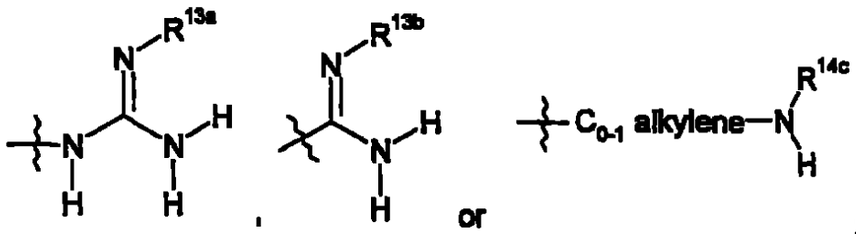


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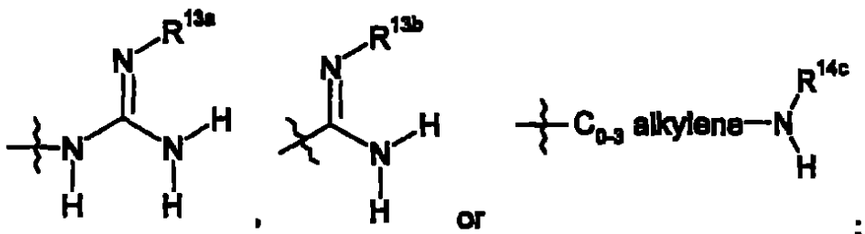
;

(17) $R^c$ represents



;

(18) $R^d$ represents H,



;

(19) $R^{13a}$ represents H, CN, $NH_2$ or $OR^{15}$;

(20) $R^{13b}$ represents H, $NH_2$, $OR^{15}$ or $C(O)OR^{16}$;

(21) $R^{13c}$ represents H or OH;

(22) $R^{15}$ represents H or $C_{1-5}$ alkyl;

(23) $R^{16}$ represents $C_{1-2}$ alkyl substituted by aryl;

(24) $R^{14a}$ represents H or $C_{1-2}$ alkyl (which latter group is optionally substituted by OH);

(25) $R^{14a}$ represents H, methyl, $C(O)O$-$C_{3-4}$ alkyl or $C(O)OCH_2$-phenyl (e.g. methyl or, preferably, H);

(26) $R^{14b}$ to $R^{14d}$ and $R^{14f}$ to $R^{14g}$ independently represent methyl or, preferably, H,

or $R^{14c}$ represents

$C_{1-2}$ alkyl substituted by one to three halo (e.g. F) atoms,

$C_{4-5}$ cycloalkyl (e.g. cyclopentyl),

$C(O)O$-$C_{3-4}$ alkyl or

$C(O)OCH_2$-phenyl (e.g. one of the latter three groups),

or $R^{14c}$ and $R^{14d}$ together represent $C_4$ *n*-alkylene;

(27) $R^{14e}$ represents H or, preferably, methyl;

(28) each aryl independently represents phenyl or naphthyl, each of which groups may be substituted by one or more substituents selected from

(a) F, Cl, Br,

(b) CN,

(c) $C_{1-6}$ alkyl, $C_{2-3}$ alkenyl (which latter two groups are optionally substituted by one or more substituents selected from F, Cl, C(O)OH, $C(O)OCH_3$ and phenyl),

(d) $C_{3-5}$ cycloalkyl,

(e) $OR^{17a}$,

(f) S-$C_{1-2}$ alkyl, $S(O)_2$-$C_{1-2}$ alkyl (the alkyl parts of which latter two groups are optionally substituted by one or more F atoms),

(g) $S(O)_2NH_2$, $S(O)_2N(H)CH_3$,

(h) $N(H)S(O)_2$-$C_{1-2}$ alkyl (the alkyl part of which latter group is optionally substituted by one or more F atoms),

(i) $NH_2$, $N(H)C_{1-2}$ alkyl,

(j) CHO, C(O)-$C_{1-4}$ alkyl (the alkyl part of which latter group is optionally substituted by one or more F or Cl atoms), C(O)OH, C(O)O-$C_{1-4}$ alkyl, $C(O)NH_2$, C(O)N(H)-$C_{1-4}$ alkyl, N(H)C(O)-$C_{1-4}$ alkyl, N(H)C(O)O-$C_{1-4}$ alkyl,

(k) phenyl (which latter group is optionally substituted by one to four substituents selected from F, Cl and Br),

(l) $Het^9$ and

(m) $Si(CH_3)_3$;

(29) $R^{17a}$ represents

(a) H,

(b) $C_{1-5}$ alkyl optionally substituted by phenyl or one or more substituents selected from F, Cl and $Het^{10}$ (e.g. one or more substituents selected from F and Cl),

(c) $C_{3-5}$ cycloalkyl or

(d) phenyl optionally substituted by one to four substituents selected from F, Cl and Br;

(30) $Het^1$ represents a 5- to 10-membered heterocyclic group containing one to three heteroatoms selected from oxygen, nitrogen and/or sulfur, which heterocyclic groups may comprise one or two rings and may be substituted by one to three substituents selected from F, Cl, Br, $C_{1-4}$ alkyl, =O and OH;

(31) $Het^3$ represents a 5- to 13-membered heterocyclic group containing one to four heteroatoms selected from oxygen, nitrogen and/or sulfur, which heterocyclic groups may comprise one, two or three rings and may be substituted by one to four substituents selected from

(a) F, Cl, Br,

(b) $C_{1-4}$ alkyl (which latter group is optionally substituted by one or more substituents selected from F, Cl and OH),

(c) $C_{3-5}$ cycloalkyl,

(d) =O,

(e) OH, O-$C_{1-2}$ alkyl (which latter group is optionally substituted by one or more substituents selected from F and Cl),

(g) $S(O)_2$-$C_{1-2}$ alkyl (which latter group is optionally substituted by one or more F atoms), $S(O)_2$-phenyl (the phenyl part of which latter group is optionally substituted by one to four substituents selected from F, Cl, Br, methyl and methoxy),

(h) $S(O)_2NH_2$, $S(O)_2N(H)$-$C_{1-2}$ alkyl,

(i) $N(H)S(O)_2$-$C_{1-2}$ alkyl,

(j) $NH_2$, N(H)-$C_{1-2}$ alkyl,

(j) C(O)-$C_{1-4}$ alkyl, C(O)-phenyl (the phenyl part of which latter group is optionally substituted by one to four substituents selected from F, Cl, Br, methyl and methoxy), C(O)OH,

$C(O)O$-$C_{1-4}$ alkyl, $C(O)NH_2$, $C(O)N(H)$-$C_{1-4}$ alkyl, $N(H)C(O)$-$C_{1-4}$ alkyl, $N(H)C(O)O$-$C_{1-4}$ alkyl,

(l) phenyl (which latter group is optionally substituted by one to four substituents selected from F, Cl and Br) and

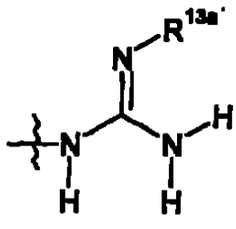
(m) $Het^c$;

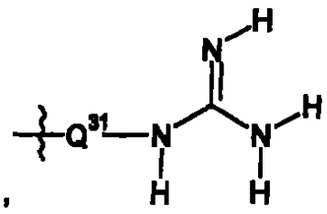
(32) $Het^9$ represents a 5- or 6-membered monocyclic heterocyclic group containing, as heteroatom(s), one sulfur or oxygen atom and/or one to three nitrogen atoms, which heterocyclic group may be substituted by one or more substituents selected from F, Cl, Br, $C_{1-4}$ alkyl, =O and OH;

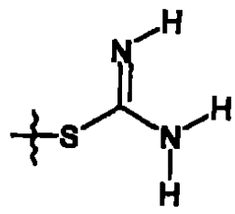
(33) $Het^{10}$ represents a 5- or 6-membered monocyclic heterocyclic group containing, as heteroatom(s), one sulfur or oxygen atom and/or one to three nitrogen atoms, which heterocyclic group may be substituted by one or more substituents selected from F, Cl, Br, $C_{1-4}$ alkyl and $C_{1-4}$ alkoxy;

(34) $Het^c$ represents a 5- or 6-membered heterocyclic group containing, as heteroatom(s), one oxygen or sulfur atom (e.g. one oxygen atom) and/or one to three (e.g. one or two) nitrogen atoms, which heterocyclic group may be substituted by one or more substituents selected from F, Cl, Br, $C_{1-4}$ alkyl and $C_{1-4}$ alkoxy (e.g. one or more substituents selected from F, Cl, Br and methyl).

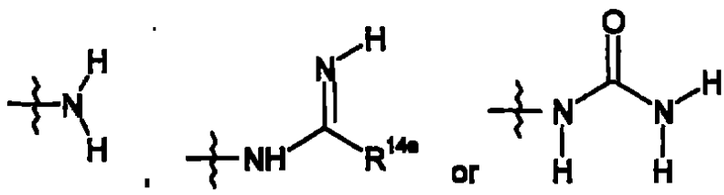
More preferred definitions of $R^{a1}$ include



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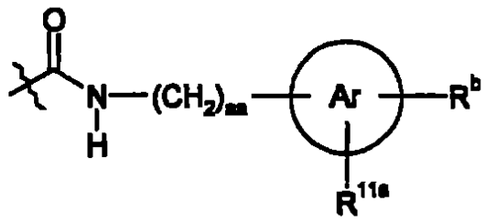


wherein $R^{13a}$ is as defined above, but preferably represents OH, CN or $NH_2$ and $Q^{31}$ and $R^{14a}$ are as defined above.

More preferred definitions of $R^{a2}$ and $R^{a3}$ include $-N(H)R^{14c}$, wherein $R^{14c}$ represents $C_{1-2}$ alkyl or, preferably, H.

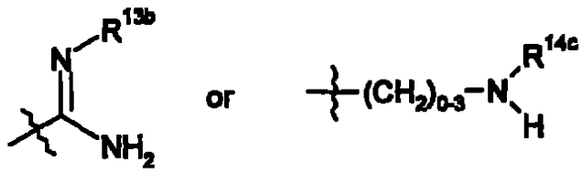
Compounds of formula I that are more preferred still include those in which the group G-L takes any of the following definitions.

(1)



wherein aa represents 0, 1 or 2 (such as 2 or, particularly, 1);

$R^b$ is as hereinbefore defined, but particularly represents tetrazol-1-yl, H,



(e.g. one of the latter three groups),

wherein $R^{13b}$ is as hereinbefore defined, but particularly represents $NH_2$ or, preferably, H;

$R^{14c}$ is as hereinbefore defined, but particularly represents $C_{1-2}$ alkyl optionally substituted by one to 3 F atoms (e.g. $CH_2CF_3$), H, cyclopentyl or $C(O)O\text{-}C_{3-4}$ alkyl (e.g. one of the latter three groups);

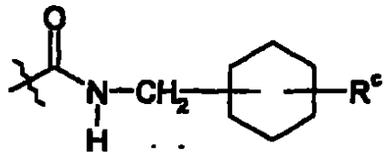
$R^{11a}$ is as hereinbefore defined, but,

(i) when $R^b$ represents H, $R^{11a}$ particularly represents one to three substituents selected from F, Cl, OH, methyl (which latter group is optionally substituted by OH or, particularly, $C(O)N(R^{12b})R^{12c}$) and methoxy (which latter group is substituted by $C(O)N(H)R^{12b}$),

(ii) when $R^b$ represents $-C(=NR^{13b})NH_2$, $R^{11a}$ particularly represents one or two substituents selected from F and OH or, preferably, $R^{11a}$ represents H,

(iii) when $R^b$ represents $-(CH_2)_{0-3}-N(H)R^{14c}$, $R^{11a}$ particularly represents H or one or two substituents selected from F, Cl, OH, methyl, methoxy and $CF_3$ (e.g. H or one or two substituents selected from Cl, OH and methyl or, preferably, a single Cl substituent).

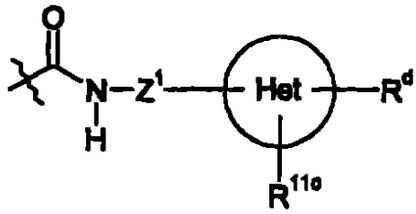
(2)



wherein $R^c$ represents $-C(=NR^{13b})NH_2$ or, particularly, $-N(H)R^{14c}$, which groups are preferably attached in the 4-position relative to the point of attachment of the $CH_2$ group;

$R^{13b}$ and $R^{14c}$ are as hereinbefore defined, but preferably represent H.

(3)



wherein $Z^1$ represents $-CH_2C\equiv C-$, $-CH=CH-$, $C(O)CH_2$ or, preferably, $C(O)$ or $-(CH_2)_{ab}-$;

when $Z^1$ represents $-CH_2C\equiv C-$, $-CH=CH-$, Het represents a 5-membered, aromatic heterocyclic group containing one or, particularly, two nitrogen atoms;

when $Z^1$ represents $C(O)CH_2$, Het represents a 6-membered, fully saturated heterocyclic group containing one or, particularly, two nitrogen atoms;

when $Z^1$ represents C(O), Het represents a 6-membered, aromatic heterocyclic group containing two nitrogen atoms or, particularly, one nitrogen atom;

when $Z^1$ represents $-(CH_2)_{ab}-$ Het represents a 5- or 6-membered monocyclic or 9- or 10-membered ring-fused bicyclic heterocyclic group containing, as heteroatom(s)

(a) a sulfur atom, or

(b) a nitrogen atom and, optionally, one or two further heteroatoms selected from nitrogen, oxygen and sulfur,

which heterocyclic group

(i) when 5- or 6-membered, is fully aromatic or fully saturated,

(ii) when 9- or 10-membered, is fully aromatic or part-aromatic;

ab represents 0 to 3, but preferably represents 1 or 2 or, when Het is 5-membered, also preferably represents 3;

$R^d$ represents H, $-C(=NR^{13b})NH_2$ or $-N(H)R^{14c}$, but $R^d$, when Het is 5 or 10-membered, particularly represents $-N(H)R^{14c}$;

$R^{11a}$ is as hereinbefore defined, but preferably represents H or

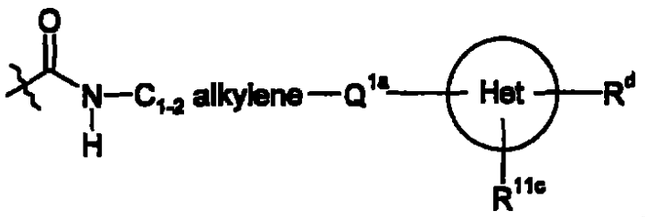
(I) when Het is 6-membered and aromatic (e.g. a pyridinyl group), one or two substituents selected from F, Cl, methyl and $CH_2OH$,

(II) when Het is 6-membered and fully saturated, a methyl or a =NH substituent;

$R^{13b}$ is as hereinbefore defined, but preferably represents H;

$R^{14a}$ is as hereinbefore defined, but preferably represents H or, when Het is 6-membered, methyl.

(4)




wherein $Q^{1a}$ represents O or $NR^{10a}$;

$R^{10a}$ represents H, methyl or $-CH_2CH_2OH$;

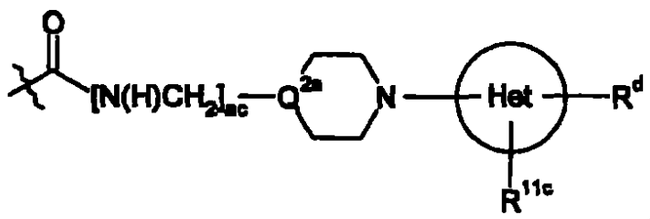
Het represents a 6-membered or 10-membered, aromatic heterocyclic group containing two nitrogen atoms or, preferably, one nitrogen atom;

$R^d$ represents H or $-N(H)R^{14c}$;

$R^{14a}$ is as hereinbefore defined, but preferably represents H;

$R^{11c}$ is as hereinbefore defined, but preferably represents H or, when Het contains two nitrogen atoms, represents Cl.

(5)



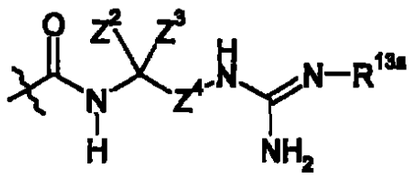

wherein $Q^{2a}$ represents N or CH;

ac represents 0 or 1, but, when $Q^{2a}$ represents CH, preferably represents 1;

Het represents a 6-membered, aromatic heterocyclic group containing two nitrogen atoms or, preferably, one nitrogen atom (e.g. a pyridinyl group, such as a pyridin-4-yl group);

$R^d$ and $R^{11a}$ are as hereinbefore defined, but preferably represent H;

(6)

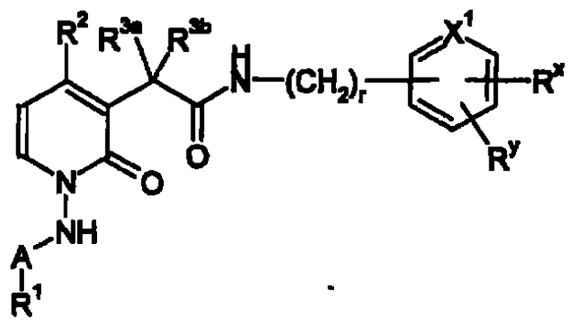


wherein $Z^2$ and $Z^3$ independently represent H or F, but, preferably, $Z^2$ and $Z^3$ both represent H or both represent F;

$Z^4$ represents $-(CH_2)_2C(O)-$ or, preferably, $-CH_2C(O)-$, $-CH_2O-$, $-CH_2-C(H)=N-$ or $-C(H)=N-$;

$R^{13a}$ is as hereinbefore defined, but preferably represents H.

Particularly preferred compounds of the invention are compounds of formula Ic



Ic

wherein $X^1$ represents CH or N;

when $X^1$ represents CH

(a) $R^x$ takes the same definitions as $R^b$ above, and

(b) $R^y$ takes the same definitions as $R^{11a}$ above;

when $X^1$ represents N

(a) $R^x$ takes the same definitions as $R^d$ above, and

(b) $R^y$ takes the same definitions as $R^{11c}$ above;

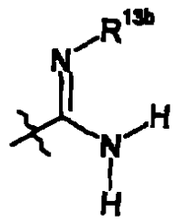
r represents 1 to 3; and

$R^1$, $R^2$, $R^{3a}$, $R^{3b}$, $R^{11a}$, $R^{11c}$, $R^b$, $R^d$ and A are as defined above,

which compounds are also referred to hereinafter as "the compounds of the invention".

Preferred compounds of formula Ic include those in which:

when $X^1$ represents CH, $R^x$ represents tetrazol-1-yl, H, $(CH_2)_{1-2}N(H)R^{14c}$ (e.g. $CH_2N(H)R^{14c}$) or



(e.g. any one of the latter three groups);

when $X^1$ represents N, $R^x$ represents H or $-N(H)R^{14c}$;

when $X^1$ represents CH, $R^y$ represents H or one to three substituents selected from halo, $C_{1-2}$ alkyl, $C_{1-2}$ alkoxy (which latter two groups are optionally substituted by one or more F atoms), OH, $CH_2OH$ and $OCH_2C(O)N(H)R^{12b}$ (e.g. H or one to three halo atoms);

when $X^1$ represents N, $R^y$ represents H or one to three substituents selected from halo and $C_{1-2}$ alkyl;

$R^{12b}$ represents H or, preferably, $C_{1-3}$ alkyl optionally substituted by $N(CH_3)_2$ (e.g. ethyl or $(CH_2)_{2-3}N(CH_3)_2$, particularly $(CH_2)_3N(CH_3)_2$);

r represents 2 or, particularly, 1.

Particularly preferred compounds of formula Ic include those in which:

A represents C(O), $S(O)_2$, C(O)NH (in which latter group the NH moiety is attached to $R^1$) or $C_{1-3}$ (e.g. $C_{1-2}$) alkylene (which latter group is optionally substituted by one or more F atoms (e.g. is unsubstituted));

$R^1$ represents

(a) $C_{1-3}$ alkyl substituted by phenyl (which latter group is optionally substituted by one or more substituents selected

from halo, $C_{1-4}$ alkyl and $C_{1-4}$ alkoxy (which latter two groups are optionally substituted by one or more F atoms)),

(b) phenyl or naphthyl (which latter two groups are optionally substituted by one or more substituents selected from CN, halo, $C_{1-4}$ alkyl, $C_{1-4}$ alkoxy (which latter two groups are optionally substituted by one or more F atoms), O-phenyl, O-$CH_2$-$Het^{10}$ and $Het^9$ (e.g. one or more substituents selected from halo, $C_{1-4}$ alkyl and $C_{1-4}$ alkoxy (which latter two groups are optionally substituted by one or more F atoms)),

(c) a 5- or 6-membered monocyclic (preferably aromatic) heterocyclic group containing, as heteroatom(s), an oxygen or sulfur atom and/or one to three nitrogen atoms, which heterocyclic group is optionally substituted by one to four substituents selected from F, Cl, Br, =O, OH, $C_{1-4}$ alkyl (which latter group is optionally substituted by one or more halo atoms or by OH), $C_{1-4}$ alkoxy, $S(O)_2$-phenyl, C(O)-phenyl, phenyl and $Het^c$ (e.g. one to four substituents selected from F, Cl, Br, $C_{1-4}$ alkyl and $C_{1-4}$ alkoxy, such as one to four substituents selected from F, Cl, Br and $C_{1-4}$ alkyl),

(d) a 9- or 10-membered bicyclic (preferably part-aromatic) heterocyclic group containing one to three heteroatoms selected from oxygen, nitrogen and/or sulfur (e.g. two oxygen atoms), which heterocyclic group is optionally substituted by one to four substituents selected from F, Cl, Br, $C_{1-4}$ alkyl and $C_{1-4}$ alkoxy,

(e) $C_{1-5}$ alkyl, or

(f) $C_{4-7}$ cycloalkyl or $C_{5-7}$ cycloalkenyl, which latter two groups are optionally substituted by one or more methyl groups

(e.g. $R^1$ represents a group as defined at (a) to (c) above);

$Het^9$ represents a 5- or 6-membered monocyclic heterocyclic group containing, as heteroatom(s), one sulfur or oxygen atom and/or one or two nitrogen atoms, which heterocyclic group may be substituted by one to three substituents selected from F, Cl and methyl;

$Het^{10}$ represents a 5- or 6-membered monocyclic, aromatic heterocyclic group containing, as heteroatom(s), one sulfur or oxygen atom and/or one or two nitrogen atoms, which heterocyclic group may be substituted by one to three substituents selected from F, Cl, methyl and methoxy;

$Het^c$ represents a 5- or 6-membered monocyclic heterocyclic group containing, as heteroatom(s), an oxygen or sulfur atom and/or or one or two nitrogen atoms, which heterocyclic group is optionally substituted by one to four substituents selected from F, Cl, Br, $C_{1-4}$ alkyl and $C_{1-4}$ alkoxy;

$R^2$ represents H, methyl or halo (such as Cl);

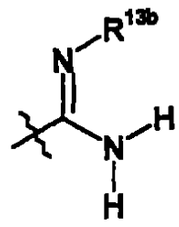
$R^{3a}$ and $R^{3b}$ both represent H;

when $X^1$ represents CH and $R^x$ represents H, then $R^y$ represents one to three substituents selected from OH, methyl, $CH_2OH$, $OCH_2C(O)N(H)R^{12b}$ and halo (particularly one to three halo atoms (e.g. one to three Cl atoms, such as two Cl atoms attached in the 2- and 5-positions relative to the point of attachment of the $(CH_2)_r$ group));

when $X^1$ represents CH and $R^x$ represents $(CH_2)_{1-2}N(H)R^{14c}$, then $R^y$ represents H or, preferably, one or two substituents selected from halo, $C_{1-2}$ alkyl and $C_{1-2}$ alkoxy (which latter two groups are optionally substituted by one or more F atoms) (and particularly $R^y$ represents one or two halo atoms (e.g. one or two Cl atoms, such as a Cl atom attached in the 3-position relative to the point of attachment of the $(CH_2)_r$ group));

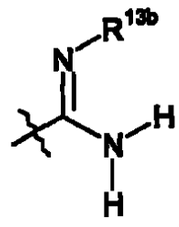
when $X^1$ represents CH and $R^x$ represents tetrazol-1-yl, then $R^y$ represents one or two halo (e.g. Cl atoms) or, preferably, H;

when $X^1$ represents CH and $R^x$ represents



then $R^y$ represents one or two F atoms or, preferably, H;

when $X^1$ represents CH, the group



if present, is attached at the 3- or, preferably, the 4-position relative to the point of attachment of the $(CH_2)_r$ group;

when $X^1$ represents CH, the group $(CH_2)_{1-2}N(H)R^{14c}$, if present, is attached at the 5-position or, preferably, the 6-position relative to the point of attachment of the $(CH_2)_r$ group;

when $X^1$ represents CH, the tetrazol-1-yl group, if present, is attached at the 5- or, preferably, the 6-position relative to the point of attachment of the $(CH_2)_r$ group;

$R^{13b}$ represents OH, $OCH_3$ or, preferably, $C(O)OCH_2$-phenyl or H;

when $X^1$ represents N and $R^x$ represents H, $R^y$ represents H or, preferably, one or two substituents selected from halo (e.g. F) and methyl;

when $X^1$ represents N and $R^x$ represents $-N(H)R^{14a}$, $R^y$ represents H or one or two methyl groups (e.g. H or methyl);

$R^{14a}$ represents $CH_2CF_3$, H, cyclopentyl or $C(O)O$-$C_4$ alkyl (e.g. one of the latter three groups, such as $C(O)O$-$C_4$ alkyl (e.g. $C(O)O$-*tert*-butyl) or, preferably, H).

Compounds of formula Ic that are more preferred still include those in which:

A represents C(O), C(O)NH (in which latter group the NH moiety is attached to $R^1$) or, particularly, $S(O)_2$ or $C_{1-3}$ (e.g. $C_{1-2}$) alkylene (which latter group is optionally gem-disubstituted by two F atoms (e.g. is unsubstituted));

$R^1$ represents

(a) $C_{1-2}$ alkyl substituted by phenyl (which latter group is optionally substituted by one or more substituents selected from F, Cl and Br), or

(b) phenyl (which latter group is optionally substituted by one or more substituents selected from F, Cl, Br, CN, $C_{1-3}$ alkyl, $C_{1-3}$ alkoxy (which latter group two groups are optionally substituted by one or more F atoms (thus forming, for example, $C_{1-2}$ alkyl, $CF_3$, $C_{1-2}$ alkoxy or $OCF_3$)), O-phenyl, O-$CH_2$-$Het^{10}$ and $Het^9$) (such as one or more substituents selected from F, Cl, Br, $C_{1-3}$ alkyl (which latter group is optionally substituted by one or more F atoms (thus forming, for example, $C_{1-2}$ alkyl or $CF_3$)) and $C_{1-3}$ alkoxy (e.g. $C_{1-2}$ alkoxy)), or

(c) naphthyl (e.g. 1-naphthyl), or

(d) pyridinyl (e.g. pyridin-2-yl or pyridin-3-yl) optionally substituted by one or two substituents selected from F, Cl, (*N*-)oxo, OH, $C_{1-4}$ alkyl (such as methyl, which $C_{1-4}$ alkyl group is optionally substituted by one or more halo atoms or by OH) or, particularly, $C_{1-4}$ alkoxy (e.g. *tert*-butoxy or methoxy) or $Het^8$, (such as pyridinyl (e.g. pyridin-3-yl) optionally substituted by one or two substituents selected from F, Cl, $C_{1-2}$ alkyl or, particularly, $C_{1-2}$ alkoxy),

(e) pyridonyl (e.g. 2-pyridon-3-yl) optionally substituted by one or two substituents selected from F, Cl, and $C_{1-4}$ alkyl (e.g. methyl);

(f) pyrazinyl (e.g. pyrazin-2-yl) optionally substituted by one or two substituents selected from F, Cl and methyl;

(g) a 5-membered aromatic heterocyclic group containing, as heteroatom(s), an oxygen or sulfur atom and/or one to three nitrogen atoms (e.g. imidazolyl, isoxazolyl, pyrazolyl, pyrrolyl, thiazolyl, or thienyl), which heterocyclic group is optionally substituted by one to four (e.g. one to three) substituents selected from F, Cl, $C_{1-4}$ alkyl (e.g. methyl or ethyl), $C_{1-4}$ alkoxy (e.g. methoxy), $S(O)_2$-phenyl, C(O)-phenyl, phenyl, morpholinyl (e.g. morpholin-4-yl), 1,3,4-triazolyl (e.g. 1,3,4-triazol-1-yl), thienyl (e.g. 2-thienyl) and pyridinyl (e.g. pyridin-2-yl),

(h) 2,3-dihydrobenzofuranyl, benzomorpholinyl, benzodioxanyl, 2,1,3-benzoxadiazolyl, or, particularly, benzodioxolyl or quinolinyl, all of which groups are optionally substituted by one or more (e.g. one to three) substituents selected from F, Cl, $C_{1-2}$ alkyl and $C_{1-2}$ alkoxy,

(i) $C_{1-4}$ alkyl (e.g. isopropyl or *tert*-butyl), or

(j) cyclopentyl, cyclohexyl or $C_7$ bicyclic cycloalkenyl (e.g. bicyclo[2.2.1]heptene, which latter three groups are optionally substituted by one to four methyl groups

(e.g. $R^1$ represents a group as defined at (a) to (d) or, particularly, (a) to (c) above);

$Het^9$ represents a 6-membered, saturated, monocyclic heterocyclic group containing, as heteroatom(s), one oxygen atom and/or one or two nitrogen atoms, which heterocyclic group may be substituted by one or two methyl substituents;

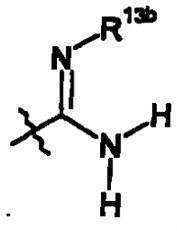
$Het^{10}$ represents a 5-membered, monocyclic, aromatic heterocyclic group containing, as heteroatom(s), one sulfur or oxygen atom and/or one or two nitrogen atoms, which heterocyclic group may be substituted by one to three substituents selected from Cl and methyl;

$Het^{c}$ represents a 6-membered, saturated, monocyclic heterocyclic group containing, as heteroatom(s), one oxygen atom and/or one or two nitrogen atoms, which heterocyclic group may be substituted by one or two methyl substituents;

$R^2$ represents methyl;

$X^1$ represents CH or N (e.g. CH);

when $X^1$ represents CH, $R^x$ represents



attached at the 4-position relative to the point of attachment of the $(CH_2)_r$ group, or $R^x$ may also represent tetrazol-1-yl or, particularly, $CH_2N(H)R^{14c}$ (which latter two groups are attached, for example, in the 6-position relative to the point of attachment of the $(CH_2)_r$ group);

$R^x$ may alternatively represent H when $X^1$ represents CH and $R^y$ represents one to three substituents selected from OH, methyl, $CH_2OH$, $OCH_2C(O)N(H)R^{12b}$ and halo;

$R^{13b}$ represents $C(O)OCH_2$-phenyl or, preferably, H;

$R^{14a}$ represents C(O)O-*tert*-butyl or, particularly, H, ethyl, $CH_2CF_3$ or cyclopentyl (e.g. H or cyclopentyl).

Other preferred compounds of formula Ia include those in which:

A represents $CH(CH_3)CH_2$ (in which latter group the $CH(CH_3)$ unit is attached to $R^1$) or, particularly, $CH_2$, $(CH_2)_2$ or $CF_2CH_2$ (in which latter group the $CF_2$ unit is attached to $R^1$);

$R^1$ represents

(a) isopropyl or *tert*-butyl,

(b) cyclopentyl, cyclohexyl or bicyclo[2.2.1]hept-5-ene,

(c) phenyl optionally substituted by one or two substituents selected from halo (e.g. F or Cl), CN, methyl, $CF_3$, methoxy, $OCF_3$, phenoxy, morpholin-4-yl or O-$CH_2$-(2-chlorothiazol-5-yl),

(d) imidazolyl optionally substituted by one to three substituents selected from Cl, methyl and phenyl,

(e) isoxazolyl (e.g. isoxazol-3-yl or isoxazol-4-yl) optionally substituted by one or two substituents selected from methyl, phenyl and 2-thienyl,

(f) thiazolyl (e.g. thiazol-5-yl) optionally substituted by one or two methyl groups,

(g) thienyl (e.g. thien-2-yl) optionally substituted by Cl or pyridinyl (e.g. pyridin-2-yl),

(h) pyrazolyl (e.g. pyrazol-4-yl) optionally substituted by one to three substituents selected from Cl, methyl, ethyl, phenyl and morpholin-4-yl,

(i) pyrrolyl (e.g. pyrrol-2-yl or pyrrol-3-yl) optionally substituted by one to three substituents selected from methyl, $S(O)_2$-phenyl, C(O)-phenyl and 1,3,4-triazol-1-yl,

(j) pyridinyl (e.g. pyridin-2yl or pyridin-3-yl) optionally substituted by OH, methoxy or morpholin-4-yl, and optionally in the form of an *N*-oxide,

(k) pyridonyl (e.g. 2-pyridon-3-yl),

(l) pyrazinyl (e.g. pyrazin-2-yl),

(m) benzodioxolyl (e.g. 5-benzodioxolyl) optionally substituted by halo (e.g. Cl),

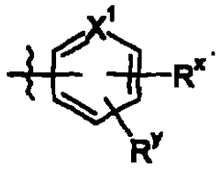
(n) benzomorpholinyl (e.g. 7-benzomorpholinyl) optionally substituted by methyl;

(o) 2,1,3-benzoxadiazolyl (e.g. 2,1,3-benzoxadiazol-5-yl),

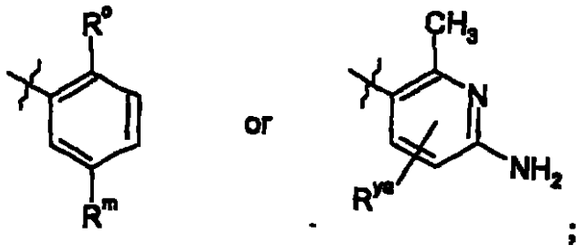
(p) 2,3-dihydrobenzofuranyl (e.g. 2,3-dihydrobenzofuran-5-yl) or

(q) quinolinyl (e.g. 8-quinolinyl);

the group



represents



;

$R^o$ represents H, F, Cl, OH, methyl or, particularly, tetrazol-1-yl, $OCH_2C(O)N(H)R^{12b}$ or $CH_2N(H)R^{14c}$;

$R^m$ represents H, methyl, $CF_3$, methoxy, F or, particularly, Cl (for example:

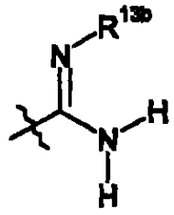
(a) when $R^o$ represents H or Cl, then $R^m$ represents Cl;

(b) when $R^o$ represents OH or methyl, then $R^m$ represents F or, particularly Cl; and

(c) when $R^o$ represents tetrazol-1-yl, $OCH_2C(O)N(H)R^{12b}$ or $CH_2N(H)R^{14c}$ then $R^m$ represents H, methyl, $CF_3$, methoxy, F or, most preferably, Cl);

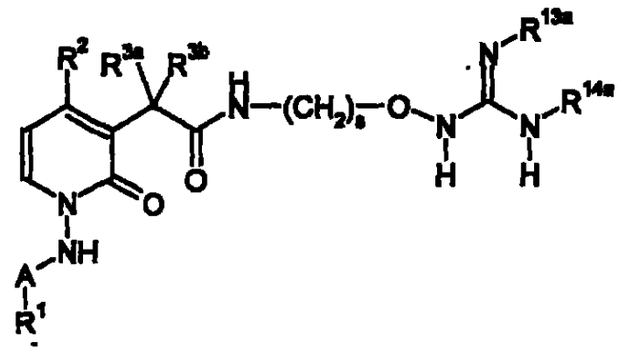
$R^{ya}$ represents H or, particularly, methyl.

In one embodiment of compounds of formula Ic that are more preferred still, $R^X$ represents

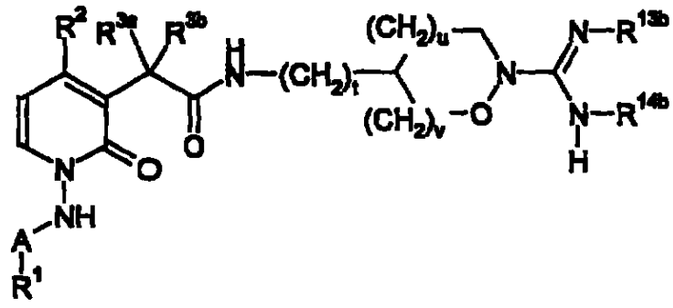


attached at the 4-position relative to the point of attachment of the $(CH_2)_r$ group.

Particularly preferred compounds of the invention are also compounds of formulae Id and Ie



Id



Ie

wherein s represents 2 to 4;

t represents 1 to 3;

u and v independently represent 0 to 2, the sum of u and v being 1 or 2; and

$R^1$, $R^2$, $R^{3a}$, $R^{3b}$, $R^{13a}$, $R^{13b}$, $R^{14a}$ and $R^{14b}$ are as defined above,

which compounds are also referred to hereinafter as "the compounds of the invention".

Preferred compounds of formula Id include those in which:
s represents 3 or, particularly, 2;
$R^{13a}$ and $R^{14a}$ both represent H.

Preferred compounds of formula Ie include those in which:
t represents 2 or, particularly, 1;
u and v both represent 1;
$R^{13b}$ and $R^{14b}$ both represent H.

For the avoidance of doubt, the preferred definitions of groups given above in relation to compounds of formula Ic, Id and Ie are also, where relevant, preferred definitions of the equivalent groups in compounds of formula I.

Preferred compounds of the invention include the compounds of the Examples disclosed hereinafter.

**Preparation**

Compounds of formula I (including compounds of formula Ic, Id and Ie) may be made in accordance with techniques well known to those skilled in the art, for example as described hereinafter.

According to a further aspect of the invention there is provided a process for the preparation of a compound of formula I, which comprises:

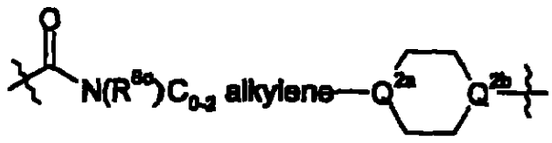
(a) for compounds of formula I in which the group G represents

(i) $C(O)N(R^{8a})$-$[CH(C(O)R^{9})]_{0-1}$-$C_{0-3}$ alkylene-$(Q^{1})_{a}$-,

(ii) $C(O)N(R^{8b})$-$C_{2-3}$ alkenylene-$(Q^1)_n$-,

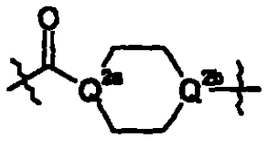
(iii) $C(O)N(R^{8b})$-$C_{2-3}$ alkynylene-$(Q^1)_n$-,

(iv)



or

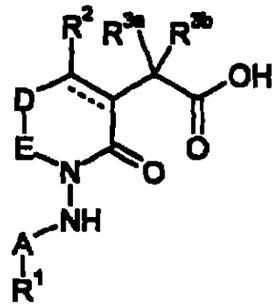
(v)



,

wherein $Q^{2a}$ represents N or NHCH,

coupling of a compound of formula II,



II

wherein the dashed line, $R^1$, $R^2$, $R^{3a}$, $R^{3b}$, A, D and E are as hereinbefore defined, with a compound of formula III,

$H\text{-}G^a\text{-}L$ III

wherein L is as hereinbefore defined and $G^a$ represents

(i) $-N(R^{8a})$-$[CH(C(O)R^9)]_{0-1}$-$C_{0-3}$ alkylene-$(Q^1)_n$-,

(ii) $-N(R^{8b})$-$C_{2-3}$ alkenylene-$(Q^1)_n$-,

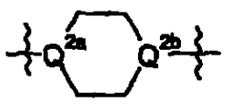
(iii) $-N(R^{8b})$-$C_{2-3}$ alkynylene-$(Q^1)_n$-,

(iv)



or

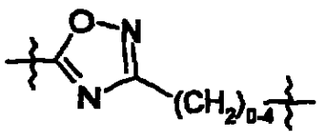
(v)



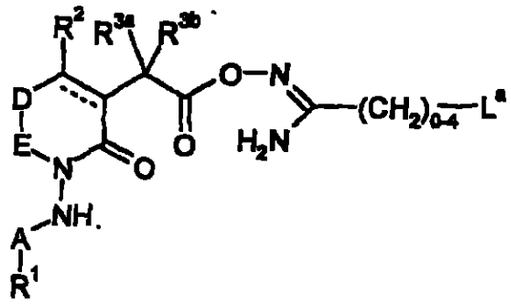
wherein $Q^{2a}$ represents N or NHCH and $R^{8a}$, $R^{8b}$, $R^{8c}$, $R^9$, $Q^1$, $Q^{2b}$ and a are as hereinbefore defined,

for example in the presence of a coupling agent (e.g. oxalyl chloride in DMF, EDC, DCC, HBTU, HATU, PyBOP or TBTU), an appropriate base (e.g. pyridine, DMAP, TEA, 2,4,6-collidine or DIPEA) and a suitable organic solvent (e.g. dichloromethane, acetonitrile, EtOAc or DMF);

(b) for compounds of formula I in which G represents



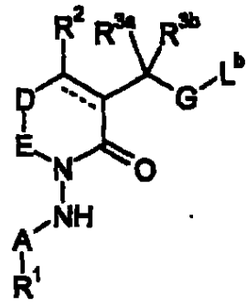
and L represents $L^a$, which latter group represents L as hereinbefore defined, except that it does not represent $C_0$ alkylene-$R^e$, cyclisation of a compound of formula IV,



IV

wherein the dashed line, $R^1$, $R^2$, $R^{3a}$, $R^{3b}$, A, D, E and $L^a$ are as hereinbefore defined, for example at elevated temperature (e.g. 60°C to reflux) in the presence of a suitable solvent (e.g. pyridine, toluene, 1,4-dioxane or THF) and optionally in the presence of a suitable catalyst (e.g. $(n\text{-Bu})_4NF$, which may particularly be employed when the reaction solvent is THF);

(c) for compounds of formula I in which $R^a$, $R^b$, $R^c$ or $R^d$ represents $-C(=NH)NH_2$, $-C(=NNH_2)NH_2$ or $-C(=NOH)NH_2$, reaction of a compound of formula V,



V

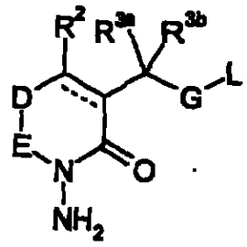
wherein $L^b$ represents L as hereinbefore defined, except that $R^a$, $R^b$, $R^c$ or $R^d$ (as appropriate) is replaced by a cyano or $-C(=NH)O-C_{1-4}$ alkyl group, and the dashed line, $R^1$, $R^2$, $R^{3a}$, $R^{3b}$, A, D, E and G are as hereinbefore defined, with a suitable source of ammonia, hydrazine or hydroxylamine (e.g. ammonia gas, ammonium acetate, hydrazine, hydrazine monohydrochloride, hydroxylamine or hydroxylamine hydrochloride) under conditions known to those skilled in the art (e.g. conditions such as those described in *Tetrahedron Lett.* 40, 7067 (1999)), for example from ambient (e.g. 15 to 25°C) to elevated temperature (e.g. 60°C to reflux) in the presence of a suitable solvent (e.g. ethanol);

(d) for compounds of formula I in which $R^{13a}$, $R^{13b}$ or $R^{13c}$ represents H, deprotection of a corresponding compound of formula I in which $R^{13a}$, $R^{13b}$ or $R^{13c}$ (as appropriate) represents $C(O)O-CH_2$aryl (e.g. C(O)O-benzyl), for example under conditions known to those skilled in the art (such as hydrogenation in the presence of an appropriate catalyst (e.g. Pt/C or, particularly, Pd/C), a suitable solvent (e.g. an alcohol such as ethanol or, particularly, methanol) and, optionally, an acid (e.g. HCl));

(e) for compounds of formula I in which $R^{14c}$ represents H, deprotection of a corresponding compound of formula I in which $R^{14c}$ represents

$C(O)O$-$C_{1-6}$ alkyl (e.g. C(O)O-*tert*-butyl), for example under conditions known to those skilled in the art (e.g. acid or base hydrolysis, such as, for deprotection of compounds in which $R^{14c}$ represents C(O)O-*tert*-butyl, reaction with HCl gas in the presence of a suitable solvent (e.g. an alcohol such as ethanol or, particularly, methanol) , or reaction with trifluoroacetic acid at sub-ambient temperature (e.g. 0 to 4°C), optionally in the presence of a suitable solvent such as DCM);

(f) reaction of a compound of formula VI,



VI

wherein the dashed line, $R^2$, $R^{3a}$, $R^{3b}$, A, D, E, G and L are as hereinbefore defined, with a compound of formula VII,

$$R^1\text{-}A\text{-}Lg^1 \qquad \text{VII}$$

wherein $Lg^1$ represents a suitable leaving group (e.g. halo, trifluoromethanesulfonate or OH) and $R^1$ and A are as hereinbefore defined, for example under conditions known to those skilled in the art (such as at sub-ambient temperature (e.g. 0°C) in the presence of an appropriate base (e.g. $K_2CO_3$ or pyridine) and a suitable solvent (e.g. DCM));

(g) for compounds of formula I in which A represents C(O)NH, reaction of a compound of formula VI, as hereinbefore defined, with a compound of formula VIII,

$$R^1\text{-}N{=}C{=}O \qquad \text{VIII}$$

wherein $R^1$ is as hereinbefore defined, for example under conditions known to those skilled in the art (such as at ambient temperature (e.g. 15 to 25°C) in the presence of a suitable solvent (e.g. DCM));

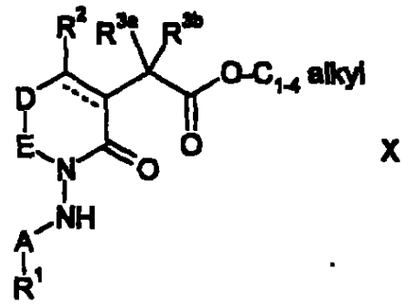
(h) for compounds of formula I in which A represents $C_{1-6}$ alkylene, reaction of a compound of formula VI, as hereinbefore defined, with a compound of formula IX,

$R^1$-$C_{0-5}$ alkylene-CHO IX

wherein $R^1$ is as hereinbefore defined, for example under conditions known to those skilled in the art (such as at reflux in the presence of a suitable solvent (e.g. ethanol), followed by reduction in the presence of a reducing agent (e.g. $NaBH_3CN$), for example under conditions known to those skilled in the art (e.g. at ambient temperature (such as 15 to 25°C) in the presence of a suitable solvent (such as ethanol); or

(i) for compounds of formula I in which $R^a$, $R^b$, $R^c$ or $R^d$ represents $-C(=NCN)NH_2$, reaction of a corresponding compound of formula I in which $R^a$, $R^b$, $R^c$ or $R^d$, respectively, represents $-C(=NH)NH_2$ with cyanogen bromide, for example under conditions known to those skilled in the art (e.g. in the presence of a suitable base (such as an alkali metal alkoxide like sodium ethoxide) and an appropriate solvent (such as a lower alkyl alcohol like ethanol).

Compounds of formula II may be prepared by hydrolysis of a compound of formula X,

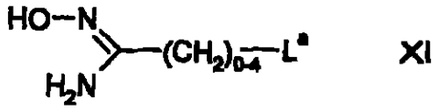



X

wherein the dashed line, $R^1$, $R^2$, $R^{3a}$, $R^{3b}$, A, D and E are as hereinbefore defined, for example under conditions known to those skilled in the art (e.g. by basic hydrolysis in the presence of an alkali metal hydroxide (e.g. LiOH

or, particularly, NaOH) and a suitable solvent (e.g. water, THF, methanol or a mixture thereof)).

Compounds of formula IV may be prepared by the coupling of a compound of formula II, as hereinbefore defined, with a compound of formula XI,

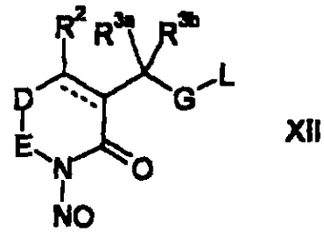


XI

wherein $L^a$ is as hereinbefore defined, for example under conditions well know to those skilled in the art (e.g. those described in WO 01/79262, such as at ambient temperature (e.g. 15 to 25°C) in the presence of a coupling agent (e.g. EDC) and a suitable solvent (e.g. DMF)).

As the skilled person will appreciate, in some instances, compounds of formula V are identical to certain compounds of formula I (e.g. compounds in which $R^b$, $R^c$ or $R^d$ represents H and $R^{11a}$, $R^{11b}$ or $R^{11c}$, respectively, represents CN). In this respect, compounds of formula V may be prepared by analogy with the procedures described herein for the preparation of compounds of formula I.

Compounds of formula VI may be prepared by reduction of a compound of formula XII,

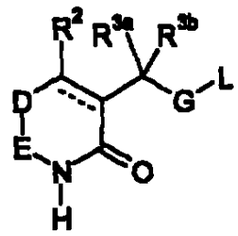


XII

wherein the dashed line, $R^2$, $R^{3a}$, $R^{3b}$, D, E, G and L are as hereinbefore defined, for example under conditions that are well known to those skilled in the art (such as by reaction with zinc metal (e.g. zinc powder or iron

metal powder) in the presence of an appropriate acid (e.g. acetic acid or hydrochloric acid) and optionally in the presence of a suitable solvent (e.g. methanol)).

Compounds of formula VI may alternatively be prepared by reaction of a compound of formula XIII,



XIII

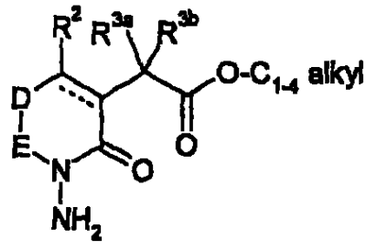
wherein the dashed line, $R^2$, $R^{3a}$, $R^{3b}$, D, E, G and L are as hereinbefore defined, with *O*-(diphenylphosphinyl)hydroxylamine, for example under conditions known to those skilled in the art (e.g. at ambient temperature (such as 15 to 25°C) in the presence of an appropriate base (such as $Cs_2CO_3$) and a suitable solvent (such as DMF)).

Compounds of formula IX may be prepared by oxidation of an alcohol of formula XIV,

$$R^1\text{-}C_{0\text{-}5}\text{ alkylene-}CH_2OH \qquad \text{XIV}$$

wherein $R^1$ is as hereinbefore defined, for example under conditions known to those skilled in the art, such as reaction with PCC, oxalyl chloride and DMSO (Swern oxidation) or, particularly, Dess-Martin periodinane in the presence of a suitable solvent (such as DCM).

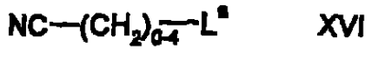
Compounds of formula X may be prepared by reaction of a compound of formula XV,



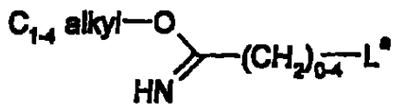
XV

wherein the dashed line, $R^2$, $R^{3a}$, $R^{3b}$, D and E are as hereinbefore defined, with a compound of formula VII, VIII or IX as hereinbefore defined, for example under conditions known to those skilled in the art (e.g. conditions described at process steps (f), (g) and (h) above in respect of compounds of formula I).

Compounds of formula XI may be prepared by methods well known to those skilled in the art. For example, compounds of formula XI may be prepared by reaction of a compound of formula XVI or XVII,



XVI



XVII

wherein $L^a$ is as hereinbefore defined, with hydroxylamine or an acid addition salt thereof, for example under conditions described at process step (c) above in respect of compounds of formula I.

Compounds of formula XII may be prepared by analogy with compounds of formulae I and XIX.

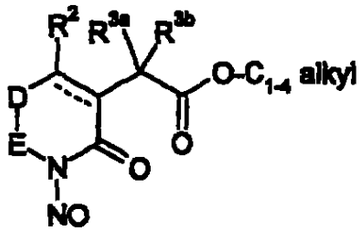
Compounds of formula XIII may be prepared by analogy with compounds of formulae I and XX.

Compounds of formula XIV may be prepared by reduction of a carboxylic acid of formula XVIII,

$R^1$-$C_{0-5}$ alkylene-C(O)OH XVIII

wherein $R^1$ is as hereinbefore defined, for example under conditions known to those skilled in the art, such as reaction with $LiAlH_4$ or, particularly, borane in the presence of a suitable solvent (such as THF).

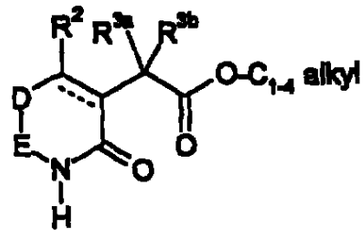
Compounds of formula XV may be prepared by reduction of a compound of formula XIX,



XIX

wherein the dashed line, $R^2$, $R^{3a}$, $R^{3b}$, D and E are as hereinbefore defined, for example under conditions described hereinbefore in respect of the preparation of compounds of formula VI.

Compounds of formula XV may alternatively be prepared by reaction of a compound of formula XX,

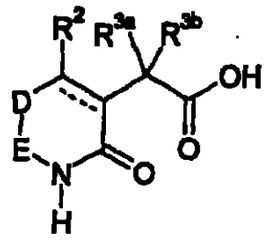


XX

wherein the dashed line, $R^2$, $R^{3a}$, $R^{3b}$, D and E are as hereinbefore defined, with *O*-(diphenylphosphinyl)hydroxylamine, for example under conditions described hereinbefore in respect of the preparation of compounds of formula VI.

Compounds of formula XIX may be prepared by nitrosation of a corresponding compound of formula XX, as hereinbefore defined, for example under conditions well known to those skilled in the art, e.g. reaction at with a nitrosating agent (such as nitrous acid, NOCl, $N_2O_3$, $N_2O_4$ or, particularly, a $C_{1-6}$ alkyl nitrite (e.g. *tert*-butyl nitrite)) in the presence of a suitable solvent (e.g. diethyl ether) and optionally in the presence of an appropriate base (e.g. pyridine).

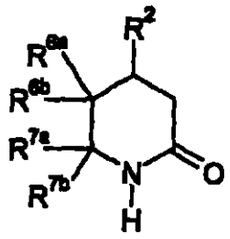
Compounds of formula XX may be prepared by esterification of a compound of formula XXI,



XXI

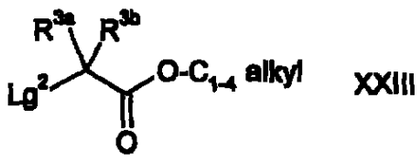
wherein $R^2$, $R^{3a}$, $R^{3b}$, D and E are as hereinbefore defined, in the presence of a $C_{1-4}$ alkyl alcohol, for example under conditions known to those skilled in the art (e.g. by esterification in the presence of an appropriate acid (e.g. HCl) and a suitable solvent (e.g. a $C_{1-4}$ alkyl alcohol (such as methanol), water, or a mixture thereof)).

Compounds of formula XX in which the dashed line is absent may alternatively be prepared by reaction of a compound of formula XXII,



XXII

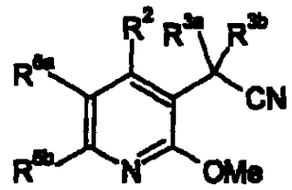
or a protected derivative thereof, wherein $R^2$, $R^{6a}$, $R^{6b}$, $R^{7a}$ and $R^{7b}$ are as hereinbefore defined, with a compound of formula XXIII,



XXIII

wherein $Lg^2$ represents a suitable leaving group (e.g. halo or $OS(O)_2R'$, wherein R' represents, for example, $C_{1-4}$ alkyl, $C_{1-4}$ perfluoroalkyl, phenyl, toluyl or benzyl) and $R^{3a}$ and $R^{3b}$ are as hereinbefore defined, in the presence of an appropriate base (e.g. a metal hydride or, particularly, a metal amide (such as lithium bis(trimethylsilyl)amide)), for example under conditions known to those skilled in the art (e.g. at low temperature (such as -78 to -10°C)) in the presence of a suitable solvent (such as THF)).

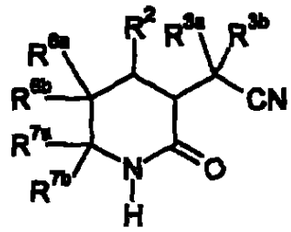
Compounds of formula XXI in which the dashed line represents a bond may be prepared by hydrolysis of a compound of formula XXIV,



XXIV

wherein $R^2$, $R^{3a}$, $R^{3b}$, $R^{5a}$ and $R^{5b}$ are as hereinbefore defined, for example under conditions known to those skilled in the art (e.g. by refluxing in concentrated HBr).

Compounds of formula XXI in which the dashed line is absent may be prepared by hydrolysis of a compound of formula XXV

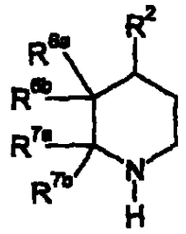


XXV

wherein $R^2$, $R^{3a}$, $R^{3b}$, $R^{6a}$, $R^{6b}$, $R^{7a}$ and $R^{7b}$ are as hereinbefore defined, for example under conditions known to those skilled in the art (e.g. those

mentioned above in relation to compounds of formula XXI in which the dashed line represents a bond).

Compounds of formula XXII may be prepared by oxidation of a compound of formula XXVI,



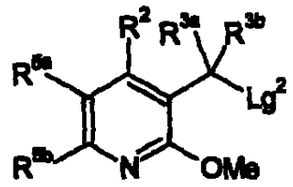
XXVI

or a protected derivative thereof, wherein $R^2$, $R^{6a}$, $R^{6b}$, $R^{7a}$ and $R^{7b}$ are as hereinbefore defined, with a suitable oxidising agent (e.g. $H_2O_2$, $(PhIO)_n$, $Hg(OAc)_2$ or, particularly, $RuO_4$, which latter reagent may be formed *in situ* by oxidation of $RuO_2$ (e.g. by an excess of $NaIO_4$)), for example under conditions known to those skilled in the art (e.g. at ambient temperature (such as 15 to 25°C) in the presence of a suitable solvent (such as ethyl acetate, water or a mixture thereof)).

As the skilled person will appreciate, the conversion of compounds of formula XXVI to corresponding compounds of formula XX may require, at any or all of the reaction steps, protection of the N-H group of the piperidone ring system. Suitable protective groups for this purpose include benzyloxycarbonyl and, particularly, *tert*-butyloxycarbonyl. The protective group may be introduced and removed under conditions that are well known to those skilled in the art. The protective group may be conveniently introduced before the compound of formula XXVI is converted to the compound of XXII (e.g. by reaction, under conditions that are well known to those skilled in the art, of a compound of XXVI with di-*tert*-butyldicarbonate). Further, the protective group may be conveniently removed, again under conditions that are well known to those skilled in the

art (e.g. by reaction with trifluoroacetic acid), once the compound of formula XX has been formed.

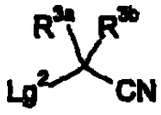
Compounds of formula XXIV may be prepared by reaction of a compound of formula XXVII,



XXVII

wherein $R^2$, $R^{3a}$, $R^{3b}$, $R^{5a}$, $R^{5b}$ and $Lg^2$ are as hereinbefore defined, with a suitable source of the cyanide ion (e.g. KCN), for example under conditions that are known to those skilled in the art (e.g. at ambient temperature (such as 15 to 25°C) in the presence of a suitable solvent (such as methanol)).

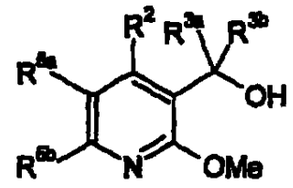
Compounds of formula XXV may be prepared by reaction of a compound of formula XXII, as hereinbefore defined, with a compound of formula XXVIII,



XXVIII

wherein $R^{3a}$, $R^{3b}$ and $Lg^2$ are as hereinbefore defined, for example under conditions know to those skilled in the art (e.g. the conditions described above in respect of the preparation of compounds of formula XX).

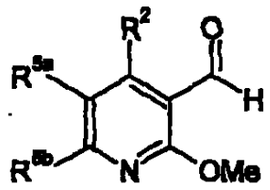
Compounds of formula XXVII in which $Lg^2$ represents halo may be prepared by halogenation of a compound of formula XXIX,



XXIX

wherein $R^2$, $R^{3a}$, $R^{3b}$, $R^{5a}$ and $R^{5b}$ are as hereinbefore defined, for example under conditions that are known to those skilled in the art (e.g. by reaction with triphenylphosphine and an *N*-halosuccinimide (such as NBS) in the presence of a suitable solvent (such as DCM)).

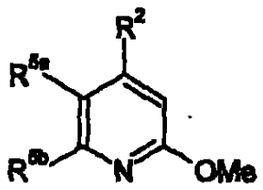
Compounds of formula XXIX in which $R^{3a}$ and $R^{3b}$ both represent H may be prepared by reduction of a corresponding compound of formula XXX,



XXX

wherein $R^2$, $R^{5a}$ and $R^{5b}$ are as hereinbefore defined, for example under conditions that are known to those skilled in the art (e.g. by reaction with sodium borohydride in the presence of a suitable solvent (such as methanol, THF or a mixture thereof)).

Compounds of formula XXX may be prepared by formylation of a corresponding compound of formula XXXI,



XXXI

wherein $R^2$, $R^{5a}$ and $R^{5b}$ are as hereinbefore defined, for example under conditions that are known to those skilled in the art (e.g. by reaction with a suitable source of the formyl group (such as DMF) in the presence of an appropriate base (such as *tert*-butyllithium or mesityllithium (which latter reagent may be formed *in situ* by reaction between *tert*-butyllithium and bromomesitylene)).

Compounds of formulae III, VII, VIII, XVI, XVII, XVIII, XXIII, XXVI, XXVIII and XXX are either commercially available, are known in the literature, or may be obtained by analogy with the processes described herein, or by conventional synthetic procedures, in accordance with standard techniques, from readily available starting materials using appropriate reagents and reaction conditions. In this respect, compounds described herein may also be obtained by analogy with synthetic procedures described in the prior art documents mentioned above (and WO 94/20467, WO 94/29336, WO 95/23609, WO 96/06832, WO 96/06849, WO 97/11693, WO 97/24135, WO 98/01422, WO 01/68605, WO 99/26920, WO 01/79155, WO 01/68605, WO 96/18644, WO 97/01338, WO 97/30708, WO 98/16547, WO 99/26926, WO 00/73302, WO 01/04117, WO 01/79262, WO 02/064140, WO 02/057225, WO 03/29224, US 5,668,289, US 5,792,779 and WO 95/35313 in particular).

Substituents on alkyl, alkenyl, cycloalkyl, cycloalkenyl, aryl and heterocyclic groups in compounds of formulae I, II, IV, V, VI, X, XII, XIII, XV, XIX, XX, XXI, XXII, XXIV, XXV, XXVI, XXVII, XXIX, XXX and XXXI may be introduced and/or interconverted using techniques well known to those skilled in the art by way of standard functional groups interconversions, in accordance with standard techniques, from readily available starting materials using appropriate reagents and reaction conditions. For example, hydroxy may be converted to alkoxy, phenyl may be halogenated to give halophenyl, halo may be displaced by cyano, etc.

The skilled person will also appreciate that various standard substituent or functional group interconversions and transformations within certain compounds of formula I will provide other compounds of formula I. For example, hydroxyamidino may be reduced to amidino.

Compounds of formula I may be isolated from their reaction mixtures using conventional techniques.

In accordance with the present invention, pharmaceutically acceptable derivatives of compounds of formula I also include "protected" derivatives, and/or compounds that act as prodrugs, of compounds of formula I.

Compounds that may act as prodrugs of compounds of formula I that may be mentioned include compounds of formula I in which $R^{13a}$, $R^{13b}$ or $R^{13c}$ is other than H or $R^{14c}$ represents C(O)O-$C_{1-6}$ alkyl, the alkyl part of which group is optionally substituted by aryl and/or one or more halo atoms (e.g. compounds in which $R^{14c}$ represents C(O)O-*tert*-butyl).

The compounds of the invention may exhibit tautomerism. All tautomeric forms and mixtures thereof are included within the scope of the invention. Particular tautomeric forms that may be mentioned include those connected with the position of the double bond in the amidine or guanidine functionalities that the groups $R^a$ to $R^d$ may represent.

Compounds of the invention may also contain one or more asymmetric carbon atoms and may therefore exhibit optical and/or diastereoisomerism. Diastereoisomers may be separated using conventional techniques, e.g. chromatography. The various stereoisomers may be isolated by separation of a racemic or other mixture of the compounds using conventional, e.g. HPLC techniques. Alternatively the desired optical isomers may be made by reaction of the appropriate optically active starting materials under conditions which will not cause racemisation or epimerisation, or by derivatisation, for example with a homochiral acid followed by separation of the diastereomeric derivatives by conventional means (e.g. HPLC,

chromatography over silica). All stereoisomers are included within the scope of the invention.

It will be appreciated by those skilled in the art that in the processes described above and hereinafter the functional groups of intermediate compounds may need to be protected by protecting groups.

Functional groups that it is desirable to protect include hydroxy, amino and carboxylic acid. Suitable protecting groups for hydroxy include optionally substituted and/or unsaturated alkyl groups (e.g. methyl, allyl, benzyl or *tert*-butyl), trialkylsilyl or diarylalkylsilyl groups (e.g. *t*-butyldimethylsilyl, *t*-butyldiphenylsilyl or trimethylsilyl) and tetrahydropyranyl. Suitable protecting groups for carboxylic acid include $C_{1-6}$ alkyl or benzyl esters. Suitable protecting groups for amino and amidino include *t*-butyloxycarbonyl, benzyloxycarbonyl or 2-trimethylsilylethoxycarbonyl (Teoc). Amidino nitrogens may also be protected by hydroxy or alkoxy groups, and may be either mono- or diprotected.

The protection and deprotection of functional groups may take place before or after coupling, or before or after any other reaction in the above-mentioned schemes.

Protecting groups may be removed in accordance with techniques that are well known to those skilled in the art and as described hereinafter.

Persons skilled in the art will appreciate that, in order to obtain compounds of the invention in an alternative, and, on some occasions, more convenient, manner, the individual process steps mentioned hereinbefore may be performed in a different order, and/or the individual reactions may be performed at a different stage in the overall route (i.e. substituents may be

added to and/or chemical transformations performed upon, different intermediates to those mentioned hereinbefore in conjunction with a particular reaction). This may negate, or render necessary, the need for protecting groups.

The type of chemistry involved will dictate the need, and type, of protecting groups as well as the sequence for accomplishing the synthesis.

The use of protecting groups is fully described in "Protective Groups in Organic Chemistry", edited by J W F McOmie, Plenum Press (1973), and "Protective Groups in Organic Synthesis", 3rd edition, T.W. Greene & P.G.M. Wutz, Wiley-Interscience (1999).

Protected derivatives of compounds of the invention may be converted chemically to compounds of the invention using standard deprotection techniques (e.g. hydrogenation). The skilled person will also appreciate that certain compounds of formula I (e.g. compounds in which $R^{13a}$, $R^{13b}$ or $R^{13c}$ is other than H) may also be referred to as being "protected derivatives" of other compounds of formula I (e.g. those in which $R^{13a}$, $R^{13b}$ or $R^{13c}$ represents H).

Those skilled in the art will also appreciate that certain compounds of formula I will be useful as intermediates in the synthesis of certain other compounds of formula I.

Some of the intermediates referred to hereinbefore are novel. According to a further aspect of the invention there is thus provided: (a) a compound of formula II, or a protected derivative thereof; (b) a compound of formula IV, or a protected derivative thereof; (c) a compound of formula V, or a protected derivative thereof; (d) a compound of formula VI, or a protected derivative

thereof; (e) a compound of formula X, or a protected derivative thereof; (f) a compound of formula XII, or a protected derivative thereof; (g) a compound of formula XV, or a protected derivative thereof; and (h) a compound of formula XIX, or a protected derivative thereof.

**Medical and pharmaceutical use**

Compounds of the invention may possess pharmacological activity as such. However, other compounds of the invention (including compounds of formula I in which $R^{13a}$, $R^{13b}$ or $R^{13c}$ is other than H or $R^{14c}$ represents C(O)O-*tert*-butyl) may not possess such activity, but may be administered parenterally or orally, and may thereafter be metabolised in the body to form compounds that are pharmacologically active (including, but not limited to, corresponding compounds of formula I in which $R^{13a}$, $R^{13b}$, $R^{13c}$ or $R^{14c}$ represents H). Such compounds (which also includes compounds that may possess some pharmacological activity, but that activity is appreciably lower than that of the "active" compounds to which they are metabolised), may therefore be described as "prodrugs" of the active compounds.

Thus, the compounds of the invention are useful because they possess pharmacological activity, and/or are metabolised in the body following oral or parenteral administration to form compounds which possess pharmacological activity. The compounds of the invention are therefore indicated as pharmaceuticals.

According to a further aspect of the invention there is thus provided the compounds of the invention for use as pharmaceuticals.

In particular, compounds of the invention are potent inhibitors of thrombin either as such and/or (e.g. in the case of prodrugs), are metabolised

following administration to form potent inhibitors of thrombin, for example as may be demonstrated in the tests described below.

By "prodrug of a thrombin inhibitor", we include compounds that form a thrombin inhibitor, in an experimentally-detectable amount, and within a predetermined time (e.g. about 1 hour), following oral or parenteral administration (see, for example, Test E below) or, alternatively, following incubation in the presence of liver microsomes (see, for example, Test F below).

The compounds of the invention are thus expected to be useful in those conditions where inhibition of thrombin is beneficial (as determined by reference to a clinically relevant end-point, e.g. conditions, such as thrombo-embolisms, where inhibition of thrombin is required or desired, and/or conditions where anticoagulant therapy is indicated), including the following:

The treatment and/or prophylaxis of thrombosis and hypercoagulability in blood and/or tissues of animals including man. It is known that hypercoagulability may lead to thrombo-embolic diseases. Conditions associated with hypercoagulability and thrombo-embolic diseases are usually designated as thrombophilia conditions. These conditions include, but are not limited to, inherited or acquired activated protein C resistance, such as the factor V-mutation (factor V Leiden), inherited or acquired deficiencies in antithrombin III, protein C, protein S, heparin cofactor II, and conditions with increased plasma levels of the coagulation factors such as caused by the prothrombin G20210A mutation. Other conditions known to be associated with hypercoagulability and thrombo-embolic disease include circulating antiphospholipid antibodies (Lupus anticoagulant), homocysteinemi, heparin induced thrombocytopenia and defects in

fibrinolysis, as well as coagulation syndromes (e.g. disseminated intravascular coagulation (DIC)) and vascular injury in general (e.g. due to trauma or surgery). Furthermore, low physical activity, low cardiac output or high age are known to increase the risk of thrombosis and hypercoagulability may be just one of several factors underlying the increased risk. These conditions include, but are not limited to, prolonged bed rest, prolonged air travelling, hospitalisation for an acute medical disorder such as cardiac insufficiency or respiratory insufficiency. Further conditions with increased risk of thrombosis with hypercoagulability as one component are pregnancy and hormone treatment (e.g. oestrogen).

The treatment of conditions where there is an undesirable excess of thrombin without signs of hypercoagulability, for example in neurodegenerative diseases such as Alzheimer's disease.

Particular disease states which may be mentioned include the therapeutic and/or prophylactic treatment of venous thrombosis (e.g. deep venous thrombosis, DVT) and pulmonary embolism, arterial thrombosis (e.g. in myocardial infarction, unstable angina, thrombosis-based stroke and peripheral arterial thrombosis), and systemic embolism usually from the atrium during atrial fibrillation (e.g. non-valvular or valvular atrial fibrillation) or from the left ventricle after transmural myocardial infarction, or caused by congestive heart failure; prophylaxis of re-occlusion (i.e. thrombosis) after thrombolysis, percutaneous trans-luminal angioplasty (PTA) and coronary bypass operations; the prevention of thrombosis after microsurgery and vascular surgery in general.

Further indications include the therapeutic and/or prophylactic treatment of disseminated intravascular coagulation caused by bacteria, multiple trauma, intoxication or any other mechanism; anticoagulant treatment when blood is

in contact with foreign surfaces in the body such as vascular grafts, vascular stents, vascular catheters, mechanical and biological prosthetic valves or any other medical device; and anticoagulant treatment when blood is in contact with medical devices outside the body such as during cardiovascular surgery using a heart-lung machine or in haemodialysis; the therapeutic and/or prophylactic treatment of idiopathic and adult respiratory distress syndrome, pulmonary fibrosis following treatment with radiation or chemotherapy, chronic obstructive lung disease, septic shock, septicemia, inflammatory responses, which include, but are not limited to, edema, acute or chronic atherosclerosis such as coronary arterial disease and the formation of atherosclerotic plaques, cardiac insufficiency, cerebral arterial disease, cerebral infarction, cerebral thrombosis, cerebral embolism, peripheral arterial disease, ischaemia, angina (including unstable angina), reperfusion damage, restenosis after percutaneous trans-luminal angioplasty (PTA) and coronary artery bypass surgery.

Compounds of the invention that inhibit trypsin and/or thrombin may also be useful in the treatment of pancreatitis.

The compounds of the invention are thus indicated both in the therapeutic and/or prophylactic treatment of these conditions.

According to a further aspect of the present invention, there is provided a method of treatment of a condition where inhibition of thrombin is required which method comprises administration of a therapeutically effective amount of a compound of the invention to a person suffering from, or susceptible to, such a condition.

The compounds of the invention will normally be administered orally, intravenously, subcutaneously, buccally, rectally, dermally, nasally,

tracheally, bronchially, by any other parenteral route or *via* inhalation, in the form of pharmaceutical preparations comprising compound of the invention either as a free base, or a pharmaceutically acceptable non-toxic organic or inorganic acid addition salt, in a pharmaceutically acceptable dosage form.

Preferred route of administration of compounds of the invention are oral.

Depending upon the disorder and patient to be treated and the route of administration, the compositions may be administered at varying doses.

The compounds of the invention may also be combined and/or co-administered with any antithrombotic agent(s) with a different mechanism of action, such as one or more of the following: the anticoagulants unfractionated heparin, low molecular weight heparin, other heparin derivatives, synthetic heparin derivatives (e.g. fondaparinux), vitamin K antagonists, synthetic or biotechnological inhibitors of other coagulation factors than thrombin (e.g. synthetic FXa, FVIIa and FIXa inhibitors, and rNAPc2), the antiplatelet agents acetylsalicylic acid, ticlopidine and clopidogrel; thromboxane receptor and/or synthetase inhibitors; fibrinogen receptor antagonists; prostacyclin mimetics; phosphodiesterase inhibitors; ADP-receptor ($P2X_1$, $P2Y_1$, $P2Y_{12}$ [$P_2T$]) antagonists; and inhibitors of carboxypeptidase U (CPU or TAFIa) and inhibitors of plasminogen activator inhibitor-1 (PAI-1).

The compounds of the invention may further be combined and/or co-administered with thrombolytics such as one or more of tissue plasminogen activator (natural, recombinant or modified), streptokinase, urokinase, prourokinase, anisoylated plasminogen-streptokinase activator complex

(APSAC), animal salivary gland plasminogen activators, and the like, in the treatment of thrombotic diseases, in particular myocardial infarction.

According to a further aspect of the invention there is thus provided a pharmaceutical formulation including a compound of the invention, in admixture with a pharmaceutically acceptable adjuvant, diluent or carrier.

Suitable daily doses of the compounds of the invention in therapeutic treatment of humans are about 0.001-100 mg/kg body weight at peroral administration and 0.001-50 mg/kg body weight at parenteral administration.

For the avoidance of doubt, as used herein, the term "treatment" includes therapeutic and/or prophylactic treatment.

Compounds of the invention have the advantage that they may be more efficacious, be less toxic, be longer acting, have a broader range of activity, be more selective (e.g. for inhibiting thrombin over other serine proteases, in particular trypsin and those involved in haemostasis), be more potent, produce fewer side effects, be more easily absorbed, and/or have a better pharmacokinetic profile (e.g. higher oral bioavailability and/or lower clearance), than, and/or have other useful pharmacological, physical, or chemical, properties over, compounds known in the prior art.

**Biological Tests**

The following test procedures may be employed.

Test A

Determination of Thrombin Clotting Time (TT)

The inhibitor solution (25 µL) is incubated with plasma (25 µL) for three minutes. Human thrombin (T 6769; Sigma Chem. Co or Hematologic Technologies) in buffer solution, pH 7.4 (25 µL, 4.0 NIH units/mL), is then added and the clotting time measured in an automatic device (KC 10; Amelung).

The thrombin clotting time (TT) is expressed as absolute values (seconds) as well as the ratio of TT without inhibitor ($TT_0$) to TT with inhibitor ($TT_i$). The latter ratios (range 1-0) are plotted against the concentration of inhibitor (log transformed) and fitted to sigmoidal dose-response curves according to the equation

$$y = a/[1+(x/IC_{50})^s]$$

where: a = maximum range, i.e. 1; s = slope of the dose-response curve; and $IC_{50}$ = the concentration of inhibitor that doubles the clotting time. The calculations are processed on a PC using the software program GraFit Version 3, setting equation equal to: Start at 0, define end = 1 (Erithacus Software, Robin Leatherbarrow, Imperial College of Science, London, UK).

Test B

Determination of Thrombin Inhibition with a Chromogenic, Robotic Assay

The thrombin inhibitor potency is measured with a chromogenic substrate method, in a Plato 3300 robotic microplate processor (Rosys AG, CH-8634 Hombrechtikon, Switzerland), using 96-well, half volume microtitre plates (Costar, Cambridge, MA, USA; Cat No 3690). Stock solutions of test substance in DMSO (72 µL), 0.1 - 1 mmol/L, are diluted serially 1:3 (24 + 48 µL) with DMSO to obtain ten different concentrations, which are analysed as samples in the assay. 2 µL of test sample is diluted with 124 µL assay buffer, 12 µL of chromogenic substrate solution (S-2366,

Chromogenix, Mölndal, Sweden) in assay buffer and finally 12 µL of α-thrombin solution (Human α-thrombin, Sigma Chemical Co. or Hematologic Technologies) in assay buffer, are added, and the samples mixed. The final assay concentrations are: test substance 0.00068 - 133 µmol/L, S-2366 0.30 mmol/L, α-thrombin 0.020 NIHU/mL. The linear absorbance increment during 40 minutes incubation at 37°C is used for calculation of percentage inhibition for the test samples, as compared to blanks without inhibitor. The $IC_{50}$-robotic value, corresponding to the inhibitor concentration which causes 50% inhibition of the thrombin activity, is calculated from a log concentration vs. % inhibition curve.

Test C

Determination of the Inhibition Constant $K_i$ for Human Thrombin

$K_i$-determinations are made using a chromogenic substrate method, performed at 37°C on a Cobas Bio centrifugal analyser (Roche, Basel, Switzerland). Residual enzyme activity after incubation of human α-thrombin with various concentrations of test compound is determined at three different substrate concentrations, and is measured as the change in optical absorbance at 405 nm.

Test compound solutions (100 µL; normally in buffer or saline containing BSA 10 g/L) are mixed with 200 µL of human α-thrombin (Sigma Chemical Co) in assay buffer (0.05 mol/L Tris-HCl pH 7.4, ionic strength 0.15 adjusted with NaCl) containing BSA (10 g/L), and analysed as samples in the Cobas Bio. A 60 µL sample, together with 20 µL of water, is added to 320 µL of the substrate S-2238 (Chromogenix AB, Mölndal, Sweden) in assay buffer, and the absorbance change (ΔA/min) is monitored. The final concentrations of S-2238 are 16, 24 and 50 µmol/L and of thrombin 0.125 NIH U/mL.

The steady state reaction rate is used to construct Dixon plots, i.e. diagrams of inhibitor concentration vs. 1/(ΔA/min). For reversible, competitive inhibitors, the data points for the different substrate concentrations typically form straight lines which intercept at $x = -K_i$.

Test D

Determination of Activated Partial Thromboplastin Time (APTT)

APTT is determined in pooled normal human citrated plasma with the reagent PTT Automated 5 manufactured by Stago. The inhibitors are added to the plasma (10 µL inhibitor solution to 90 µL plasma) and incubated with the APTT reagent for 3 minutes followed by the addition of 100 µL of calcium chloride solution (0.025 M) and APTT is determined by use of the coagulation analyser KC10 (Amelung) according to the instructions of the reagent producer.

The clotting time is expressed as absolute values (seconds) as well as the ratio of APTT without inhibitor ($APTT_0$) to APTT with inhibitor ($APTT_i$). The latter ratios (range 1-0) are plotted against the concentration of inhibitor (log transformed) and fitted to sigmoidal dose-response curves according to the equation

$$y = a/[1+(x/IC_{50})^s]$$

where: a = maximum range, i.e. 1; s = slope of the dose-response curve; and $IC_{50}$ = the concentration of inhibitor that doubles the clotting time. The calculations are processed on a PC using the software program GraFit Version 3, setting equation equal to: Start at 0, define end = 1 (Erithacus Software, Robin Leatherbarrow, Imperial College of Science, London, UK). $IC_{50}$APTT is defined as the concentration of inhibitor in human plasma that doubled the Activated Partial Thromboplastin Time.

Test E

Determination of Plasma Clearance and Oral Bioavailability in Rat

Plasma clearance and oral bioavailability are estimated in female Sprague Dawley rats. The compound is dissolved in water or another appropriate vehicle. For determination of plasma clearance the compound is administered as a subcutaneous (sc) or an intravenous (iv) bolus injection at a dose of 1-4 μmol/kg. Blood samples are collected at frequent intervals up to 24 hours after drug administration. For bioavailability estimates, the compound is administered orally at 10 μmol/kg via gavage and blood samples are collected frequently up to 24 hours after dosing. The blood samples are collected in heparinized tubes and centrifuged within 30 minutes, in order to separate the plasma from the blood cells. The plasma is transferred to plastic vials with screw caps and stored at -20°C until analysis. Prior to the analysis, the plasma is thawed and 50 μL of plasma samples are precipitated with 150 μL of cold acetonitrile. The samples are centrifuged for 20 minutes at 4000 rpm. 75 μL of the supernatant is diluted with 75 μL of 0.2% formic acid. 10 μL volumes of the resulting solutions are analysed by LC-MS/MS and the concentrations of thrombin inhibitor are determined using standard curves. All pharmacokinetic calculations are performed with the computer program WinNonlinTMProfessional (Pharsight Corporation, California, USA), or an equivalent program. Area under the plasma concentration-time profiles (AUC) is estimated using the log/linear trapezoidal rule and extrapolated to infinite time. Plasma clearance (CL) of the compound is then determined as

$$CL=Dose(iv/sc)/AUC(iv/sc).$$

The oral bioavailability is calculated as

$$F= CL \times AUC(po)/Dose(po).$$

Plasma clearance is reported as mL/min/kg and oral bioavailability as percentage (%).

Test F

Determination of *in vitro* Stability

Liver microsomes are prepared from Sprague-Dawley rats and human liver samples according to internal SOPs. The compounds are incubated at 37°C at a total microsome protein concentration of 0.5 mg/mL in a 0.1 mol/L potassium phosphate buffer at pH 7.4, in the presence of the cofactor, NADPH (1.0 mmol/L). The initial concentration of compound is 1.0 µmol/L. Samples are taken for analysis at 5 time points, 0, 7, 15, 20 and 30 minutes after the start of the incubation. The enzymatic activity in the collected sample is immediately stopped by adding an equal volume of acetonitrile containing 0.8% formic acid. The concentration of compound remaining in each of the collected samples is determined by means of LC-MS/MS. The elimination rate constant (k) of the thrombin inhibitor is calculated as the slope of the plot of ln[Thrombin inhibitor] against incubation time (minutes). The elimination rate constant is then used to calculate the half-life ($T_{1/2}$) of the thrombin inhibitor, which is subsequently used to calculate the intrinsic clearance (CLint) of the thrombin inhibitor in liver microsomes as:

$$\text{CLint (in µl/min/mg)} = \frac{(\ln 2 \times \text{incubation volume})}{(T_{1/2} \times \text{protein concentration})}$$

Test G

Venous Thrombosis Model

The thrombogenic stimuli are vessel damage and blood flow stasis. Rats are anaesthetised and the abdomen is opened. A partial occlusion on the caval vein, caudal to the left kidney-vein, is obtained with a snare around the vein and a cannula, which is than removed. A filter-paper soaked with $FeCl_3$ is placed on the external surface of the distal part of the caval vein. The abdomen is filled with saline and closed. At the end of the experiment

the rat is sacrificed, the caval vein is extirpated, the thrombus harvested and its wet weight determined.

General Experimental Details

Where Prep-HPLC is stated, either a Waters Fraction Lynx Purification System with a ACE C8 5μm 21x100 mm column or a Gilson HPLC System with a kromasil C8 10 μm 21.2x250 mm column was used. The mobile phase used with the Waters system was a gradient starting at 5% acetonitrile up to 100% in 100 mM ammonium acetate buffer. The mobile phase used with the Gilson system was a gradient starting at 0% acetonitrile up to 95% in 100 mM ammonium acetate buffer. The flow rate was 25 mL/minute. With the Waters system, MS triggered fraction collection was used. With the Gilson HPLC system ,UV triggered fraction collection was used.

Mass spectra were recorded on either a Micromass ZQ single quadrupole or a Micromass quattro micro, both equipped with a pneumatically assisted electrospay interface (LC-MS).

**Reagents**

The following lists of reagents were used in the Preparations and Examples below. Unless otherwise stated, each of these reagents is commercially available.

List 1

(a) Phenylmethanesulfonyl chloride
(b) Benzenesulfonyl chloride
(c) 4-Methoxybenzenesulfonyl chloride
(d) 2-Methoxy-4-methylbenzenesulfonyl chloride
(e) 3,4-Dichlorobenzenesulfonyl chloride

(f) 3-Methoxybenzenesulfonyl chloride

(g) 2,5-Dimethylbenzenesulfonyl chloride

(h) Naphthalene-1-sulfonyl chloride

(i) 2,4-Dimethoxybenzenesulfonyl chloride

(j) (4-Chlorophenyl)methanesulfonyl chloride

(k) 4-Ethylbenzenesulfonyl chloride

(l) 2,5-Dimethylthiophene-3-sulfonyl chloride

(m) 2,5-Dichlorobenzenesulfonyl chloride

(n) 2-Chloro-6-methylbenzenesulfonyl chloride

(o) 4-Chloro-2-fluorobenzenesulfonyl chloride

List 2

(a) Phenylacetic acid

(b) *o*-Tolylacetic acid

(c) (2,5-Dimethylphenyl)acetic acid

(d) (5-Fluoro-2-methylphenyl)acetic acid

(e) (3-Trifluoromethylphenyl)acetic acid

(f) (5-Chloro-2-fluorophenyl)acetic acid

List 3

(a) Benzaldehyde

(b) 3-Methoxybenzaldehyde

(c) 3-Pyridinecarboxaldehyde

(d) 2-Methoxynicotinaldehyde

(obtainable as described in *J. Org. Chem.* 55, 69 (1990))

List 4

(a) Isobutyraldehyde

(b) 1-Phenyl-1H-pyrazole-5-carbaldehyde

(c) 2,5-Dimethyl-1-(4H-1,2,4-triazol-4-yl)-1H-pyrrole-3-carbaldehyde

(d) 4-Benzoyl-1-methyl-1H-pyrryle-2-carbaldehyde

(e) 2,3-Dihydrobenzo[b]furan-5-carboxaldehyde

(f) 2,4-Dimethyl-1,3-thiazole-5-carbaldehyde

(g) 1,5-Dimethyl-1H-pyrazole-4-carbaldehyde

(h) 1-(Phenylsulfonyl)-1H-pyrrole-2-carbaldehyde

(i) 3,5-Dimethyl-4-isoxazolecarbaldehyde

(j) 5-Chloro-2-phenyl-3H-imidazole-4-carbaldehyde

(k) 1,3-Dihydro-2,1,3-benzoxadiazole-5-carbaldehyde

(l) 2-Pyrazinecarboxaldehyde

(m) Cyclopentanecarboxaldehyde

(n) 5-Pyridin-2-ylthiophene-2-carbaldehyde

(o) 5-Chloro-1,3-dimethyl-1H-pyrazole-4-carbaldehyde

(p) 6-Chloropiperonal

(q) 1-Methyl-1H-imidazole-2-carbaldehyde

(r) Cyclohexanecarboxaldehyde

(s) 4-Methyl-3,4-dihydro-2H-1,4-benzoxazine-7-carbaldehyde

(t) 4-Cyanobenzaldehyde

(u) 2-Phenoxybenzaldehyde

(v) 1-Ethyl-3-methyl-1H-pyrazole-4-carbaldehyde

(w) 5-Methylimidazole-4-carboxaldehyde

(x) 5-Chloro-1-methyl-3-phenyl-1H-pyrazole-4-carbaldeyhyde

(y) 2-Morpholin-4-yl-pyridine-3-carbaldehyde

(z) 3,3-Dimethylbutyraldehyde

(aa) 5-Chloro-2-thiophenecarboxaldehyde

(ab) 2-Fluoro-5-formylbenzonitrile

(ac) 5-Methyl-3-phenyl-4-isoxazolecarbaldehyde

(ad) 3-(Trifluoromethoxy)benzaldehyde

(ae) 5-Chloro-2-fluorobenzaldehyde

(af) 2-Methyl-1H-imidazole-5-carbaldehyde

(ag) 2-Fluoro-5-methoxybenzaldehyde

(ah) 2-Morpholinobenzaldehyde

(ai) 1,3-Dimethyl-5-morpholino-1H-pyrazole-4-carbaldehyde

(aj) 8-Quinolinecarbaldehyde

(ak) 5-(2-Thienyl)-3-isoxazolecarbaldehyde

(al) 2-Phenylpropionaldehyde

(am) Bicyclo[2.2.1]hept-5-ene-2-carbaldehyde

(an) 3-[(2-Chloro-1,3-thiazol-5-yl)methoxy]benzenecarbaldehyde

(ao) 3-Methyl-5-phenyl-4-isoxazolecarbaldehyde

(ap) 1,3-Dimethyl-5-morpholin-4-yl-1H-pyrazole-4-carbaldehyde

List 5

(a) [(4-Aminomethylphenyl)iminomethyl]carbamic acid benzyl ester
(obtainable as described in WO 94/29336)

(b) (5-Aminomethyl-6-methylpyridin-2-yl)carbamic acid *tert*-butyl ester
(obtainable as described in WO 97/01338)

(c) (4-Aminomethylpyridin-2-yl)carbamic acid *tert*-butyl ester
(obtainable as described in Preparation 3 below)

(d) (4-Bromomethylpyridin-2-yl)carbamic acid *tert*-butyl ester
(obtainable as described in WO 00/66557)

(e) *C*-(3-Fluoro-4-methylpyridin-2-yl)methylamine
(obtainable as described in WO 00/075134)

(f) (5-Aminomethylpyridin-2-yl)carbamic acid *tert*-butyl ester
(obtainable as described in WO 97/01338)

(g) (2-Aminomethyl-4-chlorobenzyl)carbamic acid *tert*-butyl ester
(obtainable as described in WO 02/050056)

(h) [*N,N'*-Di(*tert*-butoxycarbonyl)]2-aminoethoxyguanidine
(obtainable as described in WO 99/55355)

(i) (5-Aminomethyl-6-methylpyridin-2-yl)carbamic acid *tert*-butyl ester
(obtainable as described in, WO 97/01338).

(j) *tert*-Butyl [5-(aminomethyl)-4,6-dimethylpyridin-2-yl]carbamate

(obtainable as described in WO 97/01338)

(k) [2-(1*H*-Tetrazol-1-yl)benzyl]amine

(obtainable as described in WO 02/064211)

(l) 5-(Aminomethyl)-3,6-dimethylpyridin-2-amine

(obtainable as described in WO 99/11267)

(m) *tert*-Butyl [2-(aminomethyl)benzyl]carbamate

(obtainable as described in WO 02/057225)

(n) [5-Chloro-2-(1*H*-tetrazol-1-yl)benzyl]amine

(obtainable as described in WO 02/064559)

(o) 2-[2-(Aminomethyl)-4-chlorophenoxy]-*N*-ethylacetamide

(obtainable as described in WO 97/30708)

(p) *tert*-Butyl {2-[2-(aminomethyl)-4-chlorophenyl]ethyl}carbamate

(obtainable as described in *Bioorg. Med. Chem. Lett.*, 13, 34773 (2003))

(q) *tert*-Butyl [2-(aminomethyl)-4-fluorobenzyl]carbamate

(obtainable as described in Preparation 6 below)

(r) *tert*-Butyl [2-(aminomethyl)-4-methoxybenzyl]carbamate

(obtainable as described in Preparation 7 below)

(s) *tert*-Butyl [2-(aminomethyl)-4-methylbenzyl]carbamate

(obtainable as described in Preparation 8 below)

(t) *tert*-Butyl [2-(aminomethyl)-4-(trifluoromethyl)benzyl]carbamate

(obtainable as described in Preparation 9 below)

**Preparations**

Preparation 1

(1-Amino-4-methyl-2-oxo-1,2-dihydropyridin-3-yl)acetic acid methyl ester

(a) 2-Methoxy-4-methyl-pyridine-3-carbaldehyde

The subtitle compound was prepared from 2-methoxypyridine according to the procedures described in *J. Org. Chem.* 55, 69 (1990) and *Tetrahedron Lett.* 29, 773 (1988).

(b) (2-Methoxy-4-methyl-pyridin-3-yl)methanol

Sodium borohydride (540 mg, 14.2 mmol) was added to a solution of 2-methoxy-4-methylpyridine-3-carbaldehyde (1.8 g, 12.9 mmol; see step (a) above) in a mixture of THF and methanol (30 mL, 1:1) at 0°C. The reaction mixture was stirred at room temperature for 2 hours. Water (10 mL) was added and the aqueous layer was extracted with ethyl acetate (3 x 25 mL). The combined organic layers were dried ($Na_2SO_4$), filtered and the solvent was evaporated under reduced pressure. The residue was purified by flash chromatography ($SiO_2$, 40% ethyl acetate in hexane) to give the sub-title compound (1.68 g, 85%) as a colourless oil.

$^1$H NMR (400 MHz, $CDCl_3$) δ 2.17 (s, 3H), 3.68 (br s, 1H), 3.72 (s, 3H), 4.49 (s, 2H), 6.53 (d, 1H), 7.72 (d, 1H)

(c) 3-Bromomethyl-2-methoxy-4-methylpyridine

Triphenylphosphine (2.35 g, 13.2 mmol) and *N*-bromosuccinimide (3.46 g, 13.2 mmol) was added to a solution of (2-Methoxy-4-methylpyridin-3-yl)-methanol (1.35 g, 8.81 mmol; see step (b) above) in DCM (40 mL) at 0°C. The reaction mixture was stirred at room temperature for 5 hours. Water (20 mL) was added, the layers were separated and the aqueous layer was

extracted with DCM (3 x 20 mL). The combined organic layers were dried ($Na_2SO_4$), filtered and the solvent was evaporated under reduced pressure. Purification by flash chromatography ($SiO_2$, 10% ethyl acetate in hexane) gave the sub-title compound (1.43 g, 75%) as a colourless oil.

$^1$H NMR (400 MHz, $CDCl_3$) δ 2.38 (s, 3H), 4.00 (s, 3H), 4.58 (s, 2H), 6.74 (d, 1H), 7.98 (d, 1H)

(d) (2-Methoxy-4-methylpyridin-3-yl)acetonitrile

Potassium cyanide (633 mg, 9.70 mmol) was added to a solution of 3-bromomethyl-2-methoxy-4-methylpyridine (1.40 g, 6.48 mmol; see step (c) above) in methanol (40 mL) and the solution was stirred for 12 hours at room temperature. The solvent was evaporated under reduced pressure and the residue was partitioned between a solution of $NaHCO_3$ (sat., 10 mL) and ethyl acetate. The aqueous layer was extracted with ethyl acetate (3 x 25 mL). The combined organic layers were dried ($Na_2SO_4$), filtered and the solvent was evaporated under reduced pressure. Purification by flash chromatography ($SiO_2$, 25% ethyl acetate in hexane) gave the sub-title compound (0.95 g, 90%) as a colourless oil.

$^1$H NMR (400 MHz, $CDCl_3$) δ 2.35 (s, 3H), 3.65 (s, 2H), 3.96 (s, 3H), 6.73 (d, 1H), 7.99 (d, 1H)

(e) (4-Methyl-2-oxo-1,2-dihydropyridin-3-yl)acetic acid methyl ester

(2-Methoxy-4-methylpyridin-3-yl)acetonitrile (825 mg, 5.09 mmol; see step (d) above) was dissolved in HBr (37%, 10 mL) and the solution was heated at 100°C for 5 hours and was further stirred at room temperature for 24 hours. The solvent was evaporated under reduced pressure and the resulting carboxylic acid was used directly in the next step.

HCl (conc., 3 mL) was added to a solution of the crude acid (9.13 g, 50 mmol) in methanol (120 mL) and the reaction mixture was stirred for 10

hours at room temperature. The reaction mixture was then concentrated by evaporation under reduced pressure and the residue was dissolved in DCM and washed with $NaHCO_3$. The organic layer was dried ($Na_2SO_4$), filtered and the solvent was evaporated to give the sub-title compound (8.9 g, 97%).
$^1H$ NMR (400 MHz, $CD_3OD$) δ 2.12 (s, 3H), 3.56 (s, 2H), 3.60 (s, 3H), 6.07 (d, 1H), 7.15 (d, 1H)

(f) (1-Amino-4-methyl-2-oxo-1,2-dihydropyridin-3-yl)acetic acid methyl ester

Caesium carbonate (1.6 g, 11.6 mmol) and *O*-(diphenylphosphinyl)-hydroxylamine (1.54 g, 6.62 mmol; see *Synthesis* 592 (1988) and *Tetrahedron Lett. 23*, 3835 (1982)) were added to a solution of (4-Methyl-2-oxo-1,2-dihydropyridin-3-yl)acetic acid methyl ester (0.60 g, 3.31 mmol; see step (e) above) in DMF (10 mL). The suspension was stirred at room temperature for 18 hours, filtered and the solvent was evaporated under reduced pressure. Purification by flash chromatography (3% methanol in ethyl acetate) gave the title compound (380 mg, 60%) as a yellow oil.
$^1H$ NMR (400 MHz, $CD_3OD$) δ 2.09 (s, 3H), 3.57 (s, 2H), 3.61 (s, 3H), 5.05 (br d, 2H), 5.96 (d, 1H), 7.37 (d, 1H)

Preparation 2

The compounds (i) to (viii) listed below were prepared from the title compound of Preparation 1 by the following General Method A.
The compounds (ix) to (xiv) listed below were prepared from the title compound of Preparation 1 by the following General Method B.
Unless otherwise specified, the compounds (xv) to (xviii) listed below were prepared from the title compound of Preparation 1 by the following General Method C.

General Method A

The specific sulfonyl chloride (0.61 mmol, 1.2 mol equiv.; see List 1 above) and pyridine (125 μL, 120 mg, 1.53 mmol) was added to a solution of (1-amino-4-methyl-2-oxo-1,2-dihydropyridin-3-yl)acetic acid methyl ester (100 mg, 0.51 mmol; see Preparation 1 above) in DCM (4 mL) at 0°C. The reaction mixture was stirred at room temperature for 12 hours. Pyridine and the solvent were evaporated under reduced pressure. Purification by flash chromatography ($SiO_2$, 50-70% ethyl acetate in hexane) gave the sulfonamides listed at (i) to (viii) below (62-92%).

General Method B

Step (i)

Borane tetrahydrofuran complex (1 M solution, 1.5 eq) was added to a stirred solution of the specific acid (1.0 eq; see List 2 above) in THF (0.2 M) at 0°C. The solution was warmed to room temperature during 1 hour and stirring was continued for another hour. Water was carefully added at 0°C and the mixture was extracted with ethyl acetate. The organic phases were combined, dried and the solvent was removed under reduced pressure to give the reduced product. The crude alcohol was used without further purification.

The alcohol was dissolved in DCM (0.2 M) and Dess-Martin periodinane (1.5 eq) was added to the solution. The resulting suspension was stirred until completion (from 0.5 hour to overnight). Hexane was added to the mixture and the resulting suspension was filtered through a pad of Celite®/Silica gel. The pad was washed with a solution of 30% ethyl acetate in hexane. The solvents were removed under reduced pressure to give the corresponding aldehyde, which was used in step (ii) without further purification.

Step (ii)

The specific aldehyde (0.50 mmol; see step (i) above) was added to (1-amino-4-methyl-2-oxo-1,2-dihydropyridin-3-yl)acetic acid methyl ester (76 mg, 0.39 mmol; see Preparation 1 above) in anhydrous ethanol (1.5 mL) and the reaction mixture was heated at reflux for 12 hours. The mixture was brought back to room temperature and $NaBH_3CN$ (49 mg, 0.77 mmol) was added and stirring was continued for 4 hours. HCl (10%) was added and after stirring 10 minutes the pH was neutralised with $NaHCO_3$ (sat.). The mixture was extracted with ethyl acetate (3x10 mL). The combined organic layers were washed with brine, dried ($Na_2SO_4$), filtered and the solvent was evaporated under reduced pressure. Purification directly after work-up by flash chromatography ($SiO_2$, 45% ethyl acetate in hexane) gave the reductive amination products listed at (ix) to (xiv) below (45-69%).

General Method C

The specific aldehyde (0.52 mmol; see List 3 above) dissolved in methanol (1.5 mL) was added to (1-amino-4-methyl-2-oxo-1,2-dihydropyridin-3-yl)-acetic acid methyl ester (100 mg, 0.48 mmol; see Preparation 1 above) in methanol (1.5 mL). Sodium cyanoborohydride (63 mg, 2.85 mmol) and zinc chloride (195 mg, 1.43 mmol) were added and the reaction mixture was stirred at room temperature overnight. Another portion of sodium cyanoborohydride (90 mg, 1.43 mmol) and acetic acid (10 droplets) were added and stirring was continued for another 3 hours. Sodium hydroxide (2 M) was added and the mixture was extracted with DCM (3x10 mL). The combined organic layers were dried through a phase separator and the solvent was evaporated under reduced pressure. Purification by flash chromatography ($SiO_2$, ethyl acetate:hexane, 1:2) gave the products listed at (xv) to (xviii) below.

(i) (4-Methyl-2-oxo-1-phenylmethanesulfonylamino-1,2-dihydro-pyridin-3-yl)acetic acid methyl ester

$^1$H NMR (400 MHz, $CDCl_3$) δ 2.22 (3H, s), 3.67 (5H, s), 4.35 (2H, s), 6.15 (1H, d), 7.28-7.44 (6H, m), 9.26 (1H, br)

(ii) (1-Benzenesulfonylamino-4-methyl-2-oxo-1,2-dihydropyridin-3-yl)-acetic acid methyl ester

$^1$H NMR (400 MHz, $CDCl_3$) δ 2.17 (3H, s), 3.37 (2H, s), 3.60 (3H, s), 6.16 (1H, d), 7.41-7.63 (6H, m), 9.07 (1H, b)

(iii) [1-(4-Methoxyphenylmethanesulfonylamino)-4-methyl-2-oxo-1,2-dihydropyridin-3-yl]acetic acid methyl ester

$^1$H NMR (400 MHz, $CDCl_3$) δ 2.16 (3H, s), 3.38 (2H, s), 3.59 (3H, s), 3.87 (3H, s), 6.14 (1H, d), 6.85 (2H, d), 7.53 (2H, d), 7.61 (2H, d), 9.26 (1H, br)

(iv) [1-(2-Methoxy-4-methylbenzenesulfonylamino)-4-methyl-2-oxo-1,2-dihydropyridin-3-yl]acetic acid methyl ester

$^1$H NMR (400 MHz, $CDCl_3$) δ 2.09 (s, 2H), 2.36 (s, 3H), 3.36 (s, 2H), 3.53 (s, 3H), 4.01 (s, 3H), 6.03 (d, 1H), 6.69 (d, 1H), 6.79 (s, 1H), 7.48 (d, 1H), 7.58 (d, 1H), 9.30 (s, 1H)

(v) [1-(3,4-Dichlorobenzenesulfonylamino)-4-methyl-2-oxo-1,2-dihydro-pyridin-3-yl]acetic acid methyl ester

$^1$H NMR (400 MHz, $CDCl_3$) δ 2.20 (s, 3H), 3.44 (s, 2H), 3.63 (s, 3H), 6.20 (d, 1H), 7.38 (dd, 1H), 7.43 (d, 1H), 7.58 (d, 1H), 7.63 (d, 1H), 9.41 (s, 1H)

(vi) [1-(3-Methoxybenzenesulfonylamino)-4-methyl-2-oxo-1,2-dihydro-pyridin-3-yl]acetic acid methyl ester

$^1$H NMR (400 MHz, $CDCl_3$) δ 2.16 (s, 3H), 3.37 (s, 2H), 3.59 (s, 3H), 3.75 (s, 3H), 6.15 (d, 1H), 7.07-7.09 (m, 2H), 7.21 (d, 1H), 7.31 (t, 1H), 7.63 (d, 1H)

(vii) [1-(2,5-Dimethylbenzenesulfonylamino)-4-methyl-2-oxo-1,2-dihydro-pyridin-3-yl]acetic acid methyl ester

$^1$H NMR (400 MHz, $CDCl_3$) δ 2.14 (s, 3H), 2.22 (s, 3H), 2.59 (s, 3H), 3.36 (s, 2H), 3.57 (s, 3H), 6.08 (d, 1H), 7.14 (d, 1H), 7.22 (d, 1H), 7.45 (s, 1H), 7.52 (d, 1H)

(viii) [4-Methyl-1-(naphthalene-1-sulfonylamino)-2-oxo-1,2-dihydro-pyridin-3-yl]acetic acid methyl ester

$^1$H NMR (400 MHz, $CDCl_3$) δ 2.12 (s, 3H), 3.16 (s, 2H), 3.53 (s, 3H), 6.11 (d, 1H), 7.37-7.49 (m, 3H), 7.54 (t, 1H), 7.88 (d, 1H), 7.98 (d, 1H), 8.05 (d, 1H), 8.50 (d, 1H), 9.31 (br s, 1H)

(ix) (4-Methyl-2-oxo-1-phenethylamino-1,2-dihydro-pyridin-3-yl)acetic acid methyl ester

$^1$H NMR (400 MHz, $CD_3OD$) δ 2.18 (s, 3H), 2.85 (t, 2H), 3.28 (q, 2H), 3.67 (s, 2H), 3.70 (s, 3H), 6.03 (d, 1H), 6.12 (t, 1H), 7.19-7.36 (m, 5H)

(x) [4-Methyl-2-oxo-1-(2-*o*-tolyl-ethylamino)-1,2-dihydropyridin-3-yl]acetic acid methyl ester

$^1$H NMR (400 MHz, $CDCl_3$) δ 2.18 (s, 3H), 2.29 (s, 3H), 2.85 (t, 2H), 3.22 (t, 2H), 3.67 (s, 2H), 3.69 (s, 3H), 6.05 (d, 1H), 7.12-7.18 (m, 4H), 7.37 (d, 1H)

(xi) {1-[2-(2,5-Dimethylphenyl)ethylamino]-4-methyl-2-oxo-1,2-dihydro-pyridin-3-yl}acetic acid methyl ester

$^1$H NMR (400 MHz, $CDCl_3$) δ 2.19 (s, 3H), 2.26 (s, 3H), 2.28 (s, 3H), 2.82 (t, 2H), 3.22 (t, 2H), 3.67 (s, 2H), 3.70 (s, 3H), 6.06 (d, 1H), 6.92 (d, 1H), 6.97 (s, 1H), 7.02 (d, 1H), 7.39 (d, 1H)

(xii) {1-[2-(5-Fluoro-2-methylphenyl)ethylamino]-4-methyl-2-oxo-1,2-dihydropyridin-3-yl}acetic acid methyl ester

$^1$H NMR (400 MHz, $CDCl_3$) δ 2.17 (s, 3H), 2.24 (s, 3H), 2.81 (t, 2H), 3.22 (t, 2H), 3.66 (s, 2H), 3.69 (s, 3H), 6.05 (d, 1H), 6.50 (t, 1H), 6.50 (dd, 1H), 6.88 (dd, 1H), 7.06 (dd, 1H), 7.35 (d, 1H)

(xiii) {4-Methyl-2-oxo-1-[2-(3-trifluoromethylphenyl)ethylamino]-1,2-dihydropyridin-3-yl}acetic acid methyl ester

$^1$H NMR (400 MHz, $CDCl_3$) δ 2.18 (s, 3H), 2.92 (t, 2H), 3.30 (t, 2H), 3.66 (s, 2H), 3.69 (s, 3H), 6.04 (d, 1H), 7.33 (d, 1H), 7.40-7.43 (m, 2H), 7.46-7.48 (m, 2H)

(xiv) {1-[2-(5-Chloro-2-fluorophenyl)ethylamino]-4-methyl-2-oxo-1,2-dihydropyridin-3-yl}acetic acid methyl ester

$^1$H NMR (400 MHz, $CDCl_3$) δ 2.18 (s, 3H), 2.84 (t, 2H), 3.25 (t, 2H), 3.66 (s, 2H), 3.70 (s, 2H), 6.04 (d, 1H), 6.95 (t, 1H), 7.15 (dq, 1H), 7.21 (dd, 1H), 7.32 (d, 1H)

(xv) Methyl [1-(benzylamino)-4-methyl-2-oxo-1,2-dihydropyridin-3-yl]-acetate

Yield = 42%.

$^1$H NMR (500 MHz) δ 2.19 (s, 3H), 3.71 (s, 2H), 3.74 (s, 3H), 4.14 (s, 2H), 5.94 (d, 1H), 7.18 (d, 1H), 7.30-7.41 (m, 5H)

(xvi) Methyl {1-[(3-methoxybenzyl)amino]-4-methyl-2-oxo-1,2-dihydropyridin-3-yl}acetate

$^1$H NMR (400 MHz, $CDCl_3$) δ 2.16 (s, 3H), 3.69 (s, 2H), 3.71 (s, 3H), 3.79 (s, 3H), 4.08 (d, 2H), 5.92 (d, 1H), 6.29 (t, 1H), 6.84 (dd, 1H), 6.91 (s, 1H), 6.94 (d, 1H), 7.20 (d, 1H), 7.24 (t, 1H)

MS *m/z* 317 $(M+H)^+$

(xvii) Methyl {4-methyl-2-oxo-1-[(pyridin-3-ylmethyl)amino]-1,2-dihydropyridin-3-yl}acetate

3-Pyridinecarboxaldehyde (10.6 mmol) was added to a solution of methyl (1-amino-4-methyl-2-oxo-1,2-dihydropyridin-3-yl)acetate (2.2 mmol; see Preparation 1 above) in methanol (40 mL) and acetic acid (10 mL) and the resulting solution was stirred at room temperature. After 22 hours, the solution was concentrated and acetic acid was removed by co-concentrating the residue from toluene, hexane and methanol. Sodium cyanoborohydride (6 mmol) was added to the residue in methanol (40 mL) and acetic acid (10 mL) and the resulting solution was stirred at room temperature overnight before being concentrated. The residue was diluted with ethyl acetate and washed with $NaHCO_3$ (sat. aq.) and brine, dried, filtered and the solvent was evaporated under reduced pressure. Purification by flash chromatography ($SiO_2$, 0-10% methanol in DCM containing 0.2% acetic acid and 0.1 % TEA) gave the desired product.

$^1$H NMR (500 MHz, $CDCl_3$) δ 8.52-8.58 (m, 2H), 7.70 (d, 1H), 7.24-7.30 (m, 1H), 7.12 (d, 1H), 6.25 (t, 1H), 5.93 (d, 1H), 4.14 (d, 2H), 3.70 (s, 3H), 3.67 (s, 2H), 2.16 (s, 3H)

(xviii) Methyl (1-{[(2-methoxypyridin-3-yl)methyl]amino}-4-methyl-2-oxo-1,2-dihydropyridin-3-yl)acetate

2-Methoxynicotinaldehyde (3.6 mmol) was added to a solution of methyl (1-amino-4-methyl-2-oxo-1,2-dihydropyridin-3-yl)acetate (2.4 mmol; see Preparation 1 above) in methanol (40 mL) and acetic acid (10 mL) and the resulting solution was stirred at room temperature. After 4.5 hours sodium cyanoborohydride (7.4 mmol) was added and the resulting solution was stirred at room temperature for 3 hours before being concentrated. The residue was diluted with ethyl acetate and washed with $NaHCO_3$ (sat. aq.) and brine, dried, filtered and concentrated. Purification by flash chromatography ($SiO_2$, DCM:methanol, 900:25) gave the desired product.

$^1$H NMR (500 MHz, $CDCl_3$) δ 8.13 (d, 1H), 7.50 (d, 1H), 7.23 (d, 1H), 6.85 (dd, 1H), 6.50 (t, 1H), 5.99 (d, 1H), 4.14 (d, 2H), 3.98 (s, 3H), 3.72 (s, 3H), 3.68 (s, 2H), 2.19 (s, 3H)

Preparation 3

(4-Aminomethylpyridin-2-yl)carbamic acid *tert*-butyl ester

(a) (4-Azidomethylpyridin-2-yl)carbamic acid *tert*-butyl ester

A mixture of (4-bromomethylpyridin-2-yl)carbamic acid *tert*-butyl ester (3.0 g, 0.010 mol; obtainable as described in WO 00/66557) and sodium azide (1.36 g, 0.0209 mol) in water (20 mL) and DMF (40 mL) was stirred overnight. The reaction mixture was poured into water (300 mL) and extracted with ethyl acetate (3x). The combined organic phases were washed with water, dried ($Na_2SO_4$), filtered and the solvent was evaporated under reduced pressure. The crude product crystallised (2.6 g, 100 %) and was used without further purification.

$^1$H NMR (300 MHz, $CDCl_3$) δ 10.14 (bs, 1H), 8.36 (d, 1H), 7.99 (bs, 1H), 6.91 (m, 1H), 4.37 (bs, 2H), 1.54 (s, 9H)

(b) (4-Aminomethylpyridin-2-yl)carbamic acid *tert*-butyl ester

A solution of sodium borohydride (0.92 g, 24 mmol) in water (25 mL) was added to a slurry of Pd/C (10%, 50 mg) in water (25 mL) under stirring. Next, (4-azidomethylpyridin-2-yl)carbamic acid *tert*-butyl ester (0.40 g, 6.1 mmol; see step (a) above) in THF (75 mL) was added dropwise rather rapidly under ice-cooling. The reaction was stirred at room temperature for 4 hours. An aqueous solution of sodium hydrogensulfate was added slowly to give an acidic pH. The reaction mixture was suction filtered through a Celite® pad which was further washed with water. The combined aqueous layer was washed with ethyl acetate, made alkaline by addition of NaOH (aq.) and extracted with ethyl acetate (3x). The combined organic phases were washed with water, dried ($Na_2SO_4$), filtered and the solvent was evaporated under reduced pressure. The crude product (1.1 g, 85%) crystallised and was used without further purification.

$^1$H NMR (300 MHz, $CDCl_3$) δ 10.06 (m, 1H), 8.25 (m, 1H), 7.94 (m, 1H), 6.88 (m, 1H), 3.83 (bs, 2H), 1.50 (s, 9H).

Preparation 4

The compounds (i) to (xlii) listed below were prepared from the title compound of Preparation 1 by the following general method.

The specific aldehyde (2.0 mmol, 2 mol equiv.; see List 4 above) was dissolved in methanol/THF (5 mL, 2:1). To the resulting solution was added, under stirring, a solution of (1-amino-4-methyl-2-oxo-1,2-dihydropyridin-3-yl)acetic acid methyl ester (196 mg, 1.0 mmol; see Preparation 1 above) in methanol/THF (5 mL, 2:1). Acetic acid (1 mL) was added, and imine formation was allowed to take place by stirring at room temperature for 5 to 20 hours. Sodium cyanoborohydride (377 to 628 mg, 3 to 5 mmol, 3 to 5 mol equiv.) was added and the reaction mixture was stirred at room temperature for 18 hours (or until full conversion of the imine was observed). The solvent was evaporated under reduced pressure

and the crude product mixtures were dissolved in DCM and extracted with $NaHCO_3$ (sat.) using phase separators. Especially polar products were subsequently extracted with ethyl acetate (4x10 mL), if needed. The organic phase was eluted through a silica plug (1 g), eluting with a gradient of DCM/MeOH mixtures (1:0 through to 3:1). Alternatively, the product was purified by Biotage Horizon Flash, eluting with MeOH/DCM/$Et_3N$ (2:98:0.1). Evaporation of relevant fractions gave crude products (alkylated esters) that were used in the next stage without further purification.

(i) Methyl [1-(isobutylamino)-4-methyl-2-oxo-1,2-dihydropyridin-3-yl]-acetate

(ii) Methyl (4-methyl-2-oxo-1-{[(1-phenyl-1*H*-pyrazol-5-yl)methyl]-amino}-1,2-dihydropyridin-3-yl)acetate

(iii) Methyl [1-({[2,5-dimethyl-1-(4*H*-1,2,4-triazol-4-yl)-1*H*-pyrrol-3-yl]methyl}amino)-4-methyl-2-oxo-1,2-dihydropyridin-3-yl]acetate

(iv) Methyl (1-{[(4-benzoyl-1-methyl-1*H*-pyrrol-2-yl)methyl]amino}-4-methyl-2-oxo-1,2-dihydropyridin-3-yl)acetate

(v) Methyl (1-[(2,3-dihydro-1-benzofuran-5-ylmethyl)amino]-4-methyl-2-oxo-1,2-dihydropyridin-3-yl)acetate

(vi) Methyl (1-{[(2,4-dimethyl-1,3-thiazol-5-yl)methyl]amino}-4-methyl-2-oxo-1,2-dihydropyridin-3-yl)acetate

(vii) Methyl (1-{[(1,5-dimethyl-1*H*-pyrazol-4-yl)methyl]amino}-4-methyl-2-oxo-1,2-dihydropyridin-3-yl)acetate

(viii) Methyl [4-methyl-2-oxo-1-({[1-(phenylsulfonyl)-1*H*-pyrrol-2-yl]-methyl}amino)-1,2-dihydropyridin-3-yl]acetate

(ix) Methyl (1-{[(3,5-dimethylisoxazol-4-yl)methyl]amino}-4-methyl-2-oxo-1,2-dihydropyridin-3-yl)acetate

(x) Methyl (1-{[(4-chloro-2-phenyl-1*H*-imidazol-5-yl)methyl]amino}-4-methyl-2-oxo-1,2-dihydropyridin-3-yl)acetate

(xi) Methyl {1-[(2,1,3-Benzoxadiazol-5-ylmethyl)amino]-4-methyl-2-oxo-1,2-dihydropyridin-3-yl}acetate

(xii) Methyl {4-methyl-2-oxo-1-[(pyrazin-2-ylmethyl)amino]-1,2-dihydro-pyridin-3-yl}acetate

(xiii) Methyl {1-[(cyclopentylmethyl)amino]-4-methyl-2-oxo-1,2-dihydro-pyridin-3-yl}acetate

(xiv) Methyl (4-methyl-2-oxo-1-{[(5-pyridin-2-yl-2-thienyl)methyl]-amino}-1,2-dihydropyridin-3-yl)acetate

(xv) Methyl (1-{[(5-chloro-1,3-dimethyl-1*H*-pyrazol-4-yl)methyl]amino}-4-methyl-2-oxo-1,2-dihydropyridin-3-yl)acetate

(xvi) Methyl (1-{[(6-chloro-1,3-benzodioxol-5-yl)methyl]amino}-4-methyl-2-oxo-1,2-dihydropyridin-3-yl)acetate

(xvii) Methyl (4-methyl-1-{[(1-methyl-1*H*-imidazol-2-yl)methyl]amino}-2-oxo-1,2-dihydropyridin-3-yl)acetate

(xviii) Methyl {1-[(cyclohexylmethyl)amino]-4-methyl-2-oxo-1,2-dihydropyridin-3-yl}acetate

(xix) Methyl (4-methyl-1-{[(4-methyl-3,4-dihydro-2*H*-1,4-benzoxazin-7-yl)methyl]amino}-2-oxo-1,2-dihydropyridin-3-yl)acetate

(xx) Methyl {1-[(4-cyanobenzyl)amino]-4-methyl-2-oxo-1,2-dihydropyridin-3-yl}acetate

(xxi) Methyl {4-methyl-2-oxo-1-[(2-phenoxybenzyl)amino]-1,2-dihydropyridin-3-yl}acetate

(xxii) Methyl (1-{[(1-ethyl-3-methyl-1*H*-pyrazol-4-yl)methyl]amino}-4-methyl-2-oxo-1,2-dihydropyridin-3-yl)acetate

(xxiii) Methyl (4-methyl-1-{[(4-methyl-1*H*-imidazol-5-yl)methyl]amino}-2-oxo-1,2-dihydropyridin-3-yl)acetate

(xxiv) Methyl (1-{[(5-chloro-1-methyl-3-phenyl-1*H*-pyrazol-4-yl)methyl]-amino}-4-methyl-2-oxo-1,2-dihydropyridin-3-yl)acetate

(xxv) Methyl (4-methyl-1-{[(2-morpholin-4-ylpyridin-3-yl)methyl]amino}-2-oxo-1,2-dihydropyridin-3-yl)acetate

(xxvi) Methyl {1-[(3,3-dimethylbutyl)amino]-4-methyl-2-oxo-1,2-dihydropyridin-3-yl}acetate

(xxvii) Methyl (1-{[(5-chloro-2-thienyl)methyl]amino}-4-methyl-2-oxo-1,2-dihydropyridin-3-yl)acetate

(xxviii) Methyl {1-[(3-cyano-4-fluorobenzyl)amino]-4-methyl-2-oxo-1,2-dihydropyridin-3-yl}acetate

(xxix) Methyl (4-methyl-1-{[(5-methyl-3-phenylisoxazol-4-yl)methyl]-amino}-2-oxo-1,2-dihydropyridin-3-yl)acetate

(xxx) Methyl (4-methyl-2-oxo-1-{[3-(trifluoromethoxy)benzyl]amino}-1,2-dihydropyridin-3-yl)acetate

(xxxi) Methyl {1-[(5-chloro-2-fluorobenzyl)amino]-4-methyl-2-oxo-1,2-dihydropyridin-3-yl}acetate

(xxxii) Methyl (4-methyl-1-{[(2-methyl-1*H*-imidazol-5-yl)methyl]amino}-2-oxo-1,2-dihydropyridin-3-yl)acetate

(xxxiii) Methyl {1-[(2-fluoro-5-methoxybenzyl)amino]-4-methyl-2-oxo-1,2-dihydropyridin-3-yl}acetate

(xxxiv) Methyl {4-methyl-1-[(2-morpholin-4-ylbenzyl)amino]-2-oxo-1,2-dihydropyridin-3-yl}acetate

(xxxv) Methyl (1-{[(1,3-dimethyl-5-morpholin-4-yl-1*H*-pyrazol-4-yl)-methyl]amino}-4-methyl-2-oxo-1,2-dihydropyridin-3-yl)acetate

(xxxvi) Methyl {4-methyl-2-oxo-1-[(quinolin-8-ylmethyl)amino]-1,2-dihydropyridin-3-yl}acetate

(xxxvii) Methyl [4-methyl-2-oxo-1-({[5-(2-thienyl)isoxazol-3-yl]methyl}-amino)-1,2-dihydropyridin-3-yl]acetate

(xxxviii) Methyl {4-methyl-2-oxo-1-[(2-phenylpropyl)amino]-1,2-dihydropyridin-3-yl}acetate

(xxxix) Methyl {1-[(bicyclo[2.2.1]hept-5-en-2-ylmethyl)amino]-4-methyl-2-oxo-1,2-dihydropyridin-3-yl}acetate

(xl) Methyl [1-({3-[(2-chloro-1,3-thiazol-5-yl)methoxy]benzyl}amino)-4-methyl-2-oxo-1,2-dihydropyridin-3-yl]acetate

(xli) Methyl (4-methyl-1-{[(3-methyl-5-phenylisoxazol-4-yl)methyl]-amino}-2-oxo-1,2-dihydropyridin-3-yl)acetate

(xlii) Methyl (1-{[(1,3-dimethyl-5-morpholin-4-yl-1*H*-pyrazol-4-yl)-methyl]amino}-4-methyl-2-oxo-1,2-dihydropyridin-3-yl)acetate

Preparation 5

Methyl {1-[(2,2-difluoro-2-pyridin-2-ylethyl)amino]-4-methyl-2-oxo-1,2-dihydropyridin-3-yl}acetate

(a) 2,2-Difluoro-2-pyridin-2-ylethyl trifluoromethanesulfonate

The sub-title compound was prepared according to the method described in *J. Med. Chem.* 46, 461 (2003))

(b) Methyl {1-[(2,2-difluoro-2-pyridin-2-ylethyl)amino]-4-methyl-2-oxo-1,2-dihydropyridin-3-yl}acetate

A solution of 2,2-difluoro-2-pyridin-2-ylethyl trifluoromethanesulfonate (2.0 mmol; see step (a) above) and (1-amino-4-methyl-2-oxo-1,2-dihydropyridin-3-yl)acetic acid methyl ester (2.09 mmol; see Preparation 1 above) in 1,2-dichloroethane (40 mL) was stirred at 50°C for 3 days before

being concentrated. Purification by flash chromatography ($SiO_2$, ethyl acetate) gave the title compound.

$^1$H NMR (500 MHz, $CDCl_3$) δ 8.63 (d, 1H), 7.82 (dt, 1H), 7.69 (d, 1H), 7.37 (dd, 1H), 7.29 (d, 1H), 6.27 (t, 1H), 5.98 (d, 1H), 3.85-3.93 (m, 2H), 3.68 (s, 3H), 3.63 (s, 2H), 2.15 (s, 3H)

Preparation 6

*tert*-butyl [2-(aminomethyl)-4-fluorobenzyl]carbamate

(a) Methyl 2-bromo-5-fluorobenzoate

To a solution of 2-bromo-5-fluorobenzoic acid (3.0 g, 13.7 mmol) in methanol (4 mL) was added HCl-saturated methanol (70 mL). The reaction mixture was stirred for 24 hours and then concentrated. The excess of HCl was removed by co-evaporation from methanol to give the sub-title compound (97%), which was used in the next step without further purification.

$^1$H NMR (500 MHz, $CDCl_3$) δ 3.96 (s, 3H), 7.09 (dt, 1H), 7.55 (dd, 1H), 7.65 (dd, 1H)

(b) Methyl 2-cyano-5-fluorobenzoate

Methyl 2-bromo-5-fluorobenzoate (3.0 g, 12.87 mmol; see step (a) above) was dissolved in dry DMF (18 mL). The resulting solution was then degassed by flushing with $N_2$ gas for 5 minutes. Copper(I) cyanide (2.3 g, 25.74 mmol) was added and the reaction mixture was degased again before being refluxed for 90 minutes. NaCN (aq, 10%) was added and the mixture was extracted with DCM. The DCM phase was dried through a phase separator and the solvent was removed *in vacuo*. The crude product was dissolved in toluene and washed once with water. The organic phase was dried over $MgSO_4$ and filtered. The solvent was removed *in vacuo* to give

the crude sub-title compound (77%), which was used in the next step without further purification.

$^1$H NMR (500 MHz, $CDCl_3$) δ 4.04 (s, 3H), 7.38 (dt, 1H), 7.82-7.87 (m, 2H)

(c) [2-(Aminomethyl)-5-fluorophenyl]methanol

Lithium aluminium hydride (1.12 g, 29.5 mmol) was dispersed in dry THF (10 mL) and the resulting mixture cooled with an ice bath. Methyl 2-cyano-5-fluorobenzoate (1.76 g, 9.85 mmol; see step (b) above) was dissolved in THF (10+5 mL) and added to the reducing agent. The reaction mixture was stirred for 10 minutes and then the ice bath was removed. After 1 hour, the reaction was quenched with water (2 mL), NaOH (2M, 4 mL) and then more water (2 mL), after which the resulting mixture was stirred for 10 minutes. The mixture was diluted with diethyl ether (50 mL) and filtered. The organic phase was dried over $MgSO_4$ and filtered. The solvent was removed *in vacuo* to give the sub-title compound (81 %), which was used without further purification.

$^1$H NMR (500 MHz, $CDCl_3$) δ 4.01 (s, 2H), 4.63 (s, 2H), 6.95 (dt, 1H), 7.11 (dd, 1H), 7.23 (dd, 1H)

(d) *tert*-Butyl [4-fluoro-2-(hydroxymethyl)benzyl]carbamate

[2-(Aminomethyl)-5-fluorophenyl]methanol (1.24 g, 7.99 mmol; see step (c) above) was dissolved in DCM (20 mL) and di-*tert*-butyldicarbonate (1.74 g, 7.99 mmol), dissolved in DCM (5 mL), was added. The reaction mixture was stirred at room temperature for 2 hours. The reaction mixture was diluted with DCM and washed once with water. The DCM phase was dried through a phase separator and the solvent was removed *in vacuo*. *tert*-Butanol was coevaporated from toluene to give the sub-title compound (96%), which was used without further purification.

$^1$H NMR (500 MHz, $CDCl_3$) δ 1.45 (s, 9H), 2.83 (br s, 1H), 4.35 (d, 2H), 4.74 (s, 2H), 5.06 (br s, 1H), 6.99 (dt,1H), 7.11 (dd, 1H), 7.29-7.31 (m, 1H)

(e) *tert*-Butyl [2-(azidomethyl)-4-fluorobenzyl]carbamate

*tert*-Butyl [4-fluoro-2-(hydroxymethyl)benzyl]carbamate (1.96 g, 7.70 mmol; see step (d) above) was dissolved in dry THF (25 mL) and the resulting solution was cooled with an ice bath. Diphenylphosphoryl azide (2.75 g, 10.0 mmol) and DBU (1.52 g, 10.0 mmol) were added. The mixture was stirred under inert atmosphere and the ice bath was left to warm to room temperature overnight. The reaction mixture was diluted with water and extracted twice with ethyl acetate. The organic phase was washed with brine and dried over $MgSO_4$ and filtered before the solvent was removed *in vacuo*. Purification by flash chromatography ($SiO_2$, heptane:ethyl acetate 10:1) gave the sub-title compound (76%).

$^1$H NMR (500 MHz, $CDCl_3$) δ 1.48 (s, 9H), 4.34 (d, 2H), 4.45 (s, 2H), 4.83 (br s, 1H), 7.04 (dt,1H), 7.08 (dd, 1H), 7.32-7.39 (m, 1H)

(f) *tert*-Butyl [2-(aminomethyl)-4-fluorobenzyl]carbamate

TEA (1.76 g, 17.55 mmol) in methanol (15 mL) was added to *tert*-butyl [2-(azidomethyl)-4-fluorobenzyl]carbamate (1.64 g, 5.85 mmol; see step (e) above) and the mixture was flushed with $N_2$ gas. 1,3-Propanedithiol (1.90 g, 17.55 mmol) dissolved in methanol (15 mL) was added. The reaction mixture was stirred at room temperature for 2 days. The white precipitate that formed was filtered off and washed with methanol. The filtrate was collected and the solvent was removed *in vacuo*. Purification by flash chromatography ($SiO_2$, 2.5% methanol in DCM + 1% TEA) gave the title compound (82%).

$^1$H NMR (500 MHz, $CDCl_3$) δ 1.48 (s, 9H), 3.94 (s, 2H), 4.33 (d, 2H), 5.80 (br s, 1H), 6.94 (dt,1H), 7.06 (dd, 1H), 7.32 (dd, 1H)

Preparation 7

*tert*-Butyl [2-(aminomethyl)-4-methoxybenzyl]carbamate

The title compound was prepared by a method analogous to that described in Preparation 6, steps (b) to (f) above, using methyl 2-bromo-5-methoxybenzoate in place of methyl 2-bromo-5-fluorobenzoate in step (b), and reaction times of 2 hours, 2 hours and 1 hour for steps (b), (c) and (d), respectively.

$^1$H NMR (500 MHz, $CDCl_3$) δ 1.44 (s, 9H), 3.83 (s, 3H), 4.04 (d, 2H), 4.27 (d, 2H) 5.76 (br s, 1H), 6.83 (dd, 1H), 7.03 (d, 1H), 7.24 (d, 1H)

Preparation 8

*tert*-Butyl [2-(aminomethyl)-4-methylbenzyl]carbamate

The title compound was prepared by a method analogous to that described in Preparation 6 above, using 2-chloro-5-methylbenzoic acid in place of 2-bromo-5-fluorobenzoic acid in step (a), and the following variations to the procedures:

(I) in step (b), the mixture was initially refluxed for 18 hours, an additional portion of CuCN (1 equiv.) was then added and the reaction mixture was further refluxed for 16 hours;

(II) in step (e), toluene:ethyl acetate (15:1) was used for chromatography; and

(III) in step (f), no precipitate formed and purification was performed directly after concentration of the reaction mixture.

$^1$H NMR (500 MHz, $CDCl_3$) δ 1.46 (s, 9H), 2.36 (s, 3H), 3.92 (s, 2H), 4.35 (d, 2H), 5.98 (br s, 1H), 7.08 (d,1H), 7.13 (s, 1H), 7.24 (d, 1H)

Preparation 9

*tert*-Butyl [2-(aminomethyl)-4-(trifluoromethyl)benzyl]carbamate

The title compound was prepared by a method analogous to that described in Preparation 6 above, using 2-chloro-5-(trifluoromethyl)benzoic acid in place of 2-bromo-5-fluorobenzoic acid in step (a), and the following variations to the procedures:

(I) in step (b), the reaction mixture was refluxed for 3 days and purification by chromatography was with heptane:ethyl acetate (15:1);

(II) in step (e), the crude product was not purified before being used in step (f); and

(III) in step (f), the reaction mixture was stirred for 24 hours.

$^1$H NMR (500 MHz, $CD_3OD$) δ 1.48 (s, 9H), 3.98 (s, 2H), 4.36 (s, 2H), 7.50 (d,1H), 7.56 (d, 1H), 7.72 (s, 1H)

Examples

Example 1

Unless otherwise stated, the compounds (i) to (xxxvi) listed below were prepared from corresponding compounds of Preparation 2 by the following general method.

Sodium hydroxide (29 mg, 0.71 mmol) was added to a solution of the specific ester (0.24 mmol; see Preparation 2 above) in THF:water:methanol (3 mL, 2:2:1) and the reaction mixture was stirred at room temperature for 3 hours. The mixture was acidified (HCl, 1 M) until pH ~ 2 and extracted with ethyl acetate (3 x 5 mL). The combined organic layers were dried ($Na_2SO_4$), filtered and the solvent was evaporated under reduced pressure. The residue (the carboxylic acid) was used without further purification.

DIPEA (125 μL, 0.71 mmol) and the specific amine (0.31 mmol; see List 5 above) were added to the crude carboxylic acid (see above) in DMF (4 mL) at 0°C. After 30 minutes, EDC (69 mg, 0.36 mmol) and HOBt (49 mg, 0.36 mmol) were added and the reaction mixture was stirred at 0°C for 1 hour and then at room temperature for 2 days. DMF was removed under reduced pressure. $NaHCO_3$ (sat., 2 mL) was added and the aqueous layer was extracted with ethyl acetate (3 x 5 mL). The combined organic layers were dried ($Na_2SO_4$), filtered and the solvent was evaporated under reduced pressure. Purification by flash chromatography ($SiO_2$, 5% methanol in ethyl acetate) gave the amides listed at (i) to (xv) below as oils. The yields over two steps for these amides were 68-84%.

(i) [Amino-(4-{[2-(4-methyl-2-oxo-1-phenylmethanesulfonylamino-1,2-dihydropyridin-3-yl)acetylamino]methyl}phenyl)methylene]carbamic acid benzyl ester

$^1$H NMR (400 MHz, $CD_3OD$) δ 2.21 (3H, s), 3.35 (2H, s), 4.39 (2H, s), 4.43 (2H, s), 5.18 (2H, s), 6.17 (1H, d), 7.26-7.55 (13H, m), 7.69 (2H, d)

(ii) [Amino-(4-{[2-(1-benzenesulfonylamino-4-methyl-2-oxo-1,2-dihydro-pyridin-3-yl)acetylamino]methyl}phenyl)methylene]carbamic acid benzyl ester

$^1$H NMR (400 MHz, $CDCl_3$) δ 2.11 (s, 3H), 3.29 (s, 2H), 4.25 (s, 2H), 5.21 (s, 2H), 6.11 (d, 1H), 6.91-7.70 (m, 18H), 10.05 (br s, 1H)

(iii) {Amino-[4-({2-[1-(4-methoxybenzenesulfonylamino)-4-methyl-2-oxo-1,2-dihydropyridin-3-yl]acetylamino}methyl)phenyl[methylene}carbamic acid benzyl ester

$^1$H NMR (400 MHz, $CD_3OD$) δ 2.18 (3H, s), 3.36 (2H, s), 3.72 (3H, s), 4.32 (2H, s), 5.18 (2H, s), 6.17 (1H, d), 6.91 (2H, d), 7.26-7.54 (9H, m), 7.61 (2H, d), 7.69 (2H, d)

(iv){Amino-[4-({2-[1-(2-methoxy-4-methylbenzenesulfonylamino)-4-methyl-2-oxo-1,2-dihydropyridin-3-yl]acetylamino}methyl)phenyl]methylene}-carbamic acid benzyl ester

$^1$H NMR (400 MHz, $CDCl_3$) δ 2.19 (s, 3H), 2.33 (s, 3H), 3.38 (s, 2H), 3.92 (s, 3H), 4.32 (s, 2H), 5.19 (s, 2H), 6.20 (d, 1H), 6.73 (d, 1H), 6.97 (s, 1H), 7.30-7.38 (m, 5H), 7.41 (d, 2H), 7.48 (d, 1H), 7.54 (d, 1H), 7.80 (d, 2H)

(v) {Amino-[4-({2-[1-(3,4-dichlorobenzenesulfonylamino)-4-methyl-2-oxo-1,2-dihydropyridin-3-yl]acetylamino}methyl)phenyl]methylene}carbamic acid benzyl ester

$^1$H NMR (400 MHz, $CDCl_3$) δ 2.22 (s, 3H), 3.38 (s, 2H), 4.34 (s, 2H), 5.19 (s, 2H), 6.21 (d, 1H), 7.29-7.36 (m, 5H), 7.41-7.46 (m, 3H), 7.55 (s, 2H), 7.78 (d, 1H), 7.83 (s, 1H)

(vi) {Amino-[4-({2-[1-(3-methoxybenzenesulfonylamino)-4-methyl-2-oxo-1,2-dihydropyridin-3-yl]acetylamino}methyl)phenyl]methylene}carbamic acid benzyl ester

$^1$H NMR (400 MHz, $CD_3OD$) δ 2.30 (s, 3H), 3.30 (s, 2H), 3.70 (s, 3H), 4.25 (d, 1H), 5.20 (s, 2H), 6.17 (d, 1H), 6.89 (br s, 1H), 7.04 (d, 1H), 7.13-7.37 (m, 7H), 7.43 (d, 2H), 7.48 (d, 1H), 7.71 (d, 2H)

(vii) {Amino-[4-({2-[1-(2,5-dimethylbenzenesulfonylamino)-4-methyl-2-oxo-1,2-dihydropyridin-3-yl]acetylamino}methyl)phenyl]methylene}-carbamic acid benzyl ester

$^1$H NMR (400 MHz, $CDCl_3$) δ 2.23 (s, 3H), 2.30 (s, 3H), 2.60 (s, 3H), 3.35 (s, 2H), 4.27 (d, 2H), 5.20 (s, 2H), 6.12 (d, 1H), 6.91 (br s, 1H), 7.11-7.49 (m, 11H), 7.77 (d, 2H)

(viii) {Amino-[4-({2-[4-methyl-1-(naphthalene-1-sulfonylamino)-2-oxo-1,2-dihydropyridin-3-yl]acetylamino}methyl)phenyl]methylene}carbamic acid benzyl ester

$^1$H NMR (400 MHz, $CDCl_3$) δ 2.19 (s, 3H), 3.15 (s, 2H), 4.11 (s, 2H), 5.17 (s, 2H), 5.99 (d, 1H), 7.00 (d, 4H), 7.26-7.51 (m, 8H), 7.60 (d, 2H), 7.83 (d, 1H), 7.99 (d, 2H), 8.56 (br d, 1H)

(ix) [4-Chloro-2-({2-[4-methyl-1-(naphthalene-1-sulfonylamino)-2-oxo-1,2-dihydropyridin-3-yl]acetylamino}methyl)benzyl]carbamic acid *tert*-butyl ester

The specific ester (0.47 mmol) was hydrolysed as described in General Method C above, except that the volume of solvent was 5 mL and the reaction time was 5.5 hours. The resulting, crude carboxylic acid (0.06 mmol) was dissolved in DCM (1 mL) and TEA (2 eq.) and the specific amine (1 equiv.; see List 5 above) were added. The mixture was cooled to 0°C and PyBOP (1 equiv.) was added. The reaction mixture was stirred at 0°C for 30 minutes and then allowed to warm to room temperature and further stirred overnight. Additional portions of TEA (2 equiv.), amine (0.4 equiv) and PyBOP (0.3 equiv.) were added and the reaction was stirred for 4 hours. The solvent was removed under reduced pressure and the residue was purified by chromatography ($SiO_2$, 5% methanol in DCM) to give the product (89%).

$^1$H NMR (500 MHz, $CDCl_3$) δ 1.49 (s, 9H), 2.29 (s, 3H), 3.12 (s, 2H), 4.14 (br s, 2H), 4.21 (br s, 2H), 6.14 (d, 1H), 6.74 (t, 1H), 7.21 (bs, 2H), 7.45 (t,

1H), 7.56-7.64 (m, 2H), 7.88-7.93 (m, 1H), 8.08 (d, 1H), 8.11 (d, 1H), 8.62 (br s, 1H)

(x) [Amino-(4-{[2-(4-methyl-2-oxo-1-phenethylamino-1,2-dihydropyridin-3-yl)acetylamino]methyl}phenyl)methylene]carbamic acid benzyl ester

$^1$H NMR (400 MHz, $CD_3OD$) δ 2.32 (s, 3H), 2.81 (t, 2H, $J$ = 7.4Hz), 3.20 (q, 2H, $J$ = 7.5Hz), 3.58 (s, 2H), 4.37 (d, 2H, $J$ = 6.0Hz), 5.20 (s, 2H), 6.09-6.13 (m, 2H), 7.03-7.78 , (m, 15H), 9.50 (br s, 1H)

(xi) {Amino-[4-({2-[4-methyl-2-oxo-1-(2-o-tolylethylamino)-1,2-dihydropyridin-3-yl]acetylamino}methyl)phenyl]methylene}carbamic acid benzyl ester

$^1$H NMR (400 MHz, $CDCl_3$) δ 2.24 (s, 3H), 2.32 (s, 3H), 2.79 (t, 2H), 3.14 (q, 2H), 3.58 (s, 2H), 4.35 (d, 2H), 5.20 (s, 2H), 6.12 (d, 1H), 7.06-7.13 (m, 4H), 7.15 (d, 2H), 7.28-7.37 (m, 4H), 7.43 (d, 2H), 7.66 (d, 3H)

(xii) (Amino-{4-[(2-{1-[2-(2,5-dimethylphenyl)ethylamino]-4-methyl-2-oxo-1,2-dihydropyridin-3-yl}acetylamino)methyl]phenyl}methylene)carbamic acid benzyl ester

$^1$H NMR (400 MHz, $CDCl_3$) δ 2.20 (s, 3H), 2.25 (s, 3H), 2.31 (s, 3H), 2.76 (t, 2H), 3.14 (q, 2H), 3.58 (s, 2H), 4.35 (d, 2H), 5.19 (s, 2H), 6.11 (d, 1H), 6.18 (s, 1H), 6.91 (d, 2H), 7.00 (d, 1H), 7.14 (d, 2H), 7.26-7.36 (m, 5H), 7.43 (d, 2H), 7.67 (d, 3H), 9.27 (br s, 1H)

(xiii) {5-[(2-{1-[2-(5-Fluoro-2-methylphenyl)ethylamino]-4-methyl-2-oxo-1,2-dihydropyridin-3-yl}acetylamino)methyl]pyridin-2-yl}carbamic acid *tert*-butyl ester

$^1$H NMR (400 MHz, $CDCl_3$) δ 1.52 (s, 9H), 2.19 (s, 3H), 2.34 (s, 3H), 2.75 (t, 2H), 3.12-3.14 (m, 2H), 3.56 (s, 2H), 4.28 (d, 1H), 6.12 (d, 2H), 6.79 (s,

1H), 6.83 (d, 1H), 7.05 (d, 1H), 7.33 (d, 1H), 7.46-7.48 (m, 1H), 7.55 (s, 1H), 7.83 (d, 1H), 8.1 (d, 1H), 8.76 (s, 1H)

(xiv) {5-[(2-{4-Methyl-2-oxo-1-[2-(2-trifluoromethylphenyl)ethylamino]-1,2-dihydropyridin-3-yl}acetylamino)methyl]pyridin-2-yl}carbamic acid *tert*-butyl ester

$^1$H NMR (400 MHz, $CDCl_3$) δ 1.52 (s, 9H), 2.35 (s, 3H), 2.86-2.89 (m, 2H), 3.22-3.26 (m, 2H), 3.56 (s, 2H), 4.31 (d, 2H), 6.12 (d, 2H), 7.31 (d, 2H), 7.39-7.42 (m, 2H), 7.48-7.50 (m, 2H), 7.52-7.54 (m, 2H), 7.88 (d, 1H), 8.09 (s, 1H), 8.26 (s, 1H)

(xv) 2-{1-[2-(5-Chloro-2-fluorophenyl)ethylamino]-4-methyl-2-oxo-1,2-dihydropyridin-3-yl}-*N*-(3-fluoro-4-methylpyridin-2-ylmethyl)acetamide

$^1$H NMR (400 MHz, $CDCl_3$) δ 2.21 (s, 3H), 2.32 (s, 3H), 2.81 (t, 2H), 3.25 (t, 2H), 3.65 (s, 2H), 4.55 (s, 2H), 6.08 (d, 1H), 6.17 (br s, 1H), 6.93, 6.99 (m, 2H), 7.14-7.18 (m, 2H), 7.31 (d, 1H), 7.82 (br s, 1H), 8.1 (br s, 1H)

(xvi) *tert*-Butyl {2-[({[1-(benzylamino)-4-methyl-2-oxo-1,2-dihydropyridin-3-yl]acetyl}amino)methyl]-4-chlorobenzyl}carbamate

The corresponding ester of Preparation 2 was hydrolysed with sodium hydroxide as described in the above General Method. The amide coupling was then performed as described with respect to Example 1(ix) above, except without the extra addition of reagents. The crude residue was purified by flash chromatography and preparative HPLC to give the desired product.

$^1$H NMR (500 MHz, $CDCl_3$) δ 1.46 (s, 9H), 2.36 (s, 3H), 3.61(s, 2H), 4.08 (d, 2H), 4.27-4.32(m, 2H), 4.39 (d, 2H), 5.34 (br s, 1H), 6.03 (d, 1H), 6.38 (br s, 1H), 7.13-7.20 (m, 3H), 7.24-7.37 (m, 6H), 7.61 (br s, 1H)

MS *m/z* 525.2 $(M+H)^+$

(xvii) Di-*tert*-butyl ((*E*)-{[2-({[1-(benzylamino)-4-methyl-2-oxo-1,2-dihydropyridin-3-yl]acetyl}amino)ethoxy]amino}methylylidene)-biscarbamate

The compound was prepared according to the method described with respect to Example 1(xvi) above except that preparative HPLC was not needed to provide desired product in a sufficiently pure form.

$^1$H NMR (500 MHz, $CDCl_3$) δ 1.50 (s, 18H), 2.32 (s, 3H), 3.53 (q, 2H), 3.61 (s, 2H) 4.10 (t, 2H), 4.12 (d, 2H), 5.99 (d, 1H), 6.43 (t, 1H), 7.15 (d, 1H), 7.29-7.38 (m, 5H), 7.67-7.72 (m, 1H), 8.02 (s, 1H), 9.09 (s, 1H)

MS *m/z* 573.6 $(M+H)^+$

(xviii) *tert*-Butyl {5-[({[1-(benzylamino)-4-methyl-2-oxo-1,2-dihydropyridin-3-yl]acetyl}amino)methyl]-6-methylpyridin-2-yl}carbamate

The corresponding ester of Preparation 2 was hydrolysed as described in the above General Method, except that the reaction mixture was stirred overnight. The amide coupling was performed as described with respect to Example 1(ix) above, but without the extra addition of reagents and with the use of TBME:methanol (97:3) as eluent for the chromatography.

$^1$H NMR (500 MHz, $CDCl_3$) δ 1.49 (s, 9H), 2.33 (s, 3H), 2.35 (s, 3H), 3.59 (s, 2H), 4.01 (d, 2H), 4.31 (d, 2H), 6.01 (d, 1H), 6.27 (t, 1H), 7.07 (br s, 1H), 7.16 (d, 1H), 7.27-7.35 (m, 4H), 7.40 (d, 1H), 7.44 (t, 1H), 7.63 (d, 1H)

(xix) *tert*-Butyl (4-chloro-2-{[({4-methyl-2-oxo-1-[(2-phenylethyl)amino]-1,2-dihydropyridin-3-yl}acetyl)amino]methyl}benzyl)carbamate

The corresponding ester of Preparation 2 was hydrolysed as described in the above General Method, except that the reaction mixture was stirred overnight. The amide coupling reaction was then performed as described in respect of Example 1(ix) above, except that amine (0.1 equiv.) was the only

reagent added at the extra addition step, and the reaction mixture was stirred for 4 hours. The crude product was purified by preparative HPLC.

$^1$H NMR (500 MHz, $CDCl_3$) δ 1.46 (s, 9H), 2.36 (s, 3H), 2.85 (t, 2H), 3.24 (q, 2H), 3.59 (s, 2H), 4.20-4.30 (m, 2H), 4.37 (d, 2H), 5.28 (br s,1H), 6.12-6.20 (m, 2H), 7.10 (s, 1H), 7.14 (d, 1H), 7.19-7.26 (m, 4H), 7.28-7.33 (m, 2H), 7.36 (d, 1H), 7.60 (br s, 1H)

MS *m/z* 539 $(M+H)^+$

(xx) *tert*-Butyl (6-methyl-5-{[({4-methyl-2-oxo-1-[(2-phenylethyl)amino]-1,2-dihydropyridin-3-yl}acetyl)amino]methyl}pyridin-2-yl)carbamate

The corresponding ester of Preparation 2 was hydrolysed as described in the General Method above, except that the reaction mixture was stirred overnight. The amide coupling reaction was then performed as described in respect of Example 1(ix) above, except that amine (0.1 equiv.) was the only reagent added at the extra addition step, and the reaction mixture was stirred for 3 hours. The crude product was purified by preparative HPLC.

$^1$H NMR (500 MHz, $CDCl_3$) δ 1.52 (s, 9H), 2.34 (s, 3H), 2.36 (s, 3H), 2.84 (t, 2H), 3.21 (q, 2H), 3.58 (s, 2H), 4.30 (d, 2H), 6.10 (t, 1H), 6.13 (d, 1H), 7.14 (s, 1H), 7.19-7.26 (m, 3H), 7.29-7.40 (m, 4H), 7.44 (t, 1H), 7.63 (d, 1H)

MS *m/z* 507 $(M+H)^+$

(xxi) *tert*-Butyl (4-chloro-2-{[({1-[(3-methoxybenzyl)amino]-4-methyl-2-oxo-1,2-dihydropyridin-3-yl}acetyl)amino]methyl}benzyl)carbamate

The corresponding compound from Preparation 2 was hydrolysed as described in the above General Method. The amide coupling reaction was then performed as described with respect to Example 1(ix) above, except that 1.3 equivalents of the specific amine were used and no extra reagents were added.

$^1$H NMR (500 MHz, $CDCl_3$) δ 1.44 (s, 9H), 2.33, (s, 3H), 3.60 (s, 2H), 3.80 (s, 3H), 4.05 (d, 2H), 4.28 (d, 2H), 4.38 (d, 2H), 5.40 (br s,1H), 6.03 (d, 1H), 6.39 (br s, 1H), 6.84-6.88 (m, 3H), 7.26–7.24 (m, 5H), 7.61 (br s, 1H)
MS *m/z* 557 $(M+H)^+$

(xxii) *tert*-Butyl (5-{[({1-[(3-methoxybenzyl)amino]-4-methyl-2-oxo-1,2-dihydropyridin-3-yl}acetyl)amino]methyl}-6-methylpyridin-2-yl)carbamate
The corresponding ester from Preparation 2 was hydrolysed as described in the above General Method. The amide coupling reaction was then performed as described in the above General Method, except that TEA was used instead of DIPEA and HOAt instead of HOBt.
$^1$H NMR (500 MHz, $CDCl_3$) δ 1.50 (s, 9H), 2.33, (s, 3H), 2.34 (s, 3H), 3.40 (s, 2H), 3.80 (s, 3H), 4.00 (d, 2H), 4.30 (d, 2H), 6.02 (d, 1H), 6.36 (t, 1H), 6.83–6.87 (m, 3H), 7.20 (d, 1H), 7.23 (t, 1H), 7.38 (d, 1H), 7.40 (s, 1H), 7.48 (t, 1H), 7.63 (d, 1H)
MS *m/z* 522 $(M+H)^+$

(xxiii) *tert*-Butyl (4-chloro-2-{[({4-methyl-2-oxo-1-[(pyridin-3-ylmethyl)-amino]-1,2-dihydropyridin-3-yl}acetyl)amino]methyl}benzyl)carbamate
The corresponding ester from Preparation 2 was hydrolysed with lithium hydroxide (1 M aq., 1.5 equiv.) in THF:MeOH (1:1) and the crude carboxylate was coupled to the specific amine (see List 5 above) according to the procedure described in the above General Method, except that TEA was used instead of DIPEA and HOAt instead of HOBt.
$^1$H NMR (500 MHz, $CDCl_3$) δ 8.56 (d, 1H), 8.53 (s, 1H), 7.64 (d, 1H), 7.52 (s, 1H), 7.24-7.31 (m, 2H), 7.12-7.21 (m, 3H), 6.35 (br s, 1H), 6.04 (d, 1H), 5.35 (br s, 1H), 4.40 (d, 2H), 4.29 (d, 2H), 4.12 (d, 2H), 3.59 (d, 2H), 2.34 (s, 3H), 1.44 (s, 9H)
MS *m/z* 528 $(M+H)^+$

(xxiv) *tert*-Butyl (6-methyl-5-{[({4-methyl-2-oxo-1-[(pyridin-3-ylmethyl)-amino]-1,2-dihydropyridin-3-yl}acetyl)amino]methyl}pyridin-2-yl)-carbamate

Prepared according to the procedure described in respect of Example 1(xxiii) above.

$^1$H NMR (500 MHz, $CDCl_3$) δ 8.52-8.60 (m, 2H), 7.58-7.68 (m, 2H), 7.34-7.44 (m, 2H), 7.25-7.30 (m, 1H), 7.16 (d, 1H), 6.26-6.34 (m, 1H), 6.04 (d, 1H), 4.32 (d, 2H), 4.05 (d, 2H), 3.59 (s, 2H), 2.36 (s, 6H), 1.50 (s, 9H)

MS *m/z* 493 $(M+H)^+$

(xxv) *tert*-Butyl [5-({[(1-{[(2-methoxypyridin-3-yl)methyl]amino}-4-methyl-2-oxo-1,2-dihydropyridin-3-yl)acetyl]amino}methyl)-6-methyl-pyridin-2-yl]carbamate

Prepared according to the procedure described in respect of Example 1(xxiii) above.

$^1$H NMR (500 MHz, $CDCl_3$) δ 8.11 (dd, 1H), 7.63 (d, 1H), 7.36-7.45 (m, 3H), 7.24 (d, 1H), 7.19 (bs, 1H), 6.81 (dd, 1H), 6.57 (t, 1H), 6.08 (d, 1H), 4.29 (d, 2H), 4.06 (d, 2H), 3.94 (s, 3H), 3.57 (s, 2H), 2.34-2.37 (m, 6H), 1.50 (s, 9H)

MS *m/z* 523 $(M+H)^+$

(xxvi) *tert*-Butyl [4-chloro-2-({[(1-{[(2-methoxypyridin-3-yl)methyl]-amino}-4-methyl-2-oxo-1,2-dihydropyridin-3-yl)acetyl]amino}methyl)-benzyl]carbamate

Prepared according to the procedure described in respect of Example 1(xxiii) above.

$^1$H NMR (500 MHz, $CDCl_3$) δ 8.10 (dd, 1H), 7.57 (bs, 1H), 7.38 (d, 1H), 7.10-7.26 (m, 4H), 6.80 (dd, 1H), 6.63 (bs, 1H), 6.08 (d, 1H), 5.38 (bs, 1H),

4.36 (d, 2H), 4.28 (bd, 2H), 4.10 d, 2H), 3.93 (s, 3H), 3.57 (s, 2H), 2.34 (s, 3H), 1.44 (s, 9H)

(xxvii) 2-(1-{[(2-Methoxypyridin-3-yl)methyl]amino}-4-methyl-2-oxo-1,2-dihydropyridin-3-yl)-*N*-[2-(1*H*-tetrazol-1-yl)benzyl]acetamide

Prepared according to the procedure described in respect of Example 1(xxiii) above. The crude compound was then purified by preparative HPLC.

$^1$H NMR (500 MHz, $CD_3OD$) δ 9.54 (s, 1H), 8.04 (dd, 1H), 7.60-7.67 (m, 2H), 7.51-7.57 (m, 2H), 7.47 (d, 1H), 7.41 (d, 1H), 6.87 (dd, 1H), 6.19 (d, 1H), 4.23 (s, 2H), 4.16 (s, 2H), 3.90 (s, 3H), 3.49 (s, 2H), 2.21 (s, 3H)

MS *m/z* 461 $(M+H)^+$

(xxviii) *tert*-Butyl {5-[({[1-(benzylamino)-4-methyl-2-oxo-1,2-dihydropyridin-3-yl]acetyl}amino)methyl]-4,6-dimethylpyridin-2-yl}carbamate

Prepared according to the procedure described in respect of Example 1(xxii) above.

$^1$H NMR (500 MHz, $CDCl_3$) δ 1.48 (s, 9H), 2.29 (s, 3H), 2.33 (s, 3H), 2.40 (s, 3H), 3.54 (s, 2H), 3.94 (d, 2H), 4.34 (d, 2H), 5.99 (d, 1H), 6.19 (t, 1H), 7.04 (br s, 1H), 7.14 (d, 1H), 7.23-7.28 (m, 3H), 7.29-7.35 (m, 3H), 7.56 (s, 1H)

MS *m/z* 506 $(M+H)^+$

(xxix) 2-[1-(Benzylamino)-4-methyl-2-oxo-1,2-dihydropyridin-3-yl]-*N*-[2-(1*H*-tetrazol-1-yl)benzyl]acetamide

Prepared according to the procedure described in respect of Example 1(xxii) above.

$^1$H NMR (500 MHz, $CDCl_3$) δ 2.27 (s, 3H), 3.53 (s, 2H), 4.10 (d, 2H), 4.20 (d, 2H), 6.01 (d, 1H), 6.36 (t, 1H), 7.19 (d, 1H), 7.27-7.35 (m, 6H), 7.43 (m, 1H), 7.50-7.63 (m, 3H), 8.96 (s, 1H)

MS *m/z* 430 $(M+H)^+$

(xxx) *N*-[(6-Amino-2,5-dimethylpyridin-3-yl)methyl]-2-{1-[(3-methoxybenzyl)amino]-4-methyl-2-oxo-1,2-dihydropyridin-3-yl}acetamide

The corresponding ester from Preparation 2 was hydrolysed as described in the above General Method. The amide coupling reaction was then performed as described in the above General Method, except that 1.5 equivalents of the specific amine (see List 5 above) were used and that TEA was used instead of DIPEA and HOAt instead of HOBt.

$^1$H NMR (500 MHz, $CD_3OD$) δ 2.07 (s, 3H), 2.24 (s, 3H), 2.31 (s, 3H), 3.60 (s, 2H), 3.78 (s, 3H), 4.07 (s, 2H), 4.24 (d, 2H), 6.15 (d, 1H), 6.83–6.91 (m, 3H), 7.22 (t, 2H), 7.34 (d, 1H)

MS *m/z* 436 $(M+H)^+$

(xxxi) *tert*-Butyl (4-methoxy-2-{[({4-methyl-2-oxo-1-[(pyridin-3-ylmethyl)amino]-1,2-dihydropyridin-3-yl}acetyl)amino]methyl}benzyl)carbamate

Prepared according to the procedure described in respect of Example 1(xxiii) above.

$^1$H NMR (500 MHz, $CDCl_3$) δ 1.45 (s, 9H), 2.34 (s, 3H), 3.59 (s, 2H), 3.71 (s, 3H), 4.02 (d, 2H), 4.24-4.29 (m, 2H), 4.40 (d, 2H), 5.29 (br s, 1H), 6.01 (d, 1H), 6.32 (br s, 1H), 6.73 (d, 1H), 6.77 (br s, 1H), 7.12 (d, 1H), 7.23 (d, 1H), 7.45 (br s, 1H), 7.63 (d, 1H), 8.52 (s, 1H), 8.56 (d, 1H)

MS *m/z* 523 $(M+H)^+$

(xxxii) *tert*-Butyl [2-{[({4-methyl-2-oxo-1-[(pyridin-3-ylmethyl)amino]-1,2-dihydropyridin-3-yl}acetyl)amino]methyl}-4-(trifluoromethyl)benzyl]-carbamate

Prepared according to the procedure described in respect of Example 1(xxiii) above.

$^1$H NMR (500 MHz, $CDCl_3$) δ 1.45 (s, 9H), 2.34 (s, 3H), 3.60 (s, 2H), 4.11 (d, 2H), 4.23-4.40 (m, 2H), 4.46 (d, 2H), 5.41 (t, 1H), 6.04 (d, 1H), 6.34 (br s, 1H), 7.17 (d, 1H), 7.24-7.30 (m, 1H), 7.38 (br s, 1H), 7.42-7.50 (m, 2H), 7.59 (br s, 1H), 7.64 (d, 1H), 8.52 (s, 1H), 8.56 (d, 1H)

MS *m/z* 560 $(M+H)^+$

(xxxiii) 2-{4-Methyl-2-oxo-1-[(pyridin-3-ylmethyl)amino]-1,2-dihydro-pyridin-3-yl}-*N*-[(1-trityl-1*H*-benzimidazol-6-yl)methyl]acetamide

Prepared according to the procedure described in respect of Example 1(xxiii) above.

$^1$H NMR (500 MHz, $CDCl_3$) δ 2.31 (s, 3H), 3.49 (s, 2H), 4.09 (d, 2H), 4.16 (d, 2H), 6.02 (d, 1H), 6.25 (t, 1H), 6.34 (s, 1H), 6.99 (t, 1H), 7.04 (d, 1H), 7.12–7.20 (m, 7H), 7.26–7.36 (m, 10H), 7.62 (d, 1H), 7.70 (d, 1H), 7.90 (s, 1H), 8.54 (s, 1H), 8.57 (d, 1H)

MS *m/z* 645 $(M+H)^+$

(xxxiv) *tert*-Butyl (6-{[({4-methyl-2-oxo-1-[(pyridin-3-ylmethyl)amino]-1,2-dihydropyridin-3-yl}acetyl)amino]methyl}pyridin-3-yl)carbamate

Prepared according to the procedure described in respect of Example 1(xxiii) above.

$^1$H NMR (500 MHz, $CDCl_3$) δ 8.53 (m, 2H), 8.34 (d, 1H), 7.85 (d, 1H), 7.58-7.68 (m, 2H), 7.25 (m, 1H), 7.07-7.15 (m, 2H), 6.82 (s, 1H), 6.29 (t, 1H), 5.98 (d, 1H), 4.45 (d, 2H), 4.11 (d, 2H), 3.63 (s, 2H), 2.30 (s, 3H), 1.48 (s, 9H)

(xxxv) *tert*-Butyl (4-chloro-2-{[({1-[(2,2-difluoro-2-pyridin-2-ylethyl)-amino]-4-methyl-2-oxo-1,2-dihydropyridin-3-yl}acetyl)amino]methyl}-benzyl)carbamate

Prepared according to the procedure described in respect of Example 1(xxiii) above.

$^1$H NMR (500 MHz, $CDCl_3$) δ 8.64 (d, 1H), 7.84 (t, 1H), 7.70 (d, 1H), 7.52 (bs, 1H), 7.40 (t, 1H), 7.31 (d, 1H), 7.22 (d, 1H), 7.10-7.17 (m, 2H), 6.37 (bs, 1H), 6.08 (d, 1H), 5.36 (bs, 1H), 4.36 (d, 2H), 4.25 (s, 2H), 3.87 (dt, 2H), 3.55 (s, 2H), 2.34 (s, 3H), 1.44 (s, 9H)

(xxxvi) *tert*-Butyl [4-chloro-2-({[(1-{[2,2-difluoro-2-(1-oxidopyridin-2-yl)-ethyl]amino}-4-methyl-2-oxo-1,2-dihydropyridin-3-yl)acetyl]amino}-methyl)benzyl]carbamate

To a solution of *tert*-butyl (4-chloro-2-{[({1-[(2,2-difluoro-2-pyridin-2-ylethyl)amino]-4-methyl-2-oxo-1,2-dihydropyridin-3-yl}acetyl)amino]-methyl}benzyl)carbamate (0.20 mmol; see Example 1(xxxv) above) in DCE (1 mL) was added mCPBA (0.29 mmol) and the resulting solution was stirred at room temperature for 3 days. Then, mCPBA (0.29 mmol) and 4,4'-thiobis(2-*tert*-butyl-5-methylphenol) (0.03 mmol), together with DCE (1 mL) were added and the resulting mixture was heated to 55°C for 4 hours. The reaction mixture was diluted with DCM and washed with $NaHCO_3$ (aq.) and $Na_2SO_3$ (aq.). The aqueous layer was extracted with DCM and the combined organic layers were dried through a phase separator and concentrated. The title compound was then purified by Prep-HPLC.

$^1$H NMR (500 MHz, $CDCl_3$) δ 8.12 (br s, 1H), 7.71 (m, 1H), 7.45 (br s, 1H), 7.37 (m, 1H), 7.20-7.26 (m, 2H), 7.13-7.19 (m, 2H), 6.33 (bs, 1H), 6.02 (d, 1H), 5.36 (br s, 1H), 4.39 (d, 2H), 4.20-4.31 (m, 4H), 3.56 (s, 2H), 2.32 (s, 3H), 1.45 (s, 9H)

Example 2

Unless otherwise stated, the compounds (i) to (xi) listed below were prepared from the corresponding compounds of Example 1 by General Method A described below.

Compounds (xiii) and (xiv) below were prepared from the corresponding compounds of Example 1 by General Method B described below.

Unless otherwise stated, compounds (xv) to (xliii) were prepared from the corresponding compounds of Example 1 by General Method C described below.

General Method A

Palladium on carbon (10%, 5 mg) and HCl (conc., 2-3 drops) were added to a solution of the specific benzyloxycarbonyl-protected compound (0.06-0.007 mmol; see Example 1 above) in methanol (2 mL). The suspension was hydrogenated under atmospheric pressure at room temperature for 30 minutes. The suspension was filtered through Celite®, washed with methanol (3 x 5 mL) and the solvent was removed under reduced pressure. The residue was dissolved in a minimum volume of methanol and the deprotected product was precipitated from ethyl acetate. Yields were nearly quantitative.

General Method B

HCl gas was bubbled through a solution of the specific Boc-protected compound (0.06 mmol; see Example 1 above) in methanol (2 mL) for 5 minutes. The solution was stirred at room temperature for 30 minutes and the solvent was removed under reduced pressure to give the products as solids. Yields were nearly quantitative.

General Method C

The specific Boc-protected compound (0.04 mmol; see Example 1 above) was dissolved in ethyl acetate saturated with HCl (2 mL) and stirred at room temperature for 30 minutes. The solvent and excess of reagents were evaporated under reduced pressure to give the desired product.

(i) *N*-(4-Carbamimidoylbenzyl)-2-(4-methyl-2-oxo-1-phenylmethanesulfonylamino-1,2-dihydropyridin-3-yl)acetamide

The compound was further purified by Prep-HPLC to give the final product.

$^1$H NMR (400 MHz, $CD_3OD$) δ 2.26 (s, 3H), 3.66 (s, 2H), 4.46 (s, 4H), 6.23 (d, 1H), 7.26-7.67 (m, 10H), 8.71 (br s, 1H), 9.13 (br s, 1H)

MS *m/z* 468.1 $(M+H)^+$

(ii) 2-(1-Benzenesulfonylamino-4-methyl-2-oxo-1,2-dihydropyridin-3-yl)-*N*-(4-carbamimidoylbenzyl)acetamide

$^1$H NMR (400 MHz, $CD_3OD$) δ 2.18 (s, 3H), 3.39 (s, 2H), 4.35 (s, 2H), 6.17 (d, 1H), 7.26-7.66 (m, 9H), 8.70 (br s, 1H), 9.18 (br s, 1H)

MS *m/z* 454.4 $(M+H)^+$

(iii) *N*-(4-Carbamimidoylbenzyl)-2-[1-(4-methoxybenzenesulfonylamino)-4-methyl-2-oxo-1,2-dihydropyridin-3-yl]acetamide

$^1$H NMR (400 MHz, $CD_3OD$) δ 2.21 (s, 3H), 3.31 (s, 2H), 3.72 (s, 3H), 4.32 (s, 2H), 6.17 (d, 1H), 6.85 (d, 2H), 7.26-7.51 (m, 3H), 7.61 (d, 2H), 7.81 (d, 2H), 8.69 (br s, 1H), 9.11 (br s, 1H)

MS *m/z* 484.4 $(M+H)^+$

(iv) *N*-(4-Carbamimidoylbenzyl)-2-[1-(2-methoxy-4-methylbenzenesulfonylamino)-4-methyl-2-oxo-1,2-dihydropyridin-3-yl]acetamide

$^1$H NMR (400 MHz, $CD_3OD$) δ 2.21 (s, 3H), 2.37 (s, 3H), 3.41 (s, 2H), 3.95 (s, 3H), 4.38 (s, 2H), 6.22 (d, 1H), 6.76 (d, 1H), 7.00 (s, 1H), 7.46-7.53 (m, 4H), 7.74 (d, 1H), 8.75 (br s, 2H), 9.25 (br s, 2H)

MS *m/z* 498.4 $(M+H)^+$

(v) *N*-(4-Carbamimidoylbenzyl)-2-[1-(3,4-dichlorobenzenesulfonylamino)-4-methyl-2-oxo-1,2-dihydropyridin-3-yl]acetamide

The compound was further purified by Prep-HPLC to give the final product.

$^1$H NMR (400 MHz, $CD_3OD$) δ 2.26 (s, 3H), 3.41 (s, 2H), 4.43 (s, 2H), 6.23 (d, 1H), 7.37-7.93 (m, 9H), 8.73, (s, 1H), 9.27 (s, 1H)

MS *m/z* 522.0 $(M+H)^+$

(vi) *N*-(4-Carbamimidoylbenzyl)-2-[1-(3-methoxybenzenesulfonylamino)-4-methyl-2-oxo-1,2-dihydropyridin-3-yl]acetamide

$^1$H NMR (400 MHz, $CD_3OD$) δ 2.22 (s, 3H), 3.39 (s, 2H), 3.78 (s, 2H), 4.39 (s, 2H), 6.26 (d, 1H), 7.15 (d, 1H), 7.23 (d, 2H), 7.36 (t, 1H), 7.47 (t, 3H), 7.74 (d, 2H), 8.11 (br s, 1H), 8.76 (br s, 1H)

MS *m/z* 482.0 $(M+H)^+$

(vii) *N*-(4-Carbamimidoylbenzyl)-2-[1-(2,5-dimethylbenzenesulfonyl-amino)-4-methyl-2-oxo-1,2-dihydropyridin-3-yl]acetamide

$^1$H NMR (400 MHz, $CD_3OD$) δ 2.20 (s, 3H), 2.24 (s, 3H), 2.61 (s, 3H), 3.38 (s, 2H), 4.39 (s, 2H), 6.18 (d, 1H), 7.22 (d, 1H), 7.32 (t, 2H), 7.47 (d, 3H), 7.74 (d, 1H), 8.72 (br s, 1H), 9.22 (br s, 1H)

MS *m/z* 482.1 $(M+H)^+$

(viii) *N*-(4-Carbamimidoylbenzyl)-2-[4-methyl-1-(naphthalene-1-sulfonyl-amino)-2-oxo-1,2-dihydropyridin-3-yl]acetamide

$^1$H NMR (400 MHz, $CD_3OD$) δ 2.17 (s, 3H), 3.18 (s, 2H), 4.32 (s, 2H), 6.16 (d, 1H), 7.25 (d, 1H), 7.40 (d, 2H), 7.50 (t, 1H), 7.59-7.61 (m, 2H), 7.70 (d, 2H), 7.97-8.01 (m, 1H), 8.07 (d, 1H), 8.17 (d, 1H), 8.57-8.61 (m, 1H), 8.71 (br s, 1H), 9.18 (br s, 1H)

MS *m/z* 504.1 $(M+H)^+$

(ix) *N*-(4-Carbamimidoylbenzyl)-2-(4-methyl-2-oxo-1-phenethylamino-1,2-dihydropyridin-3-yl)acetamide

$^1$H NMR (400 MHz, $CD_3OD$) δ 2.28 (s, 3H), 2.87 (t, 2H, $J$ = 6.9Hz), 3.30-3.34 (m, 2H), 3.68 (s, 2H), 4.48 (s, 2H), 6.38 (d, 1H), 7.19-7.29 (m, 5H), 7.52 (d, 2H), 7.68 (d, 1H), 7.72 (d, 2H), 8.78 (br s, 1H), 9.24 (br s, 1H)

MS *m/z* 418.4 $(M+H)^+$

(x) *N*-(4-Carbamimidoylbenzyl)-2-[4-methyl-2-oxo-1-(2-o-tolylethylamino)-1,2-dihydropyridin-3-yl]acetamide

$^1$H NMR (400 MHz, $CD_3OD$) δ 1.30 (s, 2H), 2.27 (s, 2H), 2.81 (br s, 2H), 3.15 (br s, 2H), 3.63 (s, 3H), 4.46 (s, 3H), 6.30 (br s, 1H), 6.97-7.16 (m, 5H), 7.46-7.56 (m, 3H), 7.61 (br s, 1H), 7.68 (d, 2H), 8.71 (br s, 1H), 9.21 (br s, 1H)

MS *m/z* 432.4 $(M+H)^+$

(xi) *N*-(4-Carbamimidoylbenzyl)-2-{1-[2-(2,5-dimethylphenyl)ethylamino]-4-methyl-2-oxo-1,2-dihydropyridin-3-yl}acetamide

$^1$H NMR (400 MHz, $CD_3OD$) δ 2.20 (s, 3H), 2.23 (s, 3H), 2.25 (s, 3H), 2.78 (t, 2H), 3.18 (t, 2H), 3.64 (s, 2H), 4.44 (s, 2H), 6.27 (d, 1H), 6.89 (d, 1H), 6.94-6.99 (m, 1H), 7.44 (d, 2H), 7.58 (d, 2H), 7.66 (d, 2H)

MS *m/z* 446.5 $(M+H)^+$

(xii) *N*-(2-Aminomethyl-5-chlorobenzyl)-2-[4-methyl-1-(naphthalene-1-sulfonylamino)-2-oxo-1,2-dihydropyridin-3-yl]acetamide

The Boc-protected specific amide (0.05 mmol; see Example 1 above) was dissolved in HCl/dioxane (2 mL, 4 M) and stirred at room temperature for 2 hours. The solvent was evaporated under reduced pressure and the residue was purified by chromatography ($SiO_2$, 10% methanol in DCM + 1% TEA). The compound was dissolved in DCM and was washed with water (2x), dried through a phase separator and the solvent was evaporated under reduced pressure to give the product.

1H NMR (500 MHz, $CD_3OD$) δ 2.15 (s, 3H), 3.23 (s, 2H), 4.20 (s, 2H), 4.33 (s, 2H), 5.98 (d, 1H), 6.88 (d, 1H), 7.34-7.38 (m, 2H), 7.43 (d, 1H), 7.48 (t, 1H), 7.59-7.65 (m, 2H), 8.00 (d, 2H), 8.13 (d, 1H), 8.73 (d, 1H)

MS *m/z* 525.2 $(M+H)^+$

(xiii) *N*-(6-Aminopyridin-3-ylmethyl)-2-{1-[2-(5-fluoro-2-methylphenyl)-ethylamino]-4-methyl-2-oxo-1,2-dihydropyridin-3-yl}acetamide

$^1H$ NMR (400 MHz, $CD_3OD$) δ 2.21 (s, 3H), 2.27 (s, 3H), 2.88 (s, 2H), 3.37 (s, 2H), 3.65 (s, 2H), 4.26 (s, 2H), 6.52 (d, 1H), 6.78 (s, 1H), 6.89 (d, 1H), 6.97 (d, 1H), 7.08 (dd, 1H), 7.78-7.88 (m, 4H)

MS *m/z* 424.6 $(M+H)^+$

(xiv) *N*-(6-Aminopyridin-3-ylmethyl)-2-{4-methyl-2-oxo-1-[2-(2-trifluoro-methylphenyl)ethylamino]-1,2-dihydropyridin-3-yl}acetamide

$^1H$ NMR (400 MHz, $CD_3OD$) δ 2.23 (s, 3H), 2.81-3.01 (m, 2H), 3.31 (s, 3H), 3.59 (s, 2H), 4.27 (s, 2H), 6.16-6.33 (m, 1H), 6.95-7.01 (m, 1H), 7.49-7.54 (m, 5H), 7.75-7.81 (m 1H), 7.86-7.93 (m, 1H)

MS *m/z* 460.5 $(M+H)^+$

(xv) *N*-[2-(Aminomethyl)-5-chlorobenzyl]-2-[1-(benzylamino)-4-methyl-2-oxo-1,2-dihydropyridin-3-yl]acetamide hydrochloride

$^1$H NMR (500 MHz, $CD_3OD$) δ 2.21 (s, 3H), 3.60 (s, 2H), 4.11 (s, 2H), 4.27 (s, 2H), 4.43 (s, 2H), 6.16 (d, 1H), 7.28-7.39 (m, 7H), 7.42 (d, 1H), 7.46-7.48 (m, 1H)

MS *m/z* 425.2 $(M+H)^+$

(xvi) *N*-[2-({[Amino(imino)methyl]amino}oxy)ethyl]-2-[1-(benzylamino)-4-methyl-2-oxo-1,2-dihydropyridin-3-yl]acetamide hydrochloride

Prepared according to General Method C above, except that the reaction was stirred for 7 hours at room temperature.

$^1$H NMR (500 MHz, $CD_3OD$) δ 2.27 (s, 3H), 3.52 (t, 2H), 3.61 (s, 2H), 3.98 (t, 2H), 4.18 (s, 2H), 5.51 (s, 1H), 6.22 (d, 1H), 7.29-7.37 (m, 5H), 7.39 (d, 1H)

MS *m/z* 373.1 $(M+H)^+$

(xvii) *N*-[(6-Amino-2-methylpyridin-3-yl)methyl]-2-[1-(benzylamino)-4-methyl-2-oxo-1,2-dihydropyridin-3-yl]acetamide hydrochloride

Prepared according to General Method C above, except that the reaction was stirred for 20 hours at room temperature.

$^1$H NMR (500 MHz, $CD_3OD$) δ 2.22 (s, 3H), 2.51 (s, 3H), 3.58 (s, 2H), 4.13 (s, 2H), 4.26 (s, 2H), 6.15 (d, 1H), 6.82 (d, 1H), 7.27- 7.36 (m, 6H), 7.87 (d, 1H)

MS *m/z* 392 $(M+H)^+$

(xviii) *N*-[2-(Aminomethyl)-5-chlorobenzyl]-2-{4-methyl-2-oxo-1-[(2-phenylethyl)amino]-1,2-dihydropyridin-3-yl}acetamide hydrochloride

Prepared according to General Method C above, except that the reaction was stirred for 90 minutes at room temperature.

$^1$H NMR (500 MHz, $CD_3OD$) δ 2.24 (s, 3H), 2.86 (t, 2H), 3.32-3.34 (m, 2H), 3.61(s, 2H), 4.25 (s, 2H), 4.42 (s, 2H), 6.34 (d, 1H), 7.17-7.25 (m, 3H), 7.26-7.30 (m, 2H), 7.34 (dd, 1H), 7.40-7.47 (m, 2H), 7.63 (d, 1H)
MS *m/z* 439 $(M+H)^+$

(xix) *N*-[(6-Amino-2-methylpyridin-3-yl)methyl]-2-{4-methyl-2-oxo-1-[(2-phenylethyl)amino]-1,2-dihydropyridin-3-yl}acetamide hydrochloride
Prepared according to General Method C above, except that the reaction was stirred for 90 minutes at room temperature.
$^1$H NMR (500 MHz,$CD_3OD$) δ 2.26 (s, 3H), 2.51 (s, 3H), 2.86 (t, 2H), 3.31-3.34 (m, 2H), 3.60 (s, 2H), 4.27 (s, 2H), 6.34 (d,1H), 6.81 (d,1H), 7.17-7.25 (m, 3H), 7.26-7.31 (m, 2H), 7.63 (d, 1H), 7.86 (d, 1H)
MS *m/z* 406 $(M+H)^+$

(xx) *N*-[2-(Aminomethyl)-5-chlorobenzyl]-2-{1-[(3-methoxybenzyl)-amino]-4-methyl-2-oxo-1,2-dihydropyridin-3-yl}acetamide hydrochloride
$^1$H NMR (500 MHz, $CD_3OD$) δ 2.12 (s, 3H), 3.51 (s, 2H), 3.68 (s, 3H), 4.00 (s, 2H), 4.17 (s, 2H), 4.33 (s, 2H), 6.07 (d, 1H), 6.74–6.82 (m, 3H), 7.13 (t, 1H), 7.25–7.29 (m, 2H), 7.34 (d, 1H), 7.37 (s, 1H)
MS *m/z* 457 $(M+H)^+$

(xxi) *N*-[(6-Amino-2-methylpyridin-3-yl)methyl]-2-{1-[(3-methoxybenzyl)-amino]-4-methyl-2-oxo-1,2-dihydropyridin-3-yl}acetamide hydrochloride
$^1$H NMR (500 MHz, $CD_3OD$) δ 2.23 (s, 3H), 2.52 (s, 3H), 3.60 (s, 2H), 3.77 (s, 3H), 4.11 (s, 2H), 4.27 (s, 2H), 6.17 (d, 1H), 6.80–6.92 (m, 4H), 7.23 (t, 1H), 7.37 (d, 1H), 7.87 (s, 1H)
MS *m/z* 422 $(M+H)^+$

(xxii) *N*-[2-(Aminomethyl)-5-chlorobenzyl]-2-{4-methyl-2-oxo-1-[(pyridin-3-ylmethyl)amino]-1,2-dihydropyridin-3-yl}acetamide

Prepared according to General Method C above, except that the reaction was stirred for 3 days at room temperature.

$^1$H NMR (500 MHz, $CD_3OD$) δ 8.92 (s, 1H), 8.82 (d, 1H), 8.66 (d, 1H), 8.08 (dd, 1H), 7.54 (d, 1H), 7.48 (d, 1H), 7.44 (d, 1H), 7.38 (dd, 1H), 6.22 (d, 1H), 4.43 (s, 4H), 4.28 (s, 2H), 3.58 (s, 2H), 2.20 (s, 3H)

MS *m/z* 428 $(M+H)^+$

(xxiii) *N*-[(6-Amino-2-methylpyridin-3-yl)methyl]-2-{4-methyl-2-oxo-1-[(pyridin-3-ylmethyl)amino]-1,2-dihydropyridin-3-yl}acetamide

Prepared according to General Method C above, except that the reaction was stirred for 3 days at room temperature.

$^1$H NMR (500 MHz, $CD_3OD$) δ 8.92 (s, 1H), 8.83 (d, 1H), 8.66 (d, 1H), 8.07 (t, 1H), 7.87 (d, 1H), 7.55 (d, 1H), 6.85 (d, 1H), 6.23 (d, 1H), 4.90 (d, 2H), 4.44 (s, 2H), 4.26 (s, 2H), 3.56 (s, 2H), 2.53 (s, 3H), 2.19 (s, 3H)

MS *m/z* 393 $(M+H)^+$

(xxiv) *N*-[2-(Aminomethyl)-5-chlorobenzyl]-2-(1-{[(2-methoxypyridin-3-yl)methyl]amino}-4-methyl-2-oxo-1,2-dihydropyridin-3-yl)acetamide acetate

Prepared according to General Method C above, except that the reaction was stirred for 3 days at room temperature. The crude product was purified by preparative HPLC.

$^1$H NMR (500 MHz, $CD_3OD$) δ 8.03 (dd, 1H), 7.52 (dd, 1H), 7.34-7.43 (m, 3H), 7.30 (dd, 1H), 6.85 (dd, 1H), 6.18 (d, 1H), 4.38 (s, 2H), 4.13 (s, 2H), 4.08 (s, 2H), 3.87 (s, 3H), 3.53 (s, 2H), 2.20 (s, 3H), 1.89 (s, 3H)

MS *m/z* 458 $(M+H)^+$

(xxv) *N*-[(6-Amino-2-methylpyridin-3-yl)methyl]-2-(1-{[(2-methoxy-pyridin-3-yl)methyl]amino}-4-methyl-2-oxo-1,2-dihydropyridin-3-yl)-acetamide acetate

Prepared according to General Method C above, except that the reaction was stirred for 3 days at room temperature. The crude product was purified by preparative HPLC.

$^1$H NMR (500 MHz, $CD_3OD$) δ 8.06 (dd, 1H), 7.54 (dd, 1H), 7.37-7.41 (m, 2H), 6.88 (dd, 1H), 6.41 (d, 1H), 6.20 (d, 1H), 4.23 (s, 2H), 4.15 (s, 2H), 3.90 (s, 3H), 3.54 (s, 2H), 2.34 (s, 3H), 2.23 (s, 3H), 1.97 (s, 3H)

MS *m/z* 423 $(M+H)^+$

(xxvi) *N*-[(6-Amino-2,4-dimethylpyridin-3-yl)methyl]-2-[5-(benzylamino)-2-methyl-6-oxocyclohexa-1,3-dien-1-yl]acetamide hydrochloride

Prepared according to General Method C above, except that the reaction was stirred overnight at room temperature.

$^1$H NMR (500 MHz,$CD_3OD$) δ 2.22 (s, 3H), 2.45 (s, 3H), 2.56 (s, 3H), 3.54 (br s, 2H), 4.11 (br s, 2H), 4.32 (s, 2H), 6.14 (br s, 1H), 6.68 (s, 1H), 7.27-7.36 (m, 6H)

(xxxvii) *N*-[2-(Aminomethyl)-5-methoxybenzyl]-2-{4-methyl-2-oxo-1-[(pyridin-3-ylmethyl)amino]-1,2-dihydropyridin-3-yl}acetamide

Prepared according to the procedure described in respect of Example 2 (xxvi) above.

$^1$H NMR (500 MHz, $CD_3OD$) δ 2.24 (s, 3H), 3.61 (s, 2H), 3.75 (s, 3H), 3.80 (s, 2H), 4.18 (s, 2H), 4.42 (s, 2H), 6.15 (d, 1H), 6.80 (d, 1H), 6.89 (s, 1H), 7.25 (d, 1H), 7.36 (d, 1H), 7.41 (dd, 1H), 7.84 (d, 1H), 8.52 (s, 1H), 8.47 (s, 2H)

MS *m/z* 422 $(M+H)^+$

(xxxviii) *N*-[2-(Aminomethyl)-5-(trifluoromethyl)benzyl]-2-{4-methyl-2-oxo-1-[(pyridin-3-ylmethyl)amino]-1,2-dihydropyridin-3-yl}acetamide

Prepared according to the procedure described in respect of Example 2 (xxvi) above.

$^1$H NMR (500 MHz, $CD_3OD$) δ 2.23 (s, 3H), 3.62 (s, 2H), 3.94 (s, 2H), 4.20 (s, 2H), 4.51 (s, 2H), 6.17 (d, 1H), 7.39 (d, 1H), 7.40-7.43 (m, 1H), 7.54-7.62 (m, 3H), 7.86 (d, 1H), 8.46-8.50 (m, 2H)

MS *m/z* 460 $(M+H)^+$

(xxxix) *N*-(1*H*-Benzimidazol-6-ylmethyl)-2-{4-methyl-2-oxo-1-[(pyridin-3-ylmethyl)amino]-1,2-dihydropyridin-3-yl}acetamide

The compound of Example 1(xxxiii) above (38 mg. 0.059 mmol) was reacted with TFA:water:thioanisole:1,2-ethanedithiol (2 mL of 35:2:2:1) for 3 hours. Acetic acid was added to the reaction mixture before the solvent was evaporated under reduced pressure. The residue was triturated with diethyl ether and the crude product was purified by preparative HPLC in order to provide the title compound.

$^1$H NMR (500 MHz, $CD_3OD$) δ 2.24 (s, 3H), 3.64 (s, 2H), 4.16 (s, 2H), 4.51 (s, 2H), 6.16 (d, 1H), 7.24 (d, 1H), 7.35 (d, 1H), 7.38 (dd, 1H), 7.54–7.58 (m, 2H), 7.78 (d, 1H), 8.13 (s, 1H), 7.44–7.46 (m, 2H)

MS *m/z* 403 $(M+H)^+$

(xl) *N*-[(5-Aminopyridin-2-yl)methyl]-2-{4-methyl-2-oxo-1-[(pyridin-3-ylmethyl)amino]-1,2-dihydropyridin-3-yl}acetamide

Prepared according to the procedure described in respect of Example 2 (xxvi) above.

$^1$H NMR (500 MHz, $CD_3OD$) δ 8.91 (s, 1H), 8.82 (d, 1H), 8.68 (d, 1H), 8.05-8.09 (m, 2H), 7.73 (dd, 1H), 7.67 (d, 1H), 7.58 (d, 1H), 6.28 (d, 1H), 4.58 (s, 2H), 4.49 (s, 2H), 3.62 (s, 2H), 2.25 (s, 3H)

(xli) *N*-[2-(Aminomethyl)-5-chlorobenzyl]-2-{1-[(2,2-difluoro-2-pyridin-2-ylethyl)amino]-4-methyl-2-oxo-1,2-dihydropyridin-3-yl}acetamide

Prepared according to the procedure described in respect of Example 2 (xxvi) above.

$^1$H NMR (500 MHz, $CD_3OD$) δ 8.73 (m, 1H), 8.21 (m, 1H), 7.95 (m, 1H), 7.73 (m, 1H), 7.45 (m, d, 1H), 7.40-7.44 (m, 2H), 7.35 (dd, 1H), 6.23 (dd, 1H), 4.42 (s, 2H), 4.26 (s, 2H), 3.90 (m, 2H), 3.59 (s, 2H), 2.23 (s, 3H)

MS *m/z* 474 $(M+H)^+$

(xlii) *N*-[2-(Aminomethyl)-5-chlorobenzyl]-2-(1-{[2,2-difluoro-2-(1-oxido-pyridin-2-yl)ethyl]amino}-4-methyl-2-oxo-1,2-dihydropyridin-3-yl)-acetamide

Prepared according to the procedure described in respect of Example 2 (xxvi) above.

$^1$H NMR (500 MHz, $CD_3OD$) δ 8.26 (d, 1H), 7.92 (dd, 1H), 7.60-7.70 (m, 2H), 7.49 (d, 1H), 7.36-7.43 (m, 2H), 7.16 (d, 1H), 6.05 (d, 1H), 4.43 (s, 2H), 4.26 (s, 2H), 4.20 (m, 2H), 3.54 (s, 2H), 2.20 (s, 3H)

MS *m/z* 492 $(M+H)^+$

(xliii) *N*-[2-(Aminomethyl)-5-chlorobenzyl]-2-(4-methyl-2-oxo-1-{[(2-oxo-1,2-dihydropyridin-3-yl)methyl]amino}-1,2-dihydropyridin-3-yl)acetamide acetate

Prepared from the compound of Example 1(xxvi) by using General Method B above and employing an extended reaction time. The title compound was isolated by Prep-HPLC.

$^1$H NMR (500 MHz, $CD_3OD$) δ 7.51 (d, 1H), 7.43 (dd, 1H), 7.34-7.44 (m, 3H), 7.30 (d, 1H), 6.28 (t, 1H), 6.22 (d, 1H), 4.38 (s, 2H), 4.14 (s, 2H), 3.97 (s, 2H), 3.50 (s, 2H), 2.21 (s, 3H), 1.90 (s, 3H)

MS *m/z* 442 $(M+H)^+$

Example 3

Compounds (i) to (xiii) below were prepared according to the following general method.

The relevant esters (as obtained from Preparation 4 above) were dissolved in THF (4mL). Aqueous LiOH (2.5 mL of 0.5 M, 1.3 mmol) was added to the resultant solution. The reaction mixtures were shaken at room temperature for 5 to 25 hours. The solvent was then evaporated under reduced pressure to give the corresponding carboxylic acids as lithium salts, which were stored at -80C and used then without further purification.

The crude carboxylic acid salts were dissolved in DMF (1 mL) and *N*-methylmorpholine (88 μL, 0.8 mmol) was added. TBTU (192 mg, 0.6 mmol) was dissolved in 0.5 mL of DMF and added to each reaction mixture, and the reaction mixtures were then shaken at room temperature for 30 min. A solution of 2-[2-(aminomethyl)-4-chlorophenoxy]-*N*-ethylacetamide (1 mol equiv; see List 5 above) in DMF (1 mL) was then added to each reaction mixture. The reaction mixtures were shaken at room temperature overnight before being filtered and evaporated to dryness. The crude mixtures were purified by preparative HPLC (see General Experimental Details above) to give the amides listed below as oils or solids. The yields over three steps for these amides were 7 to 29% (Purity >85%; UV at 215nm).

(i) 2-{4-Chloro-2-[({[1-(isobutylamino)-4-methyl-2-oxo-1,2-dihydro-pyridin-3-yl]acetyl}amino)methyl]phenoxy}-*N*-ethylacetamide

$^1$H NMR (500 MHz, DMSO-$d_6$) δ 8.29 (t, 1H), 8.04 (t, 1H), 7.56 (d, 1H), 7.26 (m, 2H), 6.92 (d, 1H), 6.42 (t, 1H), 6.11 (d, 1H), 4.46 (s, 2H), 4.33 (d, 2H), 3.47 (s, 2H), 3.10 (q, 2H), 2.71 (t, 2H), 2.12 (s, 3H), 1.68 (m, 1H), 0.99 (t, 3H), 0.92 (d, 6H).

MS *m/z* 463.4 $(M+H)^+$

(ii) 2-[4-Chloro-2-({[(4-methyl-2-oxo-1-{[(1-phenyl-1*H*-pyrazol-5-yl)-methyl]amino}-1,2-dihydropyridin-3-yl)acetyl]amino}methyl)phenoxy]-*N*-ethylacetamide

$^1$H NMR (500 MHz, DMSO-$d_6$) δ 8.28 (t, 1H), 8.04 (t, 1H), 7.60 (d, 1H), 7.51 (m, 4H), 7.42 (t, 1H), 7.26 (m, 2H), 7.19 (d, 1H), 6.91 (m, 2H), 6.35 (d, 1H), 5.99 (d, 1H), 4.46 (s, 2H), 4.32 (d, 2H), 4.22 (d, 2H), 3.44 (s, 2H), 3.09 (q, 2H), 2.09 (s, 3H), 0.98 (t, 3H).

MS *m/z* 563. $(M+H)^+$

(iii) 2-{4-Chloro-2-[({[1-({[2,5-dimethyl-1-(4*H*-1,2,4-triazol-4-yl)-1*H*-pyrrol-3-yl]methyl}amino)-4-methyl-2-oxo-1,2-dihydropyridin-3-yl]-acetyl}amino)methyl]phenoxy}-*N*-ethylacetamide

$^1$H NMR (500 MHz, DMSO-$d_6$) δ 9.01 (s, 2H), 8.32 (t, 1H), 8.04 (t, 1H), 7.42 (d, 1H), 7.26 (m, 2H), 6.92 (d, 1H), 6.37 (t, 1H), 6.10 (d, 1H), 5.97 (s, 1H), 4.46 (s, 2H), 4.33 (d, 2H), 3.83 (d, 2H), 3.48 (s, 2H), 3.10 (q, 2H), 2.13 (s, 3H), 1.91 (s, 3H), 1.77 (s, 1H), 0.99 (t, 3H).

MS *m/z* 581.5 $(M+H)^+$

(iv) 2-(1-{[(4-Benzoyl-1-methyl-1*H*-pyrrol-2-yl)methyl]amino}-4-methyl-2-oxo-1,2-dihydropyridin-3-yl)-*N*-{5-chloro-2-[2-(ethylamino)-2-oxoethoxy]benzyl}acetamide

$^1$H NMR (500 MHz, DMSO-$d_6$) δ 8.31 (t, 1H), 8.05 (t, 1H), 7.70 (d, 2H), 7.58 (m, 1H), 7.47 (m, 3H), 7.29 (m, 3H), 6.92 (d, 1H), 6.70 (t, 1H), 6.30 (s, 1H), 6.05 (d, 1H), 4.47 (s, 2H), 4.33 (d, 2H), 4.10 (d, 2H), 3.76 (s, 3H), 3.49 (s, 2H), 3.11 (q, 2H), 2.12 (s, 3H), 1.00 (t, 3H).

MS *m/z* 604.5 $(M+H)^+$

(v) 2-(4-Chloro-2-{[({1-[(2,3-dihydro-1-benzofuran-5-ylmethyl)amino]-4-methyl-2-oxo-1,2-dihydropyridin-3-yl}acetyl)amino]methyl}phenoxy)-*N*-ethylacetamide

$^1$H NMR (500 MHz, DMSO-$d_6$) δ 8.29 (t, 1H), 8.05 (t, 1H), 7.40 (d, 1H), 7.26 (m, 2H), 7.20 (s, 1H), 7.00 (d, 1H), 6.92 (d, 1H), 6.68 (d, 1H), 6.59 (t, 1H), 6.04 (d, 1H), 4.50 (m, 4H), 4.33 (d, 2H), 3.96 (d, 2H), 3.48 (s, 2H), 3.12 (m, 4H), 2.11 (s, 3H), 1.00 (t, 3H).

MS *m/z* 538.8 $(M+H)^+$

(vi) 2-[4-Chloro-2-({[(1-{[(2,4-dimethyl-1,3-thiazol-5-yl)methyl]amino}-4-methyl-2-oxo-1,2-dihydropyridin-3-yl)acetyl]amino}methyl)phenoxy]-*N*-ethylacetamide

$^1$H NMR (500 MHz, DMSO-$d_6$) δ 8.29 (t, 1H), 8.05 (m, 1H), 7.28 (m, 2H), 7.22 (d, 1H), 6.92 (d, 1H), 6.84 (t, 1H), 6.01 (d, 1H), 4.47 (s, 2H), 4.33 (d, 2H), 4.19 (d, 2H), 3.48 (s, 2H), 3.11 (q, 2H), 2.55 (s, 3H), 2.11 (s, 3H), 2.03 (s, 3H), 1.00 (t, 3H).

MS *m/z* 532.2 $(M+H)^+$

(vii) 2-[4-Chloro-2-({[(1-{[(1,5-dimethyl-1*H*-pyrazol-4-yl)methyl]amino}-4-methyl-2-oxo-1,2-dihydropyridin-3-yl)acetyl]amino}methyl)phenoxy]-*N*-ethylacetamide

$^1$H NMR (500 MHz, DMSO-$d_6$) δ 8.29 (t, 1H), 8.05 (m, 1H), 7.36 (d, 1H), 7.26 (m, 2H), 7.20 (s, 1H), 6.92 (d, 1H), 6.39 (t, 1H), 6.05 (d, 1H), 4.47 (s, 2H), 4.33 (d, 2H), 3.86 (d, 2H), 3.67 (s, 3H), 3.48 (s, 2H), 3.11 (q, 2H), 2.13 (s, 3H), 2.12 (s, 3H), 1.00 (t, 3H).

MS *m/z* 514.8 $(M+H)^+$

(viii) 2-{4-Chloro-2-[({[4-methyl-2-oxo-1-({[1-(phenylsulfonyl)-1*H*-pyrrol-2-yl]methyl}amino)-1,2-dihydropyridin-3-yl]acetyl}amino)methyl]-phenoxy}-*N*-ethylacetamide

$^1$H NMR (500 MHz, DMSO-$d_6$) δ 8.26 (t, 1H), 8.04 (t, 1H), 7.96 (d, 2H), 7.27 (t, 1H), 7.61 (t, 2H), 7.43 (dd, 1H), 7.25 (m, 2H), 6.93 (m, 2H), 6.78 (t, 1H), 6.23 (t, 1H), 6.10 (m, 1H), 5.96 (d, 1H), 4.47 (s, 2H), 4.32 (d, 2H), 4.23 (d, 2H), 3.44 (s, 2H), 3.10 (q, 2H), 2.08 (s, 3H), 0.99 (t, 3H).

MS *m/z* 626.4 $(M+H)^+$

(ix) 2-[4-Chloro-2-({[(1-{[(3,5-dimethylisoxazol-4-yl)methyl]amino}-4-methyl-2-oxo-1,2-dihydropyridin-3-yl)acetyl]amino}methyl)phenoxy]-*N*-ethylacetamide

$^1$H NMR (500 MHz, DMSO-$d_6$) δ 1.01 (t, 3H), 2.10 (s, 3H), 2.12 (s, 3H), 2.16 (s, 3H), 3.12 (p, 2H), 3.47 (s, 2H), 3.89 (d, 2H), 4.32 (d, 2H), 4.48 (s, 2H), 6.02 (d, 1H), 6.67 (t, 1H), 6.93 (d, 1H), 7.21-7.31 (m, 3H), 8.05 (t, 1H), 8.31 (t, 1H)

MS *m/z* 516.4 $(M+H)^+$

(x) 2-[4-Chloro-2-({[(1-{[(4-chloro-2-phenyl-1*H*-imidazol-5-yl)methyl]-amino}-4-methyl-2-oxo-1,2-dihydropyridin-3-yl)acetyl]amino}methyl)-phenoxy]-*N*-ethylacetamide

$^1$H NMR (500 MHz, DMSO-$d_6$) δ 1.01 (t, 3H), 2.11 (s, 3H), 3.13 (p, 2H), 3.49 (s, 2H), 4.12 (d, 2H), 4.33 (d, 2H), 4.48 (s, 2H), 6.02 (d, 1H), 6.91-6.95 (m, 1H), 6.98 (t, 1H), 7.20 (d, 1H), 7.25-7.28 (m, 2H), 7.37 (t, 1H), 7.46 (t, 2H), 7.90 (d, 2H), 8.05 (t, 1H), 8.31 (t, 1H), 12.98 (s, 1H)

MS *m/z* 539.4 $(M+H)^+$

(xi) 2-{1-[(2,1,3-Benzoxadiazol-5-ylmethyl)amino]-4-methyl-2-oxo-1,2-dihydropyridin-3-yl}-*N*-{5-chloro-2-[2-(ethylamino)-2-oxoethoxy]benzyl}-acetamide

$^1$H NMR (500 MHz, DMSO-$d_6$) δ 1.00 (t, 3H), 2.09 (s, 3H), 3.10 (p, 2H), 3.46 (s, 2H), 4.25 (d, 2H), 4.32 (d, 2H), 4.48 (s, 2H), 6.02 (d, 1H), 6.93 (d, 1H), 7.14 (t, 1H), 7.24-7.28 (m, 2H), 7.45 (d, 1H), 7.68 (d, 1H), 7.83 (s, 1H), 8.00-8.07 (m, 2H), 8.28 (t, 1H)

MS *m/z* 539.4 $(M+H)^+$

(xii) 2-(4-Chloro-2-{[({4-methyl-2-oxo-1-[(pyrazin-2-ylmethyl)amino]-1,2-dihydropyridin-3-yl}acetyl)amino]methyl}phenoxy)-*N*-ethylacetamide

MS *m/z* 499.4 $(M+H)^+$

(xiii) 2-(4-Chloro-2-{[({1-[(cyclopentylmethyl)amino]-4-methyl-2-oxo-1,2-dihydropyridin-3-yl}acetyl)amino]methyl}phenoxy)-*N*-ethylacetamide

$^1$H NMR (500 MHz, DMSO-$d_6$) δ 1.00 (t, 3H), 1.18-1-26 (m, 2H), 1.43-1.59 (m, 4H), 1.69-1.77 (m, 2H), 1.91-1.99 (m,1H), 2.12 (s, 3H), 2.83 (t, 2H), 3.10 (p, 2H), 3.47 (s, 2H), 4.32 (d, 2H), 4.46 (s, 2H), 6.12 (d, 1H), 6.39 (t, 1H), 6.92 (d, 1H), 7.24-7.28 (m, 2H), 7.57 (d, 1H), 8.03 (t, 1H), 8.29 (t, 1H)

MS *m/z* 489.4 $(M+H)^+$

Example 4

Compounds (i) to (xxix) below were prepared according to the following general method.

The relevant esters (as obtained from Preparation 4 above) were dissolved in THF (4mL). Aqueous LiOH (2.5 mL of 0.5 M, 1.3 mmol) was added to the resultant solution. The reaction mixtures were shaken at room temperature for 5 to 25 hours. The solvent was then evaporated under

reduced pressure to give the corresponding carboxylic acids as lithium salts, which were stored at -80C and used then without further purification.

The crude carboxylic acid salts were dissolved in DMF (1 mL) and *N*-methylmorpholine (88 μL, 0.8 mmol) was added. TBTU (192 mg, 0.6 mmol) was dissolved in 0.5 mL of DMF and added to each reaction mixture, and the reaction mixtures were then shaken at room temperature for 30 min. A solution of the specific amine (1 mol equiv; see List 5 above) in DMF (1 mL) was then added to each reaction mixture. The reaction mixtures were shaken at room temperature overnight before being filtered and evaporated to dryness.

The resulting residues (Boc-protected amides) were dissolved in TFA (1.5 mL), shaken at room temperature for 1 hour and then concentrated in vacuo. The crude mixtures were purified by preparative HPLC (see General Experimental Details above) to give the amides listed below as oils or solids. The yields over four steps for these amides were 2 to 47% (Purity >87%; UV at 215nm).

(i) *N*-[2-(Aminomethyl)-5-chlorobenzyl]-2-(4-methyl-2-oxo-1-{[(5-pyridin-2-yl-2-thienyl)methyl]amino}-1,2-dihydropyridin-3-yl)acetamide

$^1$H NMR (500 MHz, DMSO-$d_6$) δ 2.11 (s, 3H), 3.48 (s, 2H), 3.83 (s, 2H), 4.27-4.35 (m, 4H), 6.03 (d, 1H), 6.91 (d, 1H), 7.03 (t, 1H), 7.24-7.29 (m, 2H), 7.30 (s, 1H), 7.38-7.42 (m, 2H), 7.60 (d, 1H), 7.81 (dt, 1H), 7.86 (d, 1H), 8.38 (t, 1H), 8.51 (d, 1H).

MS *m/z* 508.4 $(M+H)^+$

(ii) *N*-[2-(Aminomethyl)-5-chlorobenzyl]-2-(1-{[(5-chloro-1,3-dimethyl-1*H*-pyrazol-4-yl)methyl]amino}-4-methyl-2-oxo-1,2-dihydropyridin-3-yl)-acetamide

$^1$H NMR (500 MHz, DMSO-$d_6$) δ 2.04 (s, 3H), 2.13 (s, 3H), 3.48 (s, 2H), 3.67 (s, 3H), 3.72 (s, 2H), 3.88 (d, 2H), 4.29 (d, 2H), 6.02 (d, 1H), 6.61 (t, 1H), 7.17 (d, 1H), 7.24-7.28 (m, 2H), 7.39 (d, 1H), 8.32 (t, 1H)
MS *m/z* 476.7 $(M+H)^+$

(iii) *N*-[2-(Aminomethyl)-5-chlorobenzyl]-2-(1-{[(6-chloro-1,3-benzodioxol-5-yl)methyl]amino}-4-methyl-2-oxo-1,2-dihydropyridin-3-yl)-acetamide
$^1$H NMR (500 MHz, DMSO-$d_6$) δ 8.32 (t, 1H), 7.35-7.41 (m, 2H), 7.24-7.29 (m, 2H), 7.04 (s, 1H), 7.01 (s, 1H), 6.87 (t, 1H), 6.06 (m, 3H), 4.29 (d, 2H), 4.10 (d, 2H), 3.73 (s, 2H), 3.47 (s, 2H), 2.13 (s, 3H)
MS *m/z* 502.7 $(M+H)^+$

(iv) *N*-[(6-amino-2,4-dimethylpyridin-3-yl)methyl]-2-(4-methyl-1-{[(1-methyl-1*H*-imidazol-2-yl)methyl]amino}-2-oxo-1,2-dihydropyridin-3-yl)-acetamide
$^1$H NMR (500 MHz, DMSO-$d_6$) δ 7.79 (t, 1H), 7.18 (d, 1H), 7.09 (s, 1H), 6.80 (t, 1H), 6.74 (s, 1H), 6.10 (s, 1H), 5.99 (d, 1H), 5.62 (s, 2H), 4.11 (m, 4H), 3.66 (s, 2H), 2.27 (s, 3H), 2.13 (s, 3H), 2.09 (s, 3H)
MS *m/z* 409.8 $(M+H)^+$

(v) *N*-[(6-Amino-2,4-dimethylpyridin-3-yl)methyl]-2-{1-[(cyclohexylmethyl)amino]-4-methyl-2-oxo-1,2-dihydropyridin-3-yl}acetamide
$^1$H NMR (500 MHz, DMSO-$d_6$) δ 7.76 (t, 1H), 7.52 (d, 1H), 6.41 (t, 1H), 6.09-6.13 (m, 2H), 5.65 (s, 2H), 4.10 (d, 2H), 3.39 (s, 2H), 2.71 (t, 2H), 2.25 (s, 3H), 2.11 (s, 6H), 1.77 (d, 2H), 1.57-1.71 (m, 3H), 1.39 (m, 1H), 1.10-1.25 (m, 3H), 0.88-0.98 (m, 2H)
MS *m/z* 412.4 $(M+H)^+$

(vi) *N*-[(6-Amino-2,4-dimethylpyridin-3-yl)methyl]-2-(4-methyl-1-{[(4-methyl-3,4-dihydro-2*H*-1,4-benzoxazin-7-yl)methyl]amino}-2-oxo-1,2-dihydropyridin-3-yl)acetamide

MS *m/z* 477.5 $(M+H)^+$

(vii) *N*-[(6-Amino-2,4-dimethylpyridin-3-yl)methyl]-2-{1-[(4-cyano-benzyl)amino]-4-methyl-2-oxo-1,2-dihydropyridin-3-yl}acetamide

$^1$H NMR (500 MHz, DMSO-$d_6$) δ 7.74-7.80 (m, 3H), 7.51 (d, 2H), 7.33-7.37 (m, 1H), 7.06 (t, 1H), 6.10 (s, 1H), 6.00 (d, 1H), 5.63 (s, 2H), 4.15 (d, 2H), 4.11 (d, 2H), 3.38 (s, 2H), 2.26 (s, 3H), 2.13 (s, 3H), 2.08 (s, 3H)

MS *m/z* 430.8 $(M+H)^+$

(viii) *N*-[(6-Amino-2-methylpyridin-3-yl)methyl]-2-{4-methyl-2-oxo-1-[(2-phenoxybenzyl)amino]-1,2-dihydropyridin-3-yl}acetamide

$^1$H NMR (500 MHz, DMSO-$d_6$) δ 7.95 (t, 1H), 7.45 (d, 1H), 7.25-7.36 (m, 4H), 7.08-7.19 (m, 3H), 6.96 (t, 1H), 6.89 (d, 1H), 6.81 (d, 1H), 6.21 (d, 1H), 6.00 (d, 1H), 5.69 (s, 2H), 4.13 (d, 2H), 4.03 (d, 2H), 3.36 (s, 2H), 2.21 (s, 3H), 2.09 (s, 3H)

MS *m/z* 484.4 $(M+H)^+$

(ix) *N*-[2-(Aminomethyl)-5-chlorobenzyl]-2-(1-{[(1-ethyl-3-methyl-1*H*-pyrazol-4-yl)methyl]amino}-4-methyl-2-oxo-1,2-dihydropyridin-3-yl)-acetamide

$^1$H NMR (500 MHz, DMSO-$d_6$) δ 8.33 (t, 1H), 7.46 (s, 1H), 7.21-7.41 (m, 4H), 6.45 (t, 1H), 6.05 (d, 1H), 4.29 (d, 2H), 3.97 (q, 2H), 3.88 (d, 2H), 3.72 (s, 2H), 3.48 (s, 2H), 2.13 (s, 3H), 2.08 (s, 3H), 1.28 (t, 3H)

MS *m/z* 456.8 $(M+H)^+$

(x) *N*-[2-(Aminomethyl)-5-chlorobenzyl]-2-(4-methyl-1-{[(4-methyl-1*H*-imidazol-5-yl)methyl]amino}-2-oxo-1,2-dihydropyridin-3-yl)acetamide
MS *m/z* 428.8 $(M+H)^+$

(xi) *N*-[2-(Aminomethyl)-5-chlorobenzyl]-2-(1-{[(5-chloro-1-methyl-3-phenyl-1*H*-pyrazol-4-yl)methyl]amino}-4-methyl-2-oxo-1,2-dihydropyridin-3-yl)acetamide
$^1$H NMR (500 MHz, DMSO-$d_6$) δ 2.11 (s, 3H), 3.46 (s, 2H), 3.73 (s, 2H), 3.80 (s, 3H), 4.05 (d, 2H), 4.30 (d, 2H), 5.97 (d, 1H), 6.85 (t, 1H), 7.08 (d, 1H), 7.26 (s, 2H), 7.36-7.41 (m, 3H), 7.44 (t, 1H), 7.78 (d, 2H), 8.33 (t, 1H)
MS *m/z* 538.8 $(M+H)^+$

(xii) *N*-[2-(Aminomethyl)-5-chlorobenzyl]-2-(4-methyl-1-{[(2-morpholin-4-ylpyridin-3-yl)methyl]amino}-2-oxo-1,2-dihydropyridin-3-yl)acetamide
$^1$H NMR (500 MHz, DMSO-$d_6$) δ 2.13 (s, 3H), 3.08 (t, 4H), 3.46 (s, 2H), 3.66-3.76 (m, 6H), 4.12 (d, 2H), 4.30 (d, 2H), 6.07 (d, 1H), 6.97-7.04 (m, 2H), 7.23-7.29 (m, 2H), 7.40 (t, 2H), 7.69 (dd, 1H), 8.21 (dd, 1H), 8.33 (t, 1H)
MS *m/z* 510.8 $(M+H)^+$

(xiii) *N*-[2-(Aminomethyl)-5-chlorobenzyl]-2-{1-[(3,3-dimethylbutyl)-amino]-4-methyl-2-oxo-1,2-dihydropyridin-3-yl}acetamide
$^1$H NMR (500 MHz, DMSO-$d_6$) δ 0.86 (s, 9H), 1.36 (t, 2H), 2.14 (t, 3H), 2.86-2.96 (m, 2H), 3.48 (s, 2H), 3.80 (s, 2H), 4.30 (d, 2H), 6.16 (d, 1H), 6.36 (t, 1H), 7.22-7.29 (m, 2H), 7.39 (d, 1H), 7.60 (d, 1H), 8.37 (t, 1H)
MS *m/z* 419.4 $(M+H)^+$

(xiv) *N*-[2-(Aminomethyl)-5-chlorobenzyl]-2-(1-{[(5-chloro-2-thienyl)-methyl]amino}-4-methyl-2-oxo-1,2-dihydropyridin-3-yl)acetamide

MS *m/z* 464.7 $(M+H)^+$

(xv) *N*-[2-(Aminomethyl)-5-chlorobenzyl]-2-{1-[(3-cyano-4-fluorobenzyl)-amino]-4-methyl-2-oxo-1,2-dihydropyridin-3-yl}acetamide

$^1$H NMR (500 MHz, DMSO-$d_6$) δ 2.11 (s, 3H), 3.46 (s, 2H), 3.74 (s, 2H), 4.14 (d, 2H), 4.29 (d, 2H), 6.05 (d, 1H), 7.02 (t, 1H), 7.15-7.20 (m, 1H), 7.22-.730 (m, 2H), 7.36-7.49 (m, 3H), 7.67-7.74 (m, 1H), 7.88 (dd, 1H), 8.32 (t, 1H)

MS *m/z* 467.7 $(M+H)^+$

(xvi) *N*-[2-(Aminomethyl)-5-chlorobenzyl]-2-(4-methyl-1-{[(5-methyl-3-phenylisoxazol-4-yl)methyl]amino}-2-oxo-1,2-dihydropyridin-3-yl)-acetamide

$^1$H NMR (500 MHz, DMSO-$d_6$) δ 2.12 (s, 3H), 2.17 (s, 3H), 3.46 (s, 2H), 3.73 (s, 2H), 4.00 (d, 2H), 4.30 (d, 2H), 5.99 (d, 1H), 6.87 (t, 1H), 7.14 (d, 1H), 7.24-7.29 (m, 2H), 7.39 (d, 1H), 7.49-7.56 (m, 3H), 7.79-7.85 (m, 2H), 8.37 (t, 1H).

MS *m/z* 505.8 $(M+H)^+$

(xvii) *N*-[2-(Aminomethyl)-5-chlorobenzyl]-2-(4-methyl-2-oxo-1-{[3-(trifluoromethoxy)benzyl]amino}-1,2-dihydropyridin-3-yl)acetamide

$^1$H NMR (500 MHz, DMSO-$d_6$) δ 2.11 (t, 3H), 3.47 (s, 2H), 3.83 (s, 2H), 4.16 (d, 2H), 4.30 (d, 2H), 6.04 (d, 1H), 6.96 (t, 1H), 7.23-7.37 (m, 6H), 7.38-7.49 (m, 4H), 8.38 (t, 1H)

MS *m/z* 509.4 $(M+H)^+$

(xviii) *N*-[2-(Aminomethyl)-5-chlorobenzyl]-2-{1-[(5-chloro-2-fluoro-benzyl)amino]-4-methyl-2-oxo-1,2-dihydropyridin-3-yl}acetamide

$^1$H NMR (500 MHz, DMSO-$d_6$) δ 2.12 (s, 3H), 3.46 (s, 2H), 3.86 (s, 2H), 4.14 (d, 2H), 4.29 (d, 2H), 6.07 (d, 1H), 6.98 (t, 1H), 7.22 (t, 1H), 7.25-7.29 (m, 2H), 7.35-7.44 (m, 3H), 7.49 (dd, 1H), 8.35 (t, 1H).
MS *m/z* 477.3 $(M+H)^+$

(xix) *N*-[2-(Aminomethyl)-5-chlorobenzyl]-2-(4-methyl-1-{[(2-methyl-1*H*-imidazol-5-yl)methyl]amino}-2-oxo-1,2-dihydropyridin-3-yl)acetamide
$^1$H NMR (500 MHz, DMSO-$d_6$) δ 2.12 (s, 3H), 2.22 (s, 3H), 3.48 (s, 2H), 3.72 (s, 2H), 3.92 (d, 2H), 4.29 (d, 2H), 6.05 (d, 1H), 6.64 (t, 1H), 6.71 (s, 1H), 7.24-7.27 (m, 2H), 7.37-7.41 (m, 2H), 8.32 (t, 1H).
MS *m/z* 428.8 $(M+H)^+$

(xx) *N*-[2-(Aminomethyl)-5-chlorobenzyl]-2-{1-[(2-fluoro-5-methoxy-benzyl)amino]-4-methyl-2-oxo-1,2-dihydropyridin-3-yl}acetamide
$^1$H NMR (500 MHz, DMSO-$d_6$) δ 2.12 (s, 3H), 3.47 (s, 2H), 3.69 (s, 3H), 3.83 (s, 2H), 4.13 (d, 2H), 4.30 (d, 2H), 6.04 (d, 1H), 6.83-6.87 (m, 1H), 6.90-6.94 (m, 2H), 7.07 (t, 1H), 7.26-7.31 (m, 2H), 7.36 (d, 1H), 7.40 (d, 1H), 8.38 (t, 1H).
MS *m/z* 473.4 $(M+H)^+$

(xxi) *N*-[2-(Aminomethyl)-5-chlorobenzyl]-2-{4-methyl-1-[(2-morpholin-4-ylbenzyl)amino]-2-oxo-1,2-dihydropyridin-3-yl}acetamide
MS *m/z* 509.8 $(M+H)^+$

(xxii) *N*-[2-(Aminomethyl)-5-chlorobenzyl]-2-(1-{[(1,3-dimethyl-5-morpholin-4-yl-1*H*-pyrazol-4-yl)methyl]amino}-4-methyl-2-oxo-1,2-dihydropyridin-3-yl)acetamide
$^1$H NMR (500 MHz, DMSO-$d_6$) δ 1.94 (s, 3H), 2.14 (s, 3H), 2.98-3.02 (m, 4H), 3.50 (s, 2H), 3.55 (s, 3H), 3.65-3.69 (m, 4H), 3.72 (s, 2H), 3.91 (d,

2H), 4.29 (d, 2H), 6.05 (d, 1H), 6.41 (t , 1H), 7.23-7.27 (m, 2H), 7.29 (d, 1H), 7.39 (d, 1H), 8.35 (t, 1H).
MS *m/z* 527.8 $(M+H)^+$

(xxiii) *N*-[2-(Aminomethyl)-5-chlorobenzyl]-2-{4-methyl-2-oxo-1-[(quinolin-8-ylmethyl)amino]-1,2-dihydropyridin-3-yl}acetamide
MS *m/z* 475.8 $(M+H)^+$

(xxiv) *N*-[2-(Aminomethyl)-5-chlorobenzyl]-2-[4-methyl-2-oxo-1-({[5-(2-thienyl)isoxazol-3-yl]methyl}amino)-1,2-dihydropyridin-3-yl]acetamide
$^1$H NMR (500 MHz, DMSO-$d_6$) δ 2.11 (s, 3H), 3.47 (s, 2H), 3.72 (s, 2H), 4.23 (d, 2H), 4.28 (d, 2H), 6.05 (d, 1H), 6.91 (s , 1H), 7.14 (t 1H), 7.22-7.27 (m, 3H), 7.39 (d, 1H), 7.46 (d, 1H), 7.69 (d, 1H), 7.82 (d, 1H), 8.33 (t, 1H).
MS *m/z* 497.7 $(M+H)^+$

(xxv) *N*-[2-(Aminomethyl)-5-fluorobenzyl]-2-{4-methyl-2-oxo-1-[(2-phenylpropyl)amino]-1,2-dihydropyridin-3-yl}acetamide
$^1$H NMR (500 MHz, DMSO-$d_6$) δ 1.25 (d, 3H), 2.13 (s, 3H), 2.86-2.92 (m, 1H), 3.03-3.09 (m, 1H), 3.13-3.19 (m, 1H), 3.46 (s, 2H), 3.75 (s, 2H), 4.30 (d, 2H), 6.11 (d, 1H), 6.38 (t , 1H), 6.99-7.05 (m, 2H), 7.18-7.32 (m, 5H), 7.37 (dd, 1H), 7.48 (d, 1H), 8.35 (t, 1H).
MS *m/z* 437.5 $(M+H)^+$

(xxvi) *N*-[2-(Aminomethyl)-5-methylbenzyl]-2-{1-[(bicyclo[2.2.1]hept-5-en-2-ylmethyl)amino]-4-methyl-2-oxo-1,2-dihydropyridin-3-yl}acetamide
MS *m/z* 421.4 $(M+H)^+$

(xxvii) *N*-[2-(Aminomethyl)-5-methylbenzyl]-2-[1-({3-[(2-chloro-1,3-thiazol-5-yl)methoxy]benzyl}amino)-4-methyl-2-oxo-1,2-dihydropyridin-3-yl]acetamide

MS *m/z* 552.4 $(M+H)^+$

(xxviii) *N*-[2-(Aminomethyl)-5-methylbenzyl]-2-(4-methyl-1-{[(3-methyl-5-phenylisoxazol-4-yl)methyl]amino}-2-oxo-1,2-dihydropyridin-3-yl)-acetamide

$^1$H NMR (500 MHz, DMSO-$d_6$) δ 2.09 (s, 3H), 2.19 (s, 3H), 2.24 (s, 3H), 3.42 (s, 2H), 3.76 (s, 2H), 4.06 (d, 2H), 4.28 (d, 2H), 5.99 (d, 1H), 6.91 (t, 1H), 7.03 (d, 1H), 7.07 (s, 1H), 7.23 (d, 1H), 7.25 (d, 1H), 7.49-7.56 (m, 3H), 7.76 (d, 1H), 7.80 (d, 1H), 8.36 (t, 1H).

MS *m/z* 486.5 $(M+H)^+$

(xxix) *N*-[2-(Aminomethyl)-5-methylbenzyl]-2-(1-{[(1,3-dimethyl-5-morpholin-4-yl-1*H*-pyrazol-4-yl)methyl]amino}-4-methyl-2-oxo-1,2-dihydropyridin-3-yl)acetamide

MS *m/z* 508.5 $(M+H)^+$

Example 5

The following compounds were prepared, from appropriate intermediates (such as those described hereinbefore), according to or by analogy with methods described herein:

(1) *N*-[(6-amino-2-methylpyridin-3-yl)methyl]-2-(4-methyl-1-{[(3-methyl-5-phenylisoxazol-4-yl)methyl]amino}-2-oxo-1,2-dihydropyridin-3-yl)-acetamide;

(2) *N*-[(6-amino-2,4-dimethylpyridin-3-yl)methyl]-2-(1-{[(5-chloro-2-thienyl)methyl]amino}-4-methyl-2-oxo-1,2-dihydropyridin-3-yl)acetamide;

(3) *N*-[2-(aminomethyl)-5-chlorobenzyl]-2-(1-{[(5-chloro-2-phenyl-1*H*-imidazol-4-yl)methyl]amino}-4-methyl-2-oxo-1,2-dihydropyridin-3-yl)acetamide;

(4) *N*-[2-(aminomethyl)-5-chlorobenzyl]-2-(1-{[(1,5-dimethyl-1*H*-pyrazol-4-yl)methyl]amino}-4-methyl-2-oxo-1,2-dihydropyridin-3-yl)acetamide;

(5) 2-[4-chloro-2-({[(4-methyl-1-{[(4-methyl-1*H*-imidazol-5-yl)methyl]-amino}-2-oxo-1,2-dihydropyridin-3-yl)acetyl]amino}methyl)phenoxy]-*N*-ethylacetamide;

(6) 2-(4-chloro-2-{[({4-methyl-2-oxo-1-[(pyridin-2-ylmethyl)amino]-1,2-dihydropyridin-3-yl}acetyl)amino]methyl}phenoxy)-*N*-ethylacetamide;

(7) 2-[4-chloro-2-({[(4-methyl-1-{[(1-methyl-1*H*-imidazol-2-yl)methyl]-amino}-2-oxo-1,2-dihydropyridin-3-yl)acetyl]amino}methyl)phenoxy]-*N*-ethylacetamide;

(8) 2-(1-{[(6-chloro-1,3-benzodioxol-5-yl)methyl]amino}-4-methyl-2-oxo-1,2-dihydropyridin-3-yl)-*N*-{5-chloro-2-[2-(ethylamino)-2-oxoethoxy]-benzyl}acetamide;

(9) 2-[4-chloro-2-({[(4-methyl-1-{[(2-methyl-1*H*-imidazol-5-yl)methyl]-amino}-2-oxo-1,2-dihydropyridin-3-yl)acetyl]amino}methyl)phenoxy]-*N*-ethylacetamide;

(10) 2-(4-chloro-2-{[({4-methyl-2-oxo-1-[(2-phenoxybenzyl)amino]-1,2-dihydropyridin-3-yl}acetyl)amino]methyl}phenoxy)-*N*-ethylacetamide;

(11) 2-{4-chloro-2-[({[1-({3-[(2-chloro-1,3-thiazol-5-yl)methoxy]benzyl}-amino)-4-methyl-2-oxo-1,2-dihydropyridin-3-yl]acetyl}amino)methyl]-phenoxy}-*N*-ethylacetamide;

(12) *N*-[2-(aminomethyl)-5-fluorobenzyl]-2-(4-methyl-1-{[(2-morpholin-4-ylpyridin-3-yl)methyl]amino}-2-oxo-1,2-dihydropyridin-3-yl)acetamide;

(13) *N*-[2-(aminomethyl)-5-methylbenzyl]-2-(1-{[(5-chloro-1,3-dimethyl-1*H*-pyrazol-4-yl)methyl]amino}-4-methyl-2-oxo-1,2-dihydropyridin-3-yl)-acetamide;

(14) *N*-[2-(aminomethyl)-5-fluorobenzyl]-2-(4-methyl-2-oxo-1-{[(1-phenyl-1*H*-pyrazol-5-yl)methyl]amino}-1,2-dihydropyridin-3-yl)acetamide;

(15) *N*-[2-(aminomethyl)-5-fluorobenzyl]-2-(4-methyl-1-{[(1-methyl-1*H*-imidazol-2-yl)methyl]amino}-2-oxo-1,2-dihydropyridin-3-yl)acetamide;

(16) *N*-[2-(aminomethyl)-5-fluorobenzyl]-2-{1-[(3-cyano-4-fluorobenzyl)-amino]-4-methyl-2-oxo-1,2-dihydropyridin-3-yl}acetamide;

(17) *N*-[2-(aminomethyl)-5-methylbenzyl]-2-(1-{[(1,3-dimethyl-5-morpholin-4-yl-1*H*-pyrazol-4-yl)methyl]amino}-4-methyl-2-oxo-1,2-dihydropyridin-3-yl)acetamide;

(18) *N*-[2-(aminomethyl)-5-methylbenzyl]-2-[4-methyl-2-oxo-1-({[5-(2-thienyl)isoxazol-3-yl]methyl}amino)-1,2-dihydropyridin-3-yl]acetamide;

(19) *N*-[2-(aminomethyl)-5-methylbenzyl]-2-{1-[(4-cyanobenzyl)amino]-4-methyl-2-oxo-1,2-dihydropyridin-3-yl}acetamide;

(20) 2-[4-chloro-2-({[(1-{[(1,3-dimethyl-5-morpholin-4-yl-1*H*-pyrazol-4-yl)methyl]amino}-4-methyl-2-oxo-1,2-dihydropyridin-3-yl)acetyl]amino}-methyl)phenoxy]-*N*-ethylacetamide;

(21) *N*-[(6-amino-2,4-dimethylpyridin-3-yl)methyl]-2-(1-{[(1,3-dimethyl-5-morpholin-4-yl-1*H*-pyrazol-4-yl)methyl]amino}-4-methyl-2-oxo-1,2-dihydropyridin-3-yl)acetamide;

(22) *N*-[2-(aminomethyl)-5-methylbenzyl]-2-(1-{[(1,5-dimethyl-1*H*-pyrazol-4-yl)methyl]amino}-4-methyl-2-oxo-1,2-dihydropyridin-3-yl)-acetamide;

(23) *N*-[(6-amino-2,4-dimethylpyridin-3-yl)methyl]-2-(1-{[(1,5-dimethyl-1*H*-pyrazol-4-yl)methyl]amino}-4-methyl-2-oxo-1,2-dihydropyridin-3-yl)-acetamide;

(24) *N*-[(6-amino-2-methylpyridin-3-yl)methyl]-2-(1-{[(1,5-dimethyl-1*H*-pyrazol-4-yl)methyl]amino}-4-methyl-2-oxo-1,2-dihydropyridin-3-yl)-acetamide;

(25) 2-[4-chloro-2-({[(1-{[(1-ethyl-3-methyl-1*H*-pyrazol-4-yl)methyl]-amino}-4-methyl-2-oxo-1,2-dihydropyridin-3-yl)acetyl]amino}methyl)-phenoxy]-*N*-ethylacetamide;

(26) *N*-[2-(aminomethyl)-5-fluorobenzyl]-2-(1-{[(1-ethyl-3-methyl-1*H*-pyrazol-4-yl)methyl]amino}-4-methyl-2-oxo-1,2-dihydropyridin-3-yl)-acetamide;

(27) *N*-[(6-amino-2,4-dimethylpyridin-3-yl)methyl]-2-(1-{[(1-ethyl-3-methyl-1*H*-pyrazol-4-yl)methyl]amino}-4-methyl-2-oxo-1,2-dihydro-pyridin-3-yl)acetamide;

(28) *N*-[(6-amino-2-methylpyridin-3-yl)methyl]-2-(1-{[(1-ethyl-3-methyl-1*H*-pyrazol-4-yl)methyl]amino}-4-methyl-2-oxo-1,2-dihydropyridin-3-yl)-acetamide;

(29) *N*-[2-(aminomethyl)-5-chlorobenzyl]-2-(4-methyl-1-{[(1-methyl-1*H*-imidazol-2-yl)methyl]amino}-2-oxo-1,2-dihydropyridin-3-yl)acetamide;

(30) *N*-[(6-amino-2-methylpyridin-3-yl)methyl]-2-(4-methyl-1-{[(1-methyl-1*H*-imidazol-2-yl)methyl]amino}-2-oxo-1,2-dihydropyridin-3-yl)acetamide;

(31) *N*-[2-(aminomethyl)-5-chlorobenzyl]-2-(4-methyl-2-oxo-1-{[(1-phenyl-1*H*-pyrazol-5-yl)methyl]amino}-1,2-dihydropyridin-3-yl)acetamide;

(32) *N*-[(6-amino-2,4-dimethylpyridin-3-yl)methyl]-2-(4-methyl-2-oxo-1-{[(1-phenyl-1*H*-pyrazol-5-yl)methyl]amino}-1,2-dihydropyridin-3-yl)-acetamide;

(33) *N*-[(6-amino-2-methylpyridin-3-yl)methyl]-2-(4-methyl-2-oxo-1-{[(1-phenyl-1*H*-pyrazol-5-yl)methyl]amino}-1,2-dihydropyridin-3-yl)acetamide;

(34) *N*-[2-(aminomethyl)-5-chlorobenzyl]-2-{1-[(2,1,3-benzoxadiazol-5-yl-methyl)amino]-4-methyl-2-oxo-1,2-dihydropyridin-3-yl}acetamide;

(35) *N*-[2-(aminomethyl)-5-methylbenzyl]-2-{1-[(2,1,3-benzoxadiazol-5-yl-methyl)amino]-4-methyl-2-oxo-1,2-dihydropyridin-3-yl}acetamide;

(36) *N*-[(6-amino-2,4-dimethylpyridin-3-yl)methyl]-2-{1-[(2,1,3-benzoxadiazol-5-ylmethyl)amino]-4-methyl-2-oxo-1,2-dihydropyridin-3-yl}acetamide;

(37) *N*-[(6-amino-2-methylpyridin-3-yl)methyl]-2-{1-[(2,1,3-benzoxadiazol-5-yl-methyl)amino]-4-methyl-2-oxo-1,2-dihydropyridin-3-yl}acetamide;

(38) *N*-[2-(aminomethyl)-5-chlorobenzyl]-2-(1-{[(2,4-dimethyl-1,3-thiazol-5-yl)methyl]amino}-4-methyl-2-oxo-1,2-dihydropyridin-3-yl)acetamide;

(39) *N*-[2-(aminomethyl)-5-fluorobenzyl]-2-(1-{[(2,4-dimethyl-1,3-thiazol-5-yl)methyl]amino}-4-methyl-2-oxo-1,2-dihydropyridin-3-yl)acetamide;

(40) *N*-[(6-amino-2,4-dimethylpyridin-3-yl)methyl]-2-(1-{[(2,4-dimethyl-1,3-thiazol-5-yl)methyl]amino}-4-methyl-2-oxo-1,2-dihydropyridin-3-yl)-acetamide;

(41) *N*-[(6-amino-2-methylpyridin-3-yl)methyl]-2-(1-{[(2,4-dimethyl-1,3-thiazol-5-yl)methyl]amino}-4-methyl-2-oxo-1,2-dihydropyridin-3-yl)-acetamide;

(42) 2-(4-chloro-2-{[({1-[(2-chloro-5-fluorobenzyl)amino]-4-methyl-2-oxo-1,2-dihydropyridin-3-yl}acetyl)amino]methyl}phenoxy)-*N*-ethylacetamide;

(43) *N*-[(6-amino-2,4-dimethylpyridin-3-yl)methyl]-2-{1-[(2-chloro-5-fluorobenzyl)amino]-4-methyl-2-oxo-1,2-dihydropyridin-3-yl}acetamide;

(44) *N*-[2-(aminomethyl)-5-fluorobenzyl]-2-{1-[(2-chloro-5-fluorobenzyl)-amino]-4-methyl-2-oxo-1,2-dihydropyridin-3-yl}acetamide;

(45) *N*-[(6-amino-2-methylpyridin-3-yl)methyl]-2-{1-[(2-chloro-5-fluoro-benzyl)amino]-4-methyl-2-oxo-1,2-dihydropyridin-3-yl}acetamide;

(46) 2-(4-chloro-2-{[({1-[(2-fluoro-5-methoxybenzyl)amino]-4-methyl-2-oxo-1,2-dihydropyridin-3-yl}acetyl)amino]methyl}phenoxy)-*N*-ethyl-acetamide;

(47) *N*-[2-(aminomethyl)-5-methylbenzyl]-2-{1-[(2-fluoro-5-methoxy-benzyl)amino]-4-methyl-2-oxo-1,2-dihydropyridin-3-yl}acetamide;

(48) *N*-[(6-amino-2,4-dimethylpyridin-3-yl)methyl]-2-{1-[(2-fluoro-5-methoxybenzyl)amino]-4-methyl-2-oxo-1,2-dihydropyridin-3-yl}acetamide;

(49) *N*-[(6-amino-2-methylpyridin-3-yl)methyl]-2-{1-[(2-fluoro-5-methoxy-benzyl)amino]-4-methyl-2-oxo-1,2-dihydropyridin-3-yl}acetamide;

(50) *N*-[(6-amino-2-methylpyridin-3-yl)methyl]-2-(1-{[(2-methoxypyridin-3-yl)methyl]amino}-4-methyl-2-oxo-1,2-dihydropyridin-3-yl)acetamide;

(51) 2-(1-{[(2-methoxypyridin-3-yl)methyl]amino}-4-methyl-2-oxo-1,2-dihydropyridin-3-yl)-*N*-[2-(1*H*-tetrazol-1-yl)benzyl]acetamide;

(52) *N*-[(6-amino-2,4-dimethylpyridin-3-yl)methyl]-2-(4-methyl-1-{[(2-methyl-1*H*-imidazol-5-yl)methyl]amino}-2-oxo-1,2-dihydropyridin-3-yl)-acetamide;

(53) *N*-[(6-amino-2-methylpyridin-3-yl)methyl]-2-(4-methyl-1-{[(2-methyl-1*H*-imidazol-5-yl)methyl]amino}-2-oxo-1,2-dihydropyridin-3-yl)acetamide;

(54) 2-(4-chloro-2-{[({4-methyl-1-[(2-morpholin-4-ylbenzyl)amino]-2-oxo-1,2-dihydropyridin-3-yl}acetyl)amino]methyl}phenoxy)-*N*-ethylacetamide;

(55) *N*-[(6-amino-2,4-dimethylpyridin-3-yl)methyl]-2-{4-methyl-1-[(2-morpholin-4-ylbenzyl)amino]-2-oxo-1,2-dihydropyridin-3-yl}acetamide;

(56) *N*-[(6-amino-2-methylpyridin-3-yl)methyl]-2-{4-methyl-1-[(2-morpholin-4-ylbenzyl)amino]-2-oxo-1,2-dihydropyridin-3-yl}acetamide;

(57) 2-[4-chloro-2-({[(4-methyl-1-{[(2-morpholin-4-ylpyridin-3-yl)methyl]-amino}-2-oxo-1,2-dihydropyridin-3-yl)acetyl]amino}methyl)phenoxy]-*N*-ethylacetamide;

(58) *N*-[(6-amino-2,4-dimethylpyridin-3-yl)methyl]-2-(4-methyl-1-{[(2-morpholin-4-ylpyridin-3-yl)methyl]amino}-2-oxo-1,2-dihydropyridin-3-yl)-acetamide;

(59) *N*-[(6-amino-2-methylpyridin-3-yl)methyl]-2-(4-methyl-1-{[(2-morpholin-4-ylpyridin-3-yl)methyl]amino}-2-oxo-1,2-dihydropyridin-3-yl)-acetamide;

(60) *N*-[2-(aminomethyl)-5-chlorobenzyl]-2-{4-methyl-2-oxo-1-[(2-phenoxybenzyl)amino]-1,2-dihydropyridin-3-yl}acetamide;

(61) *N*-[(6-amino-2,4-dimethylpyridin-3-yl)methyl]-2-{4-methyl-2-oxo-1-[(2-phenoxybenzyl)amino]-1,2-dihydropyridin-3-yl}acetamide;

(62) *N*-[2-(aminomethyl)-5-methylbenzyl]-2-{4-methyl-2-oxo-1-[(2-phenoxybenzyl)amino]-1,2-dihydropyridin-3-yl}acetamide;

(63) *N*-[2-(aminomethyl)-5-chlorobenzyl]-2-(1-{[(3,5-dimethylisoxazol-4-yl)methyl]amino}-4-methyl-2-oxo-1,2-dihydropyridin-3-yl)acetamide;

(64) *N*-[2-(aminomethyl)-5-methylbenzyl]-2-(1-{[(3,5-dimethylisoxazol-4-yl)methyl]amino}-4-methyl-2-oxo-1,2-dihydropyridin-3-yl)acetamide;

(65) *N*-[(6-amino-2-methylpyridin-3-yl)methyl]-2-(1-{[(3,5-dimethylisoxazol-4-yl)methyl]amino}-4-methyl-2-oxo-1,2-dihydropyridin-3-yl)-acetamide;

(66) *N*-[2-(aminomethyl)-5-chlorobenzyl]-2-{1-[(3-methoxybenzyl)amino]-4-methyl-2-oxo-1,2-dihydropyridin-3-yl}acetamide;

(67) *N*-[2-(aminomethyl)-5-methylbenzyl]-2-{1-[(3-methoxybenzyl)amino]-4-methyl-2-oxo-1,2-dihydropyridin-3-yl}acetamide;

(68) *N*-[(6-amino-2,4-dimethylpyridin-3-yl)methyl]-2-{1-[(3-methoxybenzyl)amino]-4-methyl-2-oxo-1,2-dihydropyridin-3-yl}acetamide;

(69) *N*-[(6-amino-2-methylpyridin-3-yl)methyl]-2-{1-[(3-methoxybenzyl)amino]-4-methyl-2-oxo-1,2-dihydropyridin-3-yl}acetamide;

(70) *N*-[2-(aminomethyl)-5-chlorobenzyl]-2-(4-methyl-1-{[(3-methyl-5-phenylisoxazol-4-yl)methyl]amino}-2-oxo-1,2-dihydropyridin-3-yl)-acetamide;

(71) 2-[4-chloro-2-({[(4-methyl-1-{[(3-methyl-5-phenylisoxazol-4-yl)-methyl]amino}-2-oxo-1,2-dihydropyridin-3-yl)acetyl]amino}methyl)-phenoxy]-*N*-ethylacetamide;

(72) *N*-[(6-amino-2,4-dimethylpyridin-3-yl)methyl]-2-(4-methyl-1-{[(3-methyl-5-phenylisoxazol-4-yl)methyl]amino}-2-oxo-1,2-dihydropyridin-3-yl)acetamide;

(73) *N*-[(6-amino-2,4-dimethylpyridin-3-yl)methyl]-2-(4-methyl-1-{[(4-methyl-1*H*-imidazol-5-yl)methyl]amino}-2-oxo-1,2-dihydropyridin-3-yl)-acetamide;

(74) *N*-[(6-amino-2-methylpyridin-3-yl)methyl]-2-(4-methyl-1-{[(4-methyl-1*H*-imidazol-5-yl)methyl]amino}-2-oxo-1,2-dihydropyridin-3-yl)acetamide;

(75) *N*-[(6-amino-2-methylpyridin-3-yl)methyl]-2-(4-methyl-1-{[(4-methyl-3,4-dihydro-2*H*-1,4-benzoxazin-7-yl)methyl]amino}-2-oxo-1,2-dihydropyridin-3-yl)-acetamide;

(76) 2-[4-chloro-2-({[(1-{[(5-chloro-1,3-dimethyl-1*H*-pyrazol-4-yl)methyl]amino}-4-methyl-2-oxo-1,2-dihydropyridin-3-yl)acetyl]amino}methyl)phenoxy]-*N*-ethylacetamide;

(77) *N*-[(6-amino-2,4-dimethylpyridin-3-yl)methyl]-2-(1-{[(5-chloro-1,3-dimethyl-1*H*-pyrazol-4-yl)methyl]amino}-4-methyl-2-oxo-1,2-dihydropyridin-3-yl)acetamide;

(78) *N*-[(6-amino-2-methylpyridin-3-yl)methyl]-2-(1-{[(5-chloro-1,3-dimethyl-1*H*-pyrazol-4-yl)methyl]amino}-4-methyl-2-oxo-1,2-dihydropyridin-3-yl)acetamide;

(79) 2-[4-chloro-2-({[(1-{[(5-chloro-1-methyl-3-phenyl-1*H*-pyrazol-4-yl)methyl]amino}-4-methyl-2-oxo-1,2-dihydropyridin-3-yl)acetyl]amino}methyl)phenoxy]-*N*-ethylacetamide;

(80) *N*-[2-(aminomethyl)-5-fluorobenzyl]-2-(1-{[(5-chloro-1-methyl-3-phenyl-1*H*-pyrazol-4-yl)methyl]amino}-4-methyl-2-oxo-1,2-dihydropyridin-3-yl)acetamide;

(81) *N*-[(6-amino-2,4-dimethylpyridin-3-yl)methyl]-2-(1-{[(5-chloro-1-methyl-3-phenyl-1*H*-pyrazol-4-yl)methyl]amino}-4-methyl-2-oxo-1,2-dihydropyridin-3-yl)acetamide;

(82) *N*-[(6-amino-2-methylpyridin-3-yl)methyl]-2-(1-{[(5-chloro-1-methyl-3-phenyl-1*H*-pyrazol-4-yl)methyl]amino}-4-methyl-2-oxo-1,2-dihydropyridin-3-yl)acetamide;

(83) 2-(4-chloro-2-{[({1-[(5-chloro-2-fluorobenzyl)amino]-4-methyl-2-oxo-1,2-dihydropyridin-3-yl}acetyl)amino]methyl}phenoxy)-*N*-ethylacetamide;

(84) *N*-[2-(aminomethyl)-5-methylbenzyl]-2-{1-[(5-chloro-2-fluorobenzyl)amino]-4-methyl-2-oxo-1,2-dihydropyridin-3-yl}acetamide;

(85) *N*-[(6-amino-2,4-dimethylpyridin-3-yl)methyl]-2-{1-[(5-chloro-2-fluorobenzyl)amino]-4-methyl-2-oxo-1,2-dihydropyridin-3-yl}acetamide;

(86) *N*-[(6-amino-2-methylpyridin-3-yl)methyl]-2-{1-[(5-chloro-2-fluorobenzyl)amino]-4-methyl-2-oxo-1,2-dihydropyridin-3-yl}acetamide;

(87) *N*-[2-(aminomethyl)-5-methylbenzyl]-2-(1-{[(5-chloro-2-phenyl-1*H*-imidazol-4-yl)methyl]amino}-4-methyl-2-oxo-1,2-dihydropyridin-3-yl)-acetamide;

(88) *N*-[(6-amino-2,4-dimethylpyridin-3-yl)methyl]-2-(1-{[(5-chloro-2-phenyl-1*H*-imidazol-4-yl)methyl]amino}-4-methyl-2-oxo-1,2-dihydropyridin-3-yl)acetamide;

(89) *N*-[(6-amino-2-methylpyridin-3-yl)methyl]-2-(1-{[(5-chloro-2-phenyl-1*H*-imidazol-4-yl)methyl]amino}-4-methyl-2-oxo-1,2-dihydropyridin-3-yl)-acetamide;

(90) 2-[4-chloro-2-({[(1-{[(5-chloro-2-thienyl)methyl]amino}-4-methyl-2-oxo-1,2-dihydropyridin-3-yl)acetyl]amino}methyl)phenoxy]-*N*-ethyl-acetamide;

(91) *N*-[(6-amino-2-methylpyridin-3-yl)methyl]-2-(1-{[(5-chloro-2-thienyl)-methyl]amino}-4-methyl-2-oxo-1,2-dihydropyridin-3-yl)acetamide;

(92) 2-[4-chloro-2-({[(4-methyl-1-{[(5-methyl-3-phenylisoxazol-4-yl)-methyl]amino}-2-oxo-1,2-dihydropyridin-3-yl)acetyl]amino}methyl)-phenoxy]-*N*-ethylacetamide;

(93) *N*-[(6-amino-2,4-dimethylpyridin-3-yl)methyl]-2-(4-methyl-1-{[(5-methyl-3-phenylisoxazol-4-yl)methyl]amino}-2-oxo-1,2-dihydropyridin-3-yl)acetamide;

(94) *N*-[(6-amino-2-methylpyridin-3-yl)methyl]-2-(4-methyl-1-{[(5-methyl-3-phenylisoxazol-4-yl)methyl]amino}-2-oxo-1,2-dihydropyridin-3-yl)-acetamide;

(95) 2-[4-chloro-2-({[(4-methyl-2-oxo-1-{[(5-pyridin-2-yl-2-thienyl)-methyl]amino}-1,2-dihydropyridin-3-yl)acetyl]amino}methyl)phenoxy]-*N*-ethylacetamide;

(96) *N*-[(6-amino-2,4-dimethylpyridin-3-yl)methyl]-2-(4-methyl-2-oxo-1-{[(5-pyridin-2-yl-2-thienyl)methyl]amino}-1,2-dihydropyridin-3-yl)-acetamide;

(97) *N*-[2-(aminomethyl)-5-fluorobenzyl]-2-(4-methyl-2-oxo-1-{[(5-pyridin-2-yl-2-thienyl)methyl]amino}-1,2-dihydropyridin-3-yl)acetamide;

(98) *N*-[(6-amino-2-methylpyridin-3-yl)methyl]-2-(4-methyl-2-oxo-1-{[(5-pyridin-2-yl-2-thienyl)methyl]amino}-1,2-dihydropyridin-3-yl)acetamide;

(99) *N*-[2-(aminomethyl)-5-fluorobenzyl]-2-(1-{[(6-chloro-1,3-benzodioxol-5-yl)methyl]amino}-4-methyl-2-oxo-1,2-dihydropyridin-3-yl)-acetamide;

(100) *N*-[(6-amino-2,4-dimethylpyridin-3-yl)methyl]-2-(1-{[(6-chloro-1,3-benzodioxol-5-yl)methyl]amino}-4-methyl-2-oxo-1,2-dihydropyridin-3-yl)-acetamide;

(101) *N*-[(6-amino-2-methylpyridin-3-yl)methyl]-2-(1-{[(6-chloro-1,3-benzodioxol-5-yl)methyl]amino}-4-methyl-2-oxo-1,2-dihydropyridin-3-yl)-acetamide;

(102) 2-[4-chloro-2-({[(4-methyl-2-oxo-1-{[3-(trifluoromethoxy)benzyl]-amino}-1,2-dihydropyridin-3-yl)acetyl]amino}methyl)phenoxy]-*N*-ethyl-acetamide;

(103) *N*-[(6-amino-2,4-dimethylpyridin-3-yl)methyl]-2-(4-methyl-2-oxo-1-{[3-(trifluoromethoxy)benzyl]amino}-1,2-dihydropyridin-3-yl)acetamide;

(104) *N*-[2-(aminomethyl)-5-fluorobenzyl]-2-(4-methyl-2-oxo-1-{[3-(trifluoromethoxy)benzyl]amino}-1,2-dihydropyridin-3-yl)acetamide;

(105) *N*-[(6-amino-2-methylpyridin-3-yl)methyl]-2-(4-methyl-2-oxo-1-{[3-(trifluoromethoxy)benzyl]amino}-1,2-dihydropyridin-3-yl)acetamide;

(106) 2-{4-chloro-2-[({[4-methyl-2-oxo-1-({[5-(2-thienyl)isoxazol-3-yl]-methyl}amino)-1,2-dihydropyridin-3-yl]acetyl}amino)methyl]phenoxy}-*N*-ethylacetamide;

(107) *N*-[(6-amino-2,4-dimethylpyridin-3-yl)methyl]-2-[1-({3-[(2-chloro-1,3-thiazol-5-yl)methoxy]benzyl}amino)-4-methyl-2-oxo-1,2-dihydropyridin-3-yl]acetamide;

(108) *N*-[(6-amino-2-methylpyridin-3-yl)methyl]-2-[1-({3-[(2-chloro-1,3-thiazol-5-yl)methoxy]benzyl}amino)-4-methyl-2-oxo-1,2-dihydropyridin-3-yl]acetamide;

(109) *N*-[2-(aminomethyl)-5-chlorobenzyl]-2-(1-{[(1R,4S)-bicyclo[2.2.1]-hept-5-en-2-ylmethyl]amino}-4-methyl-2-oxo-1,2-dihydropyridin-3-yl)-acetamide;

(110) *N*-[(6-amino-2,4-dimethylpyridin-3-yl)methyl]-2-(1-{[(1R,4S)-bicyclo[2.2.1]hept-5-en-2-ylmethyl]amino}-4-methyl-2-oxo-1,2-dihydropyridin-3-yl)acetamide;

(111) 2-(4-chloro-2-{[({1-[(cyclohexylmethyl)amino]-4-methyl-2-oxo-1,2-dihydropyridin-3-yl}acetyl)amino]methyl}phenoxy)-*N*-ethylacetamide;

(112) *N*-[2-(aminomethyl)-5-chlorobenzyl]-2-{1-[(cyclohexylmethyl)-amino]-4-methyl-2-oxo-1,2-dihydropyridin-3-yl}acetamide;

(113) *N*-[2-(aminomethyl)-5-fluorobenzyl]-2-{1-[(cyclohexylmethyl)-amino]-4-methyl-2-oxo-1,2-dihydropyridin-3-yl}acetamide;

(114) *N*-[(6-amino-2-methylpyridin-3-yl)methyl]-2-{1-[(cyclohexylmethyl)-amino]-4-methyl-2-oxo-1,2-dihydropyridin-3-yl}acetamide;

(115) *N*-[2-(aminomethyl)-5-methylbenzyl]-2-{1-[(cyclopentylmethyl)-amino]-4-methyl-2-oxo-1,2-dihydropyridin-3-yl}acetamide;

(116) *N*-[(6-amino-2,4-dimethylpyridin-3-yl)methyl]-2-{1-[(cyclopentyl-methyl)amino]-4-methyl-2-oxo-1,2-dihydropyridin-3-yl}acetamide;

(117) *N*-[(6-amino-2-methylpyridin-3-yl)methyl]-2-{1-[(cyclopentyl-methyl)amino]-4-methyl-2-oxo-1,2-dihydropyridin-3-yl}acetamide;

(118) *N*-[(6-amino-2,4-dimethylpyridin-3-yl)methyl]-2-{4-methyl-2-oxo-1-[(pyridin-2-ylmethyl)amino]-1,2-dihydropyridin-3-yl}acetamide;

(119) *N*-[(6-amino-2-methylpyridin-3-yl)methyl]-2-{4-methyl-2-oxo-1-[(pyridin-2-ylmethyl)amino]-1,2-dihydropyridin-3-yl}acetamide;

(120) *N*-[2-(aminomethyl)-5-chlorobenzyl]-2-{4-methyl-2-oxo-1-[(pyridin-3-ylmethyl)amino]-1,2-dihydropyridin-3-yl}acetamide;

(121) 2-(4-chloro-2-{[({4-methyl-2-oxo-1-[(pyridin-3-ylmethyl)amino]-1,2-dihydropyridin-3-yl}acetyl)amino]methyl}phenoxy)-*N*-ethylacetamide;

(122) *N*-[2-(aminomethyl)-5-methylbenzyl]-2-{4-methyl-2-oxo-1-[(pyridin-3-ylmethyl)amino]-1,2-dihydropyridin-3-yl}acetamide;

(123) *N*-[2-(aminomethyl)-5-fluorobenzyl]-2-{4-methyl-2-oxo-1-[(pyridin-3-ylmethyl)amino]-1,2-dihydropyridin-3-yl}acetamide;

(124) *N*-[(6-amino-2,4-dimethylpyridin-3-yl)methyl]-2-{4-methyl-2-oxo-1-[(pyridin-3-ylmethyl)amino]-1,2-dihydropyridin-3-yl}acetamide;

(125) *N*-[(6-amino-2-methylpyridin-3-yl)methyl]-2-{4-methyl-2-oxo-1-[(pyridin-3-ylmethyl)amino]-1,2-dihydropyridin-3-yl}acetamide;

(126) *N*-[2-(aminomethyl)-5-methylbenzyl]-2-{4-methyl-2-oxo-1-[(quinolin-8-ylmethyl)amino]-1,2-dihydropyridin-3-yl}acetamide;

(127) 2-(4-chloro-2-{[({4-methyl-2-oxo-1-[(quinolin-8-ylmethyl)amino]-1,2-dihydropyridin-3-yl}acetyl)amino]methyl}phenoxy)-*N*-ethylacetamide;

(128) *N*-[(6-amino-2,4-dimethylpyridin-3-yl)methyl]-2-{4-methyl-2-oxo-1-[(quinolin-8-ylmethyl)amino]-1,2-dihydropyridin-3-yl}acetamide;

(129) 2-[4-chloro-2-({[(1-{[2,2-difluoro-2-(1-oxidopyridin-2-yl)ethyl]-amino}-4-methyl-2-oxo-1,2-dihydropyridin-3-yl)acetyl]amino}methyl)-phenoxy]-*N*-ethylacetamide;

(130) 2-(4-chloro-2-{[({1-[(2,2-difluoro-2-pyridin-2-ylethyl)amino]-4-methyl-2-oxo-1,2-dihydropyridin-3-yl}acetyl)amino]methyl}phenoxy)-*N*-ethylacetamide;

(131) *N*-[(6-amino-2,4-dimethylpyridin-3-yl)methyl]-2-{1-[(2,2-difluoro-2-pyridin-2-ylethyl)amino]-4-methyl-2-oxo-1,2-dihydropyridin-3-yl}-acetamide;

(132) *N*-[2-(aminomethyl)-5-methylbenzyl]-2-{4-methyl-2-oxo-1-[(2-phenylethyl)amino]-1,2-dihydropyridin-3-yl}acetamide;

(133) *N*-[2-(aminomethyl)-5-methoxybenzyl]-2-{4-methyl-2-oxo-1-[(2-phenylethyl)amino]-1,2-dihydropyridin-3-yl}acetamide;

(134) 2-(4-chloro-2-{[({4-methyl-2-oxo-1-[(2-phenylethyl)amino]-1,2-dihydropyridin-3-yl}acetyl)amino]methyl}phenoxy)-*N*-ethylacetamide;

(135) *N*-[(6-amino-2,4-dimethylpyridin-3-yl)methyl]-2-{4-methyl-2-oxo-1-[(2-phenylethyl)amino]-1,2-dihydropyridin-3-yl}acetamide;

(136) *N*-[(6-amino-2-methylpyridin-3-yl)methyl]-2-{4-methyl-2-oxo-1-[(2-phenylethyl)amino]-1,2-dihydropyridin-3-yl}acetamide;

(137) *N*-[2-(aminomethyl)-5-chlorobenzyl]-2-{4-methyl-2-oxo-1-[(2-phenylpropyl)amino]-1,2-dihydropyridin-3-yl}acetamide;

(138) 2-(4-chloro-2-{[({4-methyl-2-oxo-1-[(2-phenylpropyl)amino]-1,2-dihydropyridin-3-yl}acetyl)amino]methyl}phenoxy)-*N*-ethylacetamide;

(139) *N*-[(6-amino-2,4-dimethylpyridin-3-yl)methyl]-2-{4-methyl-2-oxo-1-[(2-phenylpropyl)amino]-1,2-dihydropyridin-3-yl}acetamide;

(140) *N*-[(6-amino-2-methylpyridin-3-yl)methyl]-2-{4-methyl-2-oxo-1-[(2-phenylpropyl)amino]-1,2-dihydropyridin-3-yl}acetamide;

(141) *N*-[(6-amino-2-methylpyridin-3-yl)methyl]-2-(4-methyl-2-oxo-1-{[(2-oxo-1,2-dihydropyridin-3-yl)methyl]amino}-1,2-dihydropyridin-3-yl)-acetamide;

(142) 2-(4-chloro-2-{[({1-[(3,3-dimethylbutyl)amino]-4-methyl-2-oxo-1,2-dihydropyridin-3-yl}acetyl)amino]methyl}phenoxy)-*N*-ethylacetamide;

(143) *N*-[(6-amino-2,4-dimethylpyridin-3-yl)methyl]-2-{1-[(3,3-dimethylbutyl)amino]-4-methyl-2-oxo-1,2-dihydropyridin-3-yl}acetamide;

(144) 2-(4-chloro-2-{[({1-[(4-cyanobenzyl)amino]-4-methyl-2-oxo-1,2-dihydropyridin-3-yl}acetyl)amino]methyl}phenoxy)-*N*-ethylacetamide;

(145) *N*-[2-(aminomethyl)-5-chlorobenzyl]-2-{1-[(4-cyanobenzyl)amino]-4-methyl-2-oxo-1,2-dihydropyridin-3-yl}acetamide;

(146) 2-(4-chloro-2-{[({1-[(3-cyano-4-fluorobenzyl)amino]-4-methyl-2-oxo-1,2-dihydropyridin-3-yl}acetyl)amino]methyl}phenoxy)-*N*-ethylacetamide;

(147) *N*-[(6-amino-2,4-dimethylpyridin-3-yl)methyl]-2-{1-[(3-cyano-4-fluorobenzyl)amino]-4-methyl-2-oxo-1,2-dihydropyridin-3-yl}acetamide;

(148) *N*-[(6-amino-2-methylpyridin-3-yl)methyl]-2-{1-[(3-cyano-4-fluorobenzyl)amino]-4-methyl-2-oxo-1,2-dihydropyridin-3-yl}acetamide;

(149) 2-[1-(benzylamino)-4-methyl-2-oxo-1,2-dihydropyridin-3-yl]-*N*-{5-chloro-2-[2-(ethylamino)-2-oxoethoxy]benzyl}acetamide;

(150) *N*-[2-(aminomethyl)-5-fluorobenzyl]-2-[1-(benzylamino)-4-methyl-2-oxo-1,2-dihydropyridin-3-yl]acetamide;

(151) *N*-[(6-amino-2,4-dimethylpyridin-3-yl)methyl]-2-[1-(benzylamino)-4-methyl-2-oxo-1,2-dihydropyridin-3-yl]acetamide;

(152) *N*-[2-(aminomethyl)-5-chlorobenzyl]-2-[1-(isobutylamino)-4-methyl-2-oxo-1,2-dihydropyridin-3-yl]acetamide;

(153) *N*-[2-(aminomethyl)-5-methylbenzyl]-2-[1-(isobutylamino)-4-methyl-2-oxo-1,2-dihydropyridin-3-yl]acetamide; and

(154) *N*-[(6-amino-2,4-dimethylpyridin-3-yl)methyl]-2-[1-(isobutylamino)-4-methyl-2-oxo-1,2-dihydropyridin-3-yl]acetamide.

Example 6

Compounds of the Examples were tested in Test B above and were found to exhibit $IC_{50}$TT values of less than 50 μM. Indeed, the compounds of Examples 2(xi) and 2(xii) were found to exhibit $IC_{50}$ values of 92.2 nM and 0.62 μM, respectively.

**Abbreviations**

| | | |
|---|---|---|
| aq. | = | aqueous |
| AUC | = | area under the curve |
| Boc | = | *tert*-butyloxycarbonyl |
| BSA | = | bovine serum albumin |
| d | = | (in relation to NMR) doublet |

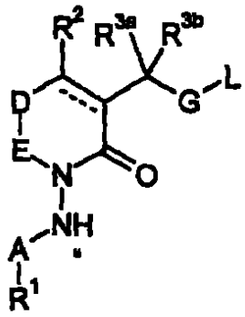
| | | | |
|---|---|---|---|
| | DCC | = | dicyclohexyl carbodiimide |
| | DCE | = | 1,2-dichloroethane |
| | DCM | = | dichloromethane |
| | DIPEA | = | diisopropylethylamine |
| | DMAP | = | 4-(*N,N*-dimethyl amino) pyridine |
| | DMF | = | dimethylformamide |
| | DMSO | = | dimethylsulfoxide |
| | DVT | = | deep vein thrombosis |
| | EDC | = | 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide |
| | | | hydrochloride |
| | Et | = | ethyl |
| | ether | = | diethyl ether |
| | $Et_3N$ | = | triethylamine |
| | EtOAc | = | ethyl acetate |
| | EtOH | = | ethanol |
| | $Et_2O$ | = | diethyl ether |
| | h | = | hour(s) |
| | HATU | = | *O*-(azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate |
| | HBTU | = | [*N,N,N',N'*-tetramethyl-*O*-(benzotriazol-1-yl)uronium hexafluorophosphate] |
| | HCl | = | hydrochloric acid, hydrogen chloride gas or hydrochloride salt (depending on context) |
| | HOAt | = | 1-hydroxy-7-azabenzotriazole |
| | HOBt | = | 1-hydroxybenzotriazole |
| | HPLC | = | high performance liquid chromatography |
| | LC | = | liquid chromatography |
| | mCPBA | = | *meta*-chloroperbenzoic acid |
| | Me | = | methyl |
| | MeOH | = | methanol |

| | | |
|---|---|---|
| min | = | minute(s) |
| MS | = | mass spectroscopy |
| NADH | = | nicotinamide adenine dinucleotide, reduced form |
| NADPH | = | nicotinamide adenine dinucleotide phosphate, reduced form |
| NBS | = | *N*-Bromosuccinimide |
| NIH | = | National Institute of Health (US) |
| NIHU | = | National Institute of Health units |
| OAc | = | acetate |
| PCC | = | pyridinium chlorochromate |
| Ph | = | phenyl |
| Pr | = | propyl |
| PyBOP | = | (benzotriazol-1-yloxy)tripyrrolidinophosphonium hexafluorophosphate |
| rt/RT | = | room temperature |
| SOPs | = | standard operating procedures |
| TBME | = | *tert*-butyl methyl ether |
| TBTU | = | [*N*,*N*,*N'*,*N'*-tetramethyl-*O*-(benzotriazol-1-yl)uronium tetrafluoroborate] |
| TEA | = | triethylamine |
| TFA | = | trifluoroacetic acid |
| THF | = | tetrahydrofuran |

Prefixes *n*, *s*, *i* and *t* have their usual meanings: normal, secondary, iso and tertiary. The prefix *c* means cyclo.

## Claims

1. A compound of formula I



I

wherein

the dashed line is absent or represents a bond;

A represents C(O), $S(O)_2$, C(O)O (in which latter group the O moiety is attached to $R^1$), C(O)NH, $S(O)_2NH$ (in which latter two groups the NH moiety is attached to $R^1$) or $C_{1-6}$ alkylene;

$R^1$ represents

(a) $C_{1-10}$ alkyl, $C_{2-10}$ alkenyl, $C_{2-10}$ alkynyl (which latter three groups are optionally substituted by one or more substituents selected from halo, CN, $C_{3-10}$ cycloalkyl (optionally substituted by one or more substituents selected from halo, OH, =O, $C_{1-6}$ alkyl, $C_{1-6}$ alkoxy and aryl), $OR^{4a}$, $S(O)_nR^{4b}$, $S(O)_2N(R^{4c})(R^{4d})$, $N(R^{4e})S(O)_2R^{4f}$, $N(R^{4g})(R^{4h})$, $B^1$-C(O)-$B^2$-$R^{4i}$, aryl and $Het^1$),

(b) $C_{3-10}$ cycloalkyl or $C_{4-10}$ cycloalkenyl, which latter two groups are optionally substituted by one or more substituents selected from halo, =O, CN, $C_{1-10}$ alkyl, $C_{3-10}$ cycloalkyl (optionally substituted by one or more substituents selected from halo, OH, =O, $C_{1-6}$ alkyl, $C_{1-6}$ alkoxy and aryl), $OR^{4a}$, $S(O)_nR^{4b}$, $S(O)_2N(R^{4c})(R^{4d})$, $N(R^{4e})S(O)_2R^{4f}$, $N(R^{4g})(R^{4h})$, $B^3$-C(O)-$B^4$-$R^{4i}$, aryl and $Het^2$,

(c) aryl, or

(d) $Het^3$;

$R^{4a}$ to $R^{4l}$ independently represent, at each occurrence,

(a) H,

(b) $C_{1-10}$ alkyl, $C_{2-10}$ alkenyl, $C_{2-10}$ alkynyl (which latter three groups are optionally substituted by one or more substituents selected from halo, OH, $C_{1-6}$ alkoxy, aryl and $Het^4$),

(c) $C_{3-10}$ cycloalkyl, $C_{4-10}$ cycloalkenyl (which latter two groups are optionally substituted by one or more substituents selected from halo, OH, =O, $C_{1-6}$ alkyl, $C_{1-6}$ alkoxy, aryl and $Het^5$),

(d) aryl or

(e) $Het^6$,

provided that $R^{4b}$ does not represent H when n is 1 or 2;

the group -D-E-

(a) when the dashed line represents a bond, represents $-C(R^{5a})=C(R^{5b})-$, or

(b) when the dashed line is absent, represents $-C(R^{6a})(R^{6b})-C(R^{7a})(R^{7b})-$;

$R^{5a}$ and $R^{5b}$ independently represent H, halo, OH, $C_{1-4}$ alkyl, $(CH_2)_{0-4}O(C_{1-3}$ alkyl) (which latter two groups are optionally substituted by one OH group or one or more F atoms);

$R^{6a}$, $R^{6b}$, $R^{7a}$ and $R^{7b}$ independently represent H, F or methyl;

or $R^{5a}$ and $R^{5b}$ together represent $C_{2-4}$ *n*-alkylene;

or one of $R^{6a}$ and $R^{6b}$, together with one of $R^{7a}$ and $R^{7b}$, represents $C_{1-4}$ *n*-alkylene;

$R^2$ represents

(a) H,

(b) halo;

(c) $C_{1-6}$ alkyl, $C_{2-6}$ alkenyl, $C_{2-6}$ alkynyl, $C_{1-6}$ alkoxy (which latter four groups are optionally substituted by one or more substituents selected from halo, OH, CN, $C_{1-4}$ alkoxy, C(O)OH, C(O)O-$C_{1-4}$ alkyl and OC(O)-$C_{1-4}$ alkyl) or

(d) together with $R^{3a}$, $R^2$ represents $C_{2-3}$ *n*-alkylene, $T^1$-($C_{1-2}$ *n*-alkylene) or ($C_{1-2}$ *n*-alkylene)-$T^1$, which latter three groups are optionally substituted by halo, or

(e) together with $R^{3a}$ and $R^{3b}$, $R^2$ represents $T^2$-[C(H)=], wherein $T^2$ is bonded to the C-atom to which the group $R^2$ is attached;

$R^{3a}$ and $R^{3b}$ independently represent H, F or methyl (which latter group is optionally substituted by one or more F atoms), or

(a) together with $R^2$, $R^{3a}$ represents $C_{2-3}$ *n*-alkylene, $T^1$-($C_{1-2}$ *n*-alkylene) or ($C_{1-2}$ *n*-alkylene)-$T^1$, which latter three groups are optionally substituted by halo, or

(b) together with $R^2$, $R^{3a}$ and $R^{3b}$ represent $T^2$-[C(H)=], wherein $T^2$ is bonded to the C-atom to which the group $R^2$ is attached;

$T^1$ and $T^2$ independently represent O, S, N(H) or N($C_{1-4}$ alkyl);

G represents

(a) -C(O)N($R^{8a}$)-[CH(C(O)$R^9$)]$_{0-1}$-$C_{0-3}$ alkylene-($Q^1$)$_a$-,

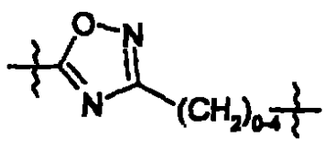
(b) -C(O)N($R^{8b}$)-$C_{2-3}$ alkenylene-($Q^1$)$_a$-,

(c)




, or

(d)



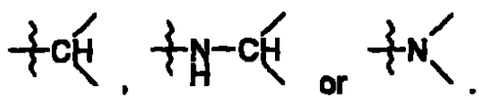
;

$R^9$ represents H or a 5- to 10-membered aromatic heterocyclic group comprising one or two rings and containing, as heteroatom(s), one sulfur or oxygen atom and/or one or more nitrogen atoms, which heterocyclic group is optionally substituted by one or more substituents selected from halo and $C_{1-6}$ alkyl;

$Q^1$ represents O, $NR^{10a}$, $[N(H)]_{0-1}C(O)$-$C_{0-2}$ alkylene, C(O)NHNHC(O), or -N=C($R^{10b}$)-;

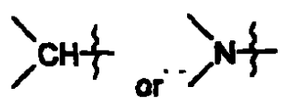
a represents 0 or 1;

$Q^{2a}$ represents



;

$Q^{2b}$ represents



;

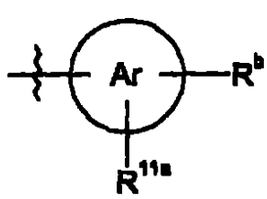
L represents

(a) $C_{0-6}$ alkylene-$R^a$,

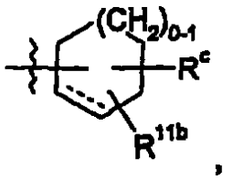
(b) $C_{0-2}$ alkylene-CH=CH-$C_{0-2}$ alkylene-$R^a$,

(c) $C_{0-2}$ alkylene-C≡C-$C_{0-2}$ alkylene-$R^a$,

(d)

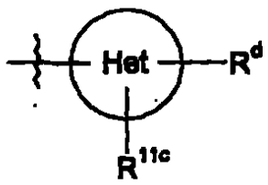


(e)



wherein the dashed line represents an optional double bond, or

(f)



;

Ar represents phenyl or naphthyl;

Het represents a 5- to 10-membered heterocyclic group comprising one or two rings and containing, as heteroatom(s), one sulfur or oxygen atom and/or one or more nitrogen atoms;

$R^{11a}$ represents H or one or more substituents selected from halo, OH, CN, $C_{1-6}$ alkyl, $C_{1-6}$ alkoxy (which latter two groups are optionally substituted by one or more substituents selected from halo, OH, $C_{1-4}$ alkoxy; $C(O)OR^{12a}$ and $C(O)N(R^{12b})R^{12a}$) and $S(O)_{0-2}R^{12d}$;

$R^{11b}$ and $R^{11c}$ independently represent H or one or more substituents selected from halo, OH, CN, $C_{1-6}$ alkyl, $C_{1-6}$ alkoxy (which latter two groups are optionally substituted by one or more substituents selected from halo, OH, $C_{1-4}$ alkoxy, $C(O)OR^{12a}$ and $C(O)N(R^{12b})R^{12a}$), $S(O)_{0-2}R^{12d}$, =O, =NH, =NOH and =N-CN;

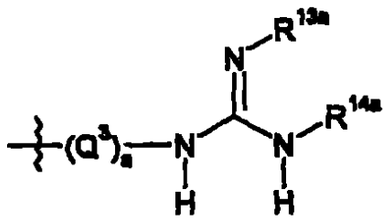
$R^{12a}$ to $R^{12c}$ independently represent H, $C_{1-6}$ alkyl or $C_{3-7}$ cycloalkyl (which latter two groups are optionally substituted by one OH or $N(R^{12e})R^{12f}$ group or by one or more halo atoms);

$R^{12d}$ represents, independently at each occurrence, $C_{1-6}$ alkyl optionally substituted by one OH or $N(R^{12e})R^{12f}$ group or by one or more halo atoms;

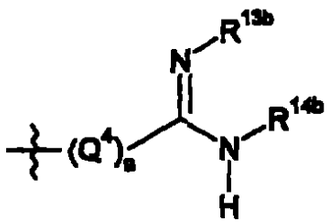
$R^{12e}$ and $R^{12f}$ represent, independently at each occurrence, H or $C_{1-4}$ alkyl optionally substituted by one or more halo atoms;

$R^a$ to $R^d$ independently represent

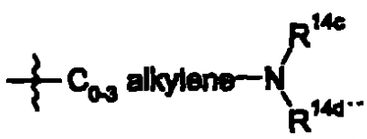
(a)



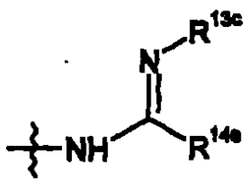
(b)



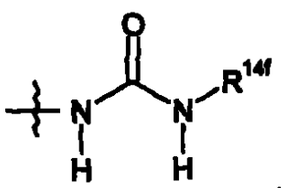
(c)



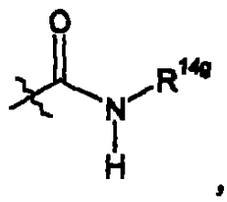
(d)



(e)



(f)



(g) $Het^x$

or $R^b$ to $R^d$ may also represent H;

$Q^3$ represents O, $N(R^{10a})$, $S(O)_2$, $S(O)_2NH$, C(O) or -CH=N-;

$Q^4$ represents O, S or $CH_2$;

a represents 0 or 1;

$Het^x$ represents a 5- or 6-membered heterocyclic group containing one to four heteroatoms selected from oxygen, nitrogen and/or sulfur, which heterocyclic group may be substituted by one or more substituents selected from halo, =O, $C_{1-6}$ alkyl and $C_{1-6}$ alkoxy (which latter two groups are optionally substituted by one or more halo atoms);

$R^{13a}$ to $R^{13c}$ independently represent

(a) H,

(b) CN,

(c) $NH_2$,

(d) $OR^{15}$ or

(e) $C(O)OR^{16}$;

$R^{15}$ represents

(a) H,

(b) $C_{1-10}$ alkyl, $C_{3-10}$ alkenyl, $C_{3-10}$ alkynyl,

(c) $C_{3-10}$ cycloalkyl, $C_{4-10}$ cycloalkenyl, which latter two groups are optionally substituted by one or more substituents selected from halo and $C_{1-6}$ alkyl, or

(d) $C_{1-3}$ alkyl, which latter group is optionally interrupted by oxygen and is substituted by aryl or -O-aryl;

$R^{16}$ represents

(a) $C_{1-10}$ alkyl, $C_{2-10}$ alkenyl, $C_{3-10}$ alkynyl, which latter three groups are optionally interrupted by one or more oxygen atoms, or

(b) $C_{3-10}$ cycloalkyl, $C_{4-10}$ cycloalkenyl, which latter two groups are optionally substituted by one or more substituents selected from halo and $C_{1-6}$ alkyl, or

(c) $C_{1-3}$ alkyl, which latter group is optionally interrupted by oxygen and is substituted by aryl or -O-aryl;

$R^{8a}$ to $R^{8c}$, $R^{10a}$ to $R^{10c}$ and $R^{14a}$ to $R^{14g}$ independently represent

(a) H or

(b) $C_{1-4}$ alkyl (which latter group is optionally substituted by one or more substituents selected from halo and OH),

or $R^{14a}$ and $R^{14b}$ independently represent C(O)O-$C_{1-6}$ alkyl (the alkyl part of which latter group is optionally substituted by aryl and/or one or more halo atoms),

or $R^{14c}$ represents

(a) $C_{1-4}$ alkyl substituted by $C_{3-7}$ cycloalkyl or aryl,

(b) $C_{3-7}$ cycloalkyl,

(c) C(O)O-$C_{1-6}$ alkyl (the alkyl part of which latter group is optionally substituted by aryl and/or one or more halo atoms),

(d) C(O)$C_{1-6}$ alkyl,

(e) C(O)N(H)-$C_{1-6}$ alkyl (the alkyl part of which latter group is optionally substituted by aryl and/or one or more halo atoms) or

(f) $S(O)_2$-$C_{1-6}$ alkyl (the alkyl part of which latter group is optionally substituted by aryl and/or one or more halo atoms),

or $R^{14c}$ and $R^{14d}$ together represent $C_{3-6}$ *n*-alkylene optionally interrupted by O, S, N(H) or N($C_{1-4}$ alkyl) and/or substituted by one or more $C_{1-4}$ alkyl groups;

each aryl independently represents a $C_{6-10}$ carbocyclic aromatic group, which group may comprise either one or two rings and may be substituted by one or more substituents selected from

(a) halo,

(b) CN,

(c) $C_{1-10}$ alkyl, $C_{2-10}$ alkenyl, $C_{2-10}$ alkynyl (which latter three groups are optionally substituted by one or more substituents selected from halo, OH, $C_{1-6}$ alkoxy, C(O)OH, C(O)O-$C_{1-6}$ alkyl, phenyl (which latter group is optionally substituted by halo) and $Het^7$),

(d) $C_{3-10}$ cycloalkyl, $C_{4-10}$ cycloalkenyl (which latter two groups are optionally substituted by one or more substituents selected from halo, OH, =O, $C_{1-6}$ alkyl, $C_{1-6}$ alkoxy, phenyl (which latter group is optionally substituted by halo) and $Het^8$),

(e) $OR^{17a}$,

(f) $S(O)_pR^{17b}$,

(g) $S(O)_2N(R^{17c})(R^{17d})$,

(h) $N(R^{17e})S(O)_2R^{17f}$,

(i) $N(R^{17g})(R^{17h})$,

(j) $B^5$-C(O)-$B^6$-$R^{17i}$,

(k) phenyl (which latter group is optionally substituted by halo),

(l) $Het^9$ and

(m) $Si(R^{18a})(R^{18b})(R^{18c})$;

$R^{17a}$ to $R^{17i}$ independently represent, at each occurrence,

(a) H,

(b) $C_{1-10}$ alkyl, $C_{2-10}$ alkenyl, $C_{2-10}$ alkynyl (which latter three groups are optionally substituted by one or more substituents selected from halo, OH, $C_{1-6}$ alkoxy, phenyl (which latter group is optionally substituted by halo) and $Het^{10}$),

(c) $C_{3-10}$ cycloalkyl, $C_{4-10}$ cycloalkenyl (which latter two groups are optionally substituted by one or more substituents selected from halo, OH, =O, $C_{1-6}$ alkyl, $C_{1-6}$ alkoxy, phenyl (which latter group is optionally substituted by halo) and $Het^{11}$),

(d) phenyl (which latter group is optionally substituted by halo) or

(e) $Het^{12}$,

provided that $R^{17b}$ does not represent H when p is 1 or 2;

$Het^{1}$ to $Het^{12}$ independently represent 4- to 14-membered heterocyclic groups containing one or more heteroatoms selected from oxygen, nitrogen and/or sulfur, which heterocyclic groups may comprise one, two or three rings and may be substituted by one or more substituents selected from

(a) halo,

(b) CN,

(c) $C_{1-10}$ alkyl, $C_{2-10}$ alkenyl, $C_{2-10}$ alkynyl (which latter four groups are optionally substituted by one or more substituents selected from halo, OH, $C_{1-6}$ alkoxy, C(O)OH, C(O)O-$C_{1-6}$ alkyl, phenyl (which latter group is optionally substituted by halo) and $Het^{a}$),

(d) $C_{3-10}$ cycloalkyl, $C_{4-10}$ cycloalkenyl (which latter two groups are optionally substituted by one or more substituents selected from halo, OH, =O, $C_{1-6}$ alkyl, $C_{1-6}$ alkoxy, phenyl (which latter group is optionally substituted by halo) and $Het^{b}$),

(e) =O,

(f) $OR^{19a}$,

(g) $S(O)_qR^{19b}$,

(h) $S(O)_2N(R^{19c})(R^{19d})$,

(i) $N(R^{19e})S(O)_2R^{19f}$,

(j) $N(R^{19g})(R^{19h})$,

(k) $B^7$-C(O)-$B^8$-$R^{19i}$,

(l) phenyl (which latter group is optionally substituted by halo),

(m) $Het^c$ and

(n) $Si(R^{20a})(R^{20b})(R^{20c})$;

$R^{19a}$ to $R^{19i}$ independently represent, at each occurrence,

(a) H,

(b) $C_{1-10}$ alkyl, $C_{2-10}$ alkenyl, $C_{2-10}$ alkynyl (which latter three groups are optionally substituted by one or more substituents selected from halo, OH, $C_{1-6}$ alkoxy, phenyl (which latter group is optionally substituted by halo) and $Het^d$),

(c) $C_{3-10}$ cycloalkyl, $C_{4-10}$ cycloalkenyl (which latter two groups are optionally substituted by one or more substituents selected from halo, OH, =O, $C_{1-6}$ alkyl, $C_{1-6}$ alkoxy, phenyl (which latter group is optionally substituted by halo) and $Het^d$),

(d) phenyl (which latter group is optionally substituted by halo) or

(e) $Het^f$,

provided that $R^{19b}$ does not represent H when q is 1 or 2;

$Het^a$ to $Het^f$ independently represent 5- or 6-membered heterocyclic groups containing one to four heteroatoms selected from oxygen, nitrogen and/or sulfur, which heterocyclic groups may be substituted by one or more substituents selected from halo, =O and $C_{1-6}$ alkyl;

$B^1$ to $B^8$ independently represent a direct bond, O, S or NH;

n, p and q independently represent 0, 1 or 2;

$R^{18a}$, $R^{18b}$, $R^{18c}$, $R^{20a}$, $R^{20b}$ and $R^{20c}$ independently represent $C_{1-6}$ alkyl or phenyl (which latter group is optionally substituted by halo or $C_{1-4}$ alkyl);

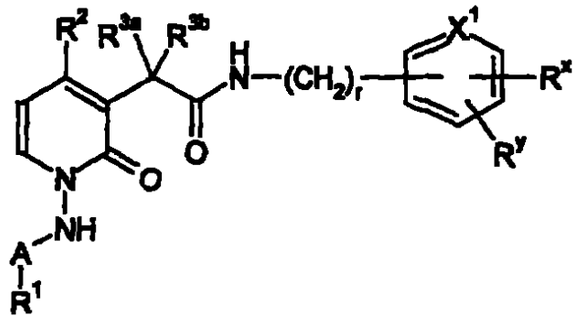
unless otherwise specified

(i) alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, alkylene and alkenylene groups, as well as the alkyl part of alkoxy groups, may be substituted by one or more halo atoms, and

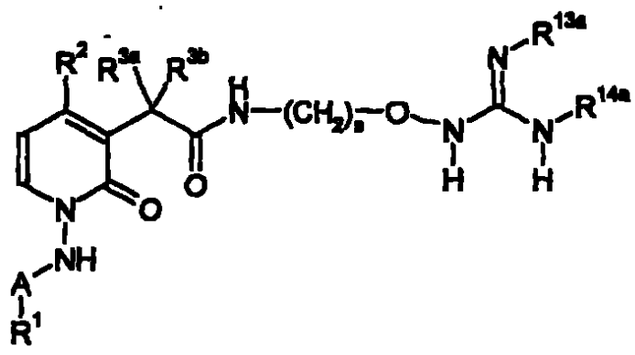
(ii) cycloalkyl and cycloalkenyl groups may comprise one or two rings and may additionally be ring-fused to one or two phenyl groups;

or a pharmaceutically-acceptable derivative thereof.

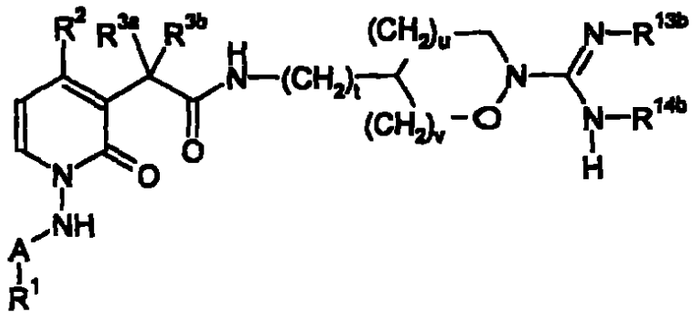
2. A compound as claimed in Claim 1, which is a compound of formula Ic, Id or Ie,



Ic



Id



Ie

wherein $X^1$ represents CH or N;

when $X^1$ represents CH

(a) $R^x$ represents $R^b$ as defined in Claim 1, and

(b) $R^y$ represents $R^{11a}$ as defined in Claim 1;

when $X^1$ represents N

(a) $R^x$ represents $R^d$ as defined in Claim 1, and

(b) $R^y$ represents $R^{11c}$ as defined in Claim 1;

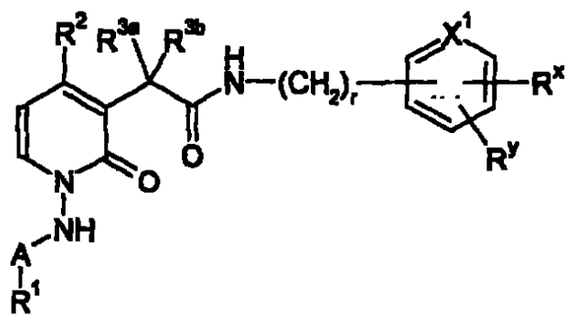
r represents 1 to 3;

s represents 2 to 4;

t represents 1 to 3;

u and v independently represent 0 to 2, the sum of u and v being 1 or 2; and $R^1$, $R^2$, $R^{3a}$, $R^{3b}$, $R^{11a}$, $R^{11c}$, $R^{13a}$, $R^{13b}$, $R^{14a}$, $R^{14b}$, $R^b$, $R^d$ and A are as defined in Claim 1.

3. A compound as claimed in Claim 2 which is a compound of formula Ic,



Ic

wherein

A represents $CH(CH_3)CH_2$ (in which latter group the $CH(CH_3)$ unit is attached to $R^1$) or $CH_2$, $(CH_2)_2$ or $CF_2CH_2$ (in which latter group the $CF_2$ unit is attached to $R^1$);

$R^1$ represents

(a) isopropyl or *tert*-butyl,

(b) cyclopentyl, cyclohexyl or bicyclo[2.2.1]hept-5-ene,

(c) phenyl optionally substituted by one or two substituents selected from halo, CN, methyl, $CF_3$, methoxy, $OCF_3$, phenoxy, morpholin-4-yl or O-$CH_2$-(2-chlorothiazol-5-yl),

(d) imidazolyl optionally substituted by one to three substituents selected from Cl, methyl and phenyl,

(e) isoxazolyl optionally substituted by one or two substituents selected from methyl, phenyl and 2-thienyl,

(f) thiazolyl optionally substituted by one or two methyl groups,

(g) thienyl optionally substituted by Cl or pyridinyl,

(h) pyrazolyl optionally substituted by one to three substituents selected from Cl, methyl, ethyl, phenyl and morpholin-4-yl,

(i) pyrrolyl optionally substituted by one to three substituents selected from methyl, $S(O)_2$-phenyl, C(O)-phenyl and 1,3,4-triazol-1-yl,

(j) pyridinyl optionally substituted by OH, methoxy or morpholin-4-yl, and optionally in the form of an *N*-oxide,

(k) pyridonyl,

(l) pyrazinyl,

(m) benzodioxolyl optionally substituted by halo,

(n) benzomorpholinyl optionally substituted by methyl;

(o) 2,1,3-benzoxadiazolyl,

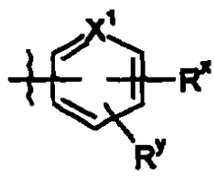
(p) 2,3-dihydrobenzofuranyl or

(q) quinolinyl;

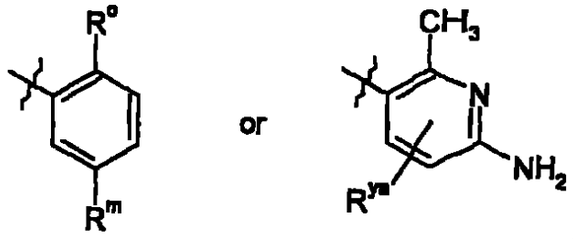
$R^5$ and $R^6$ both represent H;

r represents 1;

the group



represents



;

$R^o$ represents H, F, Cl, OH, methyl, tetrazol-1-yl, $OCH_2C(O)N(H)R^{12b}$ or $CH_2N(H)R^{14c}$;

$R^{12b}$ represents H or $C_{1-3}$ alkyl optionally substituted by $N(CH_3)_2$;

$R^{14c}$ represents C(O)O-*tert*-butyl, H, ethyl, $CH_2CF_3$ or cyclopentyl;

$R^m$ represents H, methyl, $CF_3$, methoxy, F or Cl; and

$R^{ya}$ represents H or methyl.

4. A pharmaceutical formulation including a compound as defined in any one of Claims 1 to 3, or a pharmaceutically acceptable derivative thereof, in admixture with a pharmaceutically acceptable adjuvant, diluent or carrier.

5. A compound as defined in any one of Claims 1 to 3, or a pharmaceutically acceptable derivative thereof, for use as a pharmaceutical.

6. The use of a compound as defined in any one of Claims 1 to 3, or a pharmaceutically acceptable derivative thereof, as an active ingredient for the manufacture of a medicament for the treatment of a condition where inhibition of thrombin is beneficial.

7. A method of treatment of a condition where inhibition of thrombin is beneficial, which method comprises administration of a therapeutically effective amount of a compound as defined in any one of Claims 1 to 3, or a

pharmaceutically acceptable derivative thereof, to a person suffering from, or susceptible to, such a condition.

8. A process for the preparation of a compound of formula I as defined in Claim 1, which comprises:

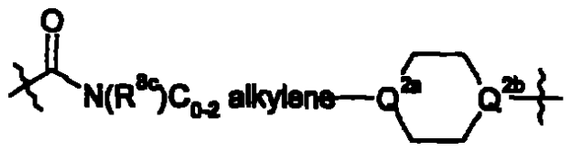
(a) for compounds of formula I in which the group G represents

(i) $C(O)N(R^{8a})$-$[CH(C(O)R^9)]_{0-1}$-$C_{0-3}$ alkylene-$(Q^1)_n$-,

(ii) $C(O)N(R^{8b})$-$C_{2-3}$ alkenylene-$(Q^1)_n$-,

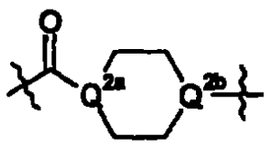
(iii) $C(O)N(R^{8b})$-$C_{2-3}$ alkynylene-$(Q^1)_n$-,

(iv)



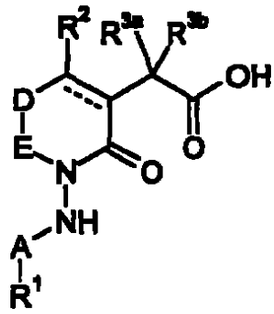
or

(v)



wherein $Q^{2a}$ represents N or NHCH,

coupling of a compound of formula II,



II

wherein the dashed line, $R^1$, $R^2$, $R^{3a}$, $R^{3b}$, A, D and E are as defined in Claim 1, with a compound of formula III,

H-$G^a$-L III

wherein L is as defined in Claim 1 and $G^a$ represents

(i) $-N(R^{8a})-[CH(C(O)R^9)]_{0-1}-C_{0-3}$ alkylene-$(Q^1)_a-$,

(ii) $-N(R^{8b})-C_{2-3}$ alkenylene-$(Q^1)_a-$,

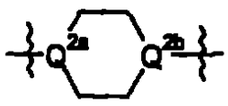
(iii) $-N(R^{8b})-C_{2-3}$ alkynylene-$(Q^1)_a-$,

(iv)



or

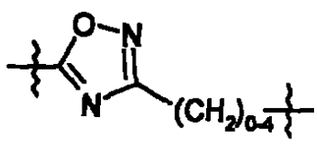
(v)



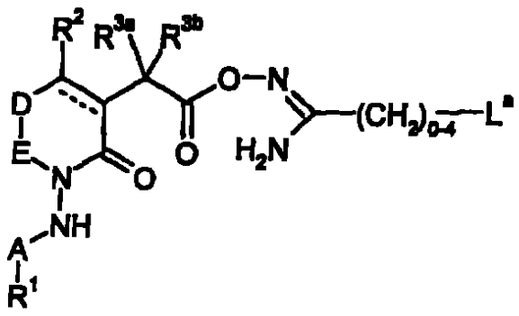
,

wherein $Q^{2a}$ represents N or NHCH and $R^{8a}$, $R^{8b}$, $R^{8c}$, $R^9$, $Q^1$, $Q^{2b}$ and a are as defined in Claim 1;

(b) for compounds of formula I in which G represents



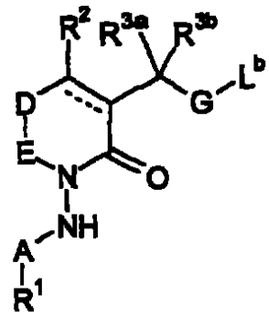
and L represents $L^a$, which latter group represents L as defined in Claim 1, except that it does not represent $C_0$ alkylene-$R^a$, cyclisation of a compound of formula IV,



IV

wherein $L^a$ is as defined above and the dashed line, $R^1$, $R^2$, $R^{3a}$, $R^{3b}$, A, D and E are as defined in Claim 1;

(c) for compounds of formula I in which $R^a$, $R^b$, $R^c$ or $R^d$ represents $-C(=NH)NH_2$, $-C(=NNH_2)NH_2$ or $-C(=NOH)NH_2$, reaction of a compound of formula V,



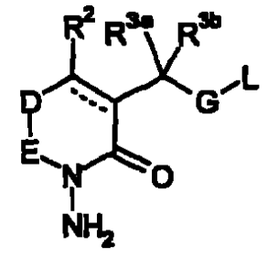
V

wherein $L^b$ represents L as defined in Claim 1, except that $R^a$, $R^b$, $R^c$ or $R^d$ (as appropriate) is replaced by a cyano or -C(=NH)O-$C_{1-4}$ alkyl group, and the dashed line, $R^1$, $R^2$, $R^{3a}$, $R^{3b}$, A, D, E and G are as defined in Claim 1, with a suitable source of ammonia, hydrazine or hydroxylamine;

(d) for compounds of formula I in which $R^{13a}$, $R^{13b}$ or $R^{13c}$ represents H, deprotection of a corresponding compound of formula I in which $R^{13a}$, $R^{13b}$ or $R^{13c}$ (as appropriate) represents C(O)O-$CH_2$aryl;

(e) for compounds of formula I in which $R^{14c}$ represents H, deprotection of a corresponding compound of formula I in which $R^{14c}$ represents C(O)O-$C_{1-6}$ alkyl;

(f) reaction of a compound of formula VI,



VI

wherein the dashed line, $R^2$, $R^{3a}$, $R^{3b}$, A, D, E, G and L are as defined in Claim 1, with a compound of formula VII,

$$R^1\text{-A-Lg}^1 \qquad \text{VII}$$

wherein $Lg^1$ represents a leaving group and $R^1$ and A are as defined in Claim 1;

(g) for compounds of formula I in which A represents C(O)NH, reaction of a compound of formula VI, as defined above, with a compound of formula VIII,

$R^1$-N=C=O VIII

wherein $R^1$ is as defined in Claim 1;

(h) for compounds of formula I in which A represents $C_{1-6}$ alkylene, reaction of a compound of formula VI, as defined above, with a compound of formula IX,

$R^1$-$C_{0-5}$ alkylene-CHO IX

wherein $R^1$ is as defined in Claim 1, followed by reduction in the presence of a reducing agent; or

(i) for compounds of formula I in which $R^a$, $R^b$, $R^c$ or $R^d$ represents -C(=NCN)$NH_2$, reaction of a corresponding compound of formula I in which $R^a$, $R^b$, $R^c$ or $R^d$, respectively, represents -C(=NH)$NH_2$ with cyanogen bromide.

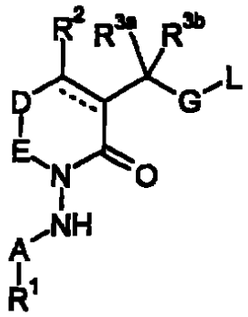
9. A compound of formula II, as defined in Claim 8, or a protected derivative thereof.

10. A compound of formula IV, as defined in Claim 8, or a protected derivative thereof.

11. A compound of formula VI, as defined in Claim 8, or a protected derivative thereof.

# ABSTRACT

There is provided a compound of formula I



I

wherein the dashed line, $R^1$, $R^2$, $R^{3a}$, $R^{3b}$, A, D, E, G and L have meanings given in the description, which compounds are useful as, or are useful as prodrugs of, competitive inhibitors of trypsin-like proteases, such as thrombin, and thus, in particular, in the treatment of conditions where inhibition of thrombin is beneficial (e.g. conditions, such as thrombo-embolisms, where inhibition of thrombin is required or desired, and/or conditions where anticoagulant therapy is indicated).

# INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 2005/000124

A. CLASSIFICATION OF SUBJECT MATTER

IPC7: C07D 211/86, A61K 31/4412, A61P 7/02
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)

IPC7: C07D

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

SE,DK,FI,NO classes as above

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

CHEM. ABS. DATA, WPI DATA

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| A | US 5792779 A (PHILIP E. SANDERSON ET AL), 11 August 1998 (11.08.1998) | 1-11 |

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

* Special categories of cited documents
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

| Date of the actual completion of the international search | Date of mailing of the international search report |
|---|---|
| 23 May 2005 | 23 -05- 2005 |
| Name and mailing address of the ISA/<br>Swedish Patent Office<br>Box 5055, S-102 42 STOCKHOLM<br>Facsimile No. +46 8 666 02 86 | Authorized officer<br>Carolina Gómez Lagerlöf/EÖ<br>Telephone No. +46 8 782 25 00 |

Form PCT/ISA/210 (second sheet) (January 2004)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 2005/000124

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

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

1. ☒ Claim Nos.: 7
because they relate to subject matter not required to be searched by this Authority, namely:

See next sheet.

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

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

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

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

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

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

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

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

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 2005/000124

Box II.1

Claim 7 relates to a method of treatment of the human or animal body by surgery or by therapy, as well as diagnostic methods /Rule 39.1(iv). Nevertheless, a search has been executed for this claim. The search has been based on the alleged effects of the compounds.

(12) SOLICITUD INTERNACIONAL PUBLICADA BAJO EL TRATADO DE COOPERACIÓN INTERNACIONAL EN MATERIA DE PATENTES (PCT)

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Oficina Internacional

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(26) Idioma de Publicación: inglés

(30) Datos relativos a la Prioridad:
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(71) Solicitante *(para todos los países destinatarios con excepción de US)*: ASTRAZENECA AB [SE/SE]; S-151 85 Södertälje (SE).

(72) Inventores, e
(75) Inventores/Solicitantes *(para US únicamente)*: BAYRAKDARIAN, Maiken [CA/CA]; AstraZeneca R & D Montreal, 7171 Frederick-Banting, St. Laurent, Montreal, Quebec H4S IZ9 (CA). BERGGREN, Kristina [SE/SE]; AstraZeneca R & D Mölndal, S-431 83 Mölndal (SE). DAVIDSSON, Öjvind [SE/SE]; AstraZeneca R & D Mölndal, S-431 83 Mölndal (SE). FJELLSTRÖM, Ola [SE/SE]; AstraZeneca R & D Mölndal, S-431 83 Mölndal (SE). GUSTAFSSON, David [SE/SE]; AstraZeneca R & D Mölndal, S-431 83 Mölndal, (SE). HANESSIAN, Stephen [CA/CA]; University of Montreal, Dep of Chemistry, C.P. 6128, Succursale Centre.-Ville, Montreal, Québec H3C 1J7 (CA). INGHARDT, Tord [SE/SE]; AstraZeneca R & D Mölndal, S-431 83 Mölndal (SE). NILSSON, Ingemar [SE/SE]; AstraZeneca R & D Mölndal, S-431 83 Mölndal (SE). NÅGÅRD, Mats [SE/SE]; AstraZeneca R & D Mölndal, S-431 83 Mölndal (SE). SIMARD, Daniel [CA/CA]; University of Montreal, Dep of Chemistry, C.P. 6128, Succursale Centre-Ville, Montreal, Québec H3C IJ7 (CA). THERRIEN, Eric [CA/CA]; University of Montreal, Dep of Chemistry, C.P. 6128, Succursale Centre-Ville, Montreal, Québec H3C IJ7 (CA).

(74) Agente: ASTRAZENECA; Global Intellectual Property, S-151 85 Södertälje (SE)

(81) Países designados *(a menos que se indique lo contrario para cada clase de protección disponible)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Países designados *(a menos que se indique lo contrario para cada clase de protección disponible)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Euroasiática (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), Europea (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Publicado:
— *con informe internacional de búsqueda*

*Para códigos de dos letras y otras abreviaturas, remítase a las "Notas Guía sobre Códigos y Abreviaturas" que aparece al comienzo de cada edición regular del Boletín Oficial PCT.*

WO 2005/075424 A1

(54) Título: NOVEDOSOS COMPUESTOS DE PIRIDIN-2-ONA ÚTILES COMO INHIBIDORES DE TROMBINA

(57) Extracto: Se provee un compuesto de fórmula I, en donde la línea discontinua, $R^1$, $R^2$, $R^{3a}$, $R^{3b}$, A, D, E, G y L tienen los significados dados en la descripción, compuestos que son útiles como, o son útiles como profármacos de, inhibidores competitivos de proteasas tipo tripsina, tales como trombina y, por consiguiente, en particular, en el tratamiento de afecciones donde es benéfica la inhibición de trombina (verbigracia, trastornos tales como tromboembolismos, donde se requiere o desea la inhibición de trombina, y/o enfermedades donde es indicada una terapia anticoagulante).

# NOVEDOSOS COMPUESTOS DE PIRIDIN-2-ONA ÚTILES COMO INHIBIDORES DE TROMBINA

## Campo de la Invención

Esta invención se relaciona con compuestos novedosos, farmacéuticamente útiles, en particular compuestos que son, y/o compuestos que se metabolizan en compuestos que son, inhibidores competitivos de serina proteasas tipo tripsina, especialmente trombina, su uso como medicamentos, composiciones farmacéuticas que los contienen y vías sintéticas para su producción.

## Antecedentes

La coagulación sanguínea es un proceso clave involucrado en la hemostasis (es decir, la prevención de pérdida de sangre de un vaso dañado) y la trombosis (es decir, la formación de un coágulo de sangre en un vaso sanguíneo, lo cual lleva a veces a una obstrucción del vaso).

La coagulación es el resultado de una serie compleja de reacciones enzimáticas. Uno de los últimos pasos en esta serie de reacciones es la conversión de la proenzima protrombina en la enzima activa trombina.

La trombina es conocida por jugar un papel central en la coagulación. Activa las plaquetas, llevando a la agregación plaquetaria, convierte fibrinógeno en monómeros de fibrina, que se polimerizan espontáneamente en polímeros de fibrina, y activa el factor XIII el que, a su vez, entrecruza los polímeros para formar fibrina insoluble. Más aún, la trombina activa el factor V, el factor VIII y el FXI que llevan a una generación con "retroalimentación positiva" de trombina a partir de protrombina.

Al inhibir la agregación de plaquetas y la formación y entrecruzamiento de fibrina, se esperaría que inhibidores efectivos de trombina exhiban actividad antitrombótica. Adicionalmente, se esperaría que la actividad antitrombótica se mejorara por la inhibición efectiva del mecanismo de retroalimentación positiva. En efecto, los efectos antitrombóticos convincentes de un inhibidor de trombina en el hombre se ha descrito recientemente por S. Schulman *y colaboradores*, en *N. Engl. J. Med.* 349, 1713-1721 **(2003)**.

**Arte Previo**

El desarrollo anterior de inhibidores de trombina de bajo peso molecular se ha descrito por Claesson en *Blood Coagul. Fibrinol.* 5, 411 **(1994)**.

Blombäck *y colaboradores* (en *J. Clin. Lab. Invest.* 24, suppl. 107, 59 **(1969)**) dieron cuenta de inhibidores de trombina basados en la secuencia de aminoácidos situados en el sitio de segmentación para la cadena Aα de fibrinógeno. De las secuencias de aminoácidos discutidas, estos autores sugerían que la secuencia de tripéptidos Phe-Val-Arg (P9-P2-P1, designada a partir de ahora la secuencia P3-P2-P1) sería el inhibidor más efectivo.

Inhibidores de trombina basados en derivados peptidilo, que presentan grupos básicos cíclicos o acíclicos en la posición P1 (por ejemplo, grupos que contienen funciones amino, amidino o guanidino), se divulgan en, por ejemplo, Solicitudes Internacionales de Patente No. WO 93/11152, WO 93/18060, WO 94/29336, WO 95/23609, WO 95/35309, WO 96/03374, WO 96/25426, WO 96/31504, WO 96/32110, WO 97/02284, WO 97/23499, WO 97/46577, WO 97/49404, WO 98/06740, WO 98/57932, WO 99/29664, WO 00/35869, WO 00/42059, WO 01/87879, WO 02/14270, WO 02/44145 y WO 03/018551, Solicitudes de Patente Europea No. 185 390, 468 231,526 877, 542 525, 559 046 y 641 779, 648 780, 669 317 y Patente de los Estados Unidos No. 4,346,078.

Se conocen también inhibidores de serina proteasas (por ejemplo, trombina) basados en cetonas electrófilas en la posición P1, tales como los compuestos divulgados en las Solicitudes de Patente Europeas No. 195 212, 362 002, 364 344 y 530 167.

Inhibidores de serina proteasas tipo tripsina basados en derivados de ácido bórico C-terminal de arginina (y sus análogos de isotiouronio) se conocen de la Solicitud de Patente Europea No. 293 881.

Inhibidores de trombina no quirales que tienen, en la posición P2 de la molécula, un grupo fenilo y un grupo básico cíclico o acíclico en la posición P3, se divulgan en las Solicitudes Internacionales de Patente No. WO 94/20467, WO 96/06832, WO 96/06849, WO 97/11693, WO 97/24135, WO 98/01422 y WO 01/68605, así como en *Bioorg Med. Chem. Lett.* 7, 1283 (1997).

Solicitudes Internacionales de Patente No. WO 99/26920 y WO 01/79155 divulgan inhibidores de trombina que tienen grupos en la posición P2 basados, respectivamente, en 2-aminofenoles y 1,4-benzoquinonas. Compuestos similares, a base de fenol, se divulgan igualmente en la Solicitud Internacional de Patente No. WO 01/68605 y WO 02/28825.

Otros inhibidores de trombina conocidos y otras serina proteasas tipo tripsina se basan (en la posición P2 de la molécula) en la unidad estructural 3-amino-2-piridona. Por ejemplo, compuestos basados en 3-amino-2-piridona, 3-amino-2-pirazinona, 5-amino-6-pirimidona, 5-amino-2,6-pirimidiona y 5-amino-1,3,4-triazin-6-ona se divulgan en las Solicitudes Internacionales de Patente No. WO 96/18644, WO 97/01338, WO 97/30708, WO 98/16547, WO 99/26926, WO 00/73302, WO 00/75134, WO 01/38323, WO 01/04117, WO 01/70229, WO 01/79262, WO 02/057225, WO 02/064140 y WO 03/29224, Patentes de los Estados

Unidos No. 5,668,289 y 5,792,779, así como en *Bioorg Med. Chem. Lett.* 8, 817 (1998) y *J. Med. Chem.* 41, 4466 (1998).

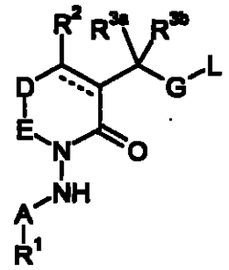
Inhibidores de trombina basados en azaheterociclos saturados 2-oxo-3-amino-sustituidos se divulgan en la Solicitud Internacional de Patente No. WO 95/35313. Más recientemente, se han divulgados inhibidores de trombina que se basan en 4-amino-3-morfolinona (véase *J. Med. Chem.* 46, 1165 (2003)).

Ninguno de los documentos ya mencionados divulgan o sugieren compuestos basados (en la posición P2) en la unidad estructural 1-amino-2-piperidona.

Más aún, subsiste una necesidad de inhibidores efectivos de serina proteasas tipo tripsina, tales como trombina. Subsiste igualmente una necesidad de compuestos que posean un perfil farmacocinético favorable. Se esperaría que sean útiles como anticoagulantes y, por lo tanto, en el tratamiento terapéutico de trombosis y trastornos relacionados.

**Divulgación de la Invención**

De acuerdo con la invención se provee un compuesto de fórmula I



I

en donde

la línea discontinua está ausente o representa un enlace;

A representa C(O), $S(O)_2$, C(O)O (en cuyo último grupo la fracción O se une a $R^1$), C(O)NH, $S(O)_2NH$ (en cuyos últimos dos grupos la fracción NH se une a $R^1$) o $C_{1-6}$ alquileno;

$R^1$ representa

(a) $C_{1-10}$ alquilo, $C_{2-10}$ alquenilo, $C_{2-10}$ alquinilo (los cuales últimos tres grupos se sustituyen opcionalmente por uno o más sustituyentes seleccionados de halo, CN, $C_{3-10}$ cicloalquilo (sustituido opcionalmente por uno o más sustituyentes seleccionados de halo, OH, =O, $C_{1-6}$ alquilo, $C_{1-6}$ alcoxi y arilo), $OR^{4a}$, $S(O)_nR^{4b}$, $S(O)_2N(R^{4c})(R^{4d})$, $N(R^{4e})S(O)_2R^{4f}$, $N(R^{4g})(R^{4h})$, $B^1$-C(O)-$B^2$-$R^{4i}$, arilo y $Het^1$),

(b) $C_{3-10}$ cicloalquilo o $C_{4-10}$ cicloalquenilo, los cuales últimos dos grupos se sustituyen opcionalmente por uno o más sustituyentes seleccionados de halo, =O, CN, $C_{1-10}$ alquilo, $C_{3-10}$ cicloalquilo (sustituido opcionalmente por uno o más sustituyentes seleccionados de halo, OH, =O, $C_{1-6}$ alquilo, $C_{1-6}$ alcoxi y arilo), $OR^{4a}$, $S(O)_nR^{4b}$, $S(O)_2N(R^{4c})(R^{4d})$, $N(R^{4e})S(O)_2R^{4f}$, $N(R^{4g})(R^{4h})$, $B^3$-C(O)-$B^4$-$R^{4i}$, arilo y $Het^2$,

(c) arilo, o

(d) $Het^3$;

$R^{4a}$ a $R^{4i}$ representan independientemente, en cada ocurrencia,

(a) H,

(b) $C_{1-10}$ alquilo, $C_{2-10}$ alquenilo, $C_{2-10}$ alquinilo (los cuales últimos tres grupos se sustituyen opcionalmente por uno o más sustituyentes seleccionados de halo, OH, $C_{1-6}$ alcoxi, arilo y $Het^4$),

(c) $C_{3-10}$ cicloalquilo, $C_{4-10}$ cicloalquenilo (los cuales últimos dos grupos se sustituyen opcionalmente por uno o más sustituyentes seleccionados de halo, OH, =O, $C_{1-6}$ alquilo, $C_{1-6}$ alcoxi, arilo y $Het^5$),

(d) arilo o

(e) $Het^6$,

siempre que $R^{4b}$ no represente H cuando n es 1 ó 2;

el grupo -D-E-

(a) cuando la línea discontinua representa un enlace, representa $-C(R^{5a})=C(R^{5b})-$, o

(b) cuando la línea dicontinua está ausente, representa $-C(R^{6a})(R^{6b})-C(R^{7a})(R^{7b})-$; $R^{5a}$ y $R^{5b}$ representan independientemente H, halo, OH, $C_{1-4}$ alquilo, $(CH_2)_{0-4}O(C_{1-3}$ alquilo) (los cuales últimos dos grupos se sustituyen de manera opcional por un grupo OH o uno o más átomos F);

$R^{6a}$, $R^{6b}$, $R^{7a}$ y $R^{7b}$ representan independientemente H, F o metilo;

o $R^{5a}$ y $R^{5b}$ juntos representan 2-4 *n*-alquileno;

o uno de $R^{6a}$ y $R^{6b}$, junto con uno de $R^{7a}$, representa $C_{1-4}$ *n*- alquileno;

$R^2$ representa

(a) H,

(b) halo,

(c) $C_{1-6}$ alquilo, $C_{2-6}$ alquenilo, $C_{2-6}$ alquinilo, $C_{1-6}$ alcoxi (los cuales últimos cuatro grupos se sustituyen opcionalmente por uno o más sustituyentes seleccionados de halo, OH, CN, $C_{1-4}$ alcoxi, C(O)OH, $C(O)O-C_{1-4}$ alquilo y $OC(O)-C_{1-4}$ alquilo) o

(d) junto con $R^{3a}$, $R^2$ representa $C_{2-3}$ *n*-alquileno, $T^1$-($C_{1-2}$ *n*-alquileno) o ($C_{1-2}$ *n*-alquileno)-$T^1$, los cuales últimos tres grupos se sustituyen opcionalmente por halo, o

(e) junto con $R^{3a}$ y $R^{3b}$, $R^2$ representa $T^2$-[C(H)=], en donde $T^2$ se enlaza al átomo C al cual se une el grupo $R^2$;

$R^{3a}$ y $R^{3b}$ representan independientemente H, F o metilo (el cual último grupo se sustituye opcionalmente por uno o más átomos F), o

(a) junto con $R^2$, $R^{3a}$ representa $C_{2-3}$ *n*-alquileno, $T^1$-($C_{1-2}$ *n*-alquileno) o ($C_{1-2}$ *n*-alquileno)-$T^1$, los cuales últimos tres grupos se sustituyen opcionalmente por halo, o

(b) junto con $R^2$, $R^{3a}$ y $R^{3b}$ representa $T^2$-[C(H)=], en donde $T^2$ se enlaza al átomo C al cual se une el grupo $R^2$;

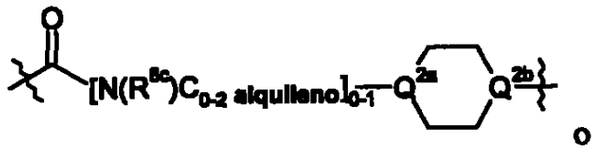
$T^1$ y $T^2$ representan independientemente O, S, N(H) o N($C_{1-4}$ alquilo);

G representa

(a) -C(O)N($R^{8a}$)-[CH(C(O)$R^9$)]$_{0-1}$-$C_{0-3}$alquileno-($Q^1$)$_a$-,

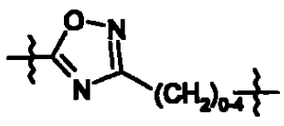
(b) -C(O)N($R^8$b)-$C_{2-3}$ alquenileno-($Q^1$)$_a$-,

(c)




o

(d)



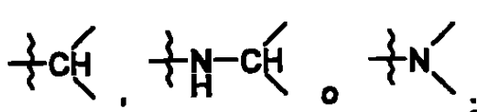

;

$R^9$ representa H o un grupo heterocíclico aromático de 5 a 10 miembros que comprende uno o dos anillos y contiene, como heteroátomo(s), un átomo de azufre u oxígeno y/o uno o más átomos de nitrógeno, grupo heterocíclico que se sustituye opcionalmente por uno o más sustituyentes seleccionados de halo y $C_{1-6}$ alquilo;

$Q^1$ representa O, $NR^{10a}$, [N(H)]$_{0-1}$C(O)-$C_{0-2}$ alquileno, C(O)NHNHC(O), o N=C($R^{10b}$)-;

a representa 0 ó 1;

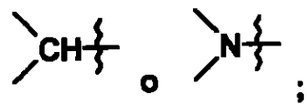
$Q^{2a}$ representa




;

$Q^{2b}$ representa

8



;

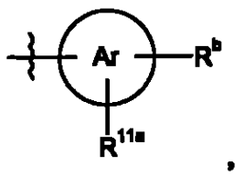
L representa

(a) $C_{0-6}$alquileno-$R^a$,

(b) $C_{0-2}$ alquileno-CH=CH-$C_{0-2}$ alquileno-$R^a$,

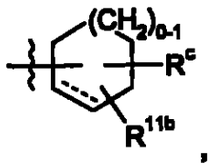
(c) $C_{0-2}$ alquileno-C≡$C_{0-2}$ alquileno-$R^a$,

(d)



,

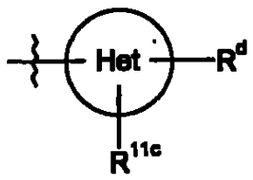
(e)



,

en donde la línea discontinua representa un doble enlace opcional, o

(f)



;

Ar representa fenilo o naftilo;

Het representa un grupo heterocíclico de 5 a 10 miembros que comprende uno o dos anillos y contiene, como heteroátomo(s), un átomo de azufre u oxígeno y/o uno o más átomos de nitrógeno;

$R^{11a}$ representa H o uno o más sustituyentes seleccionados de halo, OH, CN, $C_{1-6}$ alquilo, $C_{1-6}$ alcoxi (los cuales últimos dos grupos se sustituyen opcionalmente por uno o más sustituyentes seleccionados de halo, OH, $C_{1-4}$ alcoxi, $C(O)OR^{12a}$ y $C(O)N(R^{12b})R^{12c}$) y $S(O)_{0-2}R^{12d}$;

$R^{11b}$ y $R^{11c}$ representan independientemente H o uno o más sustituyentes seleccionados de halo, OH, CN, $C_{1-6}$ alquilo, $C_{1-6}$ alcoxi (los cuales últimos dos grupos se sustituyen opcionalmente por uno o más sustituyentes seleccionados de halo, OH, $C_{1-4}$ alcoxi, $C(O)OR^{12a}$ y $C(O)N(R^{12b})R^{12c}$), $S(O)_{0-2}R^{12d}$, =O, =NH, =NOH y =N-CN;

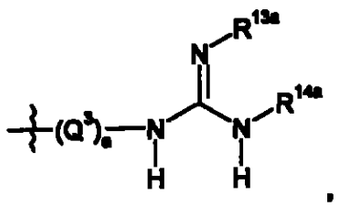
$R^{12a}$ a $R^{12c}$, representan independientemente H, $C_{1-6}$ alquilo o $C_{3-7}$ cicloalquilo (los cuales últimos dos grupos se sustituyen opcionalmente por un grupo OH ó $N(R^{12e})R^{12f}$ o por uno o más átomos halo);

$R^{12d}$ representa, independientemente en cada ocurrencia, $C_{1-6}$ alquilo sustituido opcionalmente por un grupo OH ó $N(R^{12e})R^{12f}$ o por uno o más átomos halo;

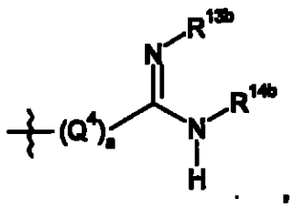
$R^{12e}$ y $R^{12f}$ representan, independientemente, en cada ocurrencia, H o $C_{1-4}$ alquilo sustituido opcionalmente por uno o más átomos halo;

$R^a$ a $R^d$ representan independientemente (a)

(a)



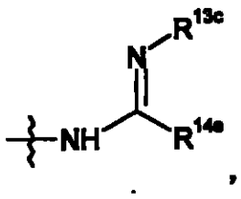
(b)



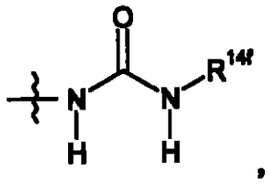
(c)



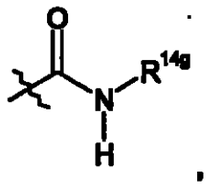
(d)



(e)



(f)



(g) $Het^x$

o $R^b$ a $R^d$ pueden representar también H;

$Q^3$ representa O, $N(R^{10c})$, $S(O)_2$, $S(O)_2NH$, C(O) o -CH=N-;

$Q^4$ representa O, S ó $CH_2$;

a representa 0 ó 1;

$Het^x$ representa un grupo heterocíclico de 5 ó 6 miembros, que contiene uno a cuatro heteroátomos seleccionados de oxígeno, nitrógeno y/o azufre, el cual grupo heterocíclico puede sustituirse por uno o más sustituyentes seleccionados de halo, =O, $C_{1-6}$ alquilo y $C_{1-6}$ alcoxi (los cuales últimos dos grupos se sustituyen de manera opcional por uno o más átomos halo);

$R^{13a}$ a $R^{13c}$ representan independientemente

(a) H,

(b) CN,

(c) $NH_2$,

(d) $OR^{15}$ o

(e) $C(O)OR^{16}$

$R^{15}$ representa

(a) H,

(b) $C_{1-10}$ alquilo, $C_{3-10}$ alquenilo, $C_{3-10}$ alquinilo,

(c) $C_{3-10}$ cicloalquilo, $C_{4-10}$ cicloalquenilo, los cuales últimos dos grupos se sustituyen opcionalmente por uno o más sustituyentes seleccionados de halo y $C_{1-6}$ alquilo, o

(d) $C_{1-3}$ alquilo, el cual último grupo se interrumpe opcionalmente por oxígeno y se sustituye por arilo o -O-arilo;

$R^{16}$ representa

(a) $C_{1-10}$ alquilo, $C_{3-10}$ alquenilo, $C_{3-10}$ alquinilo, los cuales últimos tres grupos se interrumpen opcionalmente por uno o más átomos de oxígeno, o

(b) $C_{3-10}$ cicloalquilo, $C_{4-10}$ cicloalquenilo, los cuales últimos dos grupos se sustituyen opcionalmente por uno o más sustituyentes seleccionados de halo y $C_{1-6}$ alquilo, o

(c) $C_{1-3}$ alquilo, el cual último grupo se interrumpe opcionalmente por oxígeno y se sustituye por arilo o -O-arilo;

$R^{8a}$ a $R^{8c}$, $R^{10a}$ a $R^{10c}$ y $R^{14a}$ a $R^{14g}$ representan independientemente

(a) H o

(b) $C_{1-4}$ alquilo (el cual último grupo se sustituye opcionalmente por uno o más sustituyentes seleccionados de halo y OH),

o $R^{14a}$ y $R^{14b}$ representan independientemente C(O)O-$C_{1-6}$ alquilo (la parte alquilo de cuyo último grupo se sustituye opcionalmente por arilo y/o uno o más átomos halo),

o $R^{14c}$ representa

(a) $C_{1-4}$ alquilo sustituido por $C_{3-7}$ cicloalquilo o arilo,

(b) $C_{3-7}$ cicloalquilo,

(c) C(O)O-$C_{1-6}$ alquilo (la parte alquilo de cuyo último grupo se sustituye opcionalmente por arilo y/o uno o más átomos halo),

(d) C(O)$C_{1-6}$ alquilo,

(e) C(O)N(H)-$C_{1-6}$ alquilo (la parte alquilo de cuyo último grupo se sustituye opcionalmente por arilo y/o uno o más átomos halo) o

(f) $S(O)_2$-$C_{1-6}$ alquilo (la parte alquilo de cuyo último grupo se sustituye opcionalmente por arilo y/o uno o más átomos halo),

o $R^{14c}$ y $R^{14d}$ juntos representan $C_{3-6}$ *n*-alquileno interrumpido opcionalmente por O, S, N(H) o N($C_{1-4}$ alquilo) y/o se sustituye por uno o más grupos $C_{1-4}$ alquilo;

cada arilo representa independientemente un grupo aromático carbocíclico $C_{6-10}$, grupo que puede comprender uno o dos anillos y puede sustituirse por uno o más sustituyentes seleccionados de

(a) halo,

(b) CN,

(c) $C_{1-10}$ alquilo, $C_{2-10}$ alquenilo, $C_{2-10}$ alquinilo (los cuales últimos tres grupos se sustituyen opcionalmente por uno o más sustituyentes seleccionados de halo, OH, $C_{1-6}$ alcoxi, C(O)OH, C(O)O-$C_{1-6}$ alquilo, fenilo (el cual último grupo se sustituye opcionalmente por halo) y $Het^7$),

(d) $C_{3-10}$ cicloalquilo, $C_{4-10}$ cicloalquenilo (los cuales últimos dos grupos se sustituyen opcionalmente por uno o más sustituyentes seleccionados de halo, OH, =O, $C_{1-6}$ alquilo, $C_{1-6}$ alcoxi, fenilo (el cual último grupo se sustituye opcionalmente por halo) y $Het^8$),

(e) $OR^{17a}$

(f) $S(O)_pR^{17b}$,

(g) $S(O)_2N(R^{17c})(R^{17d})$,

(h) $N(R^{17e})S(O)_2R^{17f}$,

(i) $N(R^{17g})(R^{17h})$,

(j) $B^5$-C(O)-$B^6$-$R^{17i}$,

(k) fenilo (el cual último grupo se sustituye opcionalmente por halo),

(l) $Het^9$ y

(m) $Si(R^{18a})(R^{18b})(R^{18c})$;

$R^{17a}$ a $R^{17i}$ representan independientemente, en cada ocurrencia,

(a) H,

(b) $C_{1-10}$ alquilo, $C_{2-10}$ alquenilo, $C_{2-10}$ alquinilo (los cuales últimos tres grupos se sustituyen opcionalmente por uno o más sustituyentes seleccionados de halo, OH, $C_{1-6}$ alcoxi, fenilo (el cual último grupo se sustituye opcionalmente por halo) y $Het^{10}$),

(c) $C_{3-10}$ cicloalquilo, $C_{4-10}$ cicloalquenilo (los cuales últimos dos grupos se sustituyen opcionalmente por uno o más sustituyentes seleccionados de halo, OH, =O, $C_{1-6}$ alquilo, $C_{1-6}$ alcoxi, fenilo (el cual último grupo se sustituye opcionalmente por halo) y $Het^{11}$),

(d) fenilo (el cual último grupo se sustituye opcionalmente por halo) o

(e) $Het^{12}$,

siempre que $R^{17b}$ no represente H cuando p es 1 ó 2;

$Het^{1}$ a $Het^{12}$ representan independientemente grupos heterocíclicos de 4 a 14 miembros que contienen uno o más heteroátomos seleccionados de oxígeno, nitrógeno y/o azufre, los cuales grupos heterocíclicos pueden comprender uno, dos o tres anillos y pueden sustituirse por uno o más sustituyentes seleccionados de

(a) halo,

(b) CN,

(c) $C_{1-10}$ alquilo, $C_{2-10}$ alquenilo, $C_{2-10}$ alquinilo (los cuales últimos cuatro grupos se sustituyen opcionalmente por uno o más sustituyentes seleccionados de halo, OH, $C_{1-6}$ alcoxi, C(O)OH, C(O)O-$C_{1-6}$ alquilo, fenilo (el cual último grupo se sustituye opcionalmente por halo) y $Het^{a}$),

(d) $C_{3-10}$ ciclolquilo, $C_{4-10}$ cicloalquenilo (los cuales últimos dos grupos se sustituyen opcionalmente por uno o más sustituyentes seleccionados de halo, OH, =O, $C_{1-6}$ alquilo, $C_{1-6}$ alcoxi, fenilo (el cual último grupo se sustituye opcionalmente por halo) y $Het^{b}$),

(e) =O,

(f) $OR^{19a}$,

(g) $S(O)_qR^{19b}$,

(h) $S(O)_2N(R^{19c})(R^{19d})$,

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(i) $N(R^{19c})S(O)_2R^{19f}$

(j) $N(R^{19g})(R^{19h})$,

(k) $B^7$-C(O)-$B^8$-$R^{19i}$,

(l) fenilo (el cual último grupo se sustituye opcionalmente por halo),

(m) $Het^c$ y

(n) $Si(R^{20a})(R^{20b})(R^{20c})$;

$R^{19a}$ a $R^{19i}$ representan independientemente, en cada ocurrencia,

(a) H,

(b) $C_{1-10}$ alquilo, $C_{2-10}$ alquenilo, $_{2-10}$ alquinilo (los cuales últimos tres grupos se sustituyen opcionalmente por uno o más sustituyentes seleccionados de halo, OH, $C_{1-6}$ alcoxi, fenilo (el cual último grupo se sustituye opcionalmente por halo) y $Het^d$),

(c) $C_{3-10}$ cicloalquilo, $C_{4-10}$ cicloalquenilo (los cuales últimos dos grupos se sustituyen opcionalmente por uno o más sustituyentes seleccionados de halo, OH, =O, $C_{1-6}$ alquilo, $C_{1-6}$ alcoxi, fenilo (el cual último grupo se sustituye opcionalmente por halo) y $Het^e$),

(d) fenilo (el cual último grupo se sustituye opcionalmente por halo) o

(e) $Het^f$,

siempre que $R^{19b}$ no represente H cuando q es 1 ó 2;

$Het^a$ a $Het^f$ representan independientemente grupos heterocíclicos de 5 o 6 miembros que contienen uno a cuatro heteroátomos seleccionados de oxígeno, nitrógeno y/o azufre, grupos heterocíclicos que pueden sustituirse por uno o más sustituyentes seleccionados de halo, =O y $C_{1-6}$ alquilo;

$B^1$ a $B^8$ representan independientemente un enlace directo, O, S ó NH;
n, p y q representan independientemente 0, 1 ó *2;*

$R^{18a}$, $R^{18b}$, $R^{18c}$, $R^{20a}$, $R^{20b}$ y $R^{20c}$ representan independientemente $C_{1-6}$ alquilo o fenilo (el cual último grupo se sustituye opcionalmente por halo o $C_{1-4}$ alquilo);

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a menos que se especifique otra cosa

(i) grupos alquilo, alquenilo, alquinilo, cicloalquilo, cicloalquenilo, alquileno y alquenileno, así como la parte alquilo de grupos alcoxi, pueden sustituirse por uno o más átomos halo, y

(ii) grupos cicloalquilo y cicloalquenilo pueden comprender uno o dos anillos y, adicionalmente, pueden fusionarse mediante anillo a uno o dos grupos fenilo;

o su derivado farmacéuticamente aceptable,

los cuales compuestos se designan en adelante "los compuestos de la invención".

El término "derivados farmacéuticamente aceptables" incluye sales farmacéuticamente aceptables (por ejemplo, sales de adición de ácido).

Para evitar dudas, las definiciones de los términos grupos arilo, alquilo, alquenilo, alquinilo, cicloalquilo, cicloalquenilo, alquileno, alquenileno y alcoxi, provistos más arriba, se aplican, a menos que se señale lo contrario, en cada uso de tales términos incluidos aquí.

El término "halo", cuando se emplea aquí, incluye fluoro, cloro, bromo y yodo.

Grupos heterocíclicos (Het, $Het^1$ a $Het^{12}$ y $Het^a$ a $Het^f$ y $Het^x$) pueden ser completamente saturados, parcialmente insaturados, totalmente aromáticos o parcialmente aromáticos en carácter. Valores de grupos heterocíclicos (Het, $Het^1$ a $Het^{12}$ y $Het^a$ a $Het^f$ y $Het^x$) que pueden mencionarse incluyen 1-azabiciclo[2.2.2]octanilo, benzimidazolilo, benzo[*c*]isoxazolidinilo, benzisoxazolilo, benzodioxanilo, benzodioxepanilo, benzodioxolilo, benzofuranilo, benzofurazanilo, benzomorfolinilo, 2,1,3-benzoxadiazolilo,

benzoxazolidinilo, benzoxazolilo, benzopirazolilo, benzo[*e*]pirimidina, 2,1,3-benzotiadiazolilo, benzotiazolilo, benzotienilo, benzotriazolilo, cromanilo, cromenilo, cinnolinilo, 2,3-dihidrobenzimidazolilo, 2,3-dihidrobenzo[*b*]furanilo, 1,3-dihidrobenzo-[*c*]furanilo, 1,3-dihidro-2,1-benzisoxazolil 2,3-dihidropirrolo[2,3-*b*]-piridinilo, dioxanilo, furanilo, hexahidropirimidinilo, hidantoinilo, imidazolilo, imidazo[1,2-*a*]piridinilo, imidazo[2,3-*b*]tiazolilo, indolilo, isoquinolinilo, isoxazolidinilo, isoxazolilo, maleimido, morfolinilo, nafto[1,2-*b*] furanilo, oxadiazolilo, 1,2- ó 1,3-oxazinanilo, oxazolilo, ftalazinilo, piperazinilo, piperidinilo, purinilo, piranilo, pirazinilo, pirazolilo, piridinilo, piridonilo, pirimidinilo, pirrolidinonilo, pirrolidinilo, pirrolinilo, pirrolo[2,3-*b*] piridinilo, pirrolo [5,1-*b*] piridinilo, pirrolo [2,3-*c*] piridinilo, pirrolilo, quinazolinilo, quinolinilo, sulfolanilo, 3-sulfolenilo, 4,5,6,7-tetrahidrobenzimidazolilo, 4,5,6,7-tetrahidrobenzopirazolilo, 5,6,7,8-tetrahidrobenzo-[*e*]pirimidina, tetrahidrofuranilo, tetrahidropiranilo, 3,4,5,6-tetrahidro-piridinilo, 1,2,3,4-tetrahidropirimidinilo, 3,4,5,6-tetrahidropirimidinilo, tiadiazolilo, tiazolidinilo, tiazolilo, tienilo, tieno [5,1-*c*]piridinilo, tiocromanilo, triazolilo, 1,3,4-triazolo[2,3-*b*]pirimidinilo, xantenilo y similares.

Valores de Het que pueden mencionarse incluyen 1-azabiciclo[2.2.2] octanilo, benzimidazolilo, benzo[*c*]isoxazolidinilo, benzisoxazolilo, benzo[*b*]furanilo, benzopirazolilo, benzo[*e*]pirimidina, benzotiazolilo, benzo[*b*]tienilo, benzotriazolilo, 2-oxo-2,3-dihidrobenzimidazolilo, 1,3-dihidro-2,1-benz-isoxazolilo, 2,3-dihidropirrolo[2,3-*b*]piridinilo, furanilo, 2-iminohexahidropirimidinilo, imidazolilo, imidazo[1,2-*a*] piridinilo, indolilo, isoquinolinilo, isoxazolidinilo, isoxazolilo, 1,2,4-oxadiazolilo, 1,3,4-oxadiazolilo, 1,2-oxazinanilo, 2-imino-1,3-oxazinanilo, piperazinilo, piperidinilo, 2-oxo-piperidinilo, pirazinilo, piridinilo, pirimidinilo, 2-iminopirrolidinilo, 3-pirrolinilo, pirrolo[2,3-*b*]piridinilo, pirrolo[5,1-*b*] piridinilo, pirrolo[2,3-*c*]piridinilo, pirrolilo, quinolinilo, 4,5,6,7-tetrahidrobenzimidazolilo, 4,5,6,7-tetrahidrobenzopirazolilo, 5,6,7,8-tetrahidrobenzo[*e*]pirimidina, 3,4,5,6-tetrahidro-piridinilo, 3,4,5,6-

tetrahidropirimidinilo, 2-imino-tiazolidinilo, tiazolilo, tienilo y tieno [5,1-*c*]piridinilo.

Valores de $Het^1$ que pueden mencionarse incluyen benzodioxolilo, benzo[*b*]furanilo, 2,3-dihidrobenzo[*b*]furanilo, piridinilo, pirimidinilo y tienilo.

Valores de $Het^3$ que pueden mencionarse incluyen benzodioxanilo, benzo[*b*]dioxepanilo, benzodioxolilo, benzomorfolinilo, 2,1,3-benzoxadiazolilo, 2-oxo-benzoxazolidinilo, benzopirazolilo, 2,1,3-benzotiadiazolilo, benzo[*b*]tienilo, 2-oxo- cromenilo, 2,3-dihidrobenzo[*b*]furanilo, 1-oxo-1,3-dihidrobenzo[*c*] furanilo, furanilo, imidazolilo, imidazo[2,3-*b*]tiazolilo, isoquinolinilo, isoxazolilo, nafto[1,2-*b*]furanilo, pirazinilo, pirazolilo, piridinilo, piridonilo, pirrolilo, quinolinilo, sulfolanilo, 3-sulfolenilo, 2,4-dioxo-1,2,3,4-tetrahidropirimidinilo, tiazolilo, tienilo, 1,3,4-triazolo[2,3-*b*]pirimidinilo y xantenilo.

Valores de $Het^9$ que pueden mencionarse incluyen morfolinilo, 1,3,4-oxadiazolilo, oxazolilo y pirazolilo.

Valores de $Het^{10}$ que pueden mencionarse incluyen isoxazolilo, oxazolilo y tiazolilo.

Valores de $Het^c$ que pueden mencionarse incluyen isoxazolilo, morfolinilo, oxazolilo, piridinilo, tienilo y triazolilo (verbigracia 1,3,4-triazolilo).

Valores de $Het^x$ que pueden mencionarse incluyen dihidrooxadiazolilo (verbigracia, 4,5-dihidro-1,2,4-oxadiazol-3-ilo), oxadiazolilo (verbigracia, 1,2,4-oxadiazol-3-ilo), tetrazolilo (verbigracia, triazol-1-ilo) y triazolilo (verbigracia, 1,2,4-triazol-1-ilo).

Sustituyentes de grupos heterocíclicos (Het, Het[1] a Het[12] y Het[a] a Het[f] y Het[x]) donde sea apropiado, pueden estar localizados en cualquier átomo en el sistema de anillo incluido un heteroátomo. El punto de unión de grupos heterocíclicos (Het, Het[1] a Het[12] y Het[a] a Het[f] y Het[x]) puede realizarse mediante cualquier átomo en el sistema de anillo, incluyendo (donde sea apropiado) un heteroátomo, o un átomo en cualquier anillo carbocíclico fusionado que puede estar presente como parte del sistema de anillo.

Para evitar dudas, grupo cicloalquilo y cicloalquenilo pueden ser monocíclicos o, donde lo permita el número de átomos C, bi- o tricíclicos (aunque se prefieren cicloalquilo y cicloalquenilo monocíclicos). Además, cuando un grupo cicloalquilo o cicloalquenilo se fusiona a dos grupos fenilo, los grupos fenilo pueden fusionarse igualmente entre sí (para formar un sistema de anillo tricíclico fusionado).

Compuestos de fórmula I puede exhibir tautomerismo. Todas las formas tautoméricas y sus mezclas se incluyen en el ámbito de la invención.

Compuestos de fórmula I pueden contener asimismo uno o más átomos de carbono asimétricos y, por lo tanto, pueden exhibir isomerismo óptico y/o diastereoisomerismo. Diastereoisómeros pueden separarse usando técnicas convencionales, por ejemplo cromatografía o cristalización fraccionaria. Los diferentes estereoisómeros pueden aislarse por separación de una mezcla racémica u otra mezcla de los compuestos usando técnicas convencionales, por ejemplo cristalización fraccionaria o HPLC. Alternativamente, los isómeros ópticos deseados pueden elaborarse por reacción de los materiales de partida apropiados, ópticamente activos, bajo condiciones que no causarán racemización o epimerización, o por derivación, por ejemplo con un ácido homoquiral seguido por separación de los de los ésteres diastereoméricos por medios convencionales (por ejemplo HPLC, cromatografía sobre sílice). Todos los estereoisómeros se incluyen en el ámbito de la invención.

Las abreviaturas se listan al final de esta especificación. Las líneas onduladas sobre los enlaces en fragmentos estructurales significan las posiciones de enlace de esos fragmentos.

Compuestos de fórmula I que pueden mencionarse incluyen aquellos en los cuales:

(1) $R^{5a}$ representa H, halo, OH, $C_{1-4}$ alquilo (el cual último grupo se sustituye de manera opcional por $C_{1-3}$ alcoxi) o $C_{1-4}$ alcoxi;

(2) $R^{5b}$, $R^{6a}$, $R^{6b}$, $R^{7a}$ y $R^{7b}$ representan independientemente H, F o metilo;

(3) $R^2$ representa

(a) H,

(b) halo,

(c) $C_{1-6}$ alquilo, $C_{2-6}$ alquenilo, $C_{2-6}$ alquinilo, $C_{1-6}$ alcoxi (los cuales últimos cuatro grupos se sustituyen opcionalmente por uno o más sustituyentes seleccionados de halo, OH, CN, $C_{1-4}$ alcoxi, C(O)OH, C(O)O-$C_{1-4}$ alquilo y OC(O)-$C_{1-4}$ alquilo) o

(d) junto con $R^{3a}$, $R^2$ representa $C_{2-3}$ *n*-alquileno o O-($C_{1-2}$ *n*-alquileno), los cuales últimos dos grupos se sustituyen opcionalmente por halo y en donde el átomo O del último grupo se enlaza al átomo C al cual se une el grupo $R^2$;

(4) $R^{3a}$ y $R^{3b}$ representan independientemente H, F o metil, o $R^{3a}$, junto con $R^2$, representa $C_{2-3}$ *n*-alquileno o O-($C_{1-2}$ *n*-alquileno), los cuales últimos dos grupos se sustituyen opcionalmente por halo y en donde el átomo O del último grupo se enlaza al átomo C al cual se une el grupo $R^2$;

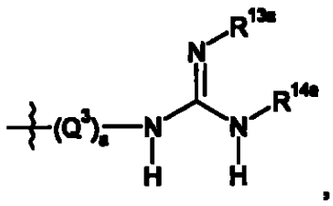
(5) $R^{11a}$ representa H o uno o más sustituyentes seleccionados de halo, OH, CN, $C_{1-6}$ alquilo y $C_{1-6}$ alcoxi (los cuales últimos dos grupos se sustituyen opcionalmente por uno o más sustituyentes seleccionados de halo, OH, $C_{1-4}$ alcoxi, C(O)O$R^{12a}$ y C(O)N($R^{12b}$)$R^{12c}$);

(6) $R^{11b}$ y $R^{11c}$ representan independientemente H o uno o más sustituyentes seleccionados de halo, OH, CN, $C_{1-6}$ alquilo, $C_{1-6}$ alcoxi (los cuales últimos dos grupos se sustituyen opcionalmente por uno o más sustituyentes seleccionados de halo, OH, $C_{1-4}$ alcoxi, $C(O)OR^{12a}$ y $C(O)N(R^{12b})R^{12c}$), =O, =NH, =NOH y =N-CN;

(7) $R^{12a}$ a $R^{12c}$ representan independientemente H, $C_{1-6}$ alquilo o $C_{3-7}$ cicloalquilo (los cuales últimos dos grupos se sustituyen opcionalmente por uno o más átomos halo);

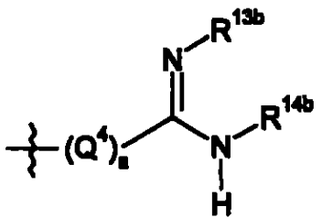
(8) $R^a$ a $R^d$, representan independientemente

(a)



,

(b)

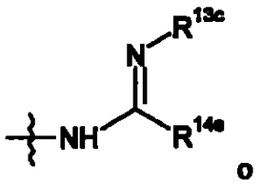


(c)



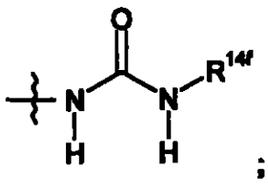
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(d)



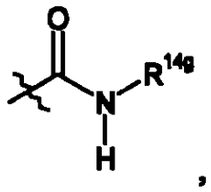
o

(e)



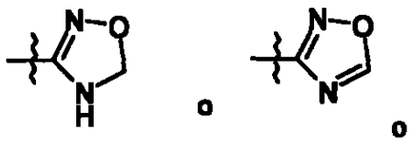
;

(f)

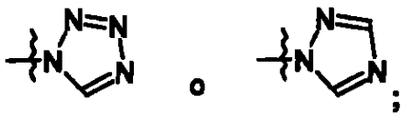


,

(g)



(h)



;

o $R^b$ a $R^d$ pueden representar igualmente H.

Otros compuestos de fórmula I, que pueden mencionarse, incluyen aquellos en los cuales:

$R^{8a}$ a $R^{8c}$, $R^{10a}$ a $R^{10c}$ y $R^{14a}$ a $R^{14g}$ representan independientemente

(a) H ó

(b) $C_{1-4}$ alquilo (el cual último grupo se sustituye opcionalmente por uno o más sustituyentes seleccionados de halo y OH),

o $R^{14c}$ representa

(a) $C_{1-4}$ alquilo sustituido por $C_{3-7}$ cicloalquilo o arilo,

(b) $C_{3-7}$ cicloalquilo,

(c) $C(O)O-C_{1-6}$ alquilo (la parte alquilo de cuyo último grupo se sustituye opcionalmente por arilo y/o uno o más átomos halo),

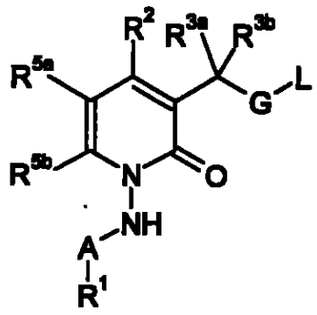
(d) C(O) $C_{1-6}$ alquilo,

(e) C(O)N(H)-$C_{1-6}$ alquilo (la parte alquilo de cuyo último grupo se sustituye opcionalmente por arilo y/o uno o más átomos halo) o

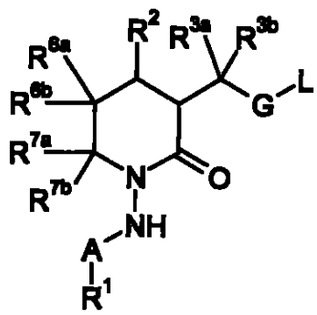
(f) $S(O)_2$-$C_{1-6}$ alquilo (la parte alquilo de cuyo último grupo se sustituye opcionalmente por arilo y/o uno o más átomos halo),

o $R^{14c}$ y $R^{14d}$ juntos representan $C_{3-6}$ *n*-alquileno interrumpido opcionalmente por O, S, N(H) o N($C_{1-4}$ alquilo) y/o se sustituye por uno o más grupos $C_{1-4}$ alquilo.

Compuestos de fórmula I pueden representarse alternativamente como compuestos de fórmulas Ia y Ib,



Ia



Ib

en donde $R^1$, $R^2$, $R^{3a}$, $R^{3b}$, $R^{5a}$, $R^{5b}$, $R^{6a}$, $R^{6b}$, $R^{7a}$, $R^{7b}$, A, G y L son como se definen más arriba en el texto.

A este respecto, el experto entenderá que las preferencias incluidas a continuación en lo concerniente a compuestos de fórmula I se aplican igualmente (donde sea apropiado) a compuestos de fórmulas Ia y Ib (ya sea de manera conjunta o por separado).

Valores preferidos de G incluyen:

(a) -C(O)N($R^{8a}$)-$C_{0-3}$ alquileno-;

(b) -C(O)N($R^{8a}$)-CH(C(O)$R^9$)-$C_{0-3}$ alquileno-;

(c) -C(O)N($R^{8a}$)-$C_{1-3}$ alquileno-$Q^1$-;

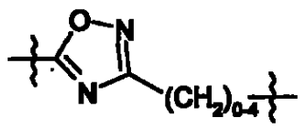
(d) -C(O)N($R^{8b}$)-$C_{2-3}$ alquenileno-;

(e)



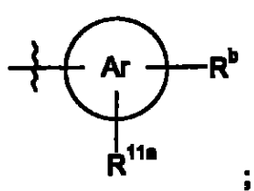
; y

(f)



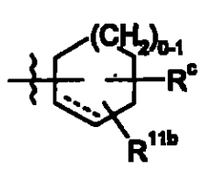
cuando G representa -C(O)N($R^{8a}$)-$C_{0-3}$ alquileno-$Q^1$-, valores preferidos de L incluyen:

(a)



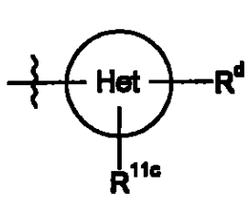
;

(b)

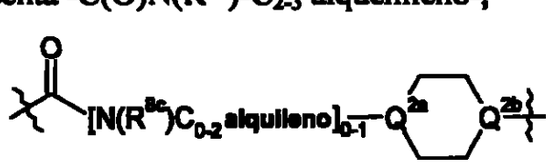


; y

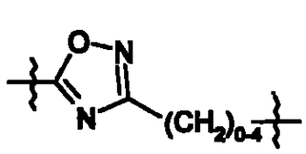
(c)



cuando G representa -C(O)N($R^{8b}$)-$C_{2-3}$ alquenileno-,



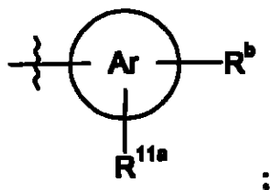
, o



,

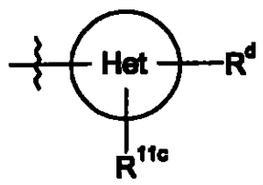
valores preferidos de L incluyen:

(a)




; y

(b)




.

Compuestos de fórmula I que se prefieren incluyen aquellos en los cuales:

(1) A representa C(O), $S(O)_2$, C(O)NH (en cuyo último grupo la fracción NH se une a $R^1$) o $C_{1-4}$ alquileno;

(2) $R^1$ representa

(a) $C_{1-6}$ alquilo, $C_{2-6}$ alquenilo, $C_{2-6}$ alquinilo (los cuales últimos tres grupos se sustituyen opcionalmente por uno o más sustituyentes seleccionados de halo, CN, $C_{3-8}$ cicloalquilo (sustituido opcionalmente por uno o más sustituyentes seleccionados de halo, OH, =O, $C_{1-6}$ alquilo, $C_{1-6}$ alcoxi y aril), $OR^{4a}$, $SR^{4b}$, $S(O)_2R^{4b}$, $S(O)_2N(H)R^{4c}$, $N(H)S(O)_2R^{4f}$, $N(R^{4g})(R^{4h})$, $C(O)R^{4i}$, $OC(O)R^{4i}$, $C(O)OR^{4i}$, $N(H)C(O)R^{4i}$, $C(O)N(H)R^{4i}$, arilo y $Het^1$),

(b) $C_{3-8}$ cicloalquilo o $C_{4-8}$ cicloalquenilo, los cuales últimos dos grupos se fusionan opcionalmente a uno o dos grupos fenilo y se sustituyen opcionalmente por uno o más sustituyentes seleccionados de halo, =O, $C_{1-6}$ alquilo, C4-6 cicloalquilo (sustituido opcionalmente por uno o más sustituyentes seleccionados de halo, $C_{1-4}$ alquilo, $C_{1-4}$ alcoxi y fenilo), $OR^{4a}$, $SR^{4b}$, $S(O)_2R^{4b}$, $S(O)_2N(H)R^{4c}$, $N(H)S(O)_2R^{4f}$, $N(R^{4g})(R^{4h})$, $OC(O)R^{4i}$, $C(O)OR^{4i}$, $N(H)C(O)R^{4i}$, $C(O)N(H)R^{4i}$, arilo y $Her^2$,

(c) arilo, o

(d) $Het^3$;

(3) $R^{4a}$ a $R^{4i}$ representan independientemente, en cada ocurrencia,

(a) H,

(b) $C_{1-6}$ alquilo, $C_{2-6}$ alquenilo, $C_{2-6}$ alquinilo (los cuales últimos tres grupos se sustituyen opcionalmente por uno o más sustituyentes seleccionados de halo, OH, $C_{1-4}$ alcoxi, arilo y $Het^4$),

(c) $C_{4-6}$ cicloalquilo, $C_{4-6}$ cicloalquenilo (los cuales últimos dos grupos se sustituyen opcionalmente por uno o más sustituyentes seleccionados de halo, =O y $C_{1-4}$ alquilo),

(d) arilo o

(e) $Het^6$,

siempre que $R^{4b}$ no represente H cuando n es 1 ó 2;

(4) $R^{5a}$ representa H, F, metilo o metoxi;

(5) $R^{5b}$ representa H;

(6) $R^{6a}$ y $R^{6b}$ ambos representan H, ambos representan metilo o ambos representan F;

(7) $R^{7a}$ y $R^{7b}$ ambos representan H;

(8) $R^2$ representa H, halo, $C_{1-4}$ alcoxi o $C_{1-4}$ alquilo (el cual último grupo se sustituye de manera opcional por uno o más sustituyentes seleccionados de halo (verbigracia, F), OH o metoxi);

(9) $R^{3a}$ y $R^{3b}$ representan independientemente H o F;

(10) el grupo G-L asume las siguientes definiciones

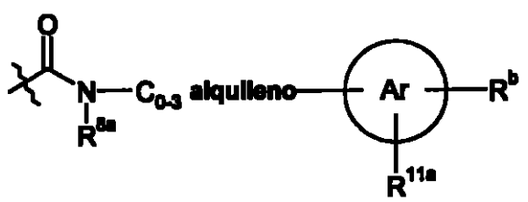
(a) $C(O)N(R^{8a})$-$C_{0-6}$ alquileno-$R^a$,

(b) $C(O)N(R^{8a})$-$CH(C(O)R^9)$-$C_{0-5}$ alquileno-$R^a$,

(c) $C(O)N(R^{8a})$-$C_{0-3}$ alquileno-CH=CH-$C_{0-2}$ alquileno-$R^a$,

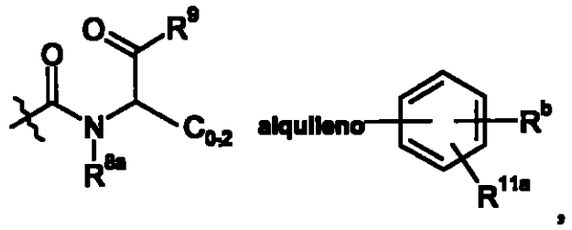
(d) $C(O)N(R^{8a})$-$C_{0-3}$ alquileno-C≡C-$C_{0-2}$ alquileno-$R^a$,

(e)




,

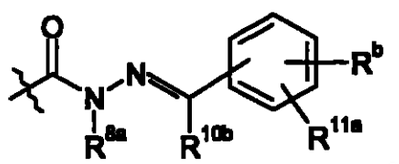
(f)



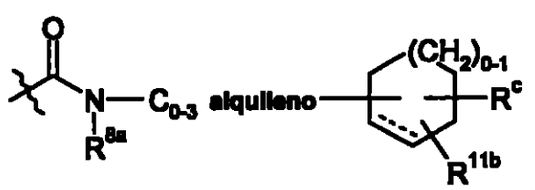
(g)



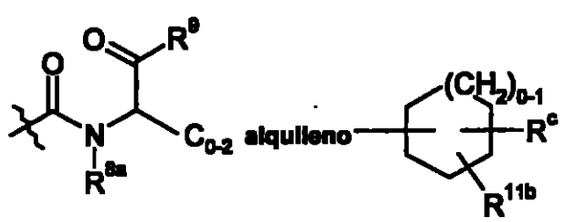
(h)



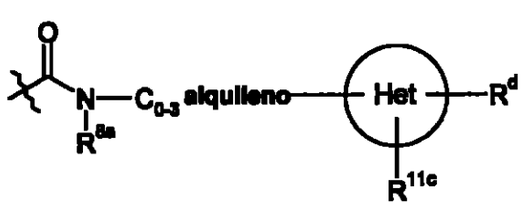
(i)



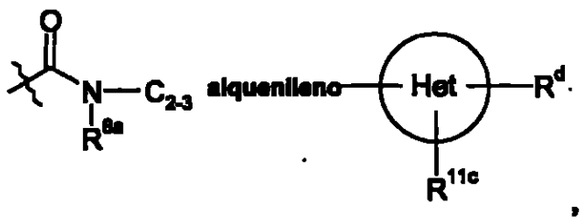
(j)



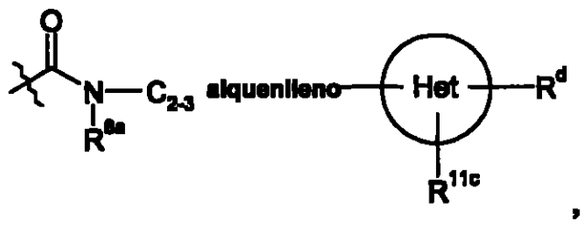
(k)



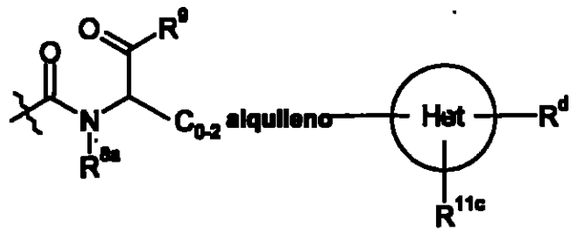
(l)



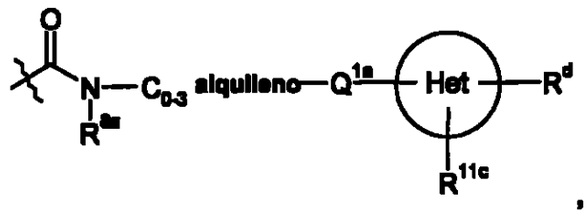
(m)



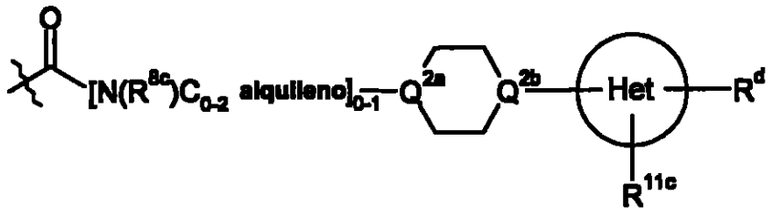
(n)



(o)



(p)



en donde $Q^{1a}$ representa O, $NR^{10a}$ ó $[N(H)]_{0-1}C(O)$-$C_{0-2}$ alquileno;

(11) $R^9$ representa un grupo heterocíclico aromático de 5 a 10 miembros que comprende uno o dos anillos y contiene, como heteroátomo(s), un átomo de azufre u oxígeno y/o uno a tres átomos de nitrógeno, grupo heterocíclico que se sustituye opcionalmente por uno o más sustituyentes seleccionados de halo y $C_{1-4}$ alquilo;

(12) Het representa un grupo heterocíclico monocíclico de 5 ó 6 miembros, o bicíclico de 8, 9 ó 10 miembros, que contiene, como heteroátomo(s), un átomo de azufre u oxígeno y/o uno a cuatro átomos de nitrógeno;

(13) $R^{11a}$ representa H o uno a tres sustituyentes seleccionados de halo, OH, CN, $C_{1-4}$ alquilo y $C_{1-4}$ alcoxi (los cuales últimos dos grupos se sustituyen opcionalmente por uno o más sustituyentes seleccionados de OH, halo, $C(O)OR^{12a}$ y $C(O)N(R^{12b})R^{12c}$ (por ejemplo uno o más sustituyentes seleccionados de los tres últimos grupos));

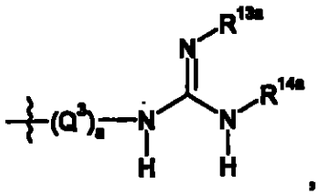
(14) $R^{11b}$ representa H o uno a tres sustituyentes seleccionados de halo, OH, $C_{1-4}$ alquilo, $C_{1-4}$ alcoxi y =O;

(15) $R^{11c}$ representa H o uno a tres sustituyentes seleccionados de halo, OH, CN, $C_{1-4}$ alquilo, $C_{1-4}$ alcoxi (los cuales últimos dos grupos se sustituyen opcionalmente por uno o más sustituyentes seleccionados de halo, OH y $C_{1-2}$ alcoxi), =O, =NH, =NOH y =N-CN;

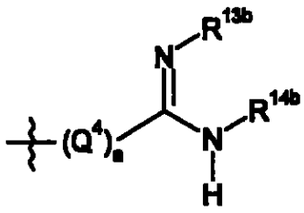
(16) $R^{12a}$ a $R^{12c}$ representan independientemente H, $C_{1-4}$ alquilo (sustituido opcionalmente por un grupo $N(R^{12e})R^{12f}$) o $C_{3-6}$ cicloalquilo (por ejemplo H, $C_{1-4}$ alquilo o $C_{3-6}$ cicloalquilo);

(17) $R^a$ representa

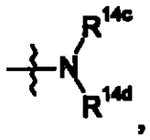
(a)



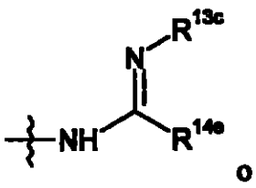
(b)



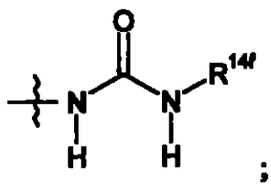
(c)



(d)



(e)

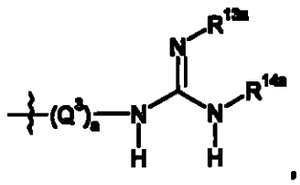


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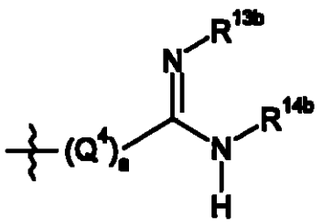
(18) $R^b$ representa

(a) H

(b)



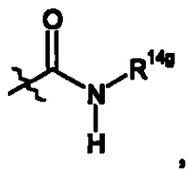
(c)



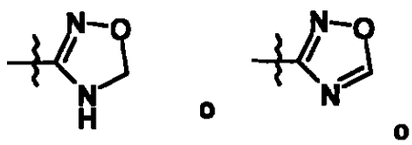
(d)



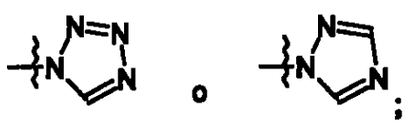
(e)



(f)

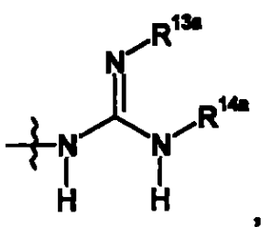


(g)

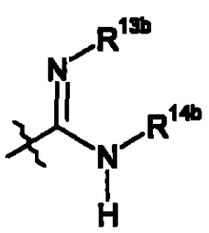


(19) $R^c$ y $R^d$ representan independientemente

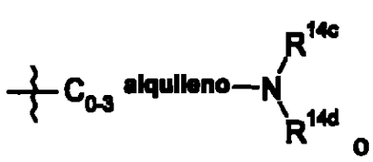
(a)



(b)



(c)



(d) $R^d$ pueden representar también H;

(20) $Q^3$ representa O, $S(O)_2$, $S(O)_2NH$, C(O) ó -CH=N-;

(21) $Q^4$ representa O ó S;

(22) $R^{15}$ representa H, $C_{1-6}$ alquilo, $C_{3-6}$ alquenilo (los cuales últimos dos grupos se interrumpen opcionalmente por un átomo de oxígeno), $C_{3-6}$

cicloalquilo o $C_{1-2}$ alquilo (el cual último grupo se sustituye por arilo);

(23) $R^{16}$ representa $C_{1-6}$ alquilo, $C_{3-6}$ alquenilo, $C_{3-6}$ cicloalquilo o $C_{1-2}$ alquilo sustituido por arilo;

(24) $R^{8a}$ a $R^{8c}$ representan H o metilo;

(25) $R^{10a}$ a $R^{10c}$ representan independientemente H o $C_{1-3}$ alquilo (el cual último grupo se sustituye opcionalmente por OH o uno o más átomos halo);

(26) $R^{14a}$ representa $C_{1-2}$ alquilo, $C(O)O$-$C_{1-5}$ alquilo (la parte alquilo de cuyo último grupo se sustituye opcionalmente por fenilo) o H (por ejemplo H ó $C_{1-2}$ alquilo);

(27) $R^{14b}$ a $R^{14g}$ representan independientementea H o $C_{1-2}$ alquilo (el cual último grupo se sustituye opcionalmente por uno o más átomos halo, pero, preferiblemente, no se sustituye), o $R^{14c}$ representa $C_{4-6}$ cicloalquilo o $C(O)O$-$C_{1-5}$ alquilo (la parte alquilo de cuyo último grupo se sustituye opcionalmente por fenilo) o $R^{14c}$ y $R^{14d}$ juntos representan $C_{4-5}$ *n*- alquileno interrumpido opcionalmente por O;

(28) cada arilo representa independientemente un fenilo o naftilo, cada uno de cuyos grupos pueden sustituirse por uno o más sustituyentes seleccionados de

(a) halo,

(b) CN,

(c) $C_{1-8}$ alquilo, $C_{2-4}$ alquenilo, $C_{2-4}$ alquinilo (los cuales últimos tres grupos se sustituyen opcionalmente por uno o más sustituyentes seleccionados de halo, OH, $C_{1-2}$ alcoxi, $C(O)OH$, $C(O)O$-$C_{1-2}$ alquilo y fenilo),

(d) $C_{3-6}$ cicloalquilo sustituido opcionalmente por uno o más sustituyentes seleccionados de halo, =O y $C_{1-4}$ alquilo,

(e) $OR^{17a}$,

(f) $SR^{17b}$, $S(O)_2R^{17b}$,

(g) $S(O)_2N(H)R^{19c}$,

(h) $N(H)S(O)_2R^{19f}$,

(i) $N(H)R^{19g}$,

(j) $C(O)R^{19i}$, $C(O)OR^{19i}$, $C(O)N(H)R^{19i}$, $N(H)C(O)R^{19i}$, $N(H)C(O)OR^{19i}$,

(k) fenilo (el cual último grupo se sustituye opcionalmente por halo) y

(l) $Het^9$ y;

(m) $Si(CH_3)_3$;

(29) $R^{17a}$ a $R^{17i}$ representan independientemente, en cada ocurrencia,

(a) H,

(b) $C_{1-8}$ alquilo sustituido opcionalmente por uno o más sustituyentes seleccionados de halo, OH, $C_{1-2}$ alcoxi, fenilo (el cual último grupo se sustituye opcionalmente por uno o más átomos halo) y $Het^{10}$ (por ejemplo uno o más sustituyentes seleccionados de halo, OH, $C_{1-2}$ alcoxi y fenilo (el cual último grupo se sustituye opcionalmente por uno o más átomos halo)),

(c) $C_{3-6}$ cicloalquilo sustituido opcionalmente por uno o más sustituyentes seleccionados de halo, =O y $C_{1-4}$ alquilo,

(d) fenilo sustituido opcionalmente por uno o más átomos halo o

(e) $Het^{12}$,

siempre que $R^{17b}$ no represente H;

(30) $Het^1$ a $Het^{12}$ representan independientemente grupos heterocíclicos de 5 a 13 miembros que contienen uno a cuatro heteroátomos seleccionados de oxígeno, nitrógeno y/o azufre, los cuales grupos heterocíclicos pueden comprender uno, dos o tres anillos y puede sustituirse por uno o más sustituyentes seleccionados de

(a) halo,

(b) CN,

(c) $C_{1-8}$ alquilo, $C_{2-4}$ alquenilo, $C_{2-4}$ alquinilo (los cuales últimos tres grupos se sustituyen opcionalmente por uno o más sustituyentes seleccionados de halo, OH y $C_{1-2}$ alcoxi),

(d) $C_{3-6}$ cicloalquilo sustituido opcionalmente por uno o más sustituyentes seleccionados de halo, =O y $C_{1-4}$ alquilo,

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(e) =O,

(f) $OR^{19a}$,

(g) $S(O)_2R^{19b}$,

(h) $S(O)_2N(H)R^{19c}$,

(i) $N(H)S(O)_2R^{19f}$,

(j) $N(H)R^{19g}$,

(j) $C(O)R^{19i}$, $C(O)OR^{19i}$, $C(O)N(H)R^{19i}$, $N(H)C(O)R^{19i}$, $N(H)C(O)OR^{19i}$,

(l) fenilo (el cual último grupo se sustituye opcionalmente por halo) y

(m) $Het^c$;

(31) $R^{19a}$ a $R^{19i}$ representan independientemente, en cada ocurrencia,

(a) H,

(b) $C_{1-6}$ alquilo sustituido opcionalmente por uno o más sustituyentes seleccionados de halo, OH, $C_{1-2}$ alcoxi y fenilo,

(c) $C_{3-6}$ cicloalquilo sustituido opcionalmente por uno o más sustituyentes seleccionados de halo, =O y $C_{1-4}$ alquilo,

(d) fenilo sustituido opcionalmente por halo o

(e) $Het^f$,

siempre que $R^{19b}$ no represente H;

(32) $Het^a$ a $Het^f$ representan independientemente grupos heterocíclicos de 5 o 6 miembros que contienen, como heteroátomos, un átomo de oxígeno o azufre y/o uno a tres átomos de nitrógeno, grupos heterocíclicos que pueden sustituirse por uno o más sustituyentes seleccionados de halo y $C_{1-4}$ alquilo;

(33) grupos alquilo, alquenilo, alquinilo, cicloalquilo, cicloalquenilo, alquileno y alquenileno, así como la parte alquilo de grupos alcoxi, pueden sustituirse por uno o más átomos de Cl o, particularmente, F.

También se prefieren compuestos de fórmula I en la cual $R^{3a}$ y $R^{3b}$ adoptan ambos la misma definición (es decir, compuestos en los cuales $R^5$ y $R^6$

ambos representan H, ambos representan F o ambos representan metilo, $CH_2F$, $CHF_2$ ó $CF_3$).

Cuando A representa C(O) o C(O)NH (en cuyo último grupo la fracción NH se une a $R^1$), compuestos preferidos de fórmula I incluyen igualmente aquellos en los cuales $R^1$ representa:

(a) $C_{1-6}$ alquilo, $C_{2-6}$ alquenilo,$_{2-6}$ alquinilo, los cuales últimos tres grupos se

(i) sustituyen por un sustituyente seleccionado de $C_{3-8}$ cicloalquilo (sustituido opcionalmente por uno o más sustituyentes seleccionados de halo, OH, =O, $C_{1-6}$ alquilo, $C_{1-6}$ alcoxi y arilo), arilo y $Het^1$, y

(ii) sustituyen opcionalmente por uno o más sustituyentes adicionales seleccionados de halo, CN, $C_{4-6}$ cicloalquilo (sustituido opcionalmente por uno o más sustituyentes seleccionados de halo y $C_{1-4}$ alquilo), $OR^{4a}$, $SR^{4b}$, $S(O)_2R^{4b}$, $S(O)_2N(H)R^{4c}$, $N(H)S(O)_2R^{4f}$, $N(R^{4g})(R^{4h})$, $OC(O)R^{4i}$, $C(O)OR^{4i}$, $N(H)C(O)R^{4i}$, $C(O)N(H)R^{4i}$, arilo y $Het^1$;

(b) $C_{3-8}$ cicloalquilo o $C_{4-8}$ cicloalquenilo, los cuales últimos dos grupos se

(i) fusionan a uno o dos grupos fenilo y se sustituyen opcionalmente por uno o más sustituyentes seleccionados de halo, $C_{1-4}$ alquilo y $C(O)OR^{4i}$, o

(ii) sustituyen por arilo y, opcionalmente, se sustituyen además por uno o más sustituyentes seleccionados de halo y $C_{1-4}$ alquilo;

(c) arilo; o

(d) $Het^3$,

en donde $R^{4a}$ a $R^{4c}$, $R^{4f}$ a $R^{4i}$ arilo y $Het^1$ son como se definen más arriba o más adelante.

Cuando A representa $S(O)_2$, compuestos preferidos de fórmula I incluyen asimismo aquellos en los cuales $R^1$ representa:

(a) $C_{1-3}$ alquilo o $C_{2-3}$ alquenilo, los cuales últimos dos grupos se sustituyen por arilo y, opcionalmente, se sustituyen además por uno o más átomos halo;

(b) $C_{1-6}$ alquilo sustituido opcionalmente por uno o más sustituyentes seleccionados de halo, $OR^{4a}$ y $S(O)_2R^{4b}$;

(c) cicloalquilo monocíclico $C_{3-6}$ sustituido opcionalmente por uno o más sustituyentes seleccionados de halo y $C_{1-4}$ alquilo;

(d) cicloalquilo bicíclico $C_{6-8}$ sustituido opcionalmente por uno o más sustituyentes seleccionados de halo, =O y $C_{1-6}$ alquilo;

(c) arilo; o

(d) $Het^3$,

en donde $R^{4a}$ y $R^{4b}$ son como se definen más arriba o más adelante.

Cuando A representa $C_{1-6}$ alquileno, compuestos preferidos de fórmula I incluyen igualmente aquellos en los cuales $R^1$ representa:

(a) $C_{1-6}$ alquilo o $C_{2-6}$ alquenilo, los cuales últimos dos grupos se sustituyen opcionalmente por uno o más sustituyentes seleccionados de halo y OH;

(b) $C_{3-8}$ cicloalquilo o $C_{4-8}$ (por ejemplo $C_{4-6}$) cicloalquenilo, los cuales últimos dos grupos se sustituyen opcionalmente por uno a cuatro sustituyentes seleccionados de halo, =O, OH, $C_{1-4}$ alquilo, O-$C_{1-4}$ alquilo (los cuales últimos dos grupos se sustituyen opcionalmente por uno o más átomos halo (por ejemplo F)) y arilo, o, particularmente,

(c) arilo (por ejemplo naftilo o, particularmente, fenilo), o

(d) $Het^3$,

(por ejemplo uno cualquiera de los grupos enumerados en (b) a (d) más arriba)

Compuestos de fórmula I que son más preferidos incluyen aquellos en los cuales G-L adopta cualquiera de las definiciones preferidas dadas en (10)(a), (c), (d), (e), (g), (h), (i), (k), (l), (m), (o) y (p) más arriba.

Compuestos de fórmula I más preferidos incluyen particularmente incluyen compuestos en los cuales:

(1) A representa C(O), $S(O)_2$, C(O)NH (en cuyo último grupo la fracción NH se une a $R^1$) ó $C_{1-3}$ alquileno;

(2) $R^1$ representa

(a) $C_{1-5}$alquilo, $C_{2-4}$ alquenilo (los cuales últimos dos grupos se sustituyen opcionalmente por uno o más sustituyentes seleccionados de halo, cicloalquilo bicíclico $C_{6-8}$, cicloalquilo monocíclico $C_{3-6}$ (los cuales últimos dos grupos se sustituyen opcionalmente por uno o más sustituyentes seleccionados de halo, =O, $C_{1-4}$ alquilo, $C_{1-4}$ alcoxi y fenilo (el cual último grupo se sustituye opcionalmente por uno o más sustituyentes seleccionados de halo, $C_{1-4}$ alquilo y $C_{1-4}$ alcoxi)), $OR^{4a}$, $SR^{4b}$, $S(O)_2R^{4b}$, $C(O)R^{4i}$, $OC(O)R^{4i}$, $C(O)OR^{4i}$, arilo y $Het^1$),

(b) $C_{3-6}$ cicloalquilo o $C_{4-8}$ cicloalquenilo (verbigracia, $C_{4-6}$), los cuales últimos dos grupos se fusionan opcionalmente a uno o dos grupos fenilo y se sustituyen opcionalmente por uno o más sustituyentes seleccionados de halo, =O, $C_{1-4}$ alquilo, $OR^{4a}$, $C(O)OR^{4i}$ y fenilo (el cual último grupo se sustituye opcionalmente por uno o más sustituyentes seleccionados de halo, $C_{1-4}$ alquilo y $C_{1-4}$ alcoxi),

(c) arilo, o

(d) $Het^3$;

(3) $R^{4a}$ a $R^{4i}$ representan independientemente, en cada ocurrencia,

(a) H,

(b) $C_{1-6}$ alquilo, $C_{2-4}$ alquenilo (los cuales últimos dos grupos se sustituyen opcionalmente por uno o más sustituyentes seleccionados de halo, OH, $C_{1-4}$ alcoxi y fenilo),

(c) $C_{4-6}$ cicloalquilo (el cual último grupo se sustituye opcionalmente por uno o más sustituyentes seleccionados de halo y $C_{1-2}$ alquilo) o

(d) fenilo (el cual último grupo se sustituye opcionalmente por uno o más sustituyentes seleccionados de halo, $C_{1-4}$ alquilo y $C_{1-4}$ alcoxi)

siempre que $R^{4b}$ no represente H;

(4) $R^2$ representa H, halo (tal como Cl) o $C_{1-3}$ alquilo (el cual último grupo se sustituye de manera opcional por F);

(5) $R^{3a}$ y $R^{3b}$ ambos representan H o ambos representan F;

(6) $R^{5a}$ representa H;

(7) $R^{6a}$ and $R^{6b}$ ambos representan H;

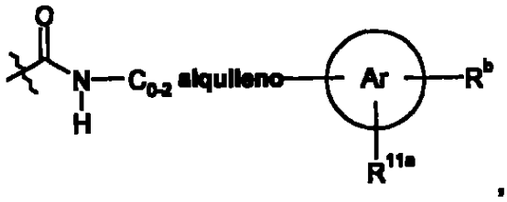
(8) el grupo G-L asume las siguientes definiciones

(i) C(O)N(H)-$C_{0-5}$ alquileno-$R^{a1}$,

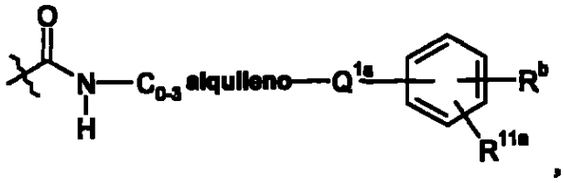
(ii) C(O)N(H)-$C_{0-3}$ alquileno-CH=CH-$R^{a2}$,

(iii) C(O)N(H)-$C_{1-3}$ alquileno-C≡C-$CH_2$-$R^{a3}$,

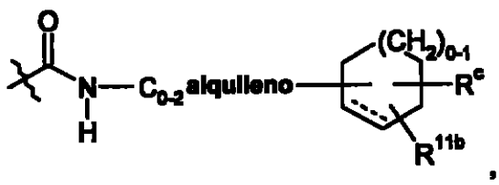
(iv)



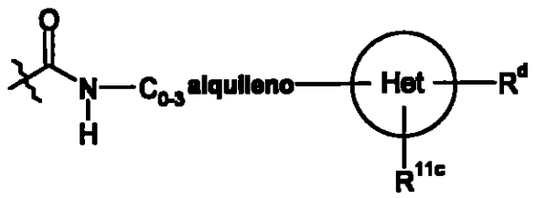

(v)



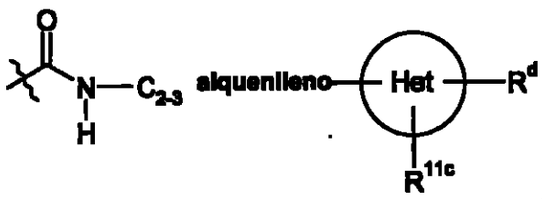

(vi)



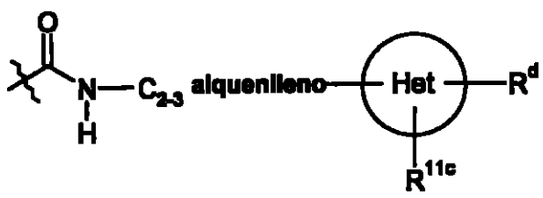
(vii)



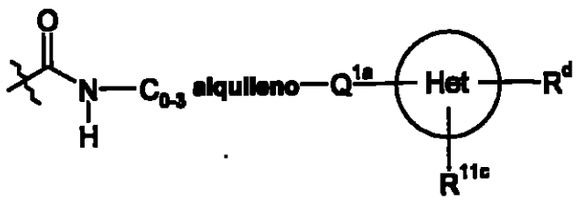
(viii)



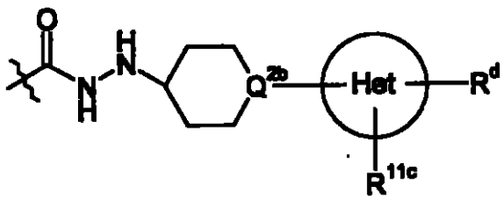
(ix)



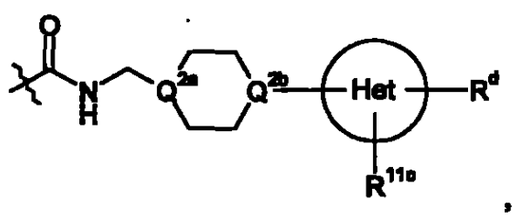
(x)



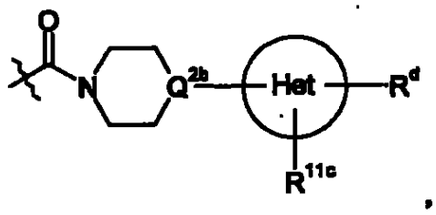
(xi)



(xii)



(xiii)



en donde $Q^{1a}$ es como se define más arriba;

(9) Het representa un grupo heterocíclico monocíclico de 5 ó 6 miembros, bicíclico de 8 miembros o bicíclico, fusionado a un anillo, de 9 ó 10 miembros que contiene, como heteroátomo(s), un átomo de azufre u oxígeno y/o uno a tres átomos de nitrógeno, grupo heterocíclico que

(i) si tiene 5 ó 6 miembros, es completamente aromático, completamente saturado o mono-insaturado,

(ii) si tiene 8 miembros, es completamente aromático o, preferiblemente, completamente saturado, o

(iii) si tiene 9 ó 10 miembros, es completamente aromático o parcialmente aromático;

(10) $R^{11a}$ representa H o uno a tres sustituyentes seleccionados de halo, OH, CN, $C_{1-3}$ alquilo y $C_{1-3}$ alcoxi (los cuales últimos dos grupos se sustituyen opcionalmente por uno o más sustituyentes seleccionados de OH, halo, $C(O)OR^{12a}$ y $C(O)N(R^{12b})R^{12c}$ (por ejemplo uno o más sustituyentes seleccionados de los tres últimos grupos));

(11) $R^{11b}$ representa uno o dos sustituyentes seleccionados de halo y $C_{1-3}$ alquilo o, preferiblemente, $R^{11b}$ representa H;

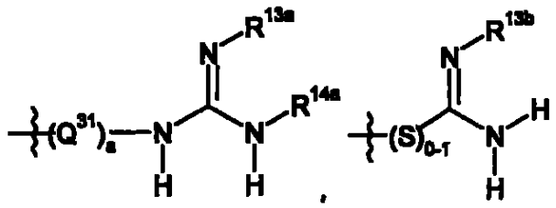
(12) $R^{11c}$ representa H o uno a tres sustituyentes seleccionados de halo, OH, CN, $C_{1-3}$ alquilo (el cual último grupo se sustituye

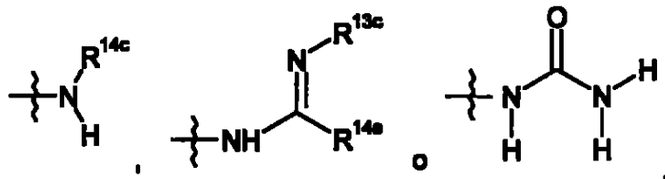
opcionalmente por uno o más sustituyentes seleccionados de halo y OH), =O, =NH y =N-CN;

(13) $R^{12a}$ a $R^{12c}$ representan independientemente H, $C_{1-3}$ alquilo (sustituido opcionalmente por un grupo $N(R^{12e})R^{12f}$) o $C_{3-5}$ cicloalquilo (por ejemplo H, $C_{1-3}$ alquilo o $C_{3-5}$ cicloalquilo);

(14) $R^{12e}$ y $R^{12f}$ representan independientemente H ó $C_{1-2}$ alquilo;

(15) $R^{a1}$, $R^{a2}$ y $R^{a3}$ representan $R^a$ como se define más arriba, pero preferiblemente representan independientemente



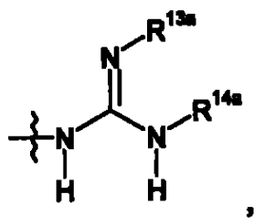


en donde $Q^{31}$ representa O, C(O) o -CH=N- y a representa 0 ó, preferiblemente, 1;

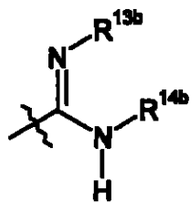
(16) $R^b$ representa

(a) H

(b)



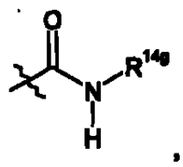
(c)



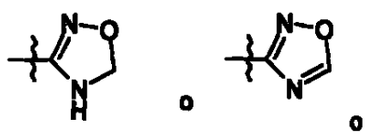
(d)



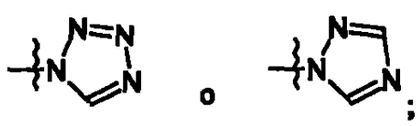
(e)



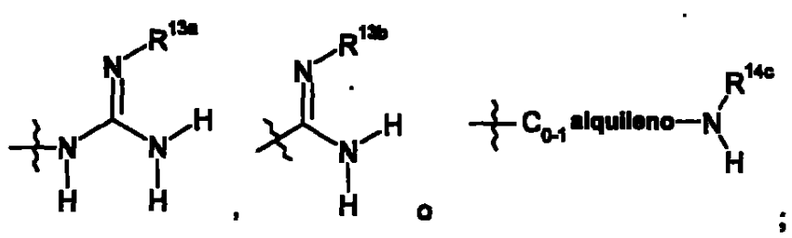
(f)



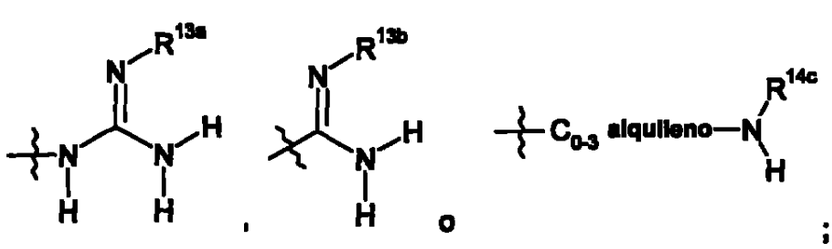
(g)



(17) $R^c$ representa



(18) $R^d$ representa H,



(19) $R^{13a}$ representa H, CN, $NH_2$ ó $OR^{15}$;

(20) $R^{13b}$ representa H, $NH_2$, $OR^{15}$ ó $C(O)OR^{16}$;

(21) $R^{13c}$ representa H ó OH;

(22) $R^{15}$ representa H ó $C_{1-5}$ alquilo;

(23) $R^{16}$ representa $C_{1-2}$ alquilo sustituido por arilo;

(24) $R^{10a}$ representa H ó $C_{1-2}$ alquilo (el cual último grupo se sustituye opcionalmente por OH);

(25) $R^{14a}$ representa H, metilo, $C(O)O$-$C_{3-4}$ alquilo o $C(O)OCH_2$-fenilo (por ejemplo metilo o, preferiblemente, H);

(26) $R^{14b}$ a $R^{14d}$ y $R^{14f}$ a $R^{14g}$ representan independientemente metilo o, preferiblemente, H,

o $R^{14c}$ representa

$C_{1-2}$ alquilo sustituido por uno a tres átomos halo (por ejemplo F),

$C_{4-5}$ cicloalquilo (por ejemplo ciclopentilo),

$C(O)O$-$C_{3-4}$ alquilo o

$C(O)OCH_2$-fenilo (por ejemplo uno de los tres últimos grupos),

o $R^{14c}$ y $R^{14d}$ juntos representan $C_4$ *n*-alquileno;

(27) $R^{14c}$ representa H o, preferiblemente, metilo;

(28) cada arilo representa independientemente un fenilo o naftilo, cada uno de cuyos grupos pueden sustituirse por uno o más sustituyentes seleccionados de

(a) F, Cl, Br,

(b) CN,

(c) $C_{1-6}$ alquilo, $C_{2-3}$ alquenilo (los cuales últimos dos grupos se sustituyen opcionalmente por uno o más sustituyentes seleccionados de F, Cl, $C(O)OH$, $C(O)OCH_3$ y fenilo),

(d) $C_{3-5}$ cicloalquilo,

(e) $OR^{17a}$,

(f) S-$C_{1-2}$ alquilo, $S(O)_2$-$C_{12}$ alquilo (las partes alquilo de cuyos últimos dos grupos se sustituyen opcionalmente por uno o más átomos F),

(g) $S(O)_2NH_2$, $S(O)_2N(H)CH_3$,

(h) $N(H)S(O)_2$-$C_{1-2}$ alquilo (la parte alquilo de cuyo último grupo se sustituye opcionalmente por uno o más átomos F),

(i) $NH_2$, $N(H)C_{1-2}$ alquilo,

(j) CHO, $C(O)$-$C_{1-4}$ alquilo (la parte alquilo de cuyo último grupo se sustituye opcionalmente por uno o más átomos F o Cl), $C(O)OH$, $C(O)O$-$C_{1-4}$ alquilo, $C(O)NH_2$, $C(O)N(H)$-$C_{1-4}$ alquilo, $N(H)C(O)$-$C_{1-4}$ alquilo, $N(H)C(O)O$-$C_{1-4}$ alquilo,

(k) fenilo (el cual último grupo se sustituye opcionalmente por uno a cuatro sustituyentes seleccionados de F, Cl y Br),

(l) $Het^9$ y

(m) $Si(CH_3)_3$;

(29) $R^{17a}$ representa

(a) H,

(b) $C_{1-5}$ alquilo opcionalmente sustituido por fenilo o uno o más sustituyentes seleccionados de F, Cl, y $Het^{10}$ (verbigracia, uno o más sustituyentes seleccionados de F y Cl),

(c) $C_{3-5}$ cicloalquilo o

(d) fenilo sustituido opcionalmente por uno a cuatro sustituyentes seleccionados de F, Cl y Br;

(30) $Het^1$ representa un grupo heterocíclico de 5 a 10 miembros que contiene uno a tres heteroátomos seleccionados de oxígeno, nitrógeno y/o azufre, los cuales grupos heterocíclicos pueden comprender uno o dos anillos y pueden sustituirse por uno a tres sustituyentes seleccionados de F, Cl, Br, $C_{1-4}$ alquilo, =O y OH;

(31) $Het^3$ representa un grupo heterocíclico de 5 a 13 miembros que contiene uno a cuatro heteroátomos seleccionados de oxígeno, nitrógeno y/o azufre, los cuales grupos heterocíclicos pueden comprender uno, dos o tres anillos y pueden sustituirse por uno a cuatro sustituyentes seleccionados de

(a) F, Cl, Br,

(b) $C_{1-4}$ alquilo (el cual último grupo se sustituye opcionalmente por uno o más sustituyentes seleccionados de F, Cl y OH),

(c) $C_{3-5}$ cicloalquilo,

(d) =O,

(e) OH, O-$C_{1-2}$ alquilo (el cual último grupo se sustituye opcionalmente por uno o más sustituyentes seleccionados de F y Cl),

(g) $S(O)_2$-$C_{1-2}$ alquilo (el cual último grupo se sustituye opcionalmente por uno o más átomos F), $S(O)_2$-fenilo (la parte fenilo de cuyo último grupo se sustituye de manera opcional por uno a cuatro sustituyentes seleccionados de F, Cl, Br, metilo y metoxi).

(h) $S(O)_2NH_2$, $S(O)_2N(H)$-$C_{1-2}$ alquilo,

(i) $N(H)S(O)_2$-$C_{1-2}$ alquilo,

(j) $NH_2$, $N(H)$-$C_{1-2}$ alquilo,

(j) $C(O)$-$C_{1-4}$ alquilo, C(O)-fenilo (la parte fenilo de cuyo último grupo se sustituye de manera opcional por uno a cuatro sustituyentes seleccionados de F, Cl, Br, metilo y metoxi), C(O)OH, $C(O)O$-$C_{1-4}$ alquilo, $C(O)NH_2$, $(O)N(H)$-$C_{1-4}$ alquilo, $N(H)C(O)$-$C_{1-4}$ alquilo, $N(H)C(O)O$-$C_{1-4}$ alquilo,

(l) fenilo (el cual último grupo se sustituye opcionalmente por uno a cuatro sustituyentes seleccionados de F, Cl y Br) y

(m) $Het^c$;

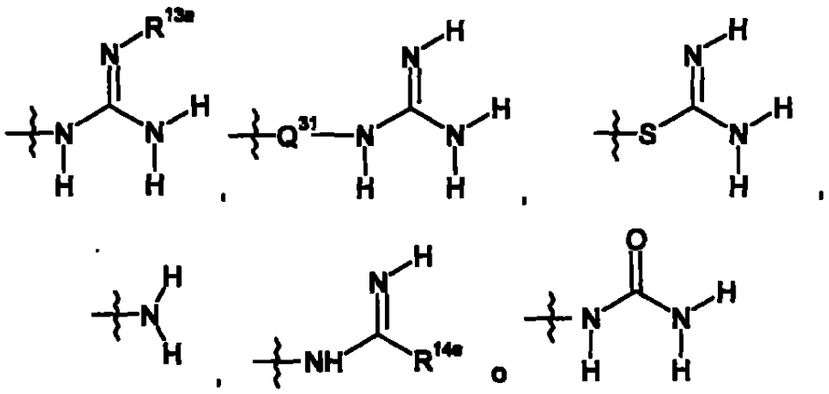
(32) $Het^9$ representa un grupo heterocíclico monocíclico de 5 ó 6 miembros que contiene, como heteroátomo(s), un átomo de azufre u oxígeno y/o uno a tres átomos de nitrógeno, los cuales grupos heterocíclicos pueden sustituirse por uno o más sustituyentes seleccionados de F, Cl, Br, $C_{1-4}$ alquilo, =O y OH;

(33) $Het^{10}$ representa grupo herocíclico monocíclico de 5 ó 6 miembros que contiene, como heteroátomo(s), un átomo de azufre u oxígeno y/o uno a tres átomos de nitrógenos, cuyo grupo heterocíclico puede sustituirse por uno o más sustituyentes seleccionados de F, Cl, Br, $C_{1-4}$ alquilo y $C_{1-4}$ alcoxi;

(34) $Het^c$ representa un grupo heterocíclico de 5 ó 6 miembros que contiene, como heteroátomo(s), un átomo de oxígeno o azufre (por ejemplo, un átomo de oxígeno) y/o uno a tres (por ejemplo, uno a

dos) átomos de nitrógeno, el cual grupo heterocíclico puede sustituirse por uno o más sustituyentes seleccionados de F, Cl, Br, $C_{1-4}$ alquilo y $C_{1-4}$ alcoxi (verbigracia, uno o más sustituyentes seleccionados de F, Cl, Br y metilo).

Definiciones más preferidas de $R^{a1}$ incluyen

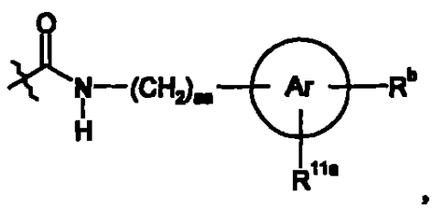


en donde $R^{13a}$ es como se define más arriba, pero preferiblemente representa OH, CN o $NH_2$ y $Q^{31}$ y $R^{14c}$ son como se define más arriba.

Definiciones más preferidas de $R^{a2}$ y $R^{a3}$ incluyen -N(H)$R^{14c}$, en donde $R^{14c}$ representa $C_{1-2}$ alquilo o, preferiblemente, H.

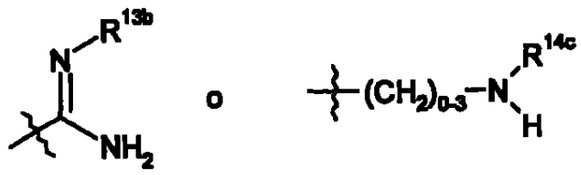
Compuestos de fórmula I que son todavía más preferida incluyen aquellos en los cuales el grupo G-L asume las siguientes definiciones.

(1)



en donde aa representa 0, 1 ó 2 (tal como 2 ó, particularmente, 1);

$R^b$ es como ya se definió, pero particularmente representa tetrazol-1-ilo, H,



(por ejemplo uno de los tres últimos grupos),

en donde $R^{13b}$ es como ya se definió, pero particularmente representa $NH_2$ ó, preferiblemente, H;

$R^{14c}$, es como ya se definió, pero particularmente representa $C_{1-2}$ alquilo sustituido opcionalmente por uno a 3 átomos F (por ejemplo $CH_2CF_3$), H, ciclopentilo o $C(O)O$-$C_{3-4}$ alquilo (por ejemplo uno de los tres últimos grupos);

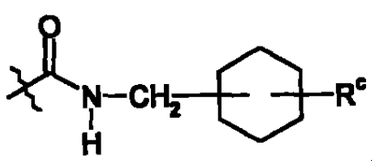
$R^{11a}$ es como ya se definió, pero,

(i) cuando $R^b$ representa H, $R^{11a}$ particularmente representa uno a tres sustituyentes seleccionados de F, Cl, OH, metilo (el cual último grupo se sustituye opcionalmente por OH o, particularmente, $C(O)N(R^{12b})R^{12c}$) y metoxi (el cual último grupo se sustituye por $C(O)N(H)R^{12b}$),

(ii) cuando $R^b$ representa $-C(=NR^{13b})NH_2$, $R^{11a}$ particularmente representa uno o dos sustituyentes seleccionados de F y OH o, preferiblemente, $R^{11a}$ representa H,

(iii) cuando $R^b$ representa $-(CH_2)_{0-3}$-$N(H)R^{14c}$, $R^{11a}$ particularmente representa H ó uno o dos sustituyentes seleccionados de F, Cl, OH, metilo, metoxi y $CF_3$ (por ejemplo H ó uno o dos sustituyentes seleccionados de Cl, OH y metilo o, preferiblemente, un solo sustituyente Cl).

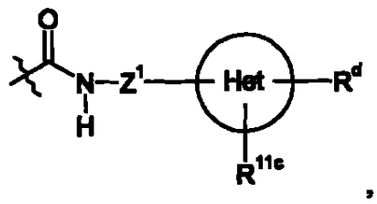
(2)



en donde $R^c$ representa $-C(=NR^{13b})NH_2$ ó, particularmente, $-N(H)R^{14c}$, grupos que preferiblemente se unen en la posición 4 en relación al punto de unión del grupo $CH_2$;

$R^{13b}$ y $R^{14c}$ son como ya se definió, pero preferiblemente representan H.

(3)




,

en donde $Z^1$ representa $-CH_2C\equiv C-$, $-CH=CH-$, $C(O)CH_2$ ó, preferiblemente, C(O) ó $-(CH_2)_{ab}-$;

cuando $Z^1$ representa $-CH_2C\equiv C-$, $-CH=CH-$, Het representa un grupo heterocíclico aromático de 5 miembros que contiene uno o, particularmente, dos átomos de nitrógeno;

cuando $Z^1$ representa $C(O)CH_2$, Het representa un grupo heterocíclico completamente saturado de 6 miembros, que contiene uno o, particularmente, dos átomos de nitrógeno;

cuando $Z^1$ representa C(O), Het representa un grupo heterocíclico a aromático de 6 miembros, que contiene dos átomos de nitrógeno o, particularmente, un átomo de nitrógeno;

cuando $Z^1$ representa $-(CH_2)_{ab}-$ Het representa un grupo heterocíclico de 5 ó 6 miembros, o bicíclico fusionado a un anillo, de 9 ó 10 miembros, que contiene, como heteroátomo(s)

(a) un átomo de azufre, o

(b) un átomo de nitrógeno y, opcionalmente, uno o dos heteroátomos adicionales seleccionados de nitrógeno, oxígeno y azufre,

grupo heterocíclico que,

(i) cuando tiene 5 ó 6 miembros, es completamente aromático o completamente saturado,

(ii) cuando tiene 9 ó 10 miembros, es completamente aromático o parcialmente aromático;

**ab** representa 0 a 3, pero preferiblemente representa 1 ó 2 o, cuando Het tiene 5 miembros, también preferiblemente representa 3;

$R^d$ representa H, $-C(=NR^{13b})NH_2$ ó $-N(H)R^{14c}-$, pero $R^d$, cuando Het tiene 5 ó 10 miembros, particularmente representa $-N(H)R^{14c}$;

$R^{11c}$ es como ya se definió, pero preferiblemente representa H ó

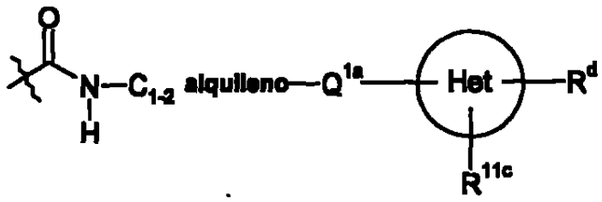
(I) cuando Het tiene 6 miembros y es aromático (por ejemplo un grupo piridinilo), uno o dos sustituyentes seleccionados de F, Cl, metilo y $CH_2OH$,

(II) cuando Het tiene 6 miembros y es completamente saturado, un metilo o un sustituyente =NH;

$R^{13b}$ es como ya se definió, pero preferiblemente representa H;

$R^{14c}$ es como ya se definió, pero preferiblemente representa H ó, cuando Het tiene 6 miembros, metilo.

(4)




en donde $Q^{1a}$ representa O ó $NR^{10a}$;

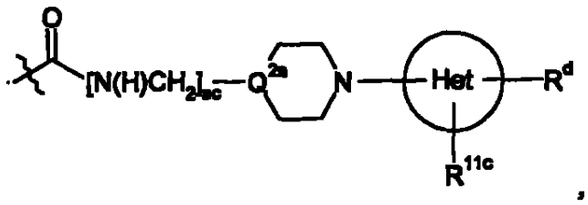
$R^{10a}$ representa H, metilo o $-CH_2CH_2OH$;

Het representa un grupo heterocíclico, aromático de 6 miembros o 10 miembros, que contiene dos átomos de nitrógeno o, preferiblemente, un átomo de nitrógeno; $R^d$ representa H ó $-N(H)R^{14c}$;

$R^{14c}$ es como ya se definió, pero preferiblemente representa H;

$R^{11c}$ es como ya se definió, pero preferiblemente representa H ó, cuando Het contiene dos átomos de nitrógeno, representa Cl.

(5)



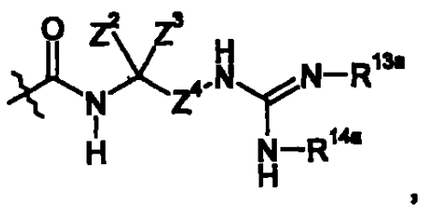
en donde $Q^{2a}$ representa N ó CH;

ac representa 0 ó 1, pero, cuando $Q^{2a}$ representa CH, preferiblemente representa 1;

Het representa un grupo heterocíclico aromático de 6 miembros, que contiene dos átomos de nitrógeno o, preferiblemente, un átomo de nitrógeno (por ejemplo un grupo piridinilo, tal como un grupo piridin-4-ilo);

$R^d$ y $R^{11c}$ son como ya se definió, pero preferiblemente representan H;

(6)

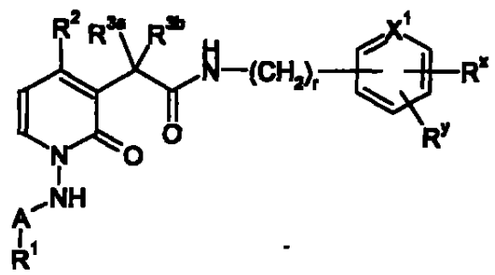


en donde $Z^2$ y $Z^3$ representan independientemente H ó F, pero, preferiblemente, $Z^2$ y $Z^3$ ambos representan H ó ambos representan F;

$Z^4$ representa- $(CH_2)_2C(O)$- ó, preferiblemente,-$CH_2C(O)$-,-$CH_2O$-, -$CH_2$-C(H)=N- ó -C(H)=N-

$R^{13a}$ es como ya se definió, pero preferiblemente representan H.

Compuestos particularmente preferidos de la invención son compuestos de fórmula Ic



Ic

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en donde $X^1$ representa CH ó N;

cuando $X^1$ representa CH

(a) $R^x$ adopta las mismas definiciones que $R^b$ más arriba, y

(b) $R^y$ adopta las mismas definiciones que $R^{11a}$ más arriba;

cuando $X^1$ representa N

(a) $R^x$ adopta las mismas definiciones que $R^d$ más arriba, y

(b) $R^y$ adopta las mismas definiciones que $R^{11c}$ más arriba;

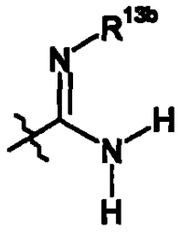
r representa 1 a 3; y

$R^1$, $R^2$, $R^{3a}$, $R^{3b}$, $R^{11a}$, $R^{11c}$, $R^b$, $R^d$ y A son como se define más arriba,

los cuales compuestos se designan también de ahora en adelante "los compuestos de la invención".

Compuestos preferidos de fórmula Ic incluyen aquellos en los que:

cuando $X^1$ representa CH, $R^x$ representa tetrazol-1-ilo, H, $(CH_2)_{1-2}N(H)R^{14c}$ (por ejemplo $CH_2N(H)R^{14c}$) ó




(por ejemplo cualquiera de los tres últimos grupos);

cuando $X^1$ representa N, $R^x$ representa H o $-N(H)R^{14c}$;

cuando $X^1$ representa CH, $R^y$ representa H o uno a tres sustituyentes seleccionados de halo, $C_{1-2}$ alquilo, $C_{1-2}$ alcoxi (los cuales últimos dos grupos se sustituyen opcionalmente por uno o más átomos F), OH, $CH_2OH$ y $OCH_2C(O)N(H)R^{12b}$ (por ejemplo H ó uno a tres átomos halo);

cuando $X^1$ representa N, $R^y$ representa H o uno a tres sustituyentes seleccionados de halo y $C_{1-2}$ alquilo;

$R^{12b}$ representa H ó, preferiblemente, $C_{1-3}$ alquilo opcionalmente sustituido por $N(CH_3)_2$ (por ejemplo etilo o $(CH_2)_{2-3}N(CH_3)_2$, particularmente $(CH_2)_3N(CH_3)_2$); r representa 2 ó, particularmente, 1.

Compuestos de fórmula Ic particularmente preferidos incluyen aquellos en los cuales:

A representa C(O), $S(O)_2$, C(O)NH (en cuyo último grupo la fracción NH se une a $R^1$) ó $C_{1-3}$ (verbigracia, $C_{1-2}$) alquileno (el cual último grupo se sustituye de manera opcional por uno o más átomos F (verbigracia, no se sustituye));

$R^1$ representa

(a) $C_{1-3}$ alquilo sustituido por fenilo (el cual último grupo se sustituye opcionalmente por uno o más sustituyentes seleccionados de halo, $C_{1-4}$ alquilo y $C_{1-4}$ alcoxi (los cuales últimos dos grupos se sustituyen opcionalmente por uno o más átomos F)),

(b) fenilo o naftilo (los cuales últimos dos grupos se sustituyen opcionalmente por uno o más sustituyentes seleccionados de CN, halo, $C_{1-4}$ alquilo y $C_{1-4}$ alcoxi (los cuales últimos dos grupos se sustituyen opcionalmente por uno o más átomos F) O-fenilo, O-$CH_2$-$Het^{10}$ y Het9 (por ejemplo uno o más sustituyentes seleccionados de halo, $C_{1-4}$ alquilo y C1-4 alcoxi (los cuales últimos dos grupos se sustituyen opcionalmente por uno o más átomos F)),

(c) un grupo heterocíclico (preferiblemente aromático) monocíclico de 5 ó 6 miembros, que contiene, como heteroátomo(s), un átomo de oxígeno o azufre y/o uno a tres átomos de nitrógeno, grupo heterocíclico que se sustituye opcionalmente por uno a cuatro sustituyentes seleccionados de F, Cl, Br, =O, OH, $C_{1-4}$ alquilo (el cual último grupo se sustituye de manera opcional por uno o más átomos halo o por OH), $C_{1-4}$ alcoxi, $S(O)_2$-fenilo, C(O)- fenilo, fenilo y $Het^c$ (por ejemplo uno a cuatro sustituyentes seleccionados de F, Cl, Br y $C_{1-4}$ alquil y $C_{1-4}$ alcoxi, tal como uno a cuatro sustituyentes seleccionados de F, Cl, Br y $C_{1-4}$ alquilo),

(d) un grupo heterocíclico (preferiblemente parcialmente aromático) bicíclico de 9 ó 10 miembros, que contiene uno a tres heteroátomos seleccionados de oxígeno, nitrógeno y/o azufre (por ejemplo dos átomos de oxígeno), grupo heterocíclico que se sustituye opcionalmente por uno a cuatro sustituyentes seleccionados de F, Cl, Br, $C_{1-4}$ alquilo y $C_{1-4}$ alcoxi

(e) $C_{1-5}$ alquilo, o

(f) $C_{4-7}$ cicloalquilo o $C_{5-7}$ cicloalquenilo, los cuales últimos dos grupos se sustituyen de manera opcional por uno o más grupos metilo

(por ejemplo $R^1$ representa un grupo como se define en (a) a (c) de arriba);

$Het^9$ representa un grupo heterocíclico monocíclico de 5 ó 6 miembros que contiene, como heteroátomo(s), un átomo de azufre u oxígeno y/o uno o dos átomos de nitrógeno, el cual grupo heterocíclico puede sustituirse por uno a tres sustituyentes seleccionados de F, Cl y metilo;

$Het^{10}$ representa un grupo heterocíclico aromático monocíclico de 5 ó 6 miembros que contiene, como heteroátomo(s), un átomo de azufre o un átomo de oxígeno y/o uno o dos átomos de nitrógeno, el cual grupo heterocíclico puede sustituirse por uno a tres sustituyentes seleccionados de F, Cl, metilo y metoxi;

$Het^c$ representa un grupo heterocíclico monocíclico de 5 ó 6 miembros que contiene, como heteroátomo(s), un átomo de oxígeno o azufre y/o uno o dos átomos de nitrógeno, el cual grupo heterocíclico puede sustituirse de manera opcional uno a cuatro sustituyentes seleccionados de F, Cl, Br, $C_{1-4}$ alquilo y $C_{1-4}$ alcoxi;

$R^2$ representa H, metilo o halo (tal como Cl);

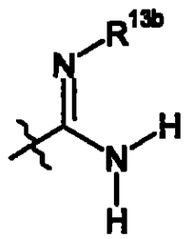
$R^{3a}$ y $R^{3b}$ ambos representan H;

cuando $X^1$ representa CH y $R^x$ representa H, entonces $R^y$ representa uno a tres sustituyentes seleccionados de OH, metilo, $CH_2OH$, $OCH_2C(O)N(H)R^{12b}$ y halo (particularmente uno a tres átomos halo (por ejemplo uno a tres átomos Cl, tal como átomos Cl unidos en las posiciones 2 y 5 relativas al punto de unión del grupo $(CH_2)_r$));

cuando $X^1$ representa CH y $R^x$ representa $(CH_2)_{1-2}N(H)R^{14c}$, entonces $R^y$ representa H ó, preferiblemente, uno o dos sustituyentes seleccionados de halo, $C_{1-2}$ alquilo y $C_{1-2}$ alcoxi (los cuales últimos dos grupos se sustituyen opcionalmente por uno o más átomos F) (y particularmente $R^y$ representa uno o dos átomos halo (por ejemplo uno o dos átomos Cl, tal como un átomo Cl unido en la posición 3 relativo al punto de unión del grupo $(CH_2)_r$));

cuando $X^1$ representa CH y $R^x$ representa tetrazol-1-ilo, entonces $R^y$ representa uno o dos halo (por ejemplo átomos Cl) o, preferiblemente, H;

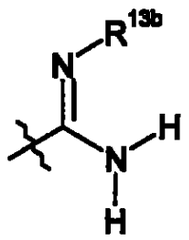
cuando $X^1$ representa CH y $R^x$ representa



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entonces $R^y$ representa uno o dos átomos F o, preferiblemente, H;

cuando $X^1$ representa CH, el grupo



,

si se encuentra presente, se une en la posición 3 ó, preferiblemente, la posición 4 relativa al punto de unión del grupo $(CH_2)_r$;

cuando $X^1$ representa CH, el grupo $(CH_2)_{1-2}N(H)R^{14c}$, si se encuentra presente, se une en la posición 5 ó, preferiblemente, la posición 6 relativa al punto de unión del grupo $(CH_2)_r$;

cuando $X^1$ representa CH, el grupo tetrazol-1-ilo, si se encuentra presente, se une en la posición 5 ó, preferiblemente, la posición 6 relativa al punto de unión del grupo $(CH_2)_r$;

$R^{13b}$ representa OH, $OCH_3$ ó, preferiblemente, $C(O)OCH_2$-fenilo o H;

cuando $X^1$ representa N y $R^x$ representa H, $R^y$ representa H ó, preferiblemente, uno o dos sustituyentes seleccionados de halo (por ejemplo F) y metilo;

cuando $X^1$ representa N y $R^x$ representa -N(H)$R^{14c}$, $R^y$ representa H o uno o dos grupos metilo (por ejemplo H o metilo);

$R^{14c}$ representa $CH_2CF_3$, H, ciclopentilo o C(O)O-$C_4$ alquilo (por ejemplo uno de los tres últimos grupos, tal como C(O)O-$C_4$ alquilo (por ejemplo C(O)O-*terc*-butilo) o, preferiblemente, H).

Compuestos de fórmula Ic que son aún más preferidos incluyen aquellos en los cuales:

A representa C(O), C(O)NH (en cuyo último grupo la fracción NH se une a $R^1$) o, particularmente, $S(O)_2$ o $C_{1-3}$ (verbigracia, $C_{1-2}$) alquileno (el cual último grupo se gem-sustituye opcionalmente por dos átomos F (verbigracia, no se sustituye));

$R^1$ representa

(a) $C_{1-2}$ alquilo sustituido por fenilo (el cual último grupo se sustituye opcionalmente por uno o más sustituyentes seleccionados de F, Cl y Br),

(b) fenilo (el cual último grupo se sustituye opcionalmente por uno o más sustituyentes seleccionados de F, Cl, Br, CN, $C_{1-3}$ alquilo y $C_{1-3}$ alcoxi (los cuales últimos dos grupos se sustituyen opcionalmente por uno o más átomos F (formando así, por ejemplo, $C_{1-2}$ alquilo, $CF_3$, $C_{1-2}$ alcoxi o $OCF_3$)), O-fenilo, O-$CH_2$-$Het^{10}$ y $Het^9$) (tal como uno o más sustituyentes seleccionados de F, Cl, Br, $C_{1-3}$ alquilo (el cual último grupo se sustituye de manera opcional por uno o más átomos F (formando así, por ejemplo, $C_{1-2}$ alquilo o $CF_3$)) y $C_{1-3}$ alcoxi (verbigracia, $C_{1-2}$ alcoxi)) o

c) naftilo (por ejemplo 1-naftilo), o

(d) piridinilo (por ejemplo piridin-2-ilo o piridin-3-ilo) sustituido opcionalmente por uno o dos sustituyentes seleccionados de F, Cl, (*N*-)oxo, OH, $C_{1-4}$ alquilo (tal como metilo, el cual grupo $C_{1-}$

$_4$ alquilo se sustituye de manera opcional por uno o más átomos halo o por OH) o, particularmente, $C_{1-4}$ alcoxi (verbigracia, *terc*-butoxi o metoxi) o Het$^c$, (tal como piridinilo (verbigracia, piridin-3-ilo) sustituido de manera opcional por uno o dos sustituyentes seleccionados de F, Cl, $C_{1-2}$ alquilo o, particularmente, $C_{1-2}$ alcoxi),

(e) piridonilo (por ejemplo 2-piridon-3-ilo) sustituido opcionalmente por uno o dos sustituyentes seleccionados de F, Cl, y $C_{1-4}$ alquilo (por ejemplo metilo);

(f) pirazinilo (verbigracia, pirazin-2-ilo) sustituido de manera opcional por uno o dos sustituyentes seleccionados de F, Cl y metilo;

(g) un grupo heterocíclico aromático de 5 miembros que contiene, como heteroátomo(s), un átomo de oxígeno o azufre y/o uno o tres átomos de nitrógeno (verbigracia, imidazolilo, isoxazolilo, pirazolilo, pirrolilo, tiazolilo, o tienilo), grupo heterocíclico que se sustituye opcionalmente por uno a cuatro (por ejemplo uno a tres) sustituyentes seleccionados de F, Cl, $C_{1-4}$ alquilo (por ejemplo metilo o etilo), $C_{1-4}$ alcoxi (por ejemplo metoxi), $S(O)_2$-fenilo, C(O)-fenilo, fenilo, morfolinilo (verbigracia, morfolin-4-ilo), 1,3,4-triazolilo (verbigracia, 1,3,4-triazol-1-ilo), tienilo (verbigracia, 2-tienilo) y piridinilo (verbigracia, piridin-2-ilo),

(h) 2,3-dihidrobenzofuranilo, benzomorfolinilo, benzodioxanilo, 2,1,3-benzoxadiazolilo, o, particularmente, benzodioxolilo o quinolinilo, todos los cuales grupos se sustituyen de manera opcional por uno o más (verbigracia, uno a tres) sustituyentes seleccionados de F, Cl, $C_{1-2}$ alquilo y $C_{1-2}$ alcoxi,

(i) $C_{1-4}$ alquilo (verbigracia, isopropilo o *terc*-butilo), o

(j) ciclopentilo, ciclohexilo o cicloalquenilo bicíclico $C_7$ (verbigracia, biciclo[2.2.1]hepteno, los cuales últimos tres grupos se sustituyen de manera opcional por uno a cuatro grupos metilo

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(verbigracia, $R^1$ representa un grupo como se define en (a) a (d) o, particularmente, (a) a (c) más arriba);

$Het^9$ representa un grupo heterocíclico monocíclico, saturado, de 6 miembros que contiene, como heteroátomo(s), un átomo de oxígeno y/o uno o dos átomos de nitrógeno, el cual grupo heterocíclico puede sustituirse por uno o dos sustituyentes metilo;

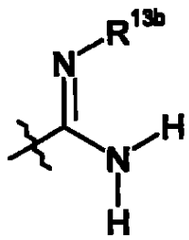
$Het^{10}$ representa un grupo heterocíclico aromático, monocíclico, de 5 miembros que contiene, como heteroátomo(s), un átomo de azufre o un átomo de oxígeno y/o uno o dos átomos de nitrógeno, el cual grupo heterocíclico puede sustituirse por uno a tres sustituyentes seleccionados de Cl y metilo;

$Het^c$ representa un grupo heterocíclico monocíclico, saturado, de 6 miembros que contiene, como heteroátomo (s), un átomo de oxígeno y/o uno o dos átomos de nitrógeno, el cual grupo heterocíclico puede sustituirse por uno o dos sustituyentes metilo;

$R^2$ representa metilo;

$X^1$ representa CH o N (verbigracia, CH);

cuando $X^1$ representa CH, $R^x$ representa




unido a la posición 4 relativa al punto de unión del grupo $(CH_2)_r$, o $R^x$ puede representar igualmente tetrazol-1-ilo o, particularmente, $CH_2N(H)R^{14c}$ (los cuales últimos dos grupos se unen are, por ejemplo, en la posición 6 relativa al punto de unión del grupo $(CH_2)_r$);

$R^x$ puede representar alternativamente H cuando $X^1$ representa CH, y $R^y$ representa uno a tres sustituyentes seleccionados de OH, metilo, $CH_2OH$, $OCH_2C(O)N(H)R^{12b}$ y halo;

$R^{13b}$ representa $C(O)OCH_2$-fenilo o, preferiblemente, H;

$R^{14c}$ representa C(O)O-*terc*-butilo o, particularmente, H, etilo, $CH_2CF_3$ o ciclopentilo (por ejemplo H o ciclopentilo).

Otros compuestos preferidos de fórmula Ia incluyen aquellos en los cuales:
A representa $CH(CH_3)CH_2$ (último grupo en el cual la unidad $CH(CH_3)$ se une a $R^1$) o, particularmente, $CH_2$, $(CH_2)_2$ ó $CF_2CH_2$ (en cuyo último grupo la unidad $CF_2$ se une a $R^1$);

$R^1$ representa

(a) isopropilo o *terc*-butilo,

(b) ciclopentilo, ciclohexilo o biciclo[2.2.1]hept-5-eno,

(c) fenilo sustituido opcionalmente por uno o dos sustituyentes seleccionados de halo (por ejemplo F o Cl), CN, metilo, $CF_3$, metoxi, $OCF_3$, fenoxi, morfolin-4-ilo o O-$CH_2$-(2-clorotiazol-5-ilo),

(d) imidazolilo sustituido de manera opcional por uno a tres sustituyentes seleccionados de Cl, metilo y fenilo,

(e) isoxazolilo (verbigracia, isoxazol-3-ilo o isoxazol-4-ilo) sustituido de manera opcional por uno o dos sustituyentes seleccionados de metilo, fenilo y 2-tienilo,

(f) tiazolilo (verbigracia, tiazol-5-il) sustituido de manera opcional por uno o dos grupos metilo,

(g) tienilo (verbigracia, tien-2-ilo) sustituido de manera opcional por Cl o piridinilo (verbigracia, piridin-2-ilo),

(h) pirazolilo (por ejemplo pirazol-4-ilo) sustituido opcionalmente por uno a tres sustituyentes seleccionados de Cl metilo, etilo, fenilo y morfolin-4-ilo,

(i) pirrolilo (verbigracia, pirrol-2-ilo o pirrol-3-ilo) sustituido de manera opcional por uno a tres sustituyentes seleccionados de metilo, $S(O)_2$-fenilo, C(O)-fenilo y 1,3,4-triazol-1-ilo,

(j) piridinilo (verbigracia, piridin-2-ilo o piridin-3-ilo) sustituido de manera opcional por OH, metoxi o morfolin-4-ilo, y de manera opcional en la forma de un *N*-óxido,

(k) piridonilo (verbigracia, 2-piridon-3-ilo),

(l) pirazinilo (verbigracia, pirazin-2-ilo),

(m) benzodioxolilo (por ejemplo 5-benzodioxolilo) opcionalmente sustituido por halo (por ejemplo Cl),

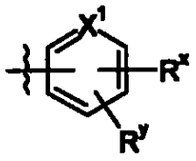
(n) benzomorfolinilo (verbigracia, 7-benzomorfolinilo) sustituido de manera opcional por metilo;

(o) 2,1,3-benzoxadiazolilo (verbigracia, 2,1,3-benzoxadiazol-5-ilo),

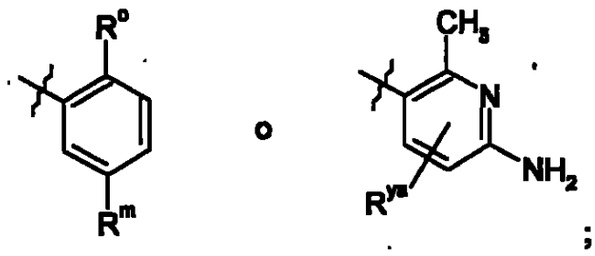
(p) 2,3-dihidrobenzofuranilo (verbigracia, 2,3-dihidrobenzofuran-5-ilo) o

(q) quinolinilo (verbigracia, 8-quinolinilo);

el grupo



representa



$R^o$ representa H, F, Cl, OH, metilo o, particularmente, tetrazol-1-ilo, $OCH_2C(O)N(H)R^{12b}$ ó $CH_2N(H)R^{14c}$;

$R^m$ representa H, metilo, $CF_3$, metoxi, F o, particularmente, Cl (por ejemplo:

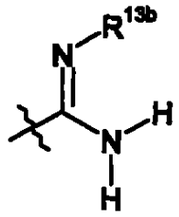
(a) cuando $R^o$ representa H o Cl, entonces $R^m$ representa Cl;

(b) cuando $R^o$ representa OH o metilo, entonces $R^m$ representa F o, particularmente Cl; y

(c) cuando $R^o$ representa tetrazol-1-ilo, $OCH_2C(O)N(H)R^{12b}$ ó $CH_2N(H)R^{14c}$ entonces $R^m$ representa H, metilo, $CF_3$, metoxi, F o, muy preferiblemente, Cl);

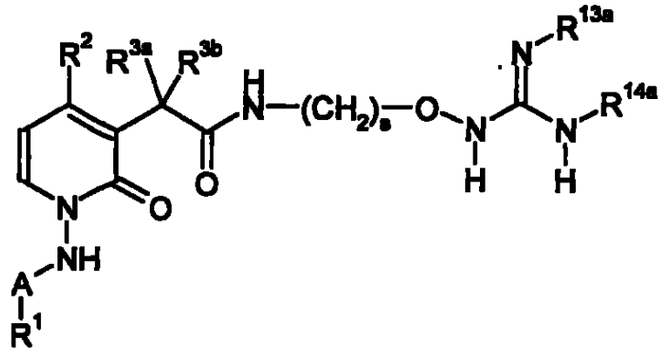
$R^{yn}$ representa H o, particularmente, metilo.

En una incorporación de compuestos de fórmula Ic que son aún más preferidos, $R^x$ representa

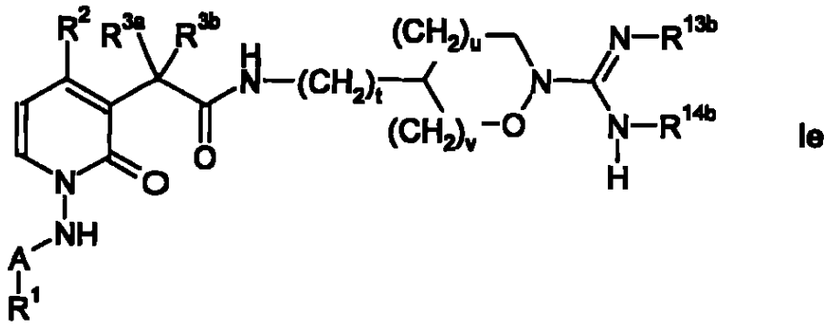


unido a la posición 4 en relación con el punto de unión del grupo $(CH_2)_r$.

Compuestos particularmente preferidos de la invención son asimismo compuestos de fórmula Id y Ic



Id



Ie

en donde s representa 2 a 4;

t representa 1 a 3;

u y v representan independientemente 0 a 2, siendo la sumatoria de u y v 1 ó 2; y $R^1$, $R^2$, $R^{3a}$, $R^{3b}$, $R^{13b}$, $R^{14a}$ y $R^{14b}$ son como se define más arriba,

los cuales compuestos se designan también en adelante "los compuestos de la invención".

Compuestos preferidos de fórmula Id incluyen aquellos en los cuales:
s representa 3 o, particularmente, 2;
$R^{13a}$ y $R^{14a}$ ambos representan H.

Compuestos preferidos de fórmula Ie incluyen aquellos en los cuales:
t representa 2 o, particularmente, 1;
u y v ambos representan 1;
$R^{13b}$ y $R^{14b}$ ambos representan H.

Para evitar dudas, las definiciones preferidas de grupos dadas más arriba en relación con compuestos de fórmula Ic, Id y Ie son también, donde sea relevante, definiciones preferidas de los grupos equivalentes en compuestos de fórmula I.

Compuestos preferidos de la invención incluyen los compuestos de los Ejemplos divulgados a continuación.

**Preparación**

Compuestos de fórmula I (incluidos los compuestos de fórmulas Ic, Id y Ie) pueden elaborarse de acuerdo con técnicas bien conocidas por los expertos en el arte, por ejemplo como se describe a continuación.

De acuerdo con un aspecto adicional de la invención se provee un proceso para la preparación de un compuesto de fórmula I, el cual comprende:

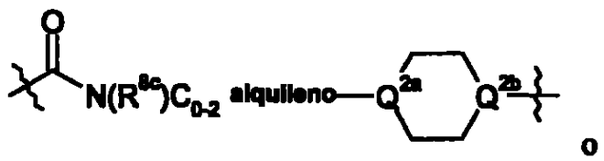
(a) para compuestos de fórmula I en la cual el grupo G representa

(i) $C(O)N(R^{8a})$-$[CH(C(O)R^9)]_{0-1}$-$C_{0-3}$ alquileno-$(Q^1)_n$-,

(ii) $C(O)N(R^{8b})$-$C_{2-3}$ alquenileno-$(Q^1)_n$-,

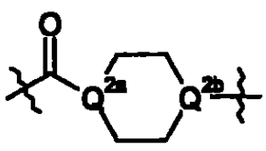
(iii) $C(O)N(R^{8b})$-$C_{2-3}$ alquinileno-$(Q^1)_n$-,

(iv)




o

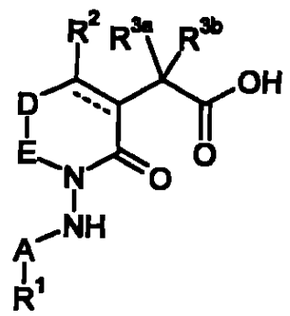
(v)




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en donde $Q^{2a}$ representa N o NHCH,

acoplamiento de un compuesto de fórmula II,




II

en donde $R^1$, $R^2$, $R^{3a}$, $R^{3b}$, A, D y E son como se define más arriba en el texto, con un compuesto de fórmula III,

H-$G^a$-L III

en donde L es como ya se definió y $G^a$ representa

(i) -$N(R^{8a})$-$[CH(C(O)R^9)]_{0-1}$-$C_{0-3}$ alquileno-$(Q^1)_n$-,

(ii) -$N(R^{8b})$-$C_{2-3}$ alquenileno-$(Q^1)_n$-,

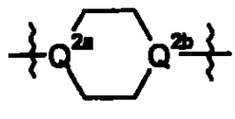
(iii) -$N(R^{8b})$-$C_{2-3}$ alquinileno-$(Q^1)_n$-,

(iv)




o

(v)

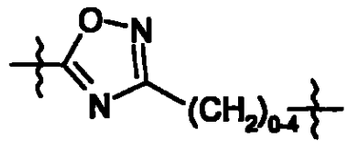


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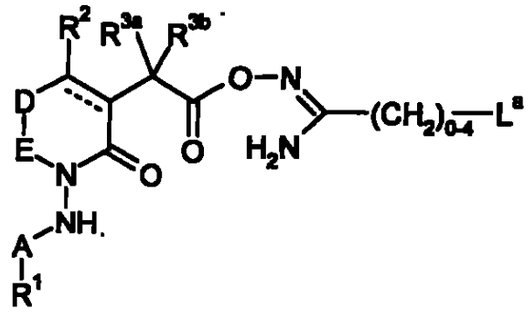
en donde $Q^{2a}$ representa N o NHCH y $R^{8a}$, $R^{8b}$, $R^{8c}$, $R^9$, $Q^1$, $Q^{2b}$ y a son como ya se definieron,

por ejemplo en la presencia de un agente de acoplamiento (por ejemplo cloruro de oxalilo en DMF, EDC, DCC, HBTU, HATU, PyBOP o TBTU), una base apropiada (por ejemplo piridina, DMAP, TEA, 2,4,6-colidina o DIPEA) y un disolvente orgánico adecuado (por ejemplo diclorometano, acetonitrilo, EtOAc o DMF);

(b) para compuestos de fórmula I en la cual G representa



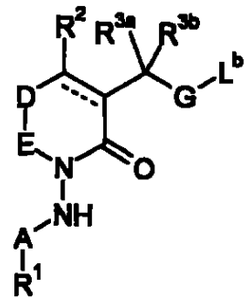
y L representa $L^a$, el cual último grupo representa L como se definió anteriormente, excepto que no represente $C_0$ alquileno-$R^a$, ciclación de un compuesto de fórmula IV,



IV

en donde la línea discontinua, $R^1$, $R^2$, $R^{3a}$, $R^{3b}$, A, D, E y L son como ya se definieron, por ejemplo a temperatura elevada (por ejemplo 60°C a reflujo) en la presencia de un disolvente adecuado (por ejemplo piridina, tolueno, 1,4-dioxano o THF) y opcionalmente en la presencia de un catalizador adecuado (por ejemplo (*n*-Bu)$_4$NF, el cual puede emplearse particularmente cuando el disolvente de reacción es THF);

(c) para compuestos de fórmula I en la cual $R^a$, $R^b$, $R^c$ o $R^d$ representa -C(=NH)$NH_2$, -C(=$NNH_2$)$NH_2$ o -C(=NOH)$NH_2$, la reacción de un compuesto de fórmula V,



V

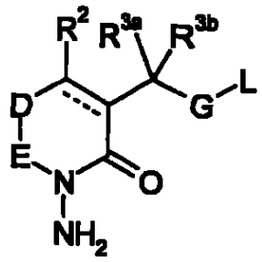
en donde $L^b$ representa L como ya se definió, excepto que $R^a$, $R^b$, $R^c$ o $R^d$ (según sea apropiado) se reemplaza por un grupo ciano o -C(=NH)O-$C_{1-4}$ alquilo, y la línea continua $R^1$, $R^2$, $R^{3a}$, $R^{3b}$, A, D, E y G son como ya se definieron, con una fuente adecuada de amoníaco, hidrazina o hidroxilamina (por ejemplo gas amoníaco, acetato de amonio, hidrazina, hidrazina monoclorhidrato, hidroxilamina o hidroxilamina clorhidrato) bajo condiciones conocidas por los expertos en el arte (por ejemplo condiciones tales como las descritas en *Tetrahedron Lett.* 40, 7067 (1999)), por ejemplo desde temperatura ambiente (por ejemplo 15 a 25°C) a temperatura elevada (por ejemplo 60°C a reflujo) en la presencia de un disolvente adecuado (por ejemplo etanol);

(d) para compuestos de fórmula I en la cual $R^{13a}$, $R^{13b}$ o $R^{13c}$ representa H, desprotección de un compuesto correspondiente de fórmula I en la cual $R^{13a}$, $R^{13b}$ o $R^{13c}$ (según sea apropiado) representa C(O)O-$CH_2$arilo (por ejemplo C(O)O-bencilo), por ejemplo bajo condiciones conocidas por los expertos en el arte (tal como hidrogenación en la presencia de un catalizador apropiado (por ejemplo Pt/C o, particularmente, Pd/C), un disolvente adecuado (por ejemplo un alcohol tal como etanol o, particularmente, metanol) y, opcionalmente, un ácido (por ejemplo HCl);

(e) para compuestos de fórmula I en la cual $R^{14c}$ representa H, desprotección de un compuesto correspondiente de fórmula I en la cual $R^{14c}$ representa

$C(O)O-C_{1-6}$ alquilo (por ejemplo C(O)O-*terc*-butilo), por ejemplo bajo condiciones conocidas por los expertos en el arte (por ejemplo acidólisis o hidrólisis de una base, tal como, para desprotección de compuestos en los cuales $R^{14c}$ representa C(O)O-*terc*-butilo, la reacción con gas HCl en la presencia de un disolvente apropiado (por ejemplo un alcohol tal como etanol o, particularmente, metanol), o la reacción con ácido trifluoroacético a temperatura por debajo de la ambiente (por ejemplo 0 a 4°C), opcionalmente en la presencia de un disolvente apropiado tal como DCM);

(f) reacción de un compuesto de fórmula VI,



VI

en donde la línea discontinua, $R^2$, $R^{3a}$, $R^{3b}$, A, D, E, G y L son como ya se definieron, con un compuesto de fórmula VII,

$$R^1\text{-}A\text{-}Lg^2 \qquad \text{VII}$$

en donde $Lg^2$ representa un grupo saliente adecuado (por ejemplo halo, trifluorometanosulfonato o OH) y $R^1$ y A son como ya se definieron, por ejemplo bajo condiciones conocidas por los expertos en el arte (tal como a temperatura por debajo de la ambiente (por ejemplo 0°C) en la presencia de una base apropiada (por ejemplo $K_2CO_3$ o piridina) y un disolvente apropiado (por ejemplo DCM));

(g) para compuestos de fórmula I en la cual A representa C(O)NH, la reacción de un compuesto de fórmula VI, como ya se definió, con un compuesto de fórmula VIII,

$$R^1\text{-}N{=}C{=}O \qquad \text{VIII}$$

en donde $R^1$ es como ya se definió, por ejemplo bajo condiciones conocidas por los expertos en el arte (tales como a temperatura ambiente (por ejemplo 15 a 25°C) en la presencia de un disolvente apropiado (por ejemplo DCM));

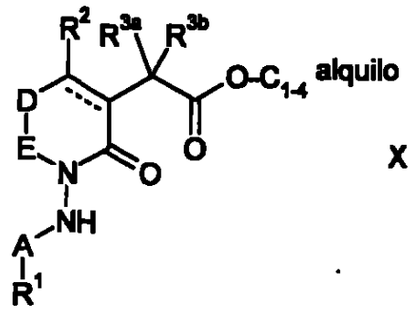
(h) para compuestos de fórmula I en la cual A representa $C_{1-6}$ alquileno, la reacción de un compuesto de fórmula VI, como ya se definió, con un compuesto de fórmula IX,

$R^1$-$C_{0-5}$ alquileno-CHO IX

en donde $R^1$ es como ya se definió, por ejemplo bajo condiciones conocidas por los expertos en el arte (tal como a reflujo, en la presencia de un disolvente apropiado (por ejemplo etanol), seguida por la reducción en la presencia de un agente reductor (por ejemplo $NaBH_3CN$), por ejemplo bajo condiciones conocidas por los expertos en el arte (por ejemplo a temperatura ambiente (tal como 15 a 25°C) en la presencia de un disolvente apropiado (tal como etanol); o

(i) para compuestos de fórmula I en la cual $R^a$, $R^b$, $R^c$ o $R^d$ representa -C(=NCN)$NH_2$, la reacción de un compuesto correspondiente de fórmula I en la cual $R^a$, $R^b$, $R^c$ o $R^d$, respectivamente, representa -C(-NH)$NH_2$ con bromuro de cianógeno, por ejemplo bajo condiciones conocidas por los expertos en el arte (por ejemplo en la presencia de una base adecuada (tal como un alcóxido de metal alcalino como etóxido de sodio) y un disolvente apropiado (tal como un alcohol alquílico inferior como etanol).

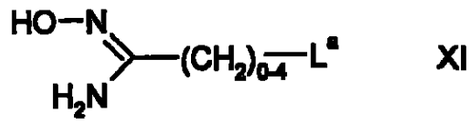
Compuestos de fórmula II pueden prepararse por hidrólisis de un compuesto de fórmula X,




X

en donde la línea discontinua, $R^1$, $R^2$, $R^{3a}$, $R^{3b}$, A, D y E son como ya se definieron, por ejemplo bajo condiciones conocidas por los expertos en el arte (por ejemplo por hidrólisis básica en la presencia de un hidróxido de metal alcalino (por ejemplo LiOH o, particularmente, NaOH) y un disolvente apropiado (por ejemplo agua, THF, metanol o su mezcla)).

Compuestos de fórmula IV pueden prepararse por el acoplamiento de un compuesto de fórmula II, como ya se definió, con un compuesto de fórmula XI,

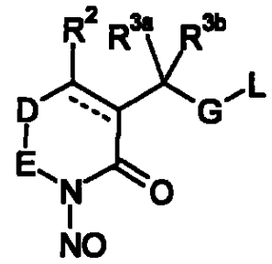


XI

en donde $L^a$ es como ya se definió, por ejemplo bajo condiciones bien conocidas por los expertos en el arte (por ejemplo los descritos en WO 01/79262, tal como a temperatura ambiente (por ejemplo 15 a 25°C) en la presencia de un agente acoplamiento (por ejemplo EDC) y un disolvente apropiado (por ejemplo DMF)).

Como observará el experto en el arte, en algunos casos, los compuestos de fórmula V son idénticos a ciertos compuestos de fórmula I (por ejemplo compuestos en los cuales $R^b$, $R^c$ o $R^d$ representa H y $R^{11a}$, $R^{11b}$ o $R^{11c}$, respectivamente, representa CN). A este respecto, los compuestos de fórmula V pueden prepararse por analogía con los procedimientos descritos aquí para la preparación de compuestos de fórmula I.

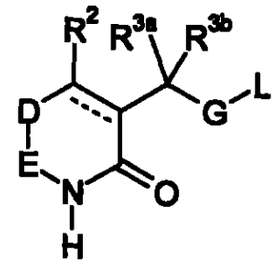
Compuestos de fórmula VI pueden prepararse mediante reducción de un compuesto de fórmula XII,



XII

en donde la línea discontinua, $R^2$, $R^{3a}$, $R^{3b}$, D, E, G y L son como ya se definieron, por ejemplo bajo condiciones que son bien conocidas por los expertos en el arte (tales como mediante reacción con metal zinc (por ejemplo polvo de zinc o polvo de hierro) en la presencia de un ácido apropiado (por ejemplo ácido acético o ácido clorhídrico) y opcionalmente en la presencia de un disolvente apropiado (por ejemplo metanol)).

Compuestos de fórmula VI pueden prepararse alternativamente por reacción de un compuesto de fórmula XIII,



XIII

en donde la línea discontinua, $R^2$, $R^{3a}$, $R^{3b}$, D, E, G y L son como se definen más arriba en el texto, con *O*-(difenilfosfinil)hidroxilamina, por ejemplo bajo condiciones conocidas por los expertos en el arte (verbigracia, a temperatura ambiente (tal como 15 a 25°C) en la presencia de una base apropiada (tal como $Cs_2CO_3$) y un disolvente apropiado (tal como DMF)).

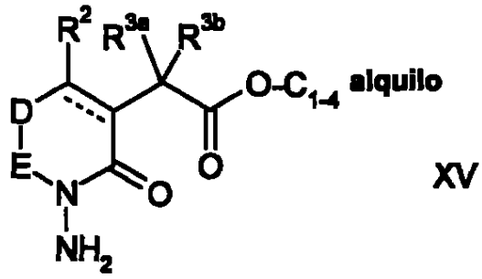
Compuestos de fórmula IX pueden prepararse por oxidación de un alcohol de fórmula XIV,

$R^1$-$C_{0-5}$ alquileno-$CH_2OH$ XIV

en donde $R^1$ es como ya se definió, por ejemplo bajo condiciones conocidas por los expertos en el arte, tales como reacción con PCC, cloruro de oxalilo

y DMSO (oxidación de Swern) o, particularmente, periodinano Dess-Martin en la presencia de un disolvente apropiado (tal como DCM).

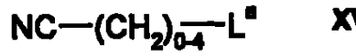
Compuestos de fórmula X pueden prepararse por reacción de un compuesto de fórmula XV,



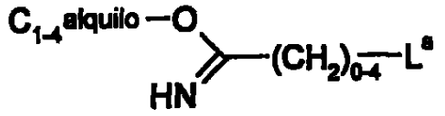

XV

en donde la línea discontinua $R^2$, $R^{3a}$, $R^{3b}$, D y E son como ya se definieron, con un compuesto de fórmula VII, VIII, o IX, como ya se definió, por ejemplo bajo condiciones conocidas por los expertos en el arte (por ejemplo bajo condiciones descritas en los pasos de proceso (f), (g) y (h) de arriba con respecto a compuestos de fórmula I).

Compuestos de fórmula XI pueden prepararse por métodos bien conocidos por los expertos en el arte. Por ejemplo, compuestos de fórmula XI pueden prepararse por reacción de un compuesto de fórmula XVI o XVII,




XVI




XVII

en donde $L^a$ es como ya se definió, con hidroxilamina o su sal de adición de ácido, por ejemplo bajo condiciones descritas en los pasos de proceso (c) de arriba con respecto a compuestos de fórmula I.

Compuestos de fórmula XII pueden prepararse por analogía con compuestos de fórmulas I y XIX.

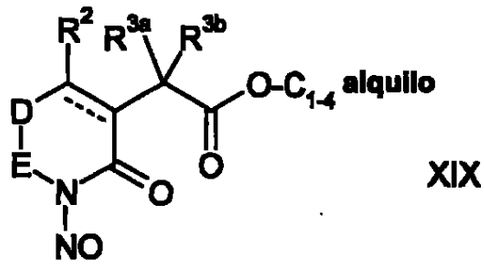
Compuestos de fórmula XIII pueden prepararse por analogía con compuestos de fórmulas I y XX.

Compuestos de fórmula XIV pueden prepararse por reducción de un ácido carboxílico de fórmula XVIII,

$R^1$-$C_{0-5}$ alquileno-C(O)OH XVIII

en donde $R^1$ es como ya se definió, por ejemplo bajo condiciones conocidas por los expertos en el arte, tales como reacción con LiAlH4 o, particularmente, borano en la presencia de un disolvente apropiado (tal como THF).

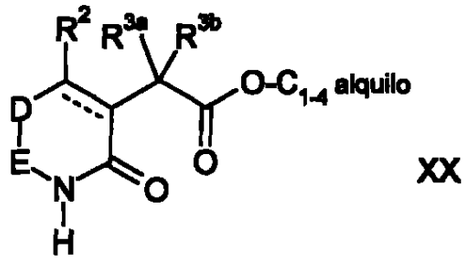
Compuestos de fórmula XV pueden prepararse por reducción de un compuesto de fórmula XIX,




XIX

en donde la línea discontinua, $R^2$, $R^{3a}$, $R^{3b}$, D y E son como ya se definieron, por ejemplo bajo condiciones ya descritas con respecto a la preparación de compuestos de fórmula VI.

Compuestos de fórmula XV pueden prepararse alternativamente por reacción de un compuesto de fórmula XX,

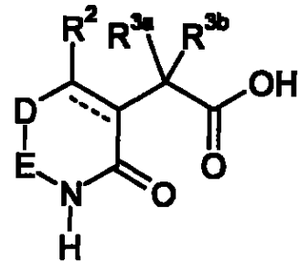



XX

en donde la línea discontinua, $R^2$, $R^{3a}$, $R^{3b}$, D y E son como se definen más arriba en el texto, con O-(difenilfosfinil)hidroxilamina, por ejemplo bajo condiciones descritas más arriba en el texto con respecto a la preparación de compuestos de fórmula VI.

Compuestos de fórmula XIX pueden prepararse por nitrosación de un compuesto correspondiente de fórmula XX, son como ya se definieron, por ejemplo bajo condiciones bien conocidas por los expertos en el arte, por ejemplo reacción con un agente nitrosante (tal como ácido nitroso, NOCl, $N_2O_3$, $N_2O_4$ o, particularmente, un nitrito de $C_{1-6}$ alquilo (por ejemplo *terc*-butilnitrito)) en la presencia de un disolvente apropiado (por ejemplo éter dietílico) y opcionalmente en la presencia de una base apropiada (por ejemplo piridina).

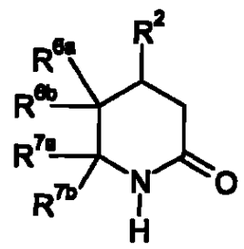
Compuestos de fórmula XX pueden prepararse por esterificación de un compuesto de fórmula XXI,



XXI

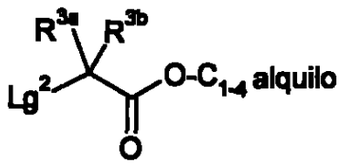
en donde $R^2$, $R^{3a}$, $R^{3b}$, D y E son como se definen más arriba en el texto, en la presencia de un alcohol $C_{1-4}$ alquílico, por ejemplo bajo condiciones conocidas por los expertos en el arte (verbigracia, por esterificación en la presencia de un ácido apropiado (verbigracia, HCl) y un disolvente apropiado (verbigracia, un alcohol $C_{1-4}$ alquílico (tal como metanol), agua, o su mezcla)).

Compuestos de fórmula XX en los cuales la línea discontinua está ausente pueden prepararse alternativamente por reacción de un compuesto de fórmula XXII,



XXII

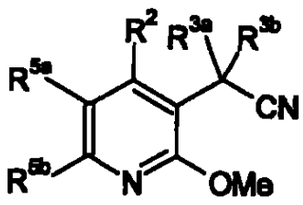
o su derivado protegido, en donde $R^2$, $R^{6a}$, $R^{6b}$, $R^{7a}$ y $R^{7b}$ son como se definen más arriba en el texto, con un compuesto de fórmula XXIII,



XXIII

en donde $Lg^2$ representa un grupo saliente apropiado (verbigracia, halo o $OS(O)_2R'$, en donde R' representa, por ejemplo, $C_{1-4}$ alquilo, $C_{1-4}$ perfluoroalquilo, fenilo, toluilo o bencilo) y $R^{3a}$ y $R^{3b}$ son como se definen más arriba en el texto, en la presencia de una base apropiada (verbigracia, un hidruro de metal o, particularmente, una amida de metal (tal como bis (trimetilsilil)amida de litio)), por ejemplo bajo condiciones conocidas por los expertos en el arte (verbigracia, a baja temperatura (tal como -78 a -10°C)) en la presencia de un disolvente apropiado (tal como THF)).

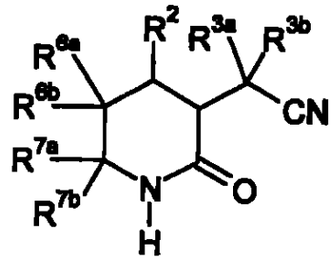
Compuestos de fórmula XXI en los cuales la línea discontinua representa un enlace pueden prepararse por hidrólisis de un compuesto de fórmula XXIV,



XXIV

en donde $R^2$, $R^{3a}$, $R^{3b}$, $R^{5a}$ y $R^{5b}$ son como se definen más arriba en el texto, por ejemplo bajo condiciones conocidas por los expertos en el arte (verbigracia, haciendo refluir en HBr concentrado).

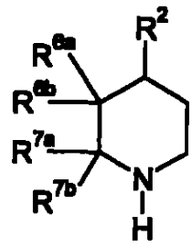
Compuestos de fórmula XXI en los cuales la línea discontinua está ausente pueden prepararse por hidrólisis de un compuesto de fórmula XXV



XXV

en donde $R^2$, $R^{3a}$, $R^{3b}$, $R^{6a}$, $R^{6b}$, $R^{7a}$ y $R^{7b}$ son como se definen más arriba en el texto, por ejemplo bajo condiciones conocidas por los expertos en el arte (verbigracia, aquellos ya mencionados en relación con compuestos de fórmula XXI en la cual la línea discontinua representa un enlace).

Compuestos de fórmula XXII pueden prepararse por oxidación de un compuesto de fórmula XXVI,



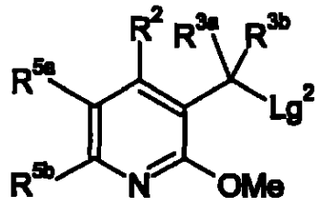
XXVI

o su derivado protegido, en donde $R^2$, $R^{6a}$, $R^{6b}$, $R^{7a}$ y $R^{7b}$ son como ya se definieron, con un agente oxidante adecuado (por ejemplo $H_2O_2$, $(PhIO)_n$, $Hg(OAc)_2$ o, particularmente, $RuO_4$, el cual último reactivo puede formarse *in situ* por oxidación de $RuO_2$ (por ejemplo por un exceso de $NaIO_4$)), por ejemplo bajo condiciones conocidas por los expertos en el arte (por ejemplo a temperatura ambiente (tal como 15 a 25°C) en la presencia de un disolvente apropiado (tal como acetato de etilo, agua o su mezcla)).

Como observará el experto en el arte, la conversión de compuestos de fórmula XXVI en los correspondientes compuestos de fórmula XX puede requerir, en cualquiera o todos los pasos de reacción, protección del grupo N-H del sistema de anillo de piperidona. Grupos protectores adecuados para este propósito incluyen benciloxicarbonilo y, particularmente, *terc*-

butiloxicarbonilo. El grupo protector puede introducirse y retirarse bajo condiciones que son bien conocidas por los expertos en el arte. El grupo protector puede introducirse convenientemente antes que el compuesto de fórmula XXVI se convierta en el compuesto de XXII (por ejemplo mediante reacción, bajo condiciones que son bien conocidas por los expertos en el arte, de un compuesto de XXVI con di-*terc*-butildicarbonato). Además, el grupo protector puede retirarse convenientemente, nuevamente bajo condiciones que son bien conocidas por los expertos en el arte (por ejemplo mediante reacción con ácido trifluoroacético), una vez se ha formado el compuesto de fórmula XX.

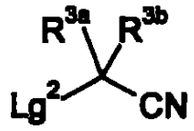
Compuestos de fórmula XXIV pueden prepararse por reacción de un compuesto de fórmula XXVII,



XXVII

en donde $R^2$, $R^{3a}$, $R^{3b}$, $R^{5a}$, $R^{5b}$ y $Lg^2$ son como se definen más arriba en el texto, con una fuente apropiada del ión cianuro (verbigracia, KCN), por ejemplo bajo condiciones que son conocidas por los expertos en el arte (verbigracia, a temperatura ambiente (tales como 15 a 25°C) en la presencia de un disolvente apropiado (tal como metanol)).

Compuestos de fórmula XXV pueden prepararse por reacción de un compuesto de fórmula XXII, como se definen más arriba en el texto, con un compuesto de fórmula XXVIII,

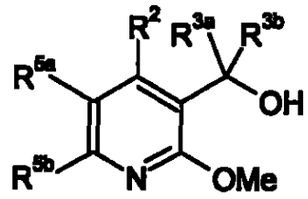


XXVIII

en donde $R^{3a}$, $R^{3b}$ y $Lg^2$ son como se definen más arriba en el texto, por ejemplo bajo condiciones conocidas por los expertos en el arte

(verbigracia, las condiciones ya descritas con respecto a la preparación de compuestos de fórmula XX).

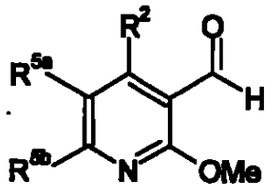
Compuestos de fórmula XXVII en la cual $Lg^2$ representa halo pueden prepararse por halogenación de un compuesto de fórmula XXIX,



XXIX

en donde $R^2$, $R^{3a}$, $R^{3b}$, $R^{5a}$ y $R^{5b}$ son como se definen más arriba en el texto, por ejemplo bajo condiciones que son conocidas por los expertos en el arte (verbigracia, por reacción con trifenilfosfina y una *N*-halosuccinimida (tal como NBS) en la presencia de un disolvente apropiado (tal como DCM)).

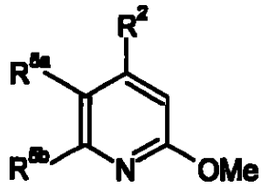
Compuestos de fórmula XXIX en la cual $R^{3a}$ y $R^{3b}$ ambos representan H pueden prepararse por reducción de un compuesto correspondiente de fórmula XXX,



XXX

en donde $R^2$, $R^{5a}$ y $R^{5b}$ son como se definen más arriba en el texto, por ejemplo bajo condiciones que son conocidas por los expertos en el arte (verbigracia, por reacción con borohidruro de sodio en la presencia de un disolvente apropiado (tal como metanol, THF o su mezcla)).

Compuestos de fórmula XXX pueden prepararse por formilación de un compuesto correspondiente de fórmula XXXI,



XXXI

en donde $R^2$, $R^{5a}$ y $R^{5b}$ son como se definen más arriba en el texto, por ejemplo bajo condiciones que son conocidas por los expertos en el arte (verbigracia, por reacción con una fuente apropiada del grupo formilo (tal como DMF) en la presencia de una base apropiada (tal como *terc*-butil litio o mesitil litio (el cual último reactivo puede formarse *in situ* por reacción entre *terc*-butil litio y bromomesitileno)).

Compuestos de fórmulas III, VII, VIII, XVI, XVII, XVIII, XXIII, XXVI, XXVIII y XXX se encuentran disponibles en el comercio, son conocidos en la literatura, o pueden obtenerse por analogía con los procesos descritos aquí, o mediante procedimientos sintéticos convencionales, de acuerdo con técnicas estándar, de materiales de partida fácilmente disponibles, usando reactivos y condiciones de reacción apropiadas. A este respecto, los compuestos descritos aquí puede obtenerse igualmente por analogía con procedimientos sintéticos descritos en documentos del arte previo mencionados más arriba (y WO 94/20467, WO 94/29336, WO 95/23609, WO 96/06832, WO 96/06849, WO 97/11693, WO 97/24135, WO 98/01422, WO 01/68605, WO 99/26920, WO 01/79155, WO 01/68605, WO96/18644, WO97/01338, WO97/30708, WO 98/16547, WO 99/26926, WO 00/73302, WO 01/04117, WO 01/79262, WO 02/064140, WO 02/057225, WO 03/29224, US 5,668,289, US 5,792,779 y WO 95/35313 en particular).

Sustituyentes en grupos alquilo, alquenilo, cicloalquilo, cicloalquenilo, arilo y heterocíclico en compuestos de fórmulas I, II, IV, V, VI, X, XII, XIII, XV, XIX, XX, XXI, XXII, XXIV, XXV, XXVI, XXVII, XXIX, XXX y XXXI pueden introducirse y/o convertirse entre sí usando técnicas bien conocidas por los expertos en el arte mediante interconversiones estándar de grupos funcionales, de acuerdo con técnicas estándar, a partir de materiales de partida disponibles fácilmente utilizando reactivos y condiciones de reacción apropiadas. Por ejemplo, hidroxi puede convertirse en alcoxi,

fenilo puede halogenarse para producir halofenilo, halo puede desplazarse por ciano, etc.

De igual manera el experto observará que diferentes interconversiones y transformaciones estándar de sustituyente o grupo funcional dentro de ciertos compuestos de fórmula I proporcionarán otros compuestos de fórmula I. Por ejemplo, hidroxiamidino puede reducirse a amidino.

Compuestos de fórmula I pueden aislarse de sus mezclas de reacción usando técnicas convencionales.

De acuerdo con la presente invención, derivados farmacéuticamente aceptables de compuestos de fórmula I incluyen asimismo derivados "protegidos", y/o compuestos que actúan como profármacos, de compuestos de fórmula I.

Compuestos que pueden actuar como profármacos de compuestos de fórmula I, que pueden mencionarse, incluyen compuestos de fórmula I en la cual $R^{13a}$, $R^{13b}$ o $R^{13c}$ es distinto de H o $R^{14c}$ representa C(O)O-$C_{1-6}$ alquilo, la parte alquilo de cuyo grupo se sustituye opcionalmente por arilo y/o uno o más átomos halo (por ejemplo compuestos en los cuales $R^{14c}$ representa C(O)O-*terc*-butilo).

Los compuestos de la invención pueden exhibir tautomerismo. Todas las formas tautoméricas y sus mezclas se incluyen en el ámbito de la invención. Formas tautoméricas particulares que pueden mencionarse incluyen aquellas conectadas con la posición del doble enlace en las funcionalidades amidina o guanidina que pueden representar los grupos $R^a$ a $R^d$.

De igual modo, compuestos de la invención pueden contener uno o más átomos de carbono asimétricos y, por lo tanto, pueden exhibir isomerismo óptico y/o diastereoisomerismo. Los diastereoisómeros pueden separarse

utilizando técnicas convencionales, por ejemplo cromatografía. Los diferentes estereoisómeros pueden aislarse por separación de una mezcla racémica u otra mezcla de los compuestos usando técnicas convencionales, por ejemplo HPLC. Alternativamente, los isómeros ópticos deseados pueden elaborarse por reacción de los materiales de partida apropiados, ópticamente activos, bajo condiciones que no causen racemización o epimerización, o por derivación, por ejemplo con un ácido homoquiral, seguida por separación de los derivados diastereoméricos por medios convencionales (por ejemplo HPLC, cromatografía sobre sílice). Todos los estereoisómeros están incluidos en el ámbito de la invención.

Se observará por los expertos en el arte que, en los procesos descritos más arriba y más adelante, los grupos funcionales de compuestos intermedios pueden necesitar que se los proteja por grupos protectores.

Grupos funcionales que es deseable proteger incluyen hidroxi, amino y ácido carboxílico. Grupos protectores adecuados para hidroxi incluyen grupos alquilo opcionalmente sustituidos y/o insaturados (por ejemplo metil, alilo, bencilo o *terc*-butilo), grupos trialquilsililo o diarilalquilsililo (por ejemplo *t*-butildimetilsililo, *t*-butildifenilsililo o trimetilsililo) y tetrahidropiranilo. Grupos protectores apropiados para ácido carboxílico incluyen ésteres $C_{1-6}$ alquílicos o bencílicos. Grupos protectores apropiados para amino y amidino incluyen *t*-butiloxicarbonilo, benciloxicarbonilo o 2-trimetilsililetoxicarbonilo (Teoc). Nitrógenos de amidino pueden protegerse igualmente por grupos hidroxi o alcoxi, y pueden ser mono- o di-protegidos.

La protección y desprotección de grupos funcionales puede tener lugar antes o después del acoplamiento, o antes o después de cualquier otra reacción en los esquemas mencionados más arriba.

Los grupos protectores pueden retirarse de acuerdo con técnicas que son bien conocidas por los expertos en el arte y como se describen a continuación.

Los expertos en el arte observarán que, con el fin de obtener compuestos de la invención en una manera alternativa y, en algunas ocasiones, más conveniente, los pasos individuales del proceso mencionados más arriba pueden realizarse en un orden diferente, y/o las reacciones individuales pueden efectuarse en una etapa diferente en la ruta general (es decir, pueden agregarse sustituyentes a, y/o llevarse a cabo transformaciones químicas sobre, intermedios diferentes a los mencionados más arriba en el texto en conjunción con una reacción particular). Esto puede anular, o hacer necesario, el requerimiento de los grupos protectores.

El tipo de química involucrada dictará la necesidad, y el tipo, de los grupos protectores, así como la secuencia para llevar a cabo la síntesis.

El uso de grupos protectores se describe completamente en "Protective Groups in Organic Chemistry", editado por J W F McOmie, Plenum Press (1973), y "Protective Groups in Organic Synthesis", 3ª edición, T.W. Greene & P.G.M. Wutz, Wiley-Interscience (1999).

Derivados protegidos de compuestos de la invención pueden convertirse químicamente en compuestos de la invención usando técnicas estándar de desprotección (por ejemplo hidrogenación). El experto observará igualmente que ciertos compuestos de fórmula I (por ejemplo compuestos en los cuales $R^{13a}$, $R^{13b}$ o $R^{13c}$ es distinto de H) pueden designarse asimismo como "derivados protegidos" de otros compuestos de fórmula I (por ejemplo aquellos en los cuales $R^{13a}$, $R^{13b}$ o $R^{13c}$ representa H).

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Los expertos en el arte se darán cuenta además que ciertos compuestos de fórmula I serán útiles como intermedios en la síntesis de algunos otros compuestos de fórmula I.

Algunos de los intermedios mencionados anteriormente son novedosos. Por consiguiente, de acuerdo con un aspecto adicional de la invención se provee: (a) un compuesto de fórmula II, o su derivado protegido; (b) un compuesto de fórmula IV, o su derivado protegido; (c) un compuesto de fórmula V, o su derivado protegido; (d) un compuesto de fórmula VI, o su derivado protegido; (e) un compuesto de fórmula X, o su derivado protegido; (f) un compuesto de fórmula XII, o su derivado protegido; (g) un compuesto de fórmula XV, o su derivado protegido; y (h) un compuesto de fórmula XIX, o su derivado protegido.

**Uso Médico y Farmacéutico**

Los compuestos de la invención pueden poseer actividad farmacológica como tales. No obstante, otros compuestos de la invención (incluidos compuestos de fórmula I en la cual $R^{13a}$, $R^{13b}$ o $R^{13c}$ es distinto de H o $R^{14c}$ representa C(O)O-*terc*-butilo) pueden no poseer tal actividad, pero pueden administrarse por vía parenteral u oral y, posteriormente, metabolizarse en el cuerpo para formar compuestos que sean farmacológicamente activos (incluidos, mas no limitados a, compuestos correspondientes de fórmula I en la cual $R^{13a}$, $R^{13b}$, $R^{13c}$ o $R^{14c}$ representa H). Tales compuestos (lo cual incluye además compuestos que pueden poseer alguna actividad farmacológica, pero esa actividad es apreciablemente menor que la de los compuestos "activos" en los cuales se metabolizan), pueden describirse por lo tanto como "profármacos" de los compuestos activos.

Por consiguiente, los compuestos de la invención son útiles porque poseen actividad farmacológica, y/o se metabolizan en el cuerpo luego de la administración oral o parenteral para formar compuestos que poseen

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actividad farmacológica. Por consiguiente, los compuestos de la invención son indicados como productos farmacéuticos.

Por lo tanto, de acuerdo con un aspecto de la invención, se proveen los compuestos de la invención para uso como productos farmacéuticos.

En particular, los compuestos de la invención son potentes inhibidores de trombina ya sea como tales y/o (por ejemplo en el caso de profármacos), se metabolizan luego de la administración para formar potentes inhibidores de trombina, por ejemplo como puede demostrarse en las pruebas descritas a continuación.

Por "profármaco de un inhibidor de trombina", incluimos compuestos que forman un inhibidor de trombina, en una cantidad experimentalmente detectable, y en un tiempo predeterminado (por ejemplo alrededor de 1 hora), luego de la administración oral o parenteral (véase, por ejemplo, Prueba E más adelante) o, alternativamente, luego de la incubación en la presencia de microsomas de hígado (véase, por ejemplo, Prueba F más adelante).

Por consiguiente, se espera que los compuestos de la invención sean útiles en aquellas condiciones donde es benéfica la inhibición de trombina (como se determina por referencia a un criterio de valoración clínicamente relevante (***"a clinically relevant end-point"***), por ejemplo afecciones tales como tromboembolias, donde se requiere o desea la inhibición de trombina, y/o enfermedades donde es indicada la terapia anticoagulante), incluidas las siguientes:

El tratamiento y/o profilaxis de trombosis e hipercoagulabilidad en la sangre y/o tejidos de animales, incluido el hombre. Se sabe que la hipercoagulabilidad puede llevar a enfermedades tromboembólicas. Trastornos asociados con hipercoagulabilidad y enfermedades

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tromboembólicas se designan usualmente enfermedades de trombofilia. Estas afecciones incluyen, pero no se limitan a, resistencia a proteína C activada, heredada o adquirida, tal como la mutación del factor V (factor V Leiden), insuficiencias heredadas o adquiridas en antitrombina III, proteína C, proteína S, cofactor II de heparina, y afecciones con niveles crecientes de plasma de los factores de coagulación tales como los causados por la mutación G20210A de protrombina. Otras afecciones conocidas por estar asociadas con hipercoagulabilidad y enfermedad tromboembólica incluyen anticuerpos antifosfolípidos en circulación (anticoagulante Lupus), homocisteinemia, trombocitopenia inducida por heparina y defectos en fibrinólisis, así como síndromes de coagulación (por ejemplo coagulación intravascular diseminada (DIC)) y lesión vascular en general (por ejemplo debida a trauma o cirugía). Más aún, una actividad física baja, gasto cardiaco bajo o edad elevada son conocidos por aumentar el riesgo de trombosis y la hipercoagulabilidad puede ser apenas uno de varios factores causantes del mayor riesgo. Estas enfermedades incluyen, pero no se limitan a, reposo en cama prolongado, viaje prolongado en avión, hospitalización por un trastorno médico agudo tal como insuficiencia cardiaca o insuficiencia respiratoria. Otras enfermedades con riesgo creciente de trombosis con hipercoagulabilidad como un componente son el embarazo y el tratamiento de hormonas (por ejemplo estrógeno).

El tratamiento de afecciones donde hay un exceso indeseable de trombina sin signos de hipercoagulabilidad, por ejemplo en enfermedades neurodegenerativas como enfermedad de Alzheimer.

Estados patológicos particulares que pueden mencionarse incluyen el tratamiento terapéutico y/o profiláctico de trombosis venosa (por ejemplo trombosis de vena profunda, DVT) y embolia pulmonar, trombosis arterial (por ejemplo en infarto del miocardio, angina inestable, apoplejía con base en trombosis o trombosis arterial periférica), y embolia sistémica usualmente de la aurícula durante la fibrilación auricular (por ejemplo fibrilación auricular valvular o no valvular) o del ventrículo izquierdo luego

de infarto del miocardio transparietal, o causada por insuficiencia cardiaca congestiva; la profilaxis de re-oclusión (es decir, trombosis) después de trombólisis, angioplastia trans-luminal percutánea (PTA) y operaciones de derivación coronaria; la prevención de trombosis después de una microcirugía y cirugía vascular en general.

Otras indicaciones incluyen el tratamiento terapéutico y/o profiláctico de coagulación intravascular diseminada, causada por bacterias, trauma múltiple, intoxicación o cualquier otro mecanismo; tratamiento anticoagulante cuando la sangre está en contacto con superficies extrañas en el cuerpo, tales como injertos vasculares, endoprótesis vasculares, catéteres vasculares, válvulas protésicas mecánicas y biológicas o cualquier otro dispositivo médico; tratamiento anticoagulante cuando la sangre está en contacto con dispositivos médicos fuera del cuerpo, tal como durante cirugía cardiovascular usando una máquina cardiovascular o en hemodiálisis; el tratamiento terapéutico y/o profiláctico de síndrome disneico agudo e idiopático en adulto, fibrosis pulmonar luego del tratamiento con radiación o quimioterapia, enfermedad pulmonar obstructiva crónica, choque septicémico, septicemia, respuestas inflamatorias, las cuales incluyen, pero no se limitan a, edema, arterioesclerosis aguda o crónica tal como arteriopatía coronaria y la formación de placas arterioescleróticas, insuficiencia cardiaca, arteriopatía cerebral, infarto cerebral, trombosis cerebral, embolia cerebral, arteriopatía periférica, isquemia, angina (incluida angina inestable), lesión por revascularización, restenosis luego de angioplastia trans-luminal percutánea (PTA) y cirugía de derivación arterial coronaria.

Los compuestos de la invención que inhiben tripsina y/o trombina pueden ser igualmente útiles en el tratamiento de pancreatitis.

Por consiguiente, los compuestos de la invención son indicados en el tratamiento terapéutico y/o profiláctico de estas afecciones.

De acuerdo con un aspecto adicional de la presente invención, se provee un método de tratamiento de una enfermedad es donde se requiere la inhibición de trombina, método que comprende la administración de una cantidad terapéuticamente efectiva de un compuesto de la invención a una persona que sufre de, o susceptible a, tal enfermedad.

Los compuestos de la invención se administrarán normalmente por vía oral, intravenosa, subcutánea, sub-lingual, rectal, dérmica, nasal, traqueal, bronquial, por cualquier otra vía parenteral o por inhalación, en la forma de preparaciones farmacéuticas que comprenden un compuesto de la invención como una base libre, o una sal de adición de ácido orgánico o inorgánico, no tóxico, farmacéuticamente aceptable, en una dosificación farmacéuticamente aceptable.

La vía preferida de administración de compuestos de la invención es la oral.

Dependiendo del trastorno y el paciente por tratar y la vía de administración, las composiciones pueden administrarse en dosis variables.

Los compuestos de la invención pueden combinarse igualmente y/o co-administrarse con cualquier agente(s) antitrombóticos con un mecanismo diferente de acción, tal como uno o más de los siguientes: los anticoagulantes heparina no fraccionaria, heparina de bajo peso molecular, otros derivados de heparina, derivados de heparina sintética (por ejemplo fondaparinux), antagonistas de vitamina K, inhibidores sintéticos o biotecnológicos de factores de coagulación distintos de trombina (por ejemplo inhibidores sintéticos de FXa, FVIIa y FIXa, y rNAPc2), los agentes antiplaquetarios ácido acetilsalicílico, ticlopidina y clopidogrel; receptor de tromboxano y/o inhibidores de sintetasa; antagonistas de receptor de fibrinógeno; miméticos de prostaciclina; inhibidores de fosfodiesterasa; antagonistas de receptor ADP ($P2X_1$, $P2Y_1$, $P2Y_{12}$ [$P_2T$]); e

inhibidores de carboxipeptidasa U (CPU o TAFIa) e inhibidores de inhibidor-1 de activador de plasminógeno (PAI-1).

Los compuestos de la invención pueden combinarse además y/o co-administrarse con trombolíticos tales como activador de plasminógeno tisular (natural, recombinante o modificado), estreptocinasa, urocinasa, prourocinasa, complejo activador de estreptocinasa-plasminógeno anisoilado (APSAC), activadores de plasminógeno de glándula salival animal, y similares, en el tratamiento de enfermedades trombóticas, en particular infarto del miocardio.

De acuerdo con un aspecto adicional de la invención se provee una formulación farmacéutica que incluye un compuesto de la invención, en mezcla con un coadyuvante, diluyente o excipiente farmacéuticamente aceptable.

Dosis diarias apropiadas de los compuestos de la invención en el tratamiento terapéutico de humanos son alrededor de 0.001-100 mg/kg de peso corporal en administración por vía oral y 0.001-50 mg/kg de peso corporal en administración parenteral.
Para evitar dudas, tal como se emplea aquí, el término "tratamiento" incluye tratamiento terapéutico y/o profiláctico.

Los compuestos de la invención tienen la ventaja de ser más eficaces, menos tóxicos, de acción más prolongada, poseer una gama más amplia de actividad, ser más selectivos (por ejemplo para inhibir trombina sobre otras serina proteasas, en particular tripsina y aquellas involucradas en hemostasis), ser más potentes, producir menores efectos secundarios, absorberse más fácilmente, y/o poseer un perfil farmacocinético mejor (por ejemplo una biodisponibilidad oral más alta y/o depuración más baja), que, y/o poseer otras propiedades farmacológicas, físicas o químicas útiles sobre, compuestos conocidos en el arte previo.

**Pruebas Biológicas**

Pueden emplearse los siguientes procedimientos de prueba.

Prueba A

Determinación del Tiempo de Coagulación de Trombina (TT)

La solución inhibidora (25 µL) se incuba con plasma (25 µL) por tres minutos. A continuación se agrega trombina humana (T 6769; Sigma Chem. Co. o Hematologic Technologies) en solución tampón, pH 7.4 (25 µL, 4.0 unidades NIH/mL), y se mide el tiempo de coagulación en un dispositivo automático (KC 10; Amelung).

El tiempo de coagulación de trombina (TT) se expresa como valores absolutos (segundos), así como la proporción de TT sin inhibidor ($TT_0$) a TT con inhibidor ($TT_i$). Las últimas proporciones (rango 1-0) se grafican contra la concentración de inhibidor (transformada logarítmicamente) y se ajustan a las curvas sigmoides de respuesta a la dosis de acuerdo con la ecuación

$$y = a/[1+(x/IC_{50})^s]$$

donde: a = rango máximo, es decir, 1; s = pendiente de la curva de respuesta a la dosis; y $IC_{50}$ = la concentración del inhibidor que dobla el tiempo de coagulación. Los cálculos se procesan en un PC usando el programa de software GraFit Versión 3, fijando la ecuación igual a: Inicio en 0, definir final en =1 (Erithacus Software, Robin Leatherbarrow, Imperial College of Science, London, UK).

Prueba B

Determinación de la Inhibición de Trombina con un Cromógeno, Análisis Robótico

La potencia del inhibidor de trombina se mide con un método de sustrato cromógeno, en un procesador robótico de microplacas Plato 3300 (Rosys AG, CH-8634 Hombrechtikon, Suiza), usando placas de microvaloración de volumen medio, con 96 pocillos (Costar, Cambridge, MA, USA; Cat No

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3690). Soluciones patrón concentradas (*"stock solutions"*) de la sustancia de prueba en DMSO (72 µL), 0.1 - 1 mmol/L, se diluyen serialmente 1:3 (24 + 48 µL) con DMSO para obtener diez concentraciones diferentes, que se analizan como muestras en el estudio. 2 µL de la muestra de prueba se diluyen con 124 µL de tampón de análisis, se agregan 12 µL de solución de sustrato cromógeno (S-2366, Cromogenix, Mölndal, Suecia) en tampón de análisis y finalmente 12 µL de solución de α-trombina (α-trombina humana, Sigma Chemical Co. o Hematologic Technologies) en tampón de análisis, y se mezclan las muestras. Las concentraciones del análisis final son: sustancia de prueba 0.00068-133 µmol/L, S-2366 0.30mmol/L, α-trombina 0.020 NIHU/mL. El incremento de la absorbencia lineal durante 40 minutos de incubación a 37°C se usa para el cálculo de la inhibición porcentual de las muestras de prueba, comparadas con blancos sin inhibidor. El valor robótico $IC_{50}$, correspondiente a la concentración del inhibidor que causa una inhibición del 50% de la actividad de la trombina, se calcula de una concentración logarítmica vs. curva de % de inhibición.

Prueba C

Determinación de la Constante de Inhibición $K_i$ para Trombina Humana

Las determinaciones de $K_i$ se hacen usando un método de sustrato cromógeno, realizado a 37°C en un analizador centrífugo Cobas Bio (Roche, Basilea, Suiza). La actividad enzimática residual luego de la incubación de α-trombina humana con varias concentraciones de compuesto de prueba se determina en tres concentraciones diferentes de sustrato, y se mide como la variación en la absorbencia óptica a 405 nm.

Soluciones del compuesto de prueba (100 µL; normalmente en tampón o solución salina que contenía BSA 10 g/L) se mezclan con 200 µL de α-trombina humana (Sigma Chemical Co) en tampón de análisis (0.05 mol/L Tris-Cl pH 7.4, concentración iónica 0.15 ajustada con NaCl) que contenía BSA (10 g/L), y se analizan como muestras en el Cobas Bio. Una muestra de 60 µL, junto con 20 µL de agua, se agrega a 320 µL del sustrato S-2238

(Cromogenix AB, Mölndal, Suecia) en tampón de análisis, y se monitorea la variación de absorbencia (ΔA/min). Las concentraciones finales de S-2238 son 16, 24 y 50 µmol/L y de la trombina 0.125 NIHU/mL.

La tasa de reacción de estado de equilibrio se usa para construir gráficos Dixon, es decir, diagramas de concentración de inhibidor vs. 1/(ΔA/min). Para inhibidores competitivos, reversibles, los puntos de los datos para las diferentes concentraciones de sustrato forman típicamente líneas rectas que se interceptan en $x = -K_i$.

Prueba D

Determinación del Tiempo de Tromboplastina Parcial Activada (APTT)

APTT se determina en plasma citrado humano normal, mezclado con el reactivo PTT Automated 5 fabricado por Stago. Los inhibidores se agregan al plasma (10 µL solución inhibidora a 90 µL plasma) y se incuban con el reactivo APTT durante 3 minutos seguido por la adición de 100 µL de solución de cloruro de calcio (0.025 M), y el APTT se determina por el uso del analizador de coagulación KC10 (Amelung) de acuerdo con las instrucciones del productor del reactivo.

El tiempo de coagulación se expresa como valores absolutos (segundos), así como la proporción de APTT sin inhibidor ($APTT_0$) a APTT con inhibidor ($APTT_i$). Las últimas proporciones (rango 1-0) se grafican contra la concentración de inhibidor (transformada logarítmicamente) y se ajustan a las curvas sigmoides de respuesta a la dosis de acuerdo con la ecuación.

$$y = a/[1+ (x/IC_{50})^s]$$

donde: a = rango máximo, es decir, 1; s = pendiente de la curva de respuesta a la dosis; y $IC_{50}$ = la concentración del inhibidor que dobla el tiempo de coagulación. Los cálculos se procesan en un PC usando el programa de software GraFit Versión 3, fijando la ecuación igual a: Inicio en 0, definir final en =1 (Erithacus Software, Robin Leatherbarrow, Imperial College of Science, London, UK). $IC_{50}$APTT se define como la concentración de

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inhibidor en plasma humana que doblaba el Tiempo de Tromboplastina Parcial Activada.

Prueba E

Determinación de la Depuración del Plasma y Biodisponibilidad Oral en Rata

La depuración del plasma y la biodisponibilidad oral se calculan en ratas hembra Sprague Dawley. El compuesto se disuelve en agua u otro vehículo apropiado. Para la determinación de la depuración del plasma el compuesto se administra como una inyección rápida subcutánea (sc) o intravenosa (iv) en una dosis de 1-4 μmol/kg. Se recogen muestras de sangre en intervalos frecuentes hasta 24 horas luego de la administración del medicamento. Para cálculos de biodisponibilidad, el compuesto se administra oralmente a 10 μmol/kg vía sonda gástrica y se recogen muestras de sangre frecuentemente hasta 24 horas luego de la dosificación. Se recogen las muestras de sangre en tubos heparinizados y se centrifugan en un período de 30 minutos, con el fin de separar el plasma de las células sanguíneas. El plasma se transfiere a frasquitos plásticos con tapas roscadas y se almacenan a -20°C hasta el análisis. Antes del análisis, el plasma se descongela y 50 μL de muestras de plasma se precipitan con 150 μL de acetonitrilo frío. Las muestras se centrifugan durante 20 minutos a 4000 rpm. Se diluyen 75 μL del sobrenadante con 75 μL de 0.2% ácido fórmico. Se analizan volúmenes de 10 μL de las soluciones resultantes por LC-MS/MS y se determinan las concentraciones de inhibidor de trombina usando curvas estándar. Todos los cálculos farmacocinéticos se realizan con el programa de computador WinNonlinTMProfessional (Pharsight Corporation, California, USA), o un programa equivalente. El área bajo la curva de los perfiles de concentración del plasma-tiempo (AUC) se calcula usando la regla trapezoidal logarítmica/lineal y se extrapola al tiempo infinito. La depuración del plasma (CL) del compuesto se determina entonces como

$$CL=\text{Dosis (iv/sc)}/\text{AUC (iv/sc)}.$$

La biodisponibilidad oral se calcula como

$$F = CL \times AUC\ (po) / Dosis\ (po).$$

La depuración del plasma se da como mL/min/kg y la biodisponibilidad oral como porcentaje (%).

Prueba F

Determinación de la Estabilidad *in vitro*

Se preparan microsomas de hígado de ratas Sprague-Dawley y muestras de hígado humano de acuerdo con SOPs internos. Los compuestos se incuban a 37°C con una concentración toral de proteína microsomal de 0.5 mg/mL en un tampón de fosfato de potasio 0.1 mol/L a pH 7.4, en la presencia del cofactor, NADPH (1.0 mmol/L). La concentración inicial del compuesto es 1.0 µmol/L. Las muestras se toman para análisis en 5 puntos de tiempo, 0, 7, 15, 20 y 30 minutos luego del inicio de la incubación. La actividad enzimática en la muestra recogida se detiene inmediatamente agregando un volumen igual de acetonitrilo que contiene 0.8% de ácido fórmico. La concentración de compuesto restante en cada una de las muestras recogidas se determina por medio de LC- MS/MS. La constante de velocidad de eliminación (k) del inhibidor de trombina se calcula como la pendiente del gráfico de ln[inhibidor de trombina] contra el tiempo de incubación (minutos). La constante de la velocidad de eliminación se usa entonces para calcular la semi-vida ($T_{1/2}$) del inhibidor de trombina, la cual se usa posteriormente para calcular la depuración intrínseca (CLint)del inhibidor de trombina en microsomas del hígado como:

$$CLint\ (en\ \mu l/min/mg) = \frac{(\ln 2 \times volumen\ de\ incubación)}{(T_{1/2} \times concentración\ de\ proteína)}$$

Prueba G

Modelo de Trombosis Venosa

Los estímulos trombógenos son daño a los vasos y estasis del flujo sanguíneo. Se anestesian las ratas y se les abre el abdomen. Se obtiene una oclusión parcial de la vena cava, caudal a la vena renal izquierda, con un

lazo alrededor de la vena y una cánula, la cual se retira luego. Un papel filtrante empapado en $FeCl_3$ se pone sobre la superficie externa de la parte distal de la vena cava. Se llena el abdomen con solución salina y se cierra. Al final del experimento se sacrifica la rata, se extirpa la vena cava, se recoge el trombo y se determina su peso húmedo.

Detalles Experimentales Generales

Donde se indica HPLC preparativa, se usó un Sistema de Purificación Waters Fraction Lynx con una columna ACE C8 5 µm 21x100 mm o un Sistema HPLC Gilson con una columna kromasil C8 10 µm 21.2x250 mm. La fase móvil utilizada con el sistema Waters fue una gradiente que se iniciaba con 5% acetonitrilo hasta 100% en 100 mM de tampón de acetato de amonio. La fase móvil usada con el sistema Gilson fue una gradiente que se iniciaba con 0% acetonitrilo hasta 95% en 100 mM tampón de acetato de amonio. El caudal fue de 25 mL/minuto.
Con el sistema Waters, se utilizó recolección de fracciones desencadenada por MS. Con el sistema HPLC Gilson, se usó recolección de fracciones desencadenada por UV.

Los espectros de masa se registraron en un Micromass ZQ single quadrupole o un Micromass quattro micro, ambos equipados con una interface de electropulverización asistida neumáticamente (LC-MS).

**Reactivos**

Los siguientes listados de reactivos se utilizaron en las Preparaciones y Ejemplos siguientes. Salvo que se indique lo contrario, cada uno de estos reactivos se encuentran disponibles en el comercio.

Listado 1

(a) Cloruro de fenilmetanosulfonilo

(b) Cloruro de bencenosulfonilo

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(c) Cloruro de 4-metoxibencenosulfonilo

(d) Cloruro de 2-metoxi-4-metilbencenosulfonilo

(e) Cloruro de 3,4-diclorobencenosulfonilo

(f) Cloruro de 3-metoxibencenosulfonilo

(g) Cloruro de 2,5-dimetilbencenosulfonilo

(h) Cloruro de naftaleno-1-sulfonilo

(i) Cloruro de 2,4-dimetoxibencenosulfonilo

(j) Cloruro de (4-clorofenil)metanosulfonilo

(k) Cloruro de 4-etilbencenosulfonilo

(l) Cloruro de 2,5-dimetiltiofen-3-sulfonilo

(m) Cloruro de 2,5-diclorobencenosulfonilo

(*n*) Cloruro de 2-cloro-6-metilbencenosulfonilo

(o) Cloruro de 4-cloro-2-fluorobencenosulfonilo

Listado 2

(a) Ácido fenilacético

(b) Ácido *o*-tolilacético

(c) Ácido (2,5-dimetilfenil)acético

(d) Ácido (5-fluoro-2-metilfenil)acético

(e) Ácido (3-trifluorometilfenil)acético

(f) Ácido (5-cloro-2-fluorofenil)acético

Listado 3

(a) Benzaldehído

(b) 3-Metoxibenzaldehído

(c) 3-Piridincarboxaldehído

(d) 2-Metoxinicotinaldehído

(obtenible como se describe en *J. Org. Chem.* 55, 69 (1990))

Listado 4

(a) Isobutiraldehído

(b) 1-Fenil-1H-pirazol-5-carbaldehído

(c) 2,5-Dimetil-1-(4H-1,2,4-triazol-4-il)-1H-pirrol-3-carbaldehído

(d) 4-Benzoil-1-metil-1H-pirrol-2-carbaldehído

(e) 2,3-Dihidrobenzo[b]furan-5-carboxaldehído

(f) 2,4-Dimetil-1,3-tiazol-5-carbaldehído

(g) 1,5-Dimetil-1H-pirazol-4-carbaldehído

(h) 1-(Fenilsulfonil)-1H-pirrol-2-carbaldehído

(i) 3,5-Dimetil-4-isoxazolcarbaldehído

(j) 5-Cloro-2-fenil-3H-imidazol-4-carbaldehído

(k) 1,3-Dihidro-2,1,3-benzoxadiazol-5-carbaldehído

(l) 2-Pirazincarboxaldehído

(m) Ciclopentancarboxaldehído

(n) 5-Piridin-2-iltiofen-2-carbaldehído

(o) 5-Cloro-1,3-dimetil-1H-pirazol-4-carbaldehído

(p) 6-Cloropiperonal

(q) 1-Metil-1H-imidazol-2-carbaldehído

(r) Ciclohexancarboxaldehído

(s) 4-Metil-3,4-dihidro-2H-1,4-benzoxazin-7-carbaldehído

(t) 4-Cianobenzaldehído

(u) 2-Fenoxibenzaldehído

(v) 1 -Etil-3-metil-1H-pirazol-4-carbaldehído

(w) 5-Metilimidazol-4-carboxaldehído

(x) 5-Cloro-1-metil-3-fenil-1H-pirazol-4-carbaldehído

(y) 2-Morfolin-4-il-piridin-3-carbaldehído

(z) 3,3-Dimetilbutiraldehído

(aa) 5-Cloro-2-tiofencarboxaldehído

(ab) 2-Fluoro-5-formilbenzonitrilo

(ac) 5-Metil-3-fenil-4-isoxazolcarbaldehído

(ad) 3-(Trifluorometoxi)benzaldehído

(ae) 5-Cloro-2-fluorobenzaldehído

(af) 2-Metil-1H-imidazol-5-carbaldehído

(ag) 2-Fluoro-5-metoxibenzaldehído

(ah) 2-Morfolinobenzaldehído

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(ai) 1,3-Dimetil-5-morfolino-1H-pirazol-4-carbaldehído

(aj) 8-Quinolincarbaldehído

(ak) 5-(2-Tienil)-3-isoxazolcarbaldehído

(al) 2-Fenilpropionaldehído

(am) Biciclo[2.2.1]hept-5-en-2-carbaldehído

(an) 3-[(2-Cloro-1,3-tiazol-5-il)metoxi]benzencarbaldehído

(ao) 3-Metil-5-fenil-4-isoxazolcarbaldehído

(ap) 1,3-Dimetil-5-morfolin-4-il-1H-pirazol-4-carbaldehído

Listado 5

(a) éster bencílico de ácido [(4-aminometilfenil)iminometil]carbámico
(obtenible como se describe en WO 94/29336)

(b) *terc*-butiléster de ácido (5-aminometil-6-metilpiridin-2-il)carbámico
(obtenible como se describe en WO 97/01338)

(c) *terc*-butiléster de ácido (4-aminometilpiridin-2-il)carbámico
(obtenible como se describe en Preparación 3 más adelante)

(d) *terc*-butiléster de ácido (4-bromometilpiridin-2-il)carbámico
(obtenible como se describe en WO 00/66557)

(e) *C*-(3-Fluoro-4-metilpiridin-2-il)metilamina
(obtenible como se describe en WO 00/075134)

(f) *terc*-butiléster de ácido (5-aminometilpiridin-2-il)carbámico
(obtenible como se describe en WO 97/01338)

(g) *terc*-butiléster de ácido (2-aminometil-4-clorobencil)carbámico
(obtenible como se describe en WO 02/050056)

(h) [N,N'-Di-(*terc*-butoxicarbonil)]-2-aminoetoxiguanidina
(obtenible como se describe en. WO 99/55355)

(i) *terc*-butiléster de ácido (5-aminometil-6-metilpiridin-2-il)carbámico
(obtenible como se describe en WO 97/01338)

(j) *terc*-Butil[5-(aminometil)-4,6-dimetilpiridin-2-il]carbamato (obtenible como se describe en WO 97/01338)

(k) [2-(1*H*-Tetrazol-1-il)bencil]amina
(obtenible como se describe en WO 02/064211)

(l) 5-(Aminometil)-3,6-dimetilpiridin-2-amina

(obtenible como se describe en WO 99/11267)

(m) *terc*-Butil [2-(aminometil)bencil]carbamato

(obtenible como se describe en WO 02/057225)

(n) [5-Cloro-2-(1*H*-tetrazol-1-il)bencil]amina

(obtenible como se describe en WO 02/064559)

(o) 2-[2-(Aminometil)-4-clorofenoxi]-*N*-etilacetamida

(obtenible como se describe en WO97/30708)

(p) *terc*-Butil {2-[2-(aminometil)-4-clorofenil]etil}carbamato

(obtenible como se describe en *Bioorg. Med. Chem. Lett.*, 13, 34773 (2003))

(q) *terc*-Butil [2-(aminometil)-4-fluorobencil]carbamato

(obtenible como se describe en preparación 6 más adelante)

(r) *terc*-Butil [2-(aminometil)-4-metoxibencil]carbamato

(obtenible como se describe en preparación 7 más adelante)

(s) *terc*-Butil [2-(aminometil)-4-metilbencil]carbamato

(obtenible como se describe en preparación 8 más adelante)

(t) *terc*-Butil [2-(aminometil)-4-(trifluorometil)bencil]carbamato

(obtenible como se describe en preparación 6 más adelante)

**Preparaciones**

Preparación 1

Metil éster de ácido (1-amino-4-metil-2-oxo-1,2-dihidropiridin-3-il)acético

(a) 2-Metoxi-4-metil-piridin-3-carbaldehído

El compuesto del subtítulo se preparó de 2-metoxipiridina de acuerdo con los procedimientos descritos en *J. Org. Chem.* 55, 69 (1990) y *Tetrahedron Lett.* 29, 773 (1988).

(b) (2-Metoxi-4-metil-piridin-3-il)metanol

Borohidruro de sodio (540 mg, 14.2 mmol) se agregó a una solución de 2-metoxi-4-metilpiridin-3-carbaldehído (1.8 g, 12.9 mmol; véase paso (a) más arriba) en una mezcla de THF y metanol (30 mL, 1:1) a 0°C. La mezcla de reacción se agitó a temperatura de la sala durante 2 horas. Se agregó agua (10 mL), y la capa acuosa se extrajo con acetato de etilo (3 x 25mL). Las capas orgánicas combinadas se secaron ($Na_2SO_4$), se filtraron, y el disolvente se evaporó bajo presión reducida. El residuo se purificó por cromatografía de destello ($SiO_2$, 40% acetato de etilo en hexano) para producir el compuesto del subtítulo (1.68 g, 85%) como un aceite incoloro.
$^1$H NMR (400 MHz, $CDCl_3$) δ 2.17 (s, 3H), 3.68 (br s, 1H), 3.72 (s, 3H), 4.49 (s, 2H), 6.53 (d, 1H), 7.72 (d, 1H)

(c) 3-Bromometil-2-metoxi-4-metilpiridina

Trifenilfosfina (2.35 g, 13.2 mmol) y *N*-bromosuccinimida (3.46 g, 13.2 mmol) se agregaron a una solución de (2-metoxi-4-metilpiridin-3-il)-metanol (1.35 g, 8.81 mmol; véase paso (b) más arriba) en DCM (40 mL) a 0°C. La mezcla de reacción se agitó a temperatura de la sala durante 5 horas. Se agregó agua (20mL), las capas se separaron y la capa acuosa se extrajo con DCM (3 x 20 mL). Las capas orgánicas combinadas se secaron ($Na_2SO_4$), se filtraron, y el disolvente se evaporó bajo presión reducida. La purificación por cromatografía de destello ($SiO_2$, 10% acetato de etilo en hexano) produjo el compuesto del subtítulo (1.43 g, 75%) como un aceite incoloro.
$^1$H NMR (400 MHz, $CDCl_3$) δ 2.38 (s, 3H), 4.00 (s, 3H), 4.58 (s, 2H), 6.74 (d, 1H), 7.98 (d, 1H)

(d) (2-Metoxi-4-metilpiridin-3-il)acetonitrilo

Cianuro de potasio (633 mg, 9.70 mmol) se agregó a una solución de 3-bromometil-2-metoxi-4-metilpiridina (1.40 g, 6.48 mmol; véase paso (c) más arriba) en metanol (40 mL), y la solución se agitó durante 12 horas a temperatura de la sala. El disolvente se evaporó bajo presión reducida y el residuo se repartió en porciones entre una solución de $NaHCO_3$ (saturado,

10 mL) y acetato de etilo. La capa acuosa se extrajo con acetato de etilo (3 x 25 mL). Las capas orgánicas combinadas se secaron ($Na_2SO_4$), se filtraron, y el disolvente se evaporó bajo presión reducida. La purificación por cromatografía de destello ($SiO_2$, 25% acetato de etilo en hexano) produjo el compuesto del subtítulo (0.95 g, 90%) como un aceite incoloro.
$^1$H NMR (400 MHz, $CDCl_3$) δ 2.35 (s, 3H), 3.65 (s, 2H), 3.96 (s, 3H), 6.73 (d, 1H), 7.99 (d, 1H)

(e) Metil éster de ácido (4-metil-2-oxo-1,2-dihidropiridin-3-il)acético
(2-Metoxi-4-metilpiridin-3-il)acetonitrilo (825 mg, 5.09 mmol; véase paso (d) más arriba) se disolvió en HBr (37%, 10mL) y la solución se calentó a 100°C durante 5 horas y se agitó aún más a temperatura de la sala durante 24 horas. El disolvente se evaporó bajo presión reducida, y el ácido carboxílico resultante se usó directamente en el siguiente paso.
HCl (concentrado, 3 mL) se agregó a una solución del ácido crudo (9.13 g, 50 mmol) en metanol (120mL), y la mezcla de reacción se agitó durante 10 horas a temperatura de la sala. La mezcla de reacción se concentró entonces por evaporación bajo presión reducida, y el residuo se disolvió en DCM y se lavó con $NaHCO_3$. La capa orgánica se secó ($Na_2SO_4$), se filtró, y el disolvente se evaporó para producir el compuesto del subtítulo (8.9 g, 97%).
$^1$H NMR (400MHz, $CD_3OD$) δ 2.12 (s, 3H), 3.56 (s, 2H), 3.60 (s, 3H), 6.07 (d, 1H), 7.15 (d, 1H)

(f) Metil éster de ácido (1-amino-4-metil-2-oxo-1,2-dihidropiridin-3-il)acético
Carbonato de cesio (1.6 g, 11.6 mmol) y *O*-(difenilfosfinil)-hidroxilamina (1.54 g, 6.62 mmol; véase Synthesis 592 (1988) y *Tetrahedron Lett.* 23, 3835 (1982)) se agregaron a una solución de metil éster de ácido (4-metil-2-oxo-1,2-dihidropiridin-3-il)acético (0.60 g, 3.31 mmol; véase paso (e) más arriba) en DMF (10 mL). La suspensión se agitó a temperatura de la sala durante 18 horas, se filtró, y el disolvente se evaporó bajo presión reducida.

La purificación por cromatografía de destello (3% metanol en acetato de etilo) produjo el compuesto del título (380 mg, 60%) como un aceite amarillo.

$^1$H NMR (400 MHz, $CD_3OD$) δ 2.09 (s, 3H), 3.57 (s, 2H), 3.61 (s, 3H), 5.05 (br d, 2H), 5.96 (d, 1H), 7.37 (d, 1H)

Preparación 2

Los compuestos (i) a (viii) listados a continuación se prepararon del compuesto del título de Preparación 1 por el siguiente Método General A.

Los compuestos (ix) a (xiv) listados a continuación se prepararon del compuesto del título de Preparación 1 por el siguiente Método General B.

A menos que se indique otra cosa, los compuestos (xv) a (xviii) listados a continuación se prepararon del compuesto del título de Preparación 1 por el siguiente Método General C.

Método General A

El cloruro de sulfonilo específico (0.61 mmol, 1.2 mol equiv.; ver Lista 1 más arriba) y piridina (125 μL, 120 mg, 1.53 mmol) se agregaron a una solución de metil éster de ácido (1-amino-4-metil-2-oxo-1,2-dihidropiridin-3-il)acético (100 mg, 0.51 mmol; ver Preparación 1 más arriba) en DCM (4 mL) a 0°C. La mezcla de reacción se agitó a temperatura de la sala durante 12 horas. La piridina y el disolvente se evaporaron bajo presión reducida. La purificación por cromatografía de destello ($SiO_2$, 50-70% acetato de etilo en hexano) produjo las sulfonamidas listadas en (i) a (viii) más adelante (62-92%).

Método General B

Paso (i)

Un complejo borano tetrahidrofurano (1 M solución, 1.5 eq) se agregó a una solución agitada del ácido específico (1.0 eq; ver Lista 2 más arriba) en THF (0.2 M) a 0°C. La solución se calentó a temperatura de la sala durante

1 hora, y la agitación se continuó durante otra hora. Se agregó cuidadosamente agua a 0°C y la mezcla se extrajo con acetato de etilo. Las fases orgánicas se combinaron, se secaron, y el disolvente se retiró bajo presión reducida para proporcionar el producto reducido. El alcohol crudo se usó sin purificación posterior. El alcohol se disolvió en DCM (0.2 M) y se agregó periodinano Dess-Martin (1.5 eq) a la solución. La suspensión resultante se agitó hasta su conclusión (desde 0.5 hora hasta la mañana). Se agregó hexano a la mezcla, y la suspensión resultante se filtró a través de una almohadilla de Celita®/gel de sílcie. La almohadilla de lavó con una solución de 30% acetato de etilo en hexano. Los disolventes se retiraron bajo presión reducida para producir el correspondiente aldehído, el cual se utilizó en paso (ii) sin purificación posterior.

Paso (ii)

El aldehído específico (0.50 mmol; véase paso (i) más arriba) se agregó a metil éster de ácido (1-amino-4-metil-2-oxo-1,2-dihidropiridin-3-il)acético (76 mg, 0.39 mmol; ver Preparación 1 más arriba) en etanol anhidro (1.5 mL), y la mezcla de reacción se calentó a reflujo durante 12 horas. La mezcla se devolvió a temperatura de la sala, y se agregó $NaBH_3CN$ (49 mg, 0.77 mmol) y la agitación se continuó durante 4 horas. Se agregó HCl (10%) y, luego de agitar durante 10 minutos, el pH se neutralizó con $NaHCO_3$ (saturado). La mezcla se extrajo con acetato de etilo (3x10mL). Las capas orgánicas combinadas se lavaron con salmuera, se secaron ($Na_2SO_4$), se filtraron, y el disolvente se evaporó bajo presión reducida. La purificación directamente luego del desarrollo por cromatografía de destello ($SiO_2$, 45% acetato de etilo en hexano) proporcionó los productos de aminación reductora listados en (ix) a (xiv) más adelante (45-69%).

Método General C

El aldehído específico (0.52 mmol; ver Lista 3 más arriba) disuelto en metanol (1.5 mL) se agregó a metil éster de ácido (1-amino-4-metil-2-oxo-1,2-dihidropiridin-3-il)-acético (100 mg, 0.48 mmol; ver Preparación 1 más

arriba) en metanol (1.5 mL). Se agregaron cianoborohidruro de sodio (63 mg, 2. 85 mmol) y cloruro de zinc (195 mg, 1.43 mmol), y la mezcla de reacción se agitó a temperatura de la sala un día para otro. Se agregó otra porción de cianoborohidruro de sodio (90 mg, 1.43 mmol) y ácido acético (10 goticas), y la agitación se continuó durante otras 3 horas. Se agregó hidróxido de sodio (2 M), y la mezcla se extrajo con DCM (3x10 mL). Las capas orgánicas combinadas se secaron a través de un separador de fase, y el disolvente se evaporó bajo presión reducida. La purificación por cromatografía de destello ($SiO_2$, acetato de etilo: hexano, 1:2) proporcionó los productos listados en (xv) a (xviii) más adelante.

(i) Metil éster de ácido (4-metil-2-oxo-1-fenilmetanesulfonilamino-1,2-dihidro-piridin-3- il)acético
$^1$H NMR (400 MHz, $CDCl_3$) δ 2.22 (3H, s), 3.67 (5H, s), 4.35 (2H,s), 6.15 (1H, d), 7.28-7.44 (6H, m), 9.26 (1H, br)

(ii) Metil éster de ácido (1-bencensulfonilamino-4-metil-2-oxo-1,2-dihidropiridin-3-il)-acético
$^1$H NMR (400 MHz, $CDCl_3$) δ 2.17 (3H, s), 3.37 (2H, s), 3.60 (3H, s), 6.16 (1H, d), 7.41-7.63 (6H, m), 9.07 (1H, b)

(iii) Metil éster de [1-(4-metoxifenilmetansulfonilamino)-4-metil-2-oxo-1,2- dihidropiridin-3-il]acético
$^1$H NMR (400 MHz, $CDCl_3$) δ 2.16 (3H,s), 3.38 (2H, s), 3.59 (3H, s), 3.87 (3H, s), 6.14 (1H, d), 6.85 (2H, d), 7.53 (2H, d), 7.61 (2H, d), 9.26 (1H, br)

(iv) Metil éster de ácido [1-(2-metoxi-4-metilbencensulfonilamino)-4-metil-2-oxo-1,2- dihidropiridin-3-il]acético
$^1$H NMR (400 MHz, $CDCl_3$) δ 2.09 (s, 2H), 2.36 (s, 3H), 3.36 (s, 2H), 3.53 (s, 3H), 4.01 (s, 3H), 6.03 (d, 1H), 6.69 (d, 1H), 6.79 (s, 1H), 7.48 (d, 1H), 7.58 (d, 1H), 9.30 (s, 1H)

(v) Metil éster de ácido [1-(3,4-diclorobencensulfonilamino)-4-metil-2-oxo-1,2-dihidro- piridin-3-il]acético

$^1$H NMR (400 MHz, $CDCl_3$) δ 2.20 (s, 3H), 3.44 (s, 2H), 3.63 (s, 3H), 6.20 (d, 1H), 7.38 (dd, 1H), 7.43 (d, 1H), 7.58 (d, 1H), 7.63 (d, 1H), 9.41 (s, 1H)

(vi) Metil éster de ácido [1-(3-metoxibencensulfonilamino)-4-metil-2-oxo-1,2-dihidro-piridin-3-il]acético

$^1$H NMR (400 MHz, $CDCl_3$) δ 2.16 (s, 3H), 3.37 (s, 2H), 3.59 (s, 3H), 3.75 (s, 3H), 6.15 (d, 1H), 7.07-7.09 (m, 2H), 7.21 (d, 1H), 7.31 (t, 1H), 7.63 (d, 1H)

(vii) Metil éster de ácido [1-(2,5-dimetilbencensulfonilamino)-4-metil-2-oxo-1,2-dihidro- piridin-3-il]acético

$^1$H NMR (400 MHz, $CDCl_3$) δ 2.14 (s, 3H), 2.22 (s, 3H), 2.59 (s, 3H), 3.36 (s, 2H), 3.57 (s, 3H), 6.08 (d, 1H), 7.14 (d, 1H), 7.22 (d, 1H), 7.45 (s, 1H), 7.52 (d, 1H)

(viii) Metil éster de ácido [4-metil-1-(naftalen-1-sulfonilamino)-2-oxo-1,2-dihidro- piridin-3-il]acético

$^1$H NMR (400 MHz, $CDCl_3$) δ 2.12 (s, 3H), 3.16 (s, 2H), 3.53 (s, 3H), 6.11 (d, 1H), 7.37-7.49 (m, 3H), 7.54 (t, 1H), 7.88 (d, 1H), 7.98 (d, 1H), 8.05 (d, 1H), 8.50 (d, 1H), 9.31 (br s, 1H)

(ix) Metil éster de ácido (4-metil-2-oxo-1-fenetilamino-1,2-dihidro-piridin-3-il)acético

$^1$H NMR (400 MHz, $CD_3OD$) δ 2.18 (s, 3H), 2.85 (t, 2H), 3.28 (q, 2H), 3.67 (s, 2H), 3.70 (s, 3H), 6.03 (d, 1H), 6.12 (t, 1H), 7.19-7.36 (m, 5H)

(x) Metil éster de ácido [4-metil-2-oxo-1-(2-*o*-tolil-etilamino)-1,2-dihidropiridin-3-il] acético

$^1$H NMR (400 MHz, $CDCl_3$) δ 2.18 (s, 3H), 2.29 (s, 3H), 2.85 (t, 2H), 3.22 (t, 2H), 3.67 (s, 2H), 3.69 (s, 3H), 6.05 (d, 1H), 7.12-7.18 (m, 4H), 7.37 (d, 1H)

(xi) Metil éster de ácido {1-[2-(2,5-dimetilfenil)etilamino]-4-metil-2-oxo-1,2-dihidro-piridin-3-il}acético

$^1$H NMR (400 MHz, $CDCl_3$) δ 2.19 (s, 3H), 2.26 (s, 3H), 2.28 (s, 3H), 2.82 (t, 2H), 3.22 (t, 2H), 3.67 (s, 2H), 3.70 (s, 3H), 6.06 (d, 1H), 6.92 (d, 1H), 6.97 (s, 1H), 7.02 (d, 1H), 7.39 (d, 1H)

(xii) Metil éster de ácido {1-[2-(5-fluoro-2-metilfenil)etilamino]-4-metil-2-oxo-1,2-dihidropiridin-3-il}acético

$^1$H NMR (400 MHz, $CDCl_3$) δ 2.17 (s, 3H), 2.24 (s, 3H), 2.81 (t, 2H), 3.22 (t, 2H), 3.66 (s, 2H), 3.69 (s, 3H), 6.05 (d, 1H), 6.50 (t, 1H), 6.50 (dd, 1H), 6.88 (dd, 1H), 7.06 (dd, 1H), 7.35 (d, 1H)

(xiii) Metil éster de ácido {4-metil-2-oxo-1-[2-(3-trifluorometilfenil)etilamino]-1,2-dihidro-piridin-3-il}acético

$^1$H NMR (400 MHz, $CDCl_3$) δ 2.18 (s, 3H), 2.92 (t, 2H), 3.30 (t, 2H), 3.66 (s, 2H), 3.69 (s, 3H), 6.04 (d, 1H), 7.33 (d, 1H), 7.40-7.43 (m, 2H), 7.46-7.48 (m, 2H)

(xiv) Metil éster de ácido {1-[2-(5-cloro-2-fluorofenil)etilamino]-4-metil-2-oxo-1,2- dihidropiridin-3-il}acético

$^1$H NMR (400 MHz, $CDCl_3$) δ 2.18 (s, 3H), 2.84 (t, 2H), 3.25 (t, 2H), 3.66 (s, 2H), 3.70 (s, 2H), 6.04 (d, 1H), 6.95 (t, 1H), 7.15 (dq, 1H), 7.21 (dd, 1H), 7.32 (d, 1H)

(xv) Metil [1-(bencilamino)-4-metil-2-oxo-1,2-dihidropiridin-3-il]-acetato

Rendimiento = 42%.

$^1$H NMR (500 MHz) δ 2.19 (s, 3H), 3.71 (s, 2H), 3.74 (s, 3H), 4.14 (s, 2H), 5.94 (d, 1H), 7.18 (d, 1H), 7.30-7.41 (m, 5H)

(xvi) Metil {1-[(3-metoxibencil)amino]-4-metil-2-oxo-1,2-dihidro-piridin-3-il}acetato

$^1$H NMR (400 MHz, $CDCl_3$) δ 2.16 (s, 3H), 3.69 (s, 2H), 3.71 (s, 3H), 3.79 (s, 3H), 4.08 (d, 2H), 5.92 (d, 1H), 6.29 (t, 1H), 6.84 (dd, 1H), 6.91 (s, 1H), 6.94 (d, 1H), 7.20 (d, 1H), 7.24 (t, 1H)

MS *m/z* 317 $(M+H)^+$

(xvii) Metil {4-metil-2-oxo-1-[(piridin-3-ilmetil)amino]-1,2-dihidro-piridin-3-il}acetato

3-Piridincarboxaldehído (10.6 mmol) se agregó a una solución de metil (1-amino-4-metil-2-oxo-1,2-dihidropiridin-3-il)acetato (2.2 mmol; ver Preparación 1 más arriba) en metanol (40 mL) y ácido acético (10 mL), y la solución resultante se agitó a temperatura de la sala. Luego de 22 horas, la solución se concentró, y ácido acético se retiró concentrando conjuntamente el residuo de tolueno, hexano y metanol. Se agregó cianoborohidruro de sodio (6 mmol) al residuo en metanol (40 mL) y ácido acético (10 mL), y la solución resultante se agitó a temperatura de la sala un día para otro antes de concentrarse. El residuo se diluyó con acetato de etilo y se lavó con $NaHCO_3$ (saturado acuoso) y salmuera, se secó, se filtró, y el disolvente se evaporó bajo presión reducida. La purificación por cromatografía de destello ($SiO_2$, 0-10% metanol en DCM que contenía 0.2% ácido acético y 0.1 % TEA) proporcionó el producto deseado.

$^1$H NMR (500 MHz, $CDCl_3$) δ 8.52-8.58 (m, 2H), 7.70 (d, 1H), 7.24-7.30 (m, 1H), 7.12 (d, 1H), 6.25 (t, 1H), 5.93 (d, 1H), 4.14 (d, 2H), 3.70 (s, 3H), 3.67 (s, 2H), 2.16 (s, 3H)

(xviii) Metil (1-{[(2-metoxipiridin-3-il)metil]amino}-4-metil-2-oxo-1,2-dihidropiridin-3-il)acetato

2-Metoxinicotinaldehído (3.6 inmol) se agregó a una solución de metil (1-amino-4-metil-2-oxo4,2-dihidropiridin-3-il)acetato (2.4 mmol; ver Preparación 1 más arriba) en metanol (40 mL) y ácido acético (10 mL), y la

solución resultante se agitó a temperatura de la sala. Luego de 4.5 horas se agregó cianoborohidruro de sodio (7.4 mmol), y la solución resultante se agitó a temperatura de la sala durante 3 horas, antes de concentrarse. El residuo se diluyó con acetato de etilo y se lavó con $NaHCO_3$ (saturado acuoso) y salmuera, se secó, se filtró y se concentró. La purificación por cromatografía de destello ($SiO_2$, DCM; metanol, 900:25) proporcionó el producto deseado. $^1H$ NMR (500 MHz, $CDCl_3$) δ 8.13 (d, 1H), 7.50 (d, 1H), 7.23 (d, 1H), 6.85 (dd, 1H), 6.50 (t, 1H), 5.99 (d, 1H), 4.14 (d, 2H), 3.98 (s, 3H), 3.72 (s, 3H), 3.68 (s, 2H), 2.19 (s, 3H)

Preparación 3

*terc*-Butil éster de ácido (4-aminometilpiridin-2-il)carbámico

(a) *terc*-Butil éster de ácido (4-azidometilpiridin-2-il)carbámico

Una mezcla de *terc*-butil éster de ácido (4-bromometilpiridin-2-il)carbámico (3.0 g, 0.010 mol; obtenible como se describe en WO 00/66557) y azida de sodio (1.36 g, 0.0209 mol) en agua (20 mL) y DMF (40 mL) se agitó un día para otro. La mezcla de reacción se vertió en agua (300 mL) y se extrajo con acetato de etilo (3x). Las fases orgánicas combinadas se lavaron con agua, se secaron ($Na_2SO_4$), se filtraron, y el disolvente se evaporó bajo presión reducida. El producto crudo se cristalizó (2.6 g, 100 %) y se usó sin purificación posterior.

$^1H$ NMR (300 MHz, $CDCl_3$) δ 10.14 (bs, 1H), 8.36 (d, 1H), 7.99 (bs, 1H), 6.91 (m, 1H), 4.37 (bs, 2H), 1.54 (s, 9H)

(b) *terc*-Butil éster de ácido (4-aminometilpiridin-2-il)carbámico

Una solución de borohidruro de sodio (0.92 g, 24 mmol) en agua (25 mL) se agregó a una mezcla de Pd/C (10% 50 mg) en agua (25 mL) bajo agitación. A continuación, *terc*-butil éster de ácido (4-azidometilpiridin-2-il)carbámico (0.40 g, 6.1 mmol; véase paso (a) más arriba) en THF (75 mL) se agregó gota a gota y no rápidamente bajo enfriamiento con hielo. La reacción se agitó a temperatura de la sala durante 4 horas. Lentamente se

productos crudos (ésteres alquilados) que se emplearon en el siguiente paso sin purificación posterior.

(i) Metil [1-(isobutilamino)-4-metil-2-oxo-1,2-dihidropiridin-3-il]-acetato

(ii) Metil(4-metil-2-oxo-1-{[(1-fenil-1*H*-pirazol-5-il)metil]-amino}-1,2-dihidropiridin-3-il)acetato

(iii) Metil[1-({[2,5-dimetil-1-(4*H*-1,2,4-triazol-4-il)-1*H*-pirrol-3-il]metil} amino)-4-metil-2-oxo-1,2-dihidropiridin-3-il]acetato

(iv) Metil (1-{[(4-benzoil-1-metil-1*H*-pirrol-2-il)metil]amino}-4-metil-2-oxo-1,2-dihidropiridin-3-il)acetato

(v) Metil (1-[(2,3-dihidro-1-benzofuran-5-ilmetil)amino]-4-metil-2-oxo-1,2-dihidropiridin-3-il)acetato

(vi) Metil (1-{[(2,4-dimetil-1,3-tiazol-5-il)metil]amino}-4-metil-2- oxo-1,2-dihidropiridin-3-il)acetato

(vii) Metil (1-{[(1,5-dimetil-1*H*-pirazol-4-il)metil]amino}-4-metil-2-oxo-1,2-dihidropiridin-3-il)acetato

(viii) Metil [4-metil-2-oxo-1-({[1-(fenilsulfonil)-1*H*-pirrol-2-il]-metil} amino)-1,2-dihidropiridin-3-il]acetato

(ix) Metil (1-[(3,5-dimetilisoxazol-4-ii)metil]amino}-4-metil-2-oxo-1,2-dihidropiridin-3-il)acetato

(x) Metil (1-[(4-cloro-2-fenil-1*H*-imidazol-5-il)metil]amino}-4-metil-2-oxo-1,2-dihidropiridin-3-il)acetato

(xi) Metil {1-[(2,1,3-benzoxadiazol-5-ilmetil)amino]-4-metil-2-oxo-1,2-dihidropiridin-3-il}acetato

(xii) Metil {4-metil-2-oxo-1-[(pirazin-2-ilmetil)amino]-1,2-dihidro-piridin-3-il}acetato

(xiii) Metil {1-[(ciclopentilmetil)amino]-4-metil-2-oxo-1,2-dihidro-piridin-3-il}acetato

(xiv) Metil (4-metil-2-oxo-1-{[(5-piridin-2-il-2-tienil)metil]-amino}-1,2-dihidropiridin-3-il)acetato

(xv) Metil (1-{[(5-cloro-1,3-dimetil-1*H*-pirazol-4-il)metil]amino}-4-metil-2-oxo-1,2-dihidropiridin-3-il)acetato

(xvi) Metil (1-{[(6-cloro-1,3-benzodioxol-5-il)metil]amino}-4-metil-2-oxo-1,2-dihidropiridin-3-il)acetato

(xvii) Metil (4-metil-1-{[(1-metil-1*H*-imidazol-2-il)metil]amino}-2-oxo-1,2-dihidropiridin-3-il)acetato

(xviii) Metil {1-[(ciclohexilmetil)amino]-4-metil-2-oxo-1,2-dihidro-piridin-3-il}acetato

(xix) Metil (4-metil-1-{[(4-metil-3,4-dihidro-2H-1,4-benzoxazin-7-il)metil] amino}-2-oxo-1,2-dihidropiridin-3-il)acetato

(xx) Metil {1-[(4-cianobencil)amino]-4-metil-2-oxo-1,2-dihidro-piridin-3-il}acetato

(xxi) Metil {4-metil-2-oxo-1-[(2-fenoxibencil)amino]-1,2-dihidro-piridin-3-il}acetato

(xxii) Metil (1-{[(1-etil-3-metil-1*H*-pirazol-4-il)metil]amino}-4-metil-2-oxo-1,2-dihidropiridin-3-il)acetato

(xxiii) Metil (4-metil-1-{[(4-metil-1*H*-imidazol-5-il)metil]amino}-2-oxo-1,2-dihidropiridin-3-il)acetato

(xxiv) Metil (1-[(5-cloro-1-metil-3-fenil-1*H*-pirazol-4-il)metil]-amino}-4-metil-2-oxo-1,2-dihidropiridin-3-il)acetato

(xxv) Metil (4-metil-1-{[(2-morfolin-4-ilpiridin-3-il)metil]amino}-2-oxo-1,2-dihidropiridin-3-il)acetato

(xxvi) Metil {1-[(3,3-dimetilbutil)amino]-4-metil-2-oxo-1,2-dihidropiridin-3-il}acetato

(xxvii) Metil (1-{[(5-cloro-2-tienil)metil]amino}-4-metil-2-oxo-1,2-dihidropiridin-3-il)acetato

(xxviii) Metil {1-[(3-ciano-4-fluorobencil)amino]-4-metil-2-oxo-1,2-dihidropiridin-3-il}acetato

(xxix) Metil (4-metil-1-{[(5-metil-3-fenilisoxazol-4-il)metil]-amino}-2-oxo-1,2-dihidropiridin-3-il)acetato

(xxx) Metil (4-metil-2-oxo-1-{[3-(trifluoronietoxi)bencil]amino}-1,2-dihidropiridin-3-il)acetato

(xxxi) Metil {1-[(5-cloro-2-fluorobencil)amino]-4-metil-2-oxo-1,2-dihidropiridin-3-il}acetato

(xxxii) Metil (4-metil-1-{[(2-metil-1*H*-imidazol-5-il)metil]amino}-2-oxo-1,2-dihidropiridin-3-il)acetato

(xxxiii) Metil {1-[(2-fluoro-5-metoxibencil)amino]-4-metil-2-oxo-1,2-dihidropiridin-3-il}acetato

(xxxiv) Metil {4-metil-1-[(2-morfolin-4-ilbencil)amino]-2-oxo-1,2-dihidropiridin-3-il}acetato

(xxxv) Metil (1-{[(1,3-dimetil-5-morfolin-4-il-1*H*-pirazol-4-il)-metil] amino}-4-metil-2-oxo-1,2-dihidropiridin-3-il)acetato

(xxxvi) Metil {4-metil-2-oxo-1-[(quinolin-8-ilmetil)amino]-1,2-dihidropiridin-3-il)acetato

(xxxvii) Metil [4-metil-2-oxo-1-({[5-(2-tienil)isoxazol-3-il]metil}-amino)-1,2-dihidropiridin-3-il]acetato

(xxxviii) Metil {4-metil-2-oxo-1-[(2-fenilpropil)amino]-1,2-dihidro-piridin-3-il}acetato

(xxxix) Metil {1-[(biciclo[2.2.1]hept-5-en-2-ilmetil)amino]-4-metil-2-oxo-1,2-dihidropiridin-3-il}acetato

(xl) Metil [1-({3-[(2-cloro-1,3-tiazol-5-il)metoxi]bencil}amino)-4-metil-2-oxo-1,2-dihidropiridin-3-il]acetato

(xli) Metil (4-metil-1-{[(3-metil-5-fenilisoxazol-4-il)metil]-amino}-2-oxo-1,2-dihidropiridin-3-il)acetato

(xlii) Metil (1-{[(1,3-dimetil-5-morfolin-4-il-1*H*-pirazol-4-il)- metil] amino}-4-metil-2-oxo-1,2-dihidropiridin-3-il)acetato

$^1$H NMR (500 MHz, $CDCl_3$) δ 3.96 (s, 3H), 7.09 (dt, 1H), 7.55 (dd, 1H), 7.65 (dd, 1H)

(b) Metil 2-ciano-5-fluorobenzoato

Metil 2-bromo-5-fluorobenzoato (3.0 g, 12.87 mmol; véase paso (a) más arriba) se disolvió en DMF seco (18 mL). La solución resultante se desgasificó entonces lavando con gas $N_2$ durante 5 minutos. Se agregó cianuro de cobre (I) (2.3 g, 25.74 mmol), y la mezcla de reacción se desgasificó nuevamente antes de hacerse refluir durante 90 minutos. Se agregó NaCN (acuoso, 10%), y la mezcla se extrajo con DCM. La fase DCM se secó a través de un separador de fase, y el disolvente se retiró *in vacuo*. El producto crudo se disolvió en tolueno y se lavó una vez con agua. La fase orgánica se secó sobre $MgSO_4$ y se filtró. El disolvente se retiró *in vacuo* para producir el compuesto crudo del subtítulo (77%), que se utilizó en el siguiente paso sin purificación posterior.

$^1$H NMR (500 MHz, $CDCl_3$) δ 4.04 (s, 3H), 7.38 (dt, 1H), 7.82-7.87 (m, 2H)

(c) [2-Aminometil)-5-fluorofenil]metanol

Hidruro de aluminio y litio (1.12 g, 29.5 mmol) se dispersó en THF seco (10mL) y la mezcla resultante se enfrió con un baño helado. Metil 2-ciano-5-fluorobenzoato (1.76 g, 9.85 mmol; véase paso (b) más arriba) se disolvió en THF (10+5mL) y se agregó al agente reductor. La mezcla de reacción se agitó durante 10 minutos y, seguidamente, se retiró el baño helado. Luego de 1 hora, la reacción se extinguió con agua (2mL), NaOH (2M, 4mL) y luego más agua (2 mL), tras lo cual la mezcla resultante se agitó durante 10 minutos. La mezcla se diluyó con éter dietílico (50 mL) y se filtró. La fase orgánica se secó sobre $MgSO_4$ y se filtró. El disolvente se retiró *in vacuo* para producir el compuesto del subtítulo (81%), el cual se usó sin purificación posterior.

$^1$H NMR (500 MHz, $CDCl_3$) δ 4.01 (s, 2H), 4.63 (s, 2H), 6.95 (dt, 1H), 7.11 (dd, 1H), 7.23 (dd, 1H)

(d) *terc*-Butil [4-fluoro-2-(hidroximetil)bencil]carbamato

[2-(Aminometil)-5-fluorofenil]metanol (1.24 g, 7.99 mmol; véase paso (c) más arriba) se disolvió en DCM (20 mL) y se agregó di-*terc*-butildicarbonato (1.74 g, 7.99 mmol), disuelto en DCM (5 mL). La mezcla de reacción se agitó a temperatura de la sala durante 2 horas. La mezcla de reacción se diluyó con DCM y se lavó una vez con agua. La fase DCM se secó a través de un separador de fase, y el disolvente se retiró *in vacuo*. *terc*-Butanol se co-evaporó de tolueno para producir el compuesto del subtítulo (96%), el cual se usó sin purificación posterior.

$^1$H NMR (500 MHz, $CDCl_3$) δ 1.45 (s, 9H), 2.83 (br s, 1H), 4.35 (d, 2H), 4.74 (s, 2H), 5.06 (br s, 1H), 6.99 (dt, 1H), 7.11 (dd, 1H), 7.29-7. 31 (m, 1H)

(e) *terc*-Butil [2-(azidometil)-4-fluorobencil]carbamato

*terc*-Butil [4-fluoro-2-(hidroximetil)bencil]carbamato (1.96 g, 7.70 mmol; véase paso (d) más arriba) se disolvió en THF seco (25 mL), y la solución resultante se enfrió con un baño helado. Se agregaron difenilfosforil azida (2.75 g, 10.0 mmol) y DBU (1.52 g, 10.0 mmol). La mezcla se agitó bajo una atmósfera inerte, y el baño helado se dejó calentar a temperatura de la sala un día para otro. La mezcla de reacción se diluyó con agua y se extrajo dos veces con acetato de etilo. La fase orgánica se lavó con salmuera y se secó sobre $MgSO_4$ y se filtró antes de retirar el disolvente *in vacuo*. La purificación por cromatografía de destello ($SiO_2$, heptano:acetato de etilo 10:1) produjo el compuesto del subtítulo (76%).

$^1$H NMR (500 MHz, $CDCl_3$) δ 1.48 (s, 9H), 4.34 (d, 2H), 4.45 (s, 2H), 4.83 (br s, 1H), 7.04 (dt, 1H), 7.08 (dd, 1H), 7.32-7.39 (m, 1H)

(f) *terc*-Butil [2- (aminometil)-4-fluorobencil]carbamato

TEA (1.76 g, 17. 55 mmol) en metanol (15mL) se agregó a *terc*-butil [2-(azidometil)-4-fluorobencil]carbamato (1.64 g, 5.85 mmol; véase paso (e) más arriba), y la mezcla se lavó con gas $N_2$. Se agregó 1,3-propanoditiol

(1.90 g, 17.55 mmol) disuelto en metanol (15 mL). La mezcla de reacción se agitó a temperatura de la sala durante 2 días. El precipitado blanco que se formó se extrajo por filtración y se lavó con metanol. El filtrado se recogió, y el disolvente se retiró *in vacuo*. La purificación por cromatografía de destello ($SiO_2$, 2.5% metanol en DCM + 1% TEA) produjo el compuesto del título (82%).

$^1$H NMR (500 MHz, $CDCl_3$) δ 1.48 (s, 9H), 3.94 (s, 2H), 4.33 (d, 2H), 5.80 (br s, 1H), 6.94 (dt, 1H), 7.06 (dd, 1H), 7.32 (dd, 1H)

Preparación 7

*terc*-Butil [2-(aminometil)-4-metoxibencil]carbamato

El compuesto del título se preparó por un método análogo al descrito en Preparación 6, pasos (b) a (f) más arriba, usando metil 2-bromo-5-metoxibenzoato en lugar de metil 2-bromo-5-fluorobenzoato en paso (b), y tiempos de reacción de 2 horas, 2 horas y 1 hora para pasos (b), (c) y (d), respectivamente.

$^1$H NMR (500 MHz, $CDCl_3$) δ 1.44 (s, 9H), 3.83 (s, 3H), 4.04 (d, 2H), 4.27 (d, 2H) 5.76 (br s, 1H), 6.83 (dd, 1H), 7.03 (d, 1H), 7.24 (d, 1H)

Preparación 8

*terc*-Butil [2-(aminometil)-4-metilbencil]carbamato

El compuesto del título se preparó por un método análogo al descrito en Preparación 6 más arriba, usando ácido 2-cloro-5-metilbenzoico en lugar de ácido 2-bromo-5-fluorobenzoico en paso (a), y las siguientes variaciones a los procedimientos:

(I) en paso (b), la mezcla se hizo inicialmente refluir durante 18 horas, a continuación se agregó una porción adicional de CuCN (1 equiv.), y la mezcla de reacción se hizo refluir aún más durante 16 horas;

(II) en paso (e), tolueno:acetato de etilo (15:1) se usó para cromatografía; y

(III) en paso (f), no se formó precipitado, y la purificación se realizó directamente luego de la concentración de la mezcla de reacción.

$^1$H NMR (500MHz, $CDCl_3$) δ 1.46 (s, 9H), 2.36 (s, 3H), 3.92 (s, 2H), 4.35 (d, 2H), 5.98 (br s, 1H), 7.08 (d, 1H), 7.13 (s, 1H), 7.24 (d, 1H)

Preparación 9

*terc*-Butil [2-(aminometil)-4-(trifluorometil)bencil]carbamato

El compuesto del título se preparó por un método análogo al descrito en Preparación 6 más arriba, usando ácido 2-cloro-5-(trifluorometil)benzoico en lugar de ácido 2-bromo-5-fluorobenzoico en paso (a), y las siguientes variaciones a los procedimientos:

(I) en paso (b), la mezcla de reacción se hizo refluir durante 3 días, y la purificación se realizó por cromatografía con heptano: acetato de etilo (15: 1);

(II) en paso (e), el producto crudo no se purificó antes de usarse en paso (f); y

(III) en paso (f), la mezcla de reacción se agitó durante 24 horas.

$^1$H NMR (500 MHz, $CD_3OD$) δ 1.48 (s, 9H), 3.98 (s, 2H), 4.36 (s, 2H), 7.50 (d, 1H), 7.56 (d, 1H), 7.72 (s, 1H)

**Ejemplos**

Ejemplo 1

A menos que se indique lo contrario, los compuestos (i) a (xxxvi) listados a continuación se prepararon de los compuestos correspondientes de Preparación 2 por el siguiente Método General.

Hidróxido de sodio (29 mg, 0.71 mmol) se agregó a una solución del éster específico (0.24 mmol; ver Preparación 2 más arriba) en THF:agua:metanol (3 mL, 2:2:1), y la mezcla de reacción se agitó a temperatura de la sala durante 3 horas. La mezcla se acidificó (HCl, 1 M) hasta pH ~ 2 y se extrajo con acetato de etilo (3x5 mL). Las capas orgánicas combinadas se secaron ($Na_2SO_4$), se filtraron, y el disolvente se evaporó bajo presión

reducida. El residuo (el ácido carboxílcio) se usó sin purificación posterior.

DIPEA (125 µL, 0.71 mmol) y la amina específica (0.31 mmol; ver Lista 5 más arriba) se agregaron a el ácido carboxílico crudo (ver más arriba) en DMF (4 mL) a 0°C. Luego de 30 minutos, se agregaron EDC (69 mg, 0.36 mmol) y HOBt (49 mg, 0.36 mmol), y la mezcla de reacción se agitó a 0°C durante 1 hora y luego a temperatura de la sala durante 2 días. Se retiró DMF bajo presión reducida. Se agregó $NaHCO_3$ (saturado, 2mL), y la capa acuosa se extrajo con acetato de etilo (3 x 5 mL). Las capas orgánicas combinadas se secaron ($Na_2SO_4$), se filtraron, y el disolvente se evaporó bajo presión reducida. La purificación por cromatografía de destello ($SiO_2$, 5% metanol en acetato de etilo) produjo las amidas listadas en (i) a (xv) a continuación en forma de aceites. Los rendimientos de los dos pasos para estas amidas fueron 68-84%.

(i) Bencil éster de ácido [amino-(4-{[2-(4-metil-2-oxo-1-fenilmetanesulfonilamino-1,2-dihidropiridin-3-il)acetilamino]metil}fenil)metilen]carbámico
$^1$H NMR (400 MHz, $CD_3OD$) δ 2.21 (3H, s), 3.35 (2H, s), 4.39 (2H, s), 4.43 (2H, s), 5.18 (2H, s), 6.17 (1H, d), 7.26-7.55 (13H, m), 7.69 (2H, d)

(ii) Bencil éster de ácido [amino-(4-{[2-(1-bencensulfonilamino-4-metil-2-oxo-1,2-dihidro-piridin-3-il)acetilamino]metil}fenil)metilen]carbámico
$^1$H NMR (400 MHz, $CDCl_3$) δ 2.11 (s, 3H), 3.29 (s, 2H), 4.25 (s, 2H), 5.21 (s, 2H), 6.11 (d, 1H), 6.91-7.70 (m, 18H), 10.05 (br s, 1H)

(iii) Bencil éster de ácido {amino-[4-({2-[1-(4-metoxibencensulfonilamino)-4-metil-2-oxo-1,2-dihidropiridin-3-il]acetilamino}metil)fenil]metilen}carbámico

$^1$H NMR (400MHz, $CD_3OD$) δ 2.18 (3H, s), 3.36 (2H, s), 3.72 (3H, s), 4.32 (2H, s), 5.18 (2H, s), 6.17 (1H, d), 6.91 (2H, d), 7.26-7.54 (9H, m), 7.61 (2H, d), 7.69 (2H, d)

(iv) Bencil éster de ácido {amino-[4-({2-[1-(2-metoxi-4-metilbencensulfonilamino)-4-metil-2-oxo-1,2-dihidropiridin-3-il]acetilamino}metil)fenil] metilene}carbámico

$^1$H NMR (400 MHz, $CDCl_3$) δ 2.19 (s, 3H), 2.33 (s, 3H), 3.38 (s, 2H), 3.92 (s, 3H), 4.32 (s, 2H), 5.19 (s, 2H), 6.20 (d, 1H), 6.73 (d, 1H), 6.97 (s, 1H), 7.30-7.38 (m, 5H), 7.41 (d, 2H), 7.48 (d, 1H), 7.54 (d, 1H), 7.80 (d, 2H)

(v) Bencil éster de ácido {amino-[4-({2-[1-(3,4-diclorobencensulfonilamino)-4-metil-2-oxo-1,2-dihidropiridin-3-il]acetilamino}metil)fenil]metilen}carbámico

$^1$H NMR (400 MHz, $CDCl_3$) δ 2.22 (s, 3H), 3.38 (s, 2H), 4.34 (s, 2H), 5.19 (s, 2H), 6.21 (d, 1H), 7.29-7.36 (m, 5H), 7.41-7.46 (m, 3H), 7.55 (s, 2H), 7.78 (d, 1H), 7.83 (s, 1H)

(vi) Bencil éster de ácido {amino-[4-({2-[1-(3-metoxibencensulfonilamino)-4-metil-2-oxo-1,2-dihidropiridin-3-il]acetilamino}metil)fenil]metilen}carbámico

$^1$H NMR (400 MHz, $CD_3OD$) δ 2.30 (s, 3H), 3.30 (s, 2H), 3.70 (s, 3H), 4.25 (d, 1H), 5.20 (s, 2H), 6.17 (d, 1H), 6.89 (br s, 1H), 7.04 (d, 1H), 7.13-7.37 (m, 7H), 7.43 (d, 2H), 7.48 (d, 1H), 7.71 (d, 2H)

(vii) Bencil éster de ácido {amino-[4-({2-[1-(2,5-dimetilbencensulfonilamino)-4-metil-2-oxo-1,2-dihidropiridin-3-il]acetilamino}metil)fenil]metilen}carbámico

$^1$H NMR (400 MHz, $CDCl_3$) δ 2.23 (s, 3H), 2.30 (s, 3H), 2.60 (s, 3H), 3.35 (s, 2H), 4.27 (d, 2H), 5.20 (s, 2H), 6.12 (d, 1H), 6.91 (br s, 1H), 7.11-7.49 (m, 11H), 7.77 (d, 2H)

(viii) Bencil éster de ácido amino-[4-(2-[4-metil-1-(naftalen-1-sulfonilamino)-2-oxo-1,2-dihidropiridin-3-il]acetilamino}metil)fenil]metilen}carbámico

$^1$H NMR (400 MHz, $CDCl_3$) δ 2.19 (s, 3H), 3.15 (s, 2H), 4.11 (s, 2H), 5.17 (s, 2H), 5.99 (d, 1H), 7.00 (d, 4H), 7.26-7.51 (m, 8H), 7.60 (d, 2H), 7.83 (d, 1H), 7.99 (d, 2H), 8.56 (br d, 1H)

(ix) *terc*-Butil éster de ácido [4-cloro-2-({2-[4-metil-1-(naftalen-1-sulfonilamino)-2-oxo-1,2-dihidropiridin-3-il]acetilamino}metil)bencil]carbámico

El éster específico (0.47 mmol) se hidrolizó como se describe en el Método General C más arriba, excepto que el volumen de disolvente fue de 5 mL y el tiempo de reacción fue de 5.5 horas. El ácido carboxílico crudo resultante (0.06 mmol) se disolvió en DCM (1 mL), y se agregaron TEA (2 eq.) y la amina específica (1 equiv.; ver Lista 5 más arriba). La mezcla se enfrió a 0°C, y se agregó PyBOP (1 equiv.). La mezcla de reacción se agitó aa 0°C durante 30 minutos y seguidamente se dejó calentar a temperatura de la sala y se agitó aún más de un día para otro. Se agregaron porciones adicionales de TEA (2 equiv.), amina (0.4 equiv) y PyBOP (0.3 equiv.), y la reacción se agitó durante 4 horas. El disolvente se retiró bajo presión reducida, y el residuo se purificó por cromatografía ($SiO_2$, 5% metanol en DCM) para proporcionar el producto (89%).

$^1$H NMR (500 MHz, $CDCl_3$) δ 1.49 (s, 9H), 2.29 (s, 3H), 3.12 (s, 2H), 4.14 (br s, 2H), 4.21 (br s, 2H), 6.14 (d, 1H), 6.74 (t, 1H), 7.21 (bs, 2H), 7.45 (t, 1H), 7.56-7.64 (m, 2H), 7.88-7.93 (m, 1H), 8.08 (d, 1H), 8.11 (d, 1H), 8.62 (br s, 1H)

(x) Bencil éster de ácido [amino-(4-{[2-(4-metil-2-oxo-1-fenetilamino-1,2-dihidropiridin-3-il)acetilamino]metil}fenil)metilen]carbámico

$^1$H NMR (400 MHz, $CD_3OD$) δ 2.32 (s, 3H), 2.81 (t, 2H, $J$ = 7.4Hz), 3.20 (q, 2H, $J$ = 7.5Hz), 3.58 (s, 2H), 4.37 (d, 2H, $J$ = 6.0Hz), 5.20 (s, 2H), 6.09-6.13 (m, 2H), 7.03-7.78, (m, 15H), 9.50 (br s, 1H)

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(xi) Bencil éster de ácido {amino-[4-(2-[4-metil-2-oxo-1-(2-o-toliletilamino)-1,2-dihidro-piridin-3-il]acetilamino}metil)fenil]metilen}carbámico

$^1$H NMR (400 MHz, $CDCl_3$) δ 2.24 (s, 3H), 2.32 (s, 3H), 2.79 (t, 2H), 3.14 (q, 2H), 3.58 (s, 2H), 4.35 (d, 2H), 5.20 (s, 2H), 6.12 (d, 1H), 7.06-7.13 (m, 4H), 7.15 (d, 2H), 7.28-7.37 (m, 4H), 7.43 (d, 2H), 7.66 (d, 3H)

(xii) Bencil éster de ácido (amino-{4-[(2-{1-[2-(2,5-dimetilfenil)etilamino]-4-metil-2-oxo-1,2-dihidropiridin-3-il}acetilamino)metil]fenil}metilen) carbámico

$^1$H NMR (400 MHz, $CDCl_3$) δ 2.20 (s, 3H), 2.25 (s, 3H), 2.31 (s, 3H), 2.76 (t, 2H), 3.14 (q, 2H), 3.58 (s, 2H), 4.35 (d, 2H), 5.19 (s, 2H), 6.11 (d, 1H), 6.18 (s, 1H), 6.91 (d, 2H), 7.00 (d, 1H), 7.14 (d, 2H), 7.26-7.36 (m, 5H), 7.43 (d, 2H), 7.67 (d, 3H), 9.27 (br s, 1H)

(xiii) *terc*-Butil éster de ácido {5-[(2-{1-[2-(5-fluoro-2-metilfenil)etilamino]-4-metil-2-oxo-1,2-dihidropiridin-3-il}acetilamino)metil]piridin-2-il}carbámico

$^1$H NMR (400 MHz, $CDCl_3$) δ 1.52 (s, 9H), 2.19 (s, 3H), 2.34 (s, 3H), 2.75 (t, 2H), 3.12-3.14 (m, 2H), 3.56 (s, 2H), 4.28 (d, 1H), 6.12 (d, 2H), 6.79 (s, 1H), 6.83 (d, 1H), 7.05 (d, 1H), 7.33 (d, 1H), 7.46-7.48 (m, 1H), 7.55 (s, 1H), 7.83 (d, 1H), 8.1 (d, 1H), 8.76 (s, 1H)

(xiv) *terc*-Butil éster de ácido {5-[(2-{4-metil-2-oxo-1-[2-(2-trifluorometilfenil)etilamino]-1,2-dihidropiridin-3-il}acetilamino)metil]piridin-2-il}carbámico

$^1$H NMR (400 MHz, $CDCl_3$) δ 1.52 (s, 9H), 2.35 (s, 3H), 2.86-2.89 (m, 2H), 3.22-3.26 (m, 2H), 3.56 (s, 2H), 4.31 (d, 2H), 6.12 (d, 2H), 7.31 (d, 2H), 7.39-7.42 (m, 2H), 7.48-7.50 (m, 2H), 7.52-7.54 (m, 2H), 7.88 (d, 1H), 8.09 (s, 1H), 8.26 (s, 1H)

(xv) 2-{1-[2-(5-Cloro-2-fluorofenil)etilamino]-4-metil-2-oxo-1,2-dihidropiridin-3-il}-*N*-(3-fluoro-4-metilpiridin-2-ilmetil)acetamida

$^1$H NMR (400 MHz, $CDCl_3$) δ 2.21 (s, 3H), 2.32 (s, 3H), 2.81 (t, 2H), 3.25 (t, 2H), 3.65 (s, 2H), 4.55 (s, 2H), 6.08 (d, 1H), 6.17 (br s, 1H), 6.93, 6.99 (m, 2H), 7.14-7.18 (m, 2H), 7.31 (d, 1H), 7.82 (br s, 1H), 8.1 (br s, 1H)

(xvi) *terc*-Butil {2-[({[1-(bencilamino)-4-metil-2-oxo-1,2-dihidro-piridin-3-il]acetil}amino)metil]-4-clorobencil}carbamato

El éster correspondiente de Preparación 2 se hidrolizó con hidróxido de sodio como se describe en el anterior Método General. El acoplamiento de la amida se realizó entonces como se describe con respecto a Ejemplo 1(ix) más arriba, excepto sin la adición extra de reactivos. El residuo crudo se purificó por cromatografía de destello y HPLC preparativa para proporcionar el producto deseado.

$^1$H NMR (500 MHz, $CDCl_3$) δ 1.46 (s, 9H), 2.36 (s, 3H), 3.61 (s, 2H), 4.08 (d, 2H), 4.27-4.32 (m, 2H), 4.39 (d, 2H), 5.34 (br s, 1H), 6.03 (d, 1H), 6.38 (br s, 1H), 7.13-7.20 (m, 3H), 7.24-7.37 (m, 6H), 7.61 (br s, 1H)

MS *m/z* 525.2 $(M+H)^+$

(xvii) Di-*terc*-butil ((E)-{[2-({[1-(bencilamino)-4-metil-2-oxo-1,2-dihidropiridin-3-il]acetil}amino)etoxi]amino}metililiden)-biscarbamato

El compuesto se preparó de acuerdo con el método descrito con respecto a Ejemplo 1(xvi) más arriba, excepto que no se necesitó HPLC preparativa para proporcionar el producto deseado en forma suficientemente pura.

$^1$H NMR (500 MHz, $CDCl_3$) δ 1.50 (s, 18H), 2. 32 (s, 3H), 3.53 (q, 2H), 3.61 (s, 2H) 4.10 (t, 2H), 4.12 (d, 2H), 5.99 (d, 1H), 6.43 (t, 1H), 7.15 (d, 1H), 7.29-7.38 (m, 5H), 7.67-7.72 (m, 1H), 8.02 (s, 1H), 9.09 (s, 1H) MS m/z 573.6 $(M+H)^+$

(xviii) *terc*-Butil {5-[([1-(bencilamino)-4-metil-2-oxo-1,2-dihidro-piridin-3-il]acetil}amino)metil]-6-metilpiridin-2-il}carbamato

El éster correspondiente de Preparación 2 se hidrolizó como se describe en el anterior Método General, excepto que la mezcla de reacción se agitó de un día para otro. El acoplamiento de la amida se realizó como se describe con respecto a Ejemplo 1(ix) más arriba, pero sin la adición extra de reactivos y con el uso de TBME: metanol (97:3) como eluyente para la cromatografía.

$^1$H NMR(500 MHz, $CDCl_3$) δ 1.49 (s, 9H), 2.33 (s, 3H), 2.35 (s, 3H), 3.59 (s, 2H), 4.01 (d, 2H), 4.31 (d, 2H), 6.01 (d, 1H), 6.27 (t, 1H), 7.07 (br s, 1H), 7.16 (d, 1H), 7.27-7.35 (m, 4H), 7.40 (d, 1H), 7.44 (t, 1H), 7.63 (d, 1H)

(xix) *terc*-Butil (4-cloro-2-{[({4-metil-2-oxo-1-[(2-feniletil)amino]- 1,2-dihidropiridin-3-il}acetil)amino]metil}bencil)carbamato

El éster correspondiente de Preparación 2 se hidrolizó como se describe en el anterior Método General, excepto que la mezcla de reacción se agitó de un día para otro. A continuación se llevó a cabo la reacción de acoplamiento de la amida como se describe con respecto a Ejemplo 1(ix) más arriba, excepto que la amina (0.1 equiv.) fue el único reactivo agregado en el paso de adición extra, y la mezcla de reacción se agitó durante 4 horas. El producto crudo se purificó por HPLC preparativa.

$^1$H NMR (500 MHz, $CDCl_3$) δ 1.46 (s, 9H), 2.36 (s, 3H), 2.85 (t, 2H), 3.24 (q, 2H), 3.59 (s, 2H), 4.20-4.30 (m, 2H), 4.37 (d, 2H), 5.28 (br s, 1H), 6.12-6.20 (m, 2H), 7.10 (s, 1H), 7.14 (d, 1H), 7.19-7.26 (m, 4H), 7.28-7.33 (m, 2H), 7.36 (d, 1H), 7.60 (br s, 1H)

MS *m/z* 539 $(M+H)^+$

(xx) *terc*-Butil (6-metil-5-{[({4-metil-2-oxo-1-[(2-feniletil)amino]-1,2-dihidropiridin-3-il}acetil)amino]metil}piridin-2-il)carbamato

El éster correspondiente de Preparación 2 se hidrolizó como se describe en el Método General más arriba, excepto que la mezcla de reacción se agitó de un día para otro. A continuación se llevó a cabo la reacción de acoplamiento de la amida como se describe con respecto a Ejemplo 1(ix)

más arriba, excepto que la amina (0.1 equiv) fue el único reactivo agregado en el paso de adición extra, y la mezcla de reacción se agitó durante 3 horas. El producto crudo se purificó por HPLC preparativa.

$^1$H NMR (500 MHz, $CDCl_3$) δ 1.52 (s, 9H), 2.34 (s, 3H), 2.36 (s, 3H), 2.84 (t, 2H), 3.21 (q, 2H), 3.58 (s, 2H), 4.30 (d, 2H), 6.10 (t, 1H), 6.13 (d, 1H), 7.14 (s, 1H), 7.19-7.26 (m, 3H), 7.29-7.40 (m, 4H), 7.44 (t, 1H), 7.63 (d, 1H)

MS *m/z* 507$(M+H)^+$

(xxi) *terc*-Butil (4-cloro-2-{[({1-[(3-metoxibencil)amino]-4-metil-2-oxo-1,2-dihidropiridin-3-il}acetil)amino]metil}bencil)carbamato

El compuesto correspondiente de Preparación 2 se hidrolizó como se describe en el anterior Método General. A continuación se llevó a cabo la reacción de acoplamiento de la amida como se describe con respecto a Ejemplo 1(ix) más arriba, excepto que se emplearon 1.3 equivalentes de la amina específica y no se agregaron reactivos extra.

$^1$H NMR (500 MHz, $CDCl_3$) δ 1.44 (s, 9H), 2.33, (s, 3H), 3.60 (s, 2H), 3.80 (s, 3H), 4.05 (d, 2H), 4.28 (d, 2H), 4.38 (d, 2H), 5.40 (br s, 1H), 6.03 (d, 1H), 6.39 (br s, 1H), 6.84-6.88 (m, 3H), 7.26-7.24 (m, 5H), 7.61 (br s, 1H)

MS *m/z* 557 $(M+H)^+$

(xxii) *terc*-Butil (5-[({1-[(3-metoxibencil)amino]-4-metil-2-oxo-1,2-dihidropiridin-3-il}acetil)amino]metil}-6-metilpiridin-2-il)carbamato El correspondiente éster de Preparación 2 se hidrolizó como se describe en el anterior Método General. A continuación se llevó a cabo la reacción de acoplamiento de la amida como se describe en el anterior Método General, excepto que se usó TEA en lugar de DIPEA y HOAt en lugar de HOBt.

$^1$H NMR (500 MHz, $CDCl_3$) δ 1.50(s, 9H), 2.33, (s, 3H), 2.34 (s, 3H), 3.40 (s, 2H), 3.80 (s, 3H), 4.00 (d, 2H), 4.30 (d, 2H), 6.02 (d, 1H), 6.36 (t, 1H), 6.83-6.87 (m, 3H), 7.20 (d, 1H), 7.23 (t, 1H), 7.38 (d, 1H), 7.40 (s, 1H), 7.48 (t, 1H), 7.63 (d, 1H)

MS *m/z* 522 $(M+H)^+$

(xxiii) *terc*-Butil (4-cloro-2-{[({4-metil-2-oxo-1-[(piridin-3-ilmetil)-amino]-1,2-dihidropiridin-3-il}acetil)amino]metil}bencil)carbamato

El correspondiente éster de Preparación 2 se hidrolizó con hidróxido de litio (1 M acuoso, 1.5 equiv.) en THF:MeOH (1:1) y el carboxilato crudo se acopló a la amina específica (ver Lista 5 más arriba) de acuerdo con el procedimiento descrito en el anterior Método General, excepto que se usó TEA en lugar de DIPEA y HOAt en lugar de HOBt.

$^1$H NMR (500 MHz, $CDCl_3$) δ 8.56 (d, 1H), 8.53 (s, 1H), 7.64 (d, 1H), 7.52 (s, 1H), 7.24-7.31(m, 2H), 7.12-7.21(m, 3H), 6.35 (br s, 1H), 6.04 (d, 1H), 5.35 (br s, 1H), 4.40 (d, 2H), 4.29 (d, 2H), 4.12 (d, 2H), 3.59 (d, 2H), 2.34 (s, 3H), 1.44 (s, 9H)

MS m/ 528$(M+H)^+$

(xxiv) *terc*-Butil (6-metil-5-{[({4-metil-2-oxo-1-[(piridin-3-ilmetil)amino]-1,2-dihidropiridin-3-il}acetil)amino]metil}piridin-2-il)carbamato Preparado de acuerdo con el procedimiento descrito con respecto a Ejemplo 1(xxiii) más arriba.

$^1$H NMR (500 MHz, $CDCl_3$) δ 8.52-8.60 (m, 2H), 7.58-7.68 (m, 2H), 7.34-7.44 (m, 2H), 7.25-7.30 (m, 1H), 7.16 (d, 1H), 6.26-6.34 (m, 1H), 6.04 (d, 1H), 4.32 (d, 2H), 4.05 (d, 2H), 3.59 (s, 2H), 2.36 (s, 6H), 1.50 (s, 9H)

MS *m/z* 493$(M+H)^+$

(xxv) *terc*-Butil [5-({[(1-{[(2-metoxipiridin-3-il)metil]amino}-4-metil-2-oxo-1,2-dihidropiridin-3-il)acetil]amino}metil)-6-metil-piridin-2-il]carbamato

Preparado de acuerdo con el procedimiento descrito con respecto a Ejemplo 1(xxiii) más arriba.

$^1$H NMR (500 MHz, $CDCl_3$ ) δ 8.11 (dd, 1H), 7.63 (d, 1H), 7.36-7.45 (m, 3H), 7.24 (d, 1H), 7.19 (bs, 1H), 6.81 (dd, 1H), 6.57 (t, 1H), 6. 08 (d, 1H), 4.29 (d, 2H), 4.06 (d, 2H), 3.94 (s, 3H), 3.57 (s, 2H), 2.34-2.37 (m, 6H), 1.50 (s, 9H)

MS *m/z* 523 $(M+H)^+$

(xxvi) *terc*-Butil [4-cloro-2-({[(1-{[(2-metoxipiridin-3-il)metil]amino}-4-metil-2-oxo-1,2-dihidropiridin-3-il)acetil]amino}metil) bencil]carbamato
Preparado de acuerdo con el procedimiento descrito con respecto a Ejemplo 1(xxiii) más arriba.
$^1$H NMR (500 MHz, $CDCl_3$) δ 8.10 (dd, 1H), 7.57 (bs, 1H), 7.38 (d, 1H), 7.10-7. 26 (m, 4H), 6.80 (dd, 1H), 6.63 (bs, 1H), 6.08 (d, 1H), 5.38 (bs, 1H), 4.36 (d, 2H), 4.28 (bd, 2H), 4.10 (d, 2H), 3.93 (s, 3H), 3.57 (s, 2H), 2.34 (s, 3H), 1.44 (s, 9H)

(xxvii) 2-(1-{[(2-Metoxipiridin-3-il)metil]amino}-4-metil-2-oxo-1,2-dihidropiridin-3-il)-*N*-[2-(1H-tetrazol-1-il)bencil]acetamida
Preparado de acuerdo con el procedimiento descrito con respecto a Ejemplo 1(xxiii) más arriba. El compuesto crudo se purificó entonces por HPLC preparativa.
$^1$H NMR (500 MHz, $CD_3OD$) δ 9.54 (s, 1H), 8.04 (dd, 1H), 7.60-7.67(m, 2H), 7.51-7.57 (m, 2H), 7.47 (d, 1H), 7.41 (d, 1H), 6.87 (dd, 1H), 6.19 (d, 1H), 4.23 (s, 2H), 4.16 (s, 2H), 3.90 (s, 3H), 3.49 (s, 2H), 2.21 (s, 3H)
MS *m/z* 461 $(M+H)^+$

(xxviii) *terc*-Butil {5-[({[1-(bencilamino)-4-metil-2-oxo-1,2-dihidro-piridin-3-il]acetil}amino)metil]-4,6-dimetilpiridin-2-il}carbamato
Preparado de acuerdo con el procedimiento descrito con respecto a Ejemplo 1(xxii) más arriba.
$^1$H NMR (500 MHz, $CDCl_3$) δ 1.48 (s, 9H), 2.29 (s, 3H), 2.33 (s, 3H), 2.40 (s, 3H), 3.54 (s, 2H), 3.94 (d, 2H), 4.34 (d, 2H), 5.99 (d, 1H), 6.19 (t, 1H), 7.04 (br s, 1H), 7.14 (d, 1H), 7.23-7.28 (m, 3H), 7.29-7.35 (m, 3H), 7.56 (s, 1H)
MS *m/z* 506 $(M+H)^+$

(xxix) 2-[1-(Bencilamino)-4-metil-2-oxo-1,2-dihidropiridin-3-il]-*N*-[2-(1*H*-tetrazol-1-il)bencil]acetamida

Preparado de acuerdo con el procedimiento descrito con respecto a Ejemplo 1(xxii) más arriba.

$^1$H NMR (500 MHz, $CDCl_3$) δ 2.27 (s, 3H), 3.53 (s, 2H), 4.10 (d, 2H), 4.20 (d, 2H), 6.01 (d, 1H), 6.36 (t, 1H), 7.19 (d, 1H), 7.27-7.35 (m, 6H), 7.43 (m, 1H), 7.50-7.63 (m, 3H), 8.96 (s, 1H)

MS *m/z* 430 $(M+H)^+$

(xxx) *N*-[(6-Amino-2,5-dimetilpiridin-3-il)metil]-2-{1-[(3-metoxi-bencil)amino]-4-metil-2-oxo-1,2-dihidropiridin-3-il}acetamida

El correspondiente éster de Preparación 2 se hidrolizó como se describe en el anterior Método General. A continuación se llevó a cabo la reacción de acoplamiento de la amida como se describe en el anterior Método General, excepto que se usaron 1.5 equivalentes de la amina específica (ver Lista 5 más arriba) y que TEA se empleó en lugar de DIPEA y HOAt en lugar de HOBt.

$^1$H NMR (500 MHz, $CD_3OD$) δ 2.07 (s, 3H), 2.24 (s, 3H), 2.31 (s, 3H), 3.60 (s, 2H), 3.78 (s, 3H), 4.07 (s, 2H), 4.24 (d, 2H), 6.15 (d, 1H), 6.83-6.91 (m, 3H), 7.22 (t, 2H), 7.34 (d, 1H)

MS *m/z* 436 $(M+H)^+$

(xxxi) *terc*-Butil (4-metoxi-2-{[({4-metil-2-oxo-1-[(piridin-3-il-metil)amino]-1,2-dihidropiridin-3-il}acetil)amino]metil}bencil)-carbamato

Preparado de acuerdo con el procedimiento descrito con respecto a Ejemplo 1(xxiii) más arriba.

$^1$H NMR (500 MHz, $CDCl_3$) δ 1.45 (s, 9H), 2.34 (s, 3H), 3.59 (s, 2H), 3.71 (s, 3H), 4.02 (d, 2H), 4.24-4.29 (m, 2H), 4.40 (d, 2H), 5.29 (br s, 1H), 6.01 (d, 1H), 6.32 (br s, 1H), 6.73 (d, 1H), 6.77 (br s, 1H), 7.12 (d, 1H), 7.23 (d, 1H), 7.45 (br s, 1H), 7.63 (d, 1H), 8.52 (s, 1H), 8.56 (d, 1H)

MS *m/z* 523 $(M+H)^+$

(xxxii) *terc*-Butil [2-{[({4-metil-2-oxo-1-[(piridin-3-ilmetil)amino]-1,2-dihidropiridin-3-il}acetil)amino]metil}-4-(trifluorometil)bencil]- carbamato
Preparado de acuerdo con el procedimiento descrito con respecto a Ejemplo 1(xxiii) más arriba.
$^1$H NMR (500 MHz, $CDCl_3$) δ 1.45 (s,9H), 2.34 (s, 3H), 3.60 (s, 2H), 4.11 (d, 2H), 4.23-4.40 (m, 2H), 4.46 (d, 2H), 5.41 (t, 1H), 6.04 (d, 1H), 6.34 (br s, 1H), 7.17 (d, 1H), 7.24-7.30 (m, 1H), 7.38 (br s, 1H), 7.42-7.50 (m, 2H), 7.59 (br s, 1H), 7.64 (d, 1H), 8.52 (s, 1H), 8.56 (d, 1H)
MS *m/z* 560 $(M+H)^+$

(xxxiii) 2-{4-Metil-2-oxo-1-[(piridin-3-ilmetil)amino]-1,2-dihidro-piridin-3-il}-*N*-[(1-tritil-1*H*-benzimidazol-6-il)metil]acetamida
Preparado de acuerdo con el procedimiento descrito con respecto a Ejemplo 1(xxiii) más arriba.
$^1$H NMR (500 MHz, $CDCl_3$) δ 2.31 (s, 3H), 3.49 (s, 2H), 4.09 (d, 2H), 4.16 (d, 2H), 6.02 (d, 1H), 6.25 (t, 1H), 6.34 (s, 1H), 6.99 (t, 1H), 7.04 (d, 1H), 7.12-7.20 (m, 7H), 7.26-7.36 (m, 10H), 7.62 (d, 1H), 7.70 (d, 1H), 7.90 (s, 1H), 8.54 (s, 1H), 8.57 (d, 1H)
MS *m/z* 645 $(M+H)^+$

(xxxiv) *terc*-Butil (6-{[({4-metil-2-oxo-1-[(piridin-3-ilmetil)amino]-1,2-dihidropiridin-3-il}acetil)amino]metil}piridin-3-il)carbamato
Preparado de acuerdo con el procedimiento descrito con respecto a Ejemplo 1 (xxiii) más arriba.
$^1$H NMR (500 MHz, $CDCl_3$) δ 8.53 (m, 2H), 8.34 (d, 1H), 7.85 (d, 1H), 7.58-7.68 (m, 2H), 7.25 (m, 1H), 7.07-7.15 (m, 2H), 6.82 (s, 1H), 6.29 (t, 1H), 5.98 (d, 1H), 4.45 (d, 2H), 4.11 (d, 2H), 3.63 (s, 2H), 2.30 (s, 3H), 1.48 (s, 9H)

(xxxv) *terc*-Butil(4-cloro-2-{[({1-[(2,2-difluoro-2-piridin-2-iletil)-amino]-4-metil-2-oxo-1,2-dihidropiridin-3-il}acetil)amino]metil}-bencil)carbamato

Preparado de acuerdo con el procedimiento descrito con respecto a Ejemplo 1(xxiii) más arriba.

$^1$H NMR (500 MHz, $CDCl_3$) δ 8.64 (d, 1H), 7.84 (t, 1H), 7.70 (d, 1H), 7.52 (bs, 1H), 7.40 (t, 1H), 7.31 (d, 1H), 7.22 (d, 1H), 7.10-7.17 (m, 2H), 6.37 (bs, 1H), 6.08 (d, 1H), 5.36 (bs, 1H), 4.36 (d, 2H), 4.25 (s, 2H), 3.87 (dt, 2H), 3.55 (s, 2H), 2.34 (s, 3H), 1.44 (s, 9H)

(xxxvi) *terc*-Butil [4-cloro-2-({[(1-{[2,2-difluoro-2-(1-oxidopiridin-2-il)-etil]amino}-4-metil-2-oxo-1,2-dihidropiridin-3-il)acetil]amino}-metil)bencil]carbamato

A una solución de *terc*-butil (4-cloro-2-{[({1-[(2,2-difluoro-2-piridin-2-iletil)amino]-4-metil-2-oxo-1,2-dihidropiridin-3-il}acetil)amino]-metil}bencil)carbamato (0.20 mmol; ver Ejemplo 1(xxxv) más arriba) en DCE (1 mL) se agregó mCPBA (0.29 mmol), y la solución resultante se agitó a temperatura de la sala durante 3 días. Seguidamente, se agregaron mCPBA (0.29 mmol) y 4,4'-tiobis (2-*terc*-butil-5-metilfenol) (0.03 mmol), junto con DCE (1mL), y la mezcla resultante se calentó a 55°C durante 4 horas. La mezcla de reacción se diluyó con DCM y se lavó con $NaHCO_3$ (acuoso) y $Na_2SO_3$ (acuoso). La capa acuosa se extrajo con DCM, y las capas orgánicas combinadas se secaron a través de un separador de fase y se concentraron. El compuesto del título se purificó entonces por HPLC preparativa.

$^1$H NMR (500 MHz, $CDCl_3$) δ 8.12 (br s, 1H), 7.71 (m, 1H), 7.45 (br s, 1H), 7.37 (m, 1H), 7.20-7.26 (m, 2H), 7.13-7.19 (m, 2H), 6.33 (bs, 1H), 6.02 (d, 1H), 5.36 (br s, 1H), 4.39 (d, 2H), 4.20-4.31 (m, 4H), 3.56 (s, 2H), 2.32 (s, 3H), 1.45 (s, 9H)

Ejemplo 2

A menos que se indique lo contrario, los compuestos (i) a (xi) listados a continuación se prepararon de los compuestos correspondientes de Ejemplo 1 por el Método General A descrito más adelante.

Compuestos (xiii) y (xiv) a continuación se prepararon de los correspondientes compuestos de Ejemplo 1 por el Método General B descrito más adelante.

A menos que se indique lo contrario, compuestos (xv) a (xliii) se prepararon de los correspondientes compuestos de Ejemplo 1 por el Método General C descrito más adelante.

Método General A

Paladio en carbón (10%, 5 mg) y HCl (concentrado, 2-3 gotas) se agregaron a una solución del compuesto específico protegido con benciloxicarbonilo (0.06- 0.007 mmol; ver Ejemplo 1 más arriba) en metanol (2 mL). La suspensión se hidrogenó bajo presión atmosférica a temperatura de la sala durante 30 minutos. La suspensión se filtró a través de Celita®, se lavó con metanol (3 x 5 mL), y el disolvente se retiró bajo presión reducida.

El residuo se disolvió en un volumen mínimo de metanol, y el producto desprotegido se precipitó de acetato de etilo. Los rendimientos fueron casi cuantitativos.

Método General B

Gas de HCl se hizo burbujerar a través de una solución del compuesto específico Boc- protegido (0.06 mmol; ver Ejemplo 1 más arriba) en metanol (2 mL) durante 5 minutos. La solución se agitó a temperatura de la sala durante 30 minutos, y el disolvente se retiró bajo presión reducida para proporcionar los productos como sólidos. Los rendimientos fueron casi cuantitativos.

Método General C

El compuesto específico Boc- protegido (0.04 mmol; ver Ejemplo 1 más arriba) se disolvió en acetato de etilo saturado con HCl (2 mL) y se agitó a temperatura de la sala durante 30 minutos. El disolvente y el exceso de reactivos se evaporaron bajo presión reducida para proporcionar el producto deseado.

(i) *N*-(4-Carbamimidoilbencil)-2-(4-metil-2-oxo-1-fenilmetanesulfonilamino-1,2-dihidropiridin-3-il)acetamida

El compuesto se purificó adicionalmente por HPLC preparativa para proporcionar el producto final.

$^1$H NMR (400 MHz, $CD_3OD$) δ 2.26 (s, 3H), 3.66 (s, 2H), 4.46 (s, 4H), 6.23 (d, 1H), 7.26-7.67 (m, 10H), 8.71 (br s, 1H), 9.13 (br s, 1H)

MS *m/z* 468.1 $(M+H)^+$

(ii) 2-(1-Bencensulfonilamino-4-metil-2-oxo-1,2-dihidropiridin-3-il)-*N*-(4-carbamimidoilbencil)acetamida

$^1$H NMR (400 MHz, $CD_3OD$) δ 2.18 (s, 3H), 3.39 (s, 2H), 4.35 (s, 2H), 6.17 (d, 1H), 7.26-7.66 (m, 9H), 8.70 (br s, 1H), 9.18 (br s, 1H)

MS *m/z* 454.4 $(M+H)^+$

(iii) *N*-(4-Carbamimidoilbencil)-2-[1-(4-metoxibencensulfonilamino)-4-metil-2-oxo-1,2-dihidropiridin-3-il]acetamida

$^1$H NMR (400 MHz, $CD_3OD$) δ 2.21 (s, 3H), 3.31 (s, 2H), 3.72 (s, 3H), 4.32 (s, 2H), 6.17 (d, 1H), 6.85 (d, 2H), 7.26-7.51 (m, 3H), 7.61 (d, 2H), 7.81 (d, 2H), 8.69 (br s, 1H), 9.11 (br s, 1H)

MS *m/z* 484.4 $(M+H)^+$

(iv) *N*-(4-Carbamimidoilbencil)-2-[1-(2-metoxi-4-metilbencensulfonil-amino)-4-metil-2-oxo-1,2-dihidropiridin-3-il] acetamida

$^1$H NMR (400 MHz, $CD_3OD$) δ 2.21 (s, 3H), 2.37 (s, 3H), 3.41 (s, 2H), 3.95 (s, 3H), 4.38 (s, 2H), 6.22 (d, 1H), 6.76 (d, 1H), 7.00 (s, 1H), 7.46-7.53 (m, 4H), 7.74 (d, 1H), 8.75 (br s, 2H), 9.25 (br s, 2H)

MS *m/z* 498.4 $(M+H)^+$

(v) *N*-(4-Carbamimidoilbencil)-2-[1-(3,4-diclorobencensulfonilamino)-4-metil-2-oxo-1,2-dihidropiridin-3-il]acetamida

El compuesto se purificó adicionalmente por HPLC preparativa para proporcionar el producto final.

$^1$H NMR (400 MHz, $CD_3OD$) δ 2.26 (s, 3H), 3.41 (s, 2H), 4.43 (s, 2H), 6.23 (d, 1H), 7.37-7.93 (m, 9H), 8.73 (s, 1H), 9.27 (s, 1H)

MS *m/z* 522.0 $(M+H)^+$

(vi) *N*-(4-Carbamimidoilbencil)-2-[1-(3-metoxibencensulfonilamino)-4-metil-2-oxo-1,2-dihidropiridin-3-il]acetamida

$^1$H NMR (400 MHz, $CD_3OD$) δ 2.22 (s, 3H), 3.39 (s, 2H), 3.78 (s, 2H), 4.39 (s, 2H), 6.26 (d, 1H), 7.15 (d, 1H), 7.23 (d, 2H), 7.36 (t, 1H), 7.47 (t, 3H), 7.74 (d, 2H), 8.11 (br s, 1H), 8.76 (br s, 1H)

MS *m/z* 482.0 $(M+H)^+$

(vii) *N*-(4-Carbamimidoilbencil)-2-[1-(2,5-dimetilbencensulfonil-amino)-4-metil-2-oxo-1,2-dihidropiridin-3-il]acetamida

$^1$H NMR (400 MHz, $CD_3OD$) δ 2.20 (s, 3H), 2.24 (s, 3H), 2.61 (s, 3H), 3.38 (s, 2H), 4.39 (s, 2H), 6.18 (d, 1H), 7.22 (d, 1H), 7.32 (t, 2H), 7.47 (d, 3H), 7.74 (d, 1H), 8.72 (br s, 1H), 9.22 (br s, 1H)

MS *m/z* 482.1 $(M+H)^+$

(viii) *N*-(4-Carbamimidoilbencil)-2-[4-metil-1-(naftalen-1-sulfonil-amino)-2-oxo-1,2-dihidropiridin-3-il]acetamida

$^1$H NMR (400 MHz,$CD_3OD$) δ 2.17 (s, 3H), 3.18 (s, 2H), 4.32 (s, 2H), 6.16 (d, 1H), 7.25 (d, 1H), 7.40 (d, 2H), 7.50 (t, 1H), 7.59-7.61 (m, 2H), 7.70 (d, 2H), 7.97-8.01 (m, 1H), 8.07 (d, 1H), 8.17 (d, 1H), 8.57-8.61 (m, 1H), 8.71 (br s, 1H), 9.18 (br s, 1H)

MS *m/z* 504.1 $(M+H)^+$

(ix) *N*-(4-Carbamimidoilbencil)-2-(4-metil-2-oxo-1-fenetilamino-1,2-dihidropiridin-3-il)acetamida

$^1$H NMR (400 MHz, $CD_3OD$) δ 2.28 (s, 3H), 2.87 (t, 2H, $J$ = 6.9Hz), 3.30-3.34 (m, 2H), 3.68 (s, 2H), 4.48 (s, 2H), 6.38 (d, 1H), 7.19-7.29 (m, 5H), 7.52 (d, 2H), 7.68 (d, 1H), 7.72 (d, 2H), 8.78 (br s, 1H), 9.24 (br s, 1H)
MS *m/z* 418.4 $(M+H)^+$

(x) *N*-(4-Carbamimidoilbencil)-2-[4-metil-2-oxo-1-(2-o-toliletilamino)-1,2-dihidropiridin-3-il]acetamida
$^1$H NMR (400 MHz, $CD_3OD$) δ 1.30 (s, 2H), 2.27 (s, 2H), 2.81 (br s, 2H), 3.15 (br s, 2H), 3.63 (s, 3H), 4.46 (s, 3H), 6.30 (br s, 1H), 6.97-7.16 (m, 5H), 7.46-7.56 (m, 3H), 7.61 (br s, 1H), 7.68 (d, 2H), 8.71 (br s, 1H), 9.21 (br s, 1H)
MS *m/z* 432.4 $(M+H)^+$

(xi) *N*-(4-Carbamimidoilbencil)-2-{1-[2-(2,5-dimetilfenil) etilamino]-4-metil-2-oxo-1,2-dihidropiridin-3-il}acetamida
$^1$H NMR (400 MHz, $CD_3OD$) δ 2.20 (s, 3H), 2.23 (s, 3H), 2.25 (s, 3H), 2.78 (t, 2H), 3.18 (t, 2H), 3.64 (s, 2H), 4.44 (s, 2H), 6.27 (d, 1H), 6.89 (d, 1H), 6.94-6.99 (m, 1H), 7.44 (d, 2H), 7.58 (d, 2H), 7.66 (d, 2H)
MS *m/z* 446.5 $(M+H)^+$

(xii) *N*-(2-Aminometil-5-clorobencil)-2-[4-metil-1-(naftalen-1-sulfonilamino)-2-oxo-1,2-dihidropiridin-3-il]acetamida
La mida específica Boc-protegida (0.05mmol; ver Ejemplo 1 más arriba) se disolvió en HCl/dioxano (2 mL, 4 M) y se agitó a temperatura de la sala durante 2 horas. El disolvente se evaporó bajo presión reducida, y el residuo se purificó por cromatografía ($SiO_2$, 10% metanol en DCM + 1% TEA). El compuesto se disolvió en DCM y se lavó con agua (2x), se secó a través de un separador de fase, y el disolvente se evaporó bajo presión reducida para proporcionar el producto.
$^1$H NMR (500 MHz, $CD_3OD$) δ 2.15 (s, 3H), 3.23 (s, 2H), 4.20 (s, 2H), 4.33 (s, 2H), 5.98 (d, 1H), 6.88 (d, 1H), 7.34-7.38 (m, 2H), 7.43 (d, 1H), 7.48 (t, 1H), 7.59-7.65 (m, 2H), 8.00 (d, 2H), 8.13 (d, 1H), 8.73 (d, 1H)

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MS *m/z* 525.2 $(M+H)^+$

(xiii) *N*-(6-Aminopiridin-3-ilmetil)-2-{1-[2-(5-fluoro-2-metilfenil)-etilamino]-4-metil-2-oxo-1,2-dihidropiridin-3-il}acetamida

$^1$H NMR (400 MHz, $CD_3OD$) δ 2.21 (s, 3H), 2.27 (s, 3H), 2.88 (s, 2H), 3.37 (s, 2H), 3.65 (s, 2H), 4.26 (s, 2H), 6.52 (d, 1H), 6.78 (s, 1H), 6.89 (d, 1H), 6.97 (d, 1H), 7.08 (dd, 1H), 7.78-7.88 (m, 4H)

MS *m/z* 424.6 $(M+H)^+$

(xiv) *N*-(6-Aminopiridin-3-ilmetil)-2-{4-metil-2-oxo-1-[2-(2-trifluoro-metilfenil)etilamino]-1,2-dihidropiridin-3-il}acetamida

$^1$H NMR (400 MHz, $CD_3OD$) δ 2.23 (s, 3H), 2.81-3.01 (m, 2H), 3.31 (s, 3H), 3.59 (s, 2H), 4.27 (s, 2H), 6.16-6.33 (m, 1H), 6.95-7.01 (m, 1H), 7.49-7.54 (m,5H), 7.75-7.81 (m 1H), 7.86-7.93 (m, 1H)

MS *m/z* 460.5 $(M+H)^+$

(xv) *N*-[2-(Aminometil)-5-clorobencil]-2-[1-(bencilamino)-4-metil-2-oxo-1,2-dihidropiridin-3-il]acetamida clorhidrato

$^1$H NMR (500 MHz,$CD_3OD$) δ 2.21 (s, 3H), 3.60 (s, 2H), 4.11 (s, 2H), 4.27 (s, 2H), 4.43 (s, 2H), 6.16 (d, 1H), 7.28-7.39 (m, 7H), 7.42 (d, 1H), 7.46-7.48 (m, 1H)

MS *m/z* 425.2 $(M+H)^+$

(xvi) *N*-[2-({[Amino(imino)metil]amino}oxi)etil]-2-[1-(bencilamino)-4-metil-2-oxo-1,2-dihidropiridin-3-il]acetamida clorhidrato

Preparado de acuerdo con Método General C más arriba, excepto que la reacción se agitó durante 7 horas a temperatura de la sala.

$^1$H NMR (500 MHz, $CD_3OD$) δ 2.27 (s, 3H), 3.52 (t, 2H), 3.61 (s, 2H), 3.98 (t, 2H), 4.18 (s, 2H), 5.51 (s, 1H), 6.22 (d, 1H), 7.29-7.37 (m, 5H), 7.39 (d, 1H)

MS *m/z* 373.1 $(M+H)^+$

(xvii) *N*-[(6-Amino-2-metilpiridin-3-il)metil]-2-[1-(bencilamino)-4-metil-2-oxo-1,2-dihidropiridin-3-il]acetamida clorhidrato

Preparado de acuerdo con Método General C más arriba, excepto que la reacción se agitó durante 20 horas a temperatura de la sala.

$^1$H NMR (500 MHz, $CD_3OD$) δ 2.22 (s, 3H), 2.51 (s, 3H), 3.58 (s, 2H), 4.13 (s, 2H), 4.26 (s, 2H), 6.15 (d, 1H), 6.82 (d, 1H), 7.27- 7.36 (m, 6H), 7.87 (d, 1H)

MS *m/z* 392 $(M+H)^+$

(xviii) *N*-[2-(Aminometil)-5-clorobencil]-2-{4-metil-2-oxo-1-[(2-feniletil)amino]-1,2-dihidropiridin-3-il}acetamida clorhidrato

Preparado de acuerdo con Método General C más arriba, excepto que la reacción se agitó durante 90 minutos a temperatura de la sala.

$^1$H NMR (500 MHz, $CD_3OD$) δ 2.24 (s, 3H), 2.86 (t, 2H), 3.32-3.34 (m, 2H), 3.61 (s, 2H), 4.25 (s, 2H), 4.42 (s, 2H), 6.34 (d, 1H), 7.17-7.25 (m, 3H), 7.26-7.30 (m, 2H), 7.34 (dd, 1H), 7.40-7.47 (m, 2H), 7.63 (d, 1H)

MS *m/z* 439 $(M+H)^+$

(xix) *N*-[(6-Amino-2-metilpiridin-3-il)metil]-2-{4-metil-2-oxo-1-[(2-feniletil)amino]-1,2-dihidropiridin-3-il}acetamida clorhidrato

Preparado de acuerdo con Método General C más arriba, excepto que la reacción se agitó durante 90 minutos a temperatura de la sala.

$^1$H NMR (500 MHz, $CD_3OD$) δ 2.26 (s, 3H), 2.51 (s, 3H), 2.86 (t, 2H), 3.31- 3.34 (m, 2H), 3.60 (s, 2H), 4.27 (s, 2H), 6.34 (d, 1H), 6.81 (d, 1H), 7.17-7.25 (m, 3H), 7.26-7.31 (m, 2H), 7.63 (d, 1H), 7.86 (d, 1H)

MS *m/z* 406 $(M+H)^+$

(xx) *N*-[2-(Aminometil)-5-clorobencil]-2-{1-[(3-metoxibencil)- amino]-4-metil-2-oxo-1,2-dihidropiridin-3-il}acetamida clorhidrato

$^1$H NMR (500 MHz, $CD_3OD$) δ 2.12 (s, 3H), 3.51 (s, 2H), 3.68 (s, 3H), 4.00 (s, 2H), 4.17 (s, 2H), 4.33 (s, 2H), 6.07 (d, 1H), 6.74-6.82 (m, 3H), 7.13 (t,- 1H), 7.25-7.29 (m, 2H), 7.34 (d, 1H), 7.37 (s, 1H)

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MS *m/z* 457 $(M+H)^+$

(xxi) *N*-[(6-Amino-2-metilpiridin-3-il)metil]-2-{1-[(3-metoxibencil)-amino]-4-metil-2-oxo-1,2-dihidropiridin-3-il}acetamida clorhidrato

$^1$H NMR (500 MHz, $CD_3OD$) δ 2.23 (s, 3H), 2.52 (s,3H), 3.60 (s, 2H), 3.77 (s, 3H), 4.11 (s, 2H), 4.27 (s, 2H), 6.17 (d, 1H), 6.80-6.92 (m, 4H), 7.23 (t, 1H), 7.37 (d, 1H), 7.87 (s, 1H)

MS *m/z* 422 $(M+H)^+$

(xxii) *N*-[2-(Aminometil)-5-clorobencil]-2-{4-metil-2-oxo-1-[(piridin-3-ilmetil)amino]-1,2-dihidropiridin-3-il}acetamida

Preparada de acuerdo con Método General C más arriba, excepto que la reacción se agitó durante 3 días a temperatura de la sala.

$^1$H NMR (500 MHz, $CD_3OD$) δ. 8.92 (s, 1H), 8.82 (d, 1H), 8.66 (d, 1H), 8.08 (dd, 1H), 7.54 (d, 1H), 7.48 (d, 1H), 7.44 (d, 1H), 7.38 (dd, 1H), 6.22 (d, 1H), 4.43 (s, 4H), 4.28 (s, 2H), 3.58 (s, 2H), 2.20 (s, 3H)

MS *m/z* 428 $(M+H)^+$

(xxiii) *N*-[(6-Amino-2-metilpiridin-3-il)metil]-2-{4-metil-2-oxo-1-[(piridin-3-ilmetil)amino]-1,2-dihidropiridin-3-il}acetamida

Preparada de acuerdo con Método General C más arriba, excepto que la reacción se agitó durante 3 días a temperatura de la sala.

$^1$H NMR (500 MHz, $CD_3OD$) δ. 8.92 (s, 1H), 8.83 (d, 1H), 8.66 (d, 1H), 8.07 (t, 1H), 7. 87 (d, 1H), 7.55 (d, 1H), 6.85 (d, 1H), 6.23 (d, 1H), 4.90 (d, 2H), 4.44 (s, 2H), 4.26 (s, 2H), 3.56 (s, 2H), 2.53 (s, 3H), 2.19 (s, 3H)

MS *m/z* 393 $(M+H)^+$

(xxiv) *N*-[2-(Aminometil)-5-clorobencil]-2-(1-{[(2-metoxipiridin-3-il)metil]amino}-4-metil-2-oxo-1,2-dihidropiridin-3-il)acetamida acetato

Preparado de acuerdo con Método General C más arriba, excepto que la reacción se agitó durante 3 días a temperatura de la sala. El producto crudo se purificó por HPLC preparativa.

$^1$H NMR (500 MHz, $CD_3OD$) δ 8.03 (dd, 1H), 7.52 (dd, 1H), 7.34-7.43 (m, 3H), 7.30 (dd, 1H), 6.85 (dd, 1H), 6.18 (d, 1H), 4.38 (s, 2H), 4.13 (s, 2H), 4.08 (s, 2H), 3.87 (s, 3H), 3.53 (s, 2H), 2.20 (s, 3H), 1.89 (s, 3H)
MS *m/z* 458 $(M+H)^+$

(xxv) *N*-[(6-Amino-2-metilpiridin-3-il)metil]-2-(1-{[(2-metoxi-piridin-3-il)metil]amino}-4-metil-2-oxo-1,2-dihidropiridin-3-il)-acetamida acetato
Preparado de acuerdo con Método General C más arriba, excepto que la reacción se agitó durante 3 días a temperatura de la sala. El producto crudo se purificó por HPLC preparativa.
$^1$H NMR (500 MHz, $CD_3OD$) δ 8.06 (dd, 1H), 7.54 (dd, 1H), 7.37-7.41 (m, 2H), 6.88 (dd, 1H), 6.41 (d, 1H), 6.20 (d, 1H), 4.23 (s, 2H), 4.15 (s, 2H), 3.90 (s, 3H), 3.54 (s, 2H), 2.34 (s, 3H), 2.23 (s, 3H), 1.97 (s, 3H)
MS *m/z* 423 $(M+H)^+$

(xxvi) *N*-[(6-Amino-2,4-dimetilpiridin-3-il)metil]-2-[5-(bencilamino)-2-metil-6-oxociclohexa-1,3-dien-1-il]acetamida clorhidrato
Preparado de acuerdo con Método General C más arriba, excepto que la reacción se agitó un día para otro a temperatura de la sala.
$^1$H NMR (500 MHz, $CD_3OD$) δ 2.22 (s, 3H), 2.45 (s, 3H), 2.56 (s, 3H), 3.54 (br s, 2H), 4.11 (br s, 2H), 4.32 (s, 2H), 6.14 (br s, 1H), 6.68 (s, 1H), 7.27-7.36 (m, 6H)

(xxxvii) *N*-[2-(Aminometil)-5-metoxibencil]-2-{4-metil-2-oxo-1- [(piridin-3-ilmetil)amino]-1,2-dihidropiridin-3-il}acetamida
Preparada de acuerdo con el procedimiento descrito con respecto a Ejemplo 2 (xxvi) más arriba.
$^1$H NMR (500 MHz, $CD_3OD$) δ 2.24 (s, 3H), 3.61 (s, 2H), 3.75 (s, 3H), 3.80 (s, 2H), 4.18 (s, 2H), 4.42 (s, 2H), 6.15 (d, 1H), 6.80 (d, 1H), 6.89 (s, 1H), 7.25 (d, 1H), 7.36 (d, 1H), 7.41 (dd, 1H), 7.84 (d, 1H), 8.52 (s, 1H), 8.47 (s, 2H)
MS *m/z* 422 $(M+H)^+$

(xxxviii) *N*-[2-(Aminometil)-5-(trifluorometil)bencil]-2-{4-metil-2- oxo-1-[(piridin-3-ilmetil)amino]-1,2-dihidropiridin-3-il}acetamida

Preparada de acuerdo con el procedimiento descrito con respecto a Ejemplo 2 (xxvi) más arriba.

$^1$H NMR (500 MHz, $CD_3OD$) δ 2.23 (s, 3H), 3.62 (s, 2H), 3.94 (s, 2H), 4.20 (s, 2H), 4.51 (s, 2H), 6.17 (d, 1H), 7.39 (d, 1H), 7.40-7.43 (m, 1H), 7.54-7.62 (m, 3H), 7.86 (d, 1H), 8.46-8.50 (m, 2H)

MS *m/z* 460 $(M+H)^+$

(xxxix) *N*-(1*H*-Benzimidazol-6-ilmetil)-2-{4-metil-2-oxo-1-[(piridin-3-ilmetil)amino]-1,2-dihidropiridin-3-il}acetamida

El compuesto de Ejemplo 1(xxxiii) más arriba (38 mg. 0.059 mmol) se hizo reaccionar con TFA:agua:tioanisol: 1,2-etanoditiol (2 mL de 35:2:2:1) durante 3 horas. Ácido acético se agregó a la mezcla de reacción antes que el disolvente se evaporara bajo presión reducida. El residuo se trituró con éter dietílico, y el producto crudo se purificó por HPLC preparativa con el fin de proporcionar el compuesto del título.

$^1$H NMR (500 MHz, $CD_3OD$) δ 2.24 (s, 3H), 3.64 (s, 2H), 4.16 (s, 2H), 4.51 (s, 2H), 6.16 (d, 1H), 7.24 (d, 1H), 7.35 (d, 1H), 7.38 (dd, 1H), 7.54-7.58 (m, 2H), 7.78 (d, 1H), 8.13 (s, 1H), 7.44-7.46 (m, 2H)

MS *m/z* 403 $(M+H)^+$

(xl) *N*-[(5-Aminopiridin-2-il)metil]-2-{4-metil-2-oxo-1-[(piridin-3-il-metil)amino]-1,2-dihidropiridin-3-il}acetamida

Preparada de acuerdo con el procedimiento descrito con respecto a Ejemplo 2(xxvi) más arriba.

$^1$H NMR (500 MHz, $CD_3OD$) δ 8.91 (s, 1H), 8.82 (d, 1H), 8.68 (d, 1H), 8.05-8.09 (m, 2H), 7.73 (dd, 1H), 7.67 (d, 1H), 7.58 (d, 1H), 6.28 (d, 1H), 4.58 (s, 2H), 4.49 (s, 2H), 3.62 (s, 2H), 2.25 (s, 3H)

(xli) *N*-[2-(Aminometil)-5-clorobencil]-2-{1-[(2,2-difluoro-2-piridin-2-iletil)amino]-4-metil-2-oxo-1,2-dihidropiridin-3-il}acetamida

Preparada de acuerdo con el procedimiento descrito con respecto a Ejemplo 2 (xxvi) más arriba.

$^1$H NMR (500 MHz, $CD_3OD$) δ 8.73 (m, 1H), 8.21 (m, 1H), 7.95 (m, 1H), 7.73 (m, 1H), 7.45 (m, d, 1H), 7.40-7.44 (m, 2H), 7.35 (dd, 1H), 6.23 (dd, 1H), 4.42 (s, 2H), 4.26 (s, 2H), 3.90 (m, 2H), 3.59 (s, 2H), 2.23 (s, 3H)

MS *m/z* 474 $(M+H)^+$

(xlii) *N*-[2-(Aminometil)-5-clorobencil]-2-(1-{[2,2-difluoro-2-(1-oxido-piridin-2-il)etil]amino}-4-metil-2-oxo-1,2-dihidropiridin-3-il) acetamida

Preparada de acuerdo con el procedimiento descrito con respecto a Ejemplo 2 (xxvi) más arriba.

$^1$H NMR (500 MHz, $CD_3OD$) δ 8.26 (d, 1H), 7.92 (dd, 1H), 7.60-7.70 (m, 2H), 7.49 (d, 1H), 7.36-7.43 (m, 2H), 7.16 (d, 1H), 6.05 (d, 1H), 4.43 (s, 2H), 4.26 (s, 2H), 4.20 (m, 2H), 3.54 (s, 2H), 2.20 (s, 3H)

MS *m/z* 492 $(M+H)^+$

(xliii) *N*-[2-(Aminometil)-5-clorobencil]-2-(4-metil-2-oxo-1-{[(2-oxo- 1,2-dihidropiridin-3-il)metil]amino}-1,2-dihidropiridin-3-il)acetamida acetato

Preparado del compuesto de Ejemplo 1(xxvi) usando el Método General B más arriba y empleando un tiempo de reacción ampliado. El compuesto del título se aisló por HPLC preparativa.

$^1$H NMR (500 MHz, $CD_3OD$) δ 7.51 (d, 1H), 7.43 (dd, 1H), 7.34-7.44 (m, 3H), 7.30 (d, 1H), 6.28 (t, 1H), 6.22 (d, 1H), 4.38 (s, 2H), 4.14 (s, 2H), 3.97 (s, 2H), 3.50 (s, 2H), 2.21 (s, 3H), 1.90 (s, 3H)

MS *m/z* 442 $(M+H)^+$

Ejemplo 3

Los compuestos (i) a (xiii) a continuación se prepararon de acuerdo con el siguiente Método General.

Los ésteres relevantes (obtenidos de la Preparación 4 más arriba) se disolvieron en THF (4mL). Se agregó LiOH acuoso (2.5 mL de 0.5 M, 1.3 mmol) a la solución resultante. Las mezclas de reacción se agitaron a temperatura de la sala durante 5 a 25 horas. A continuación el disolvente se evaporó bajo presión reducida para producir los ácidos carboxílicos correspondientes como sales de litio, las cuales se almacenaron a -80°C y se usaron luego sin purificación posterior.

Las sales crudas de ácido carboxílico se disolvieron en DMF (1mL), y se agregó *N*-metilmorfolina (88 µL, 0.8 mmol). TBTU (192 mg, 0.6 mmol) se disolvió en 0.5mL de DMF y se agregó a cada mezcla de reacción, y las mezclas de reacción se agitaron entonces a temperatura de la sala durante 30 minutos. A continuación se agregó una solución de 2-[2-(aminometil)-4-clorofenoxi]-N-etilacetamida (1 mol equiv; ver Lista 5 más arriba) en DMF (1 mL) a cada mezcla de reacción. Las mezclas de reacción se agitaron a temperatura de la sala un día para otro, antes de filtrarlas y evaporarlas por HPLC preparativa. Las mezclas crudas se purificaron por HPLC preparativa (ver Detalles Experimentales Generales más arriba) para proporcionar las amidas listadas más adelante como aceites o sólidos. Los rendimientos en tres pasos para estas amidas fueron de 7 a 29% (Pureza > 85%; UV a 215nm).

(i) 2-{4-Cloro-2-[({[1-(isobutilamino)-4-metil-2-oxo-1,2-dihidro- piridin-3-il]acetil}amino)metil]fenoxi}-*N*-etilacetamida

$^1$H NMR (500 MHz, DMSO-$d_6$) δ 8.29 (t, 1H), 8.04 (t, 1H), 7.56 (d, 1H), 7.26 (m, 2H), 6.92 (d, 1H), 6.42 (t, 1H), 6.11 (d, 1H), 4.46 (s, 2H), 4.33 (d, 2H), 3.47 (s, 2H), 3.10 (q, 2H), 2.71 (t, 2H), 2.12 (s, 3H), 1.68 (m, 1H), 0.99 (t, 3H), 0.92 (d, 6H).

MS *m/z* 463. 4 $(M+H)^+$

(ii) 2-[4-Cloro-2-({[(4-metil-2-oxo-1-{[(1-fenil-1*H*-pirazol-5-il)metil]amino}-1,2-dihidropiridin-3-il)acetil]amino}metil)fenoxi]-*N*-etilacetamida

$^1$H NMR (500 MHz, DMSO-d6) δ 8.28 (t, 1H), 8.04 (t, 1H), 7.60 (d, 1H), 7.51 (m, 4H), 7.42 (t, 1H), 7.26 (m, 2H), 7.19 (d, 1H), 6.91 (m, 2H), 6.35 (d, 1H), 5.99 (d, 1H), 4.46 (s, 2H), 4.32 (d, 2H), 4.22 (d, 2H), 3.44 (s, 2H), 3.09 (q, 2H), 2.09 (s, 3H), 0.98 (t, 3H).
MS *m/z* 563 $(M+H)^+$

(iii) 2-{4-Cloro-2-[({[1-({[2,5-dimetil-1-(4*H*-1,2,4-triazol-4-il)-1*H*-pirrol-3-il]metil}amino)-4-metil-2-oxo-1,2-dihidropiridin-3-il]acetil} amino)metil]fenoxi}-*N*-etilacetamida
$^1$H NMR (500 MHz, DMSO-$d_6$) δ 9.01 (s, 2H), 8.32 (t, 1H), 8.04 (t, 1H), 7.42 (d, 1H), 7.26 (m, 2H), 6.92 (d, 1H), 6.37 (t, 1H), 6.10 (d, 1H), 5.97 (s, 1H), 4.46 (s, 2H), 4.33 (d, 2H), 3.83 (d, 2H), 3.48 (s, 2H), 3.10 (q, 2H), 2.13 (s, 3H), 1.91 (s, 3H), 1.77 (s, 1H), 0.99 (t, 3H).
MS *m/z* 581.5 $(M+H)^+$

(iv) 2-(1-{[(4-Benzoil-1-metil-1*H*-pirrol-2-il)metil]amino}-4-metil- 2-oxo-1,2-dihidropiridin-3-il)-*N*-{5-cloro-2-[2-(etilamino)-2-oxoetoxi]bencil}acetamida
$^1$H NMR (500 MHz, DMSO-$d_6$) δ 8.31 (t, 1H), 8.05 (t, 1H), 7.70 (d, 2H), 7.58 (m, 1H), 7.47 (m, 3H), 7.29 (m, 3H), 6.92 (d, 1H), 6.70 (t, 1H), 6.30 (s, 1H), 6.05 (d, 1H), 4.47 (s, 2H), 4.33 (d, 2H), 4.10 (d, 2H), 3.76 (s, 3H), 3.49 (s, 2H), 3.11 (q, 2H), 2.12 (s, 3H), 1.00 (t, 3H).
MS *m/z* 604.5 $(M+H)^+$

(v) 2-(4-Cloro-2-{[({1-[(2,3-dihidro-1-benzofuran-5-ilmetil)amino]-4-metil-2-oxo-1,2-dihidropiridin-3-il}acetil)amino]metil}fenoxi)-*N*-etilacetamida
$^1$H NMR (500 MHz, DMSO-$d_6$) δ 8.29 (t, 1H), 8.05 (t, 1H), 7.40 (d, 1H), 7.26 (m, 2H), 7.20 (s, 1H), 7.00 (d, 1H), 6.92 (d, 1H), 6.68 (d, 1H), 6.59 (t, 1H), 6.04 (d, 1H), 4.50 (m, 4H), 4.33 (d, 2H), 3.96 (d, 2H), 3.48 (s, 2H), 3.12 (m, 4H), 2.11 (s, 3H), 1.00 (t, 3H).
MS *m/z* 538.8 $(M+H)^+$

(vi) 2-[4-Cloro-2-({[(1-{[(2,4-dimetil-1,3-tiazol-5-il)metil]amino}-4-metil-2-oxo-1,2-dihidropiridin-3-il)acetil]amino}metil)fenoxi]-*N*-etilacetamida

$^1$H NMR (500 MHz, DMSO-$d_6$) δ 8.29 (t, 1H), 8.05 (m, 1H), 7.28 (m, 2H), 7.22 (d, 1H), 6.92 (d, 1H), 6.84 (t, 1H), 6.01 (d, 1H), 4.47 (s, 2H), 4.33 (d, 2H), 4.19 (d, 2H), 3.48 (s, 2H), 3.11 (q, 2H), 2.55 (s, 3H), 2.11 (s, 3H), 2.03 (s, 3H), 1.00 (t, 3H).

MS *m/z* 532.2 $(M+H)^+$

(vii) 2-[4-Cloro-2-({[(1-{[(1,5-dimetil-1*H*-pirazol-4-il)metil]amino}-4-metil-2-oxo-1,2-dihidropiridin-3-il)acetil]amino}metil)fenoxi]-*N*-etilacetamida

$^1$H NMR (500 MHz, DMSO-$d_6$) δ 8.29 (t, 1H), 8.05 (m, 1H), 7.36 (d, 1H), 7.26 (m, 2H), 7.20 (s, 1H), 6.92 (d, 1H), 6.39 (t, 1H), 6.05 (d, 1H), 4.47 (s, 2H), 4.33 (d, 2H), 3.86 (d, 2H), 3.67 (s, 3H), 3.48 (s, 2H), 3.11 (q, 2H), 2.13 (s, 3H), 2.12 (s, 3H), 1.00 (t, 3H).

MS *m/z* 514.8 $(M+H)^+$

(viii) 2-{4-Cloro-2-[({[4-metil-2-oxo-1-({[1-(fenilsulfonil)-1*H*-pirrol-2-il]metil}amino)-1,2-dihidropiridin-3-il]acetil}amino)metil]-fenoxi}-*N*-etilacetamida

$^1$H NMR (500 MHz, DMSO-$d_6$) δ 8.26 (t, 1H), 8.04 (t, 1H), 7.96 (d, 2H), 7.27 (t, 1H), 7.61 (t, 2H), 7.43 (dd, 1H), 7.25 (m, 2H), 6.93 (m, 2H), 6.78 (t, 1H), 6.23 (t, 1H), 6.10 (m, 1H), 5.96 (d, 1H), 4.47 (s, 2H), 4.32 (d, 2H), 4.23 (d, 2H), 3.44 (s, 2H), 3.10 (q, 2H), 2.08 (s, 3H), 0.99 (t, 3H).

MS *m/z* 626.4 $(M+H)^+$

(ix) 2-[4-Cloro-2-({[(1-{[(3,5-dimetilisoxazol-4-il)metil]amino}-4-metil-2-oxo-1,2-dihidropiridin-3-il)acetil]amino}metil)fenoxi]-*N*-etilacetamida

$^1$H NMR (500 MHz, DMSO-$d_6$) δ 1.01 (t, 3H), 2.10 (s, 3H), 2.12 (s, 3H), 2.16 (s, 3H), 3.12 (p, 2H), 3.47 (s, 2H), 3.89 (d, 2H), 4.32 (d, 2H), 4.48 (s,

2H), 6.02 (d, 1H), 6.67 (t, 1H), 6.93 (d, 1H), 7.21-7.31 (m, 3H), 8.05 (t, 1H), 8.31 (t, 1H)
MS *m/z* 516.4 $(M+H)^+$

(x) 2-[4-Cloro-2-({[(1-{[(4-cloro-2-fenil-1*H*-imidazol-5-il)metil] amino}-4-metil-2-oxo-1,2-dihidropiridin-3-il)acetil]amino}metil) fenoxi]-*N*-etilacetamida
$^1$H NMR (500 MHz, DMSO-$d_6$) δ 1.01 (t, 3H), 2.11 (s, 3H), 3.13 (p, 2H), 3.49 (s, 2H), 4.12 (d, 2H), 4.33 (d, 2H), 4.48 (s, 2H), 6.02 (d, 1H), 6.91-6.95 (m, 1H), 6.98 (t, 1H), 7.20 (d, 1H), 7.25-7.28 (m, 2H), 7.37 (t, 1H), 7.46 (t, 2H), 7.90 (d, 2H), 8.05 (t, 1H), 8.31 (t, 1H), 12.98 (s, 1H)
MS *m/z* 539.4 $(M+H)^+$

(xi) 2-{1-[(2,1,3-Benzoxadiazol-5-ilmetil)amino]-4-metil-2-oxo-1,2-dihidropiridin-3-il}-*N*-{5-cloro-2-[2-(etilamino)-2-oxoetoxi]bencil}-acetamida
$^1$H NMR (500 MHz, DMSO-$d_6$) δ 1.00 (t, 3H), 2.09 (s, 3H), 3.10 (p, 2H), 3.46 (s, 2H), 4.25 (d, 2H), 4.32 (d, 2H), 4.48 (s, 2H), 6.02 (d, 1H), 6.93 (d, 1H), 7.14 (t, 1H), 7.24-7.28 (m, 2H), 7.45 (d, 1H), 7.68 (d, 1H), 7.83 (s, 1H), 8.00-8.07 (m, 2H), 8.28 (t, 1H)
MS *m/z* 539.4 $(M+H)^+$

(xii) 2-(4-Cloro-2-{[({4-metil-2-oxo-1-[(pirazin-2-ilmetil)amino]-1,2-dihidropiridin-3-il}acetil)amino]metil}fenoxi)-*N*-etilacetamida
MS *m/z* 499.4 $(M+H)^+$

(xiii) 2-(4-Cloro-2-{[({1-[(ciclopentilmetil)amino]-4-metil-2-oxo-1,2-dihidropiridin-3-il}acetil)amino]metil}fenoxi)-*N*-etilacetamida
$^1$H NMR (500 MHz, DMSO-$d_6$) δ 1.00 (t, 3H), 1.18-1-26 (m, 2H), 1.43-1.59 (m, 4H), 1.69-1.77 (m, 2H), 1.91-1.99 (m, 1H), 2.12 (s, 3H), 2.83 (t, 2H), 3.10 (p, 2H), 3.47 (s, 2H), 4.32 (d, 2H), 4.46 (s, 2H), 6.12 (d, 1H), 6.39

(t, 1H), 6.92 (d, 1H), 7.24-7.28 (m, 2H), 7.57 (d, 1H), 8.03 (t, 1H), 8.29 (t, 1H)

MS *m/z* 489.4 $(M+H)^+$

Ejemplo 4

Los compuestos (i) a (xxix), más adelante, se prepararon de acuerdo con el siguiente Método General.

Los ésteres relevantes (obtenidos de Preparación 4 más arriba) se disolvieron en THF (4mL). Se agregó LiOH acuoso (2.5 mL de 0.5 M, 1.3 mmol) a la solución resultante. Las mezclas de reacción se agitaron a temperatura de la sala durante 5 a 25 horas. A continuación el disolvente se evaporó bajo presión reducida para proporcionar los ácidos carboxílicos correspondientes como sales de litio, las cuales se almacenaron a -80°C y se usaron luego sin purificación posterior.

Las sales crudas de ácido carboxílico se disolvieron en DMF (1 mL), y se agregó *N*-metilmorfolina (88 µL, 0.8 mmol). TBTU (192 mg, 0.6 mmol) se disolvió en 0.5mL de DMF y se agregó a cada mezcla de reacción, y las mezclas de reacción se agitaron entonces a temperatura de la sala durante 30 minutos. Una solución de la amina específica (1 mol equiv; ver Lista 5 más arriba) en DMF (1 mL) se agregó entonces a cada mezcla de reacción. Las mezclas de reacción se agitaron a temperatura de la sala un día para otro, antes de filtrarlas y evaporarlas a sequedad.

Los residuos resultantes (amidas Boc-protegidas) se disolvieron en TFA (1.5 mL), se agitaron a temperatura de la sala durante 1 hora y luego se concentraron *in vacuo*. Las mezclas crudas se purificaron por HPLC preparativa (ver Detalles Experimentales Generales más arriba) para proporcionar las amidas listadas a continuación como aceites o sólidos. Los rendimientos en cuatro pasos para estas amidas fueron 2 a 47% (Pureza >87%; UV a 215nm).

(i) *N*-[2-(Aminometil)-5-clorobencil]-2-(4-metil-2-oxo-1-{[(5-piridin- 2-il-2-tienil)metil]amino}-1,2-dihidropiridin-3-il)acetamida

$^1$H NMR (500 MHz, DMSO-$d_6$) δ 2.11 (s, 3H), 3.48 (s, 2H), 3.83 (s, 2H), 4.27-4.35 (m, 4H), 6.03 (d, 1H), 6.91 (d, 1H), 7.03 (t, 1H), 7.24-7.29 (m, 2H), 7.30 (s, 1H), 7.38-7.42 (m, 2H), 7.60 (d, 1H), 7.81 (dt, 1H), 7.86 (d, 1H), 8.38 (t, 1H), 8.51 (d, 1H).
MS *m/z* 508.4 $(M+H)^+$

(ii) *N*-[2-(Aminometil)-5-clorobencil]-2-(1-{[(5-cloro-1,3-dimetil-1*H*-pirazol-4-il)metil]amino}-4-metil-2-oxo-1,2-dihidropiridin-3-il)-acetamida
$^1$H NMR (500 MHz, DMSO-$d_6$) δ 2.04 (s, 3H), 2.13 (s, 3H), 3.48 (s, 2H), 3.67 (s, 3H), 3.72 (s, 2H), 3.88 (d, 2H), 4.29 (d, 2H), 6.02 (d, 1H), 6.61 (t, 1H), 7.17 (d, 1H), 7.24-7.28 (m, 2H), 7.39 (d, 1H), 8.32 (t, 1H)
MS *m/z* 476.7 $(M+H)^+$

(iii) *N*-[2-(Aminometil)-5-clorobencil]-2-(1-{[(6-cloro-1,3-benzo- dioxol-5-il)metil]amino}-4-metil-2-oxo-1,2-dihidropiridin-3-il)- acetamida
$^1$H NMR (500 MHz, DMSO-$d_6$) δ 8.32 (t, 1H), 7.35-7.41 (m, 2H), 7.24-7.29 (m, 2H), 7.04 (s, 1H), 7.01 (s, 1H), 6.87 (t, 1H), 6.06 (m, 3H), 4.29 (d, 2H), 4.10 (d, 2H), 3.73 (s, 2H), 3.47 (s, 2H), 2.13 (s, 3H)
MS *m/z* 502.7 $(M+H)^+$

(iv) *N*-[(6-amino-2,4-dimetilpiridin-3-il)metil]-2-(4-metil-1-{[(1-metil-1*H*-imidazol-2-il)metil]amino}-2-oxo-1,2-dihidropiridin-3-il)- acetamida
$^1$H NMR (500 MHz, DMSO-$d_6$) δ 7.79 (t, 1H), 7.18 (d, 1H), 7.09 (s, 1H), 6.80 (t, 1H), 6.74 (s, 1H), 6.10 (s, 1H), 5.99 (d, 1H), 5.62 (s, 2H), 4.11 (m, 4H), 3.66 (s, 2H), 2.27 (s, 3H), 2.13 (s, 3H), 2.09 (s, 3H)
MS *m/z* 409.8 $(M+H)^+$

(v) *N*-[(6-Amino-2,4-dimetilpiridin-3-il)metil]-2-{1-[(ciclohexil-metil)amino]-4-metil-2-oxo-1,2-dihidropiridin-3-il}acetamida
$^1$H NMR (500 MHz, DMSO-$d_6$) δ 7.76 (t, 1H), 7.52 (d, 1H), 6.41 (t, 1H), 6.09-6.13 (m, 2H), 5.65 (s, 2H), 4.10 (d, 2H), 3.39 (s, 2H), 2.71 (t, 2H),

2.25 (s, 3H), 2.11 (s, 6H), 1.77 (d, 2H), 1.57-1.71 (m, 3H), 1.39 (m, 1H), 1.10-1.25 (m, 3H), 0.88-0.98 (m, 2H)
MS *m/z* 412.4 $(M+H)^+$

(vi) *N*-[(6-Amino-2,4-dimetilpiridin-3-il)metil]-2-(4-metil-1-{[(4- metil-3,4-dihidro-2*H*-1,4-benzoxazin-7-il)metil]amino}-2-oxo-1,2-dihidropiridin-3-il)acetamida
MS *m/z* 477.5 $(M+H)^+$

(vii) *N*-[(6-Amino-2,4-dimetilpiridin-3-il)metil]-2-{1-[(4-ciano-bencil)amino]-4-metil-2-oxo-1,2-dihidropiridin-3-il}acetamida
$^1$H NMR (500 MHz, DMSO-$d_6$) δ 7.74-7.80 (m, 3H), 7.51 (d, 2H), 7.33-7.37 (m, 1H), 7.06 (t, 1H), 6.10 (s, 1H), 6.00 (d, 1H), 5.63 (s, 2H), 4.15 (d, 2H), 4.11 (d, 2H), 3.38 (s, 2H), 2.26 (s, 3H), 2.13 (s, 3H), 2.08 (s, 3H)
MS *m/z* 430.8 $(M+H)^+$

(viii) *N*-[(6-Amino-2-metilpiridin-3-il)metil]-2-{4-metil-2-oxo-1-[(2-fenoxibencil)amino]-1,2-dihidropiridin-3-il}acetamida
$^1$H NMR (500 MHz, DMSO-$d_6$) δ 7.95 (t, 1H), 7.45 (d, 1H), 7.25-7.36 (m, 4H), 7.08-7.19 (m, 3H), 6.96 (t, 1H), 6.89 (d, 1H), 6.81 (d, 1H), 6.21 (d, 1H), 6.00 (d, 1H), 5.69 (s, 2H), 4.13 (d, 2H), 4.03 (d, 2H), 3.36 (s, 2H), 2.21 (s, 3H), 2.09 (s, 3H)
MS *m/z* 484.4 $(M+H)^+$

(ix) *N*-[2-(Aminometil)-5-clorobencil]-2-(1-{[(1-etil-3-metil-1*H*- pirazol-4-il)metil]amino}-4-metil-2-oxo-1,2-dihidropiridin-3-il)- acetamida
$^1$H NMR (500 MHz, DMSO-$d_6$) δ 8.33 (t, 1H), 7.46 (s, 1H), 7.21-7.41 (m, 4H), 6.45 (t, 1H), 6.05 (d, 1H), 4.29 (d, 2H), 3.97 (q, 2H), 3.88 (d, 2H), 3.72 (s, 2H), 3.48 (s, 2H), 2.13 (s, 3H), 2.08 (s, 3H), 1.28 (t, 3H)
MS *m/z* 456.8 $(M+H)^+$

(x) *N*-[2-(Aminometil)-5-clorobencil]-2-(4-metil-1-{[(4-metil-1*H*-imidazol-5-il)metil]amino}-2-oxo-1,2-dihidropiridin-3-il)acetamida
MS *m/z* 428.8 $(M+H)^+$

(xi) *N*-[2-(Aminometil)-5-clorobencil]-2-(1-{[(5-cloro-1-metil-3- fenil-1*H*-pirazol-4-il)metil]amino}-4-metil-2-oxo-1,2-dihidro-piridin-3-il)acetamida
$^1$H NMR (500 MHz, DMSO-$d_6$) δ 2.11 (s, 3H), 3.46 (s, 2H), 3.73 (s, 2H), 3.80 (s, 3H), 4.05 (d, 2H), 4.30 (d, 2H), 5.97 (d, 1H), 6.85 (t, 1H), 7.08 (d, 1H), 7.26 (s, 2H), 7.36-7.41 (m, 3H), 7.44 (t, 1H), 7.78 (d, 2H), 8.33 (t, 1H)
MS *m/z* 538.8 $(M+H)^+$

(xii) *N*-[2-(Aminometil)-5-clorobencil]-2-(4-metil-1-{[(2-morfolin- 4-ilpiridin-3-il)metil]amino}-2-oxo-1,2-dihidropiridin-3-il)acetamida
$^1$H NMR (500 MHz, DMSO-$d_6$) δ 2.13 (s, 3H), 3.08 (t, 4H), 3.46 (s, 2H), 3.66-3.76 (m, 6H), 4.12 (d, 2H), 4.30 (d, 2H), 6.07 (d, 1H), 6.97-7.04 (m, 2H), 7.23-7.29 (m, 2H), 7.40 (t, 2H), 7.69 (dd, 1H), 8.21 (dd, 1H), 8.33 (t, 1H)
MS *m/z* 510.8 $(M+H)^+$

(xiii) *N*-[2-(Aminometil)-5-clorobencil]-2-{1-[(3,3-dimetilbutil) amino]-4-metil-2-oxo-1,2-dihidropiridin-3-il}acetamida
$^1$H NMR (500 MHz, DMSO-$d_6$) δ 0.86 (s, 9H), 1.36 (t, 2H), 2.14 (t, 3H), 2.86-2.96 (m, 2H), 3.48 (s, 2H), 3.80 (s, 2H), 4.30 (d, 2H), 6.16 (d, 1H), 6.36 (t, 1H), 7.22-7.29 (m, 2H), 7.39 (d, 1H), 7.60 (d, 1H), 8.37 (t, 1H)
MS *m/z* 419.4 $(M+H)^+$

(xiv) *N*-[2-(Aminometil)-5-clorobencil]-2-(1-{[(5-cloro-2-tienil)metil] amino}-4-metil-2-oxo-1,2-dihidropiridin-3-il)acetamida
MS *m/z* 464.7 $(M+H)^+$

(xv) *N*-[2-(Aminometil)-5-clorobencil]-2-{1-[(3-ciano-4-fluorobencil)-amino]-4-metil-2-oxo-1,2-dihidropiridin-3-il}acetamida

$^1$H NMR (500 MHz, DMSO-$d_6$) δ 2.11 (s, 3H), 3.46 (s, 2H), 3.74 (s, 2H), 4.14 (d, 2H), 4.29 (d, 2H), 6.05 (d, 1H), 7.02 (t, 1H), 7.15-7.20 (m, 1H), 7.22-7.30 (m, 2H), 7.36-7.49 (m, 3H), 7.67-7.74 (m, 1H), 7.88 (dd, 1H), 8.32 (t, 1H)

MS *m/z* 467.7 $(M+H)^+$

(xvi) *N*-[2-(Aminometil)-5-clorobencil]-2-(4-metil-1-{[(5-metil-3-fenilisoxazol-4-il)metil]amino}-2-oxo-1,2-dihidropiridin-3-il)- acetamida

$^1$H NMR (500 MHz, DMSO-$d_6$) δ 2.12 (s, 3H), 2.17 (s, 3H), 3.46 (s, 2H), 3.73 (s, 2H), 4.00 (d, 2H), 4.30 (d, 2H), 5.99 (d, 1H), 6.87 (t, 1H), 7.14 (d, 1H), 7.24-7.29 (m, 2H), 7.39 (d, 1H), 7.49-7.56 (m, 3H), 7.79-7.85 (m, 2H), 8.37 (t, 1H).

MS *m/z* 505.8 $(M+H)^+$

(xvii) *N*-[2-(Aminometil)-5-clorobencil]-2-(4-metil-2-oxo-1-{[3-(trifluorometoxi)bencil]amino}-1,2-dihidropiridin-3-il)acetamida

$^1$H NMR (500 MHz, DMSO-$d_6$) δ 2.11 (t, 3H), 3.47 (s, 2H), 3.83 (s, 2H), 4.16 (d, 2H), 4.30 (d, 2H), 6.04 (d, 1H), 6.96 (t, 1H), 7.23-7.37 (m, 6H), 7.38-7.49 (m, 4H), 8.38 (t, 1H)

MS *m/z* 509.4 $(M+H)^+$

(xviii) *N*-[2-(Aminometil)-5-clorobencil]-2-{1-[(5-cloro-2-fluoro-bencil)amino]-4-metil-2-oxo-1,2-dihidropiridin-3-il}acetamida

$^1$H NMR (500 MHz, DMSO-$d_6$) δ 2.12(s, 3H), 3.46 (s, 2H), 3.86 (s, 2H), 4.14 (d, 2H), 4.29 (d, 2H), 6.07 (d, 1H), 6.98 (t, 1H), 7.22 (t, 1H), 7.25-7.29 (m, 2H), 7.35-7.44 (m, 3H), 7.49 (dd, 1H), 8.35 (t, 1H).

MS *m/z* 477.3 $(M+H)^+$

(xix) *N*-[2-(Aminometil)-5-clorobencil]-2-(4-metil-1-{[(2-metil-1*H*-imidazol-5-il)metil]amino}-2-oxo-1,2-dihidropiridin-3-il)acetamida

$^1$H NMR (500 MHz, DMSO-$d_6$) δ 2.12 (s, 3H), 2.22 (s, 3H), 3.48 (s, 2H), 3.72 (s, 2H), 3.92 (d, 2H), 4.29 (d, 2H), 6.05 (d, 1H), 6.64 (t, 1H), 6.71 (s, 1H), 7.24-7.27 (m, 2H), 7.37-7.41 (m, 2H), 8.32 (t, 1H).
MS *m/z* 428.8 $(M+H)^+$

(xx) *N*-[2-(Aminometil)-5-clorobencil]-2-{1-[(2-fluoro-5-metoxi-bencil)amino]-4-metil-2-oxo-1,2-dihidropiridin-3-il}acetamida
$^1$H NMR (500 MHz, DMSO-$d_6$) δ 2.12 (s, 3H), 3.47 (s, 2H), 3.69 (s,3H), 3.83 (s, 2H), 4.13 (d, 2H), 4.30 (d, 2H), 6.04 (d, 1H), 6.83-6.87 (m, 1H), 6.90-6.94 (m, 2H), 7.07 (t, 1H), 7.26-7.31 (m, 2H), 7.36 (d, 1H), 7.40 (d, 1H), 8.38 (t, 1H).
MS *m/z* 473.4 $(M+H)^+$

(xxi) *N*-[2-(Aminometil)-5-clorobencil]-2-{4-metil-1-[(2-morfolin-4-ilbencil)amino]-2-oxo-1,2-dihidropiridin-3-il}acetamida
MS *m/z* 509.8 $(M+H)^+$

(xxii) *N*-[2-(Aminometil)-5-clorobencil]-2-(1-{[(1,3-dimetil-5- morfolin-4-il-1*H*-pirazol-4-il)metil]amino}-4-metil-2-oxo-1,2- dihidropiridin-3-il)acetamida
$^1$H NMR (500 MHz, DMSO-$d_6$) δ 1.94 (s, 3H), 2.14 (s, 3H), 2.98-3.02 (m, 4H), 3.50 (s, 2H), 3.55 (s, 3H), 3.65-3.69 (m, 4H), 3.72 (s, 2H), 3.91 (d, 2H), 4.29 (d, 2H), 6.05 (d, 1H), 6.41 (t, 1H), 7.23-7.27 (m, 2H), 7.29 (d, 1H), 7.39 (d, 1H), 8.35 (t, 1H).
MS *m/z* 527.8 $(M+H)^+$

(xxiii) *N*-[2-(Aminometil)-5-clorobencil]-2-{4-metil-2-oxo-1- [(quinolin-8-ilmetil)amino]-1,2-dihidropiridin-3-il}acetamida
MS *m/z* 475.8 $(M+H)^+$

(xxiv) *N*-[2-(Aminometil)-5-clorobencil]-2-[4-metil-2-oxo-1-({[5-(2-tienil)isoxazol-3-il]metil}amino)-1,2-dihidropiridin-3-il]acetamida

$^1$H NMR (500 MHz, DMSO-$d_6$) δ 2.11 (s, 3H), 3.47 (s, 2H), 3.72 (s, 2H), 4.23 (d, 2H), 4.28 (d, 2H), 6.05 (d, 1H), 6.91 (s, 1H), 7.14 (t 1H), 7.22-7.27 (m, 3H), 7.39 (d, 1H), 7.46 (d, 1H), 7.69 (d, 1H), 7.82 (d, 1H), 8.33 (t, 1H).
MS *m/z* 497.7 $(M+H)^+$

(xxv) *N*-[2-(Aminometil)-5-fluorobencil]-2-{4-metil-2-oxo-1-[(2-fenilpropil)amino]-1,2-dihidropiridin-3-il}acetamida
$^1$H NMR (500 MHz, DMSO-$d_6$) δ 1.25 (d, 3H), 2.13 (s, 3H), 2.86-2.92 (m, 1H), 3.03-3.09 (m, 1H), 3.13-3.19 (m, 1H), 3.46 (s, 2H), 3.75 (s, 2H), 4.30 (d, 2H), 6.11 (d, 1H), 6.38 (t, 1H), 6.99-7.05 (m, 2H), 7.18-7.32 (m, 5H), 7.37 (dd, 1H), 7.48 (d, 1H), 8.35 (t, 1H).
MS *m/z* 437.5 $(M+H)^+$

(xxvi) *N*-[2-(Aminometil)-5-metilbencil]-2-{1-[(biciclo[2.2.1]hept-5- en-2-ilmetil)amino]-4-metil-2-oxo-1,2-dihidropiridin-3-il}acetamida
MS *m/z* 421.4 $(M+H)^+$

(xxvii) *N*-[2-(Aminometil)-5-metilbencil]-2-[1-({3-[(2-cloro-1,3- tiazol-5-il)metoxi]bencil}amino)-4-metil-2-oxo-1,2-dihidropiridin-3-il]acetamida
MS *m/z* 552.4 $(M+H)^+$

(xxviii) *N*-[2-(Aminometil)-5-metilbenzoil]-2-(4-metil-1-{[(3-metil-5-fenilisoxazol-4-il)metil]amino}-2-oxo-1,2-dihidropiridin-3-il)-acetamida
$^1$H NMR (500 MHz, DMSO-$d_6$) δ 2.09 (s, 3H), 2.19 (s, 3H), 2.24 (s, 3H), 3.42 (s, 2H), 3.76 (s, 2H), 4.06 (d, 2H), 4.28 (d, 2H), 5.99 (d, 1H), 6.91 (t, 1H), 7.03 (d, 1H), 7.07 (s, 1H), 7.23 (d, 1H), 7.25 (d, 1H), 7.49-7.56 (m, 3H), 7.76 (d, 1H), 7.80 (d, 1H), 8.36 (t, 1H).
MS *m/z* 486.5 $(M+H)^+$

(xxix) *N*-[2-(Aminometil)-5-metilbencil]-2-(1-{[(1,3-dimetil-5-morfolin-4-il-1*H*-pirazol-4-il)metil]amino}-4-metil-2-oxo-1,2-dihidropiridin-3-il)acetamida

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MS *m/z* 508.5 $(M+H)^+$

Ejemplo 5

Los siguientes compuestos se prepararon de intermedios apropiados (tales como los descritos más arriba en el texto) de acuerdo con o por analogía con métodos descritos aquí:

(1) *N*-[(6-amino-2-metilpiridin-3-il)metil]-2-(4-metil-1-{[(3-metil-5-fenilisoxazol-4-il)metil]amino}-2-oxo-1,2-dihidropiridin-3-il)- acetamida;

(2) *N*-[(6-amino-2,4-dimetilpiridin-3-il)metil]-2-(1-{[(5-cloro-2-tienil) metil]amino}-4-metil-2-oxo-1,2-dihidropiridin-3-il)acetamida;

(3) *N*-[2-(aminometil)-5-clorobenzoil]-2-(1-{[(5-cloro-2-fenil-1*H*-imidazol-4-il)metil]amino}-4-metil-2-oxo-1,2-dihidropiridin-3-il) acetamida;

(4) *N*-[2-(aminometil)-5-clorobenzoil]-2-(1-[{(1,5-dimetil-1*H*-pirazol-4-il)metil]amino}-4-metil-2-oxo-1,2-dihidropiridin-3-il)acetamida;

(5) 2-[4-cloro-2-({[(4-metil-1-{[(4-metil-1*H*-imidazol-5-il)-metil]-amino}-2-oxo-1,2-dihidropiridin-3-il)acetil]amino)metil)fenoxi]-*N*-etilacetamida;

(6) 2-(4-cloro-2-{[({4-metil-2-oxo-1-[(piridin-2-ilmetil)amino]-1,2-dihidropiridin-3-il}acetil)amino]metil}fenoxi)-*N*-etilacetamida;

(7) 2-[4-cloro-2-({[(4-metil-1-{[(2-metil-1*H*-imidazol-2-il)metil]- amino}-2-oxo-1,3-dihidroxipiridin-2-il)acetil]amino}metil)fenoxi]-*N*-etilacetamida;

(8) 2-(1-{[(6-cloro-1,3-benzodioxol-5-il)metil]amino}-4-metil-2-oxo- 1,2-dihidropiridin-3-il)-*N*-{5-cloro-2-[2-(etilamino)-2-oxoetoxi]-bencil}acetamida;

(9) 2-[4-cloro-2-({[(4-metil-1-{[(2-metil-1*H*-imidazol-5-il)metil]-amino}-2-oxo-1,2-dihidropiridin-3-il)acetil]amino}metil)fenoxi]-*N*- etilacetamida;

(10) 2-(4-cloro-2-{[({4-metil-2-oxo-1-[(2-fenoxibencil)amino]-1,2-dihidropiridin-3-il}acetil)amino]metil}fenoxi)-*N*-etilacetamida;

(11) 2-{4-cloro-2-[({[1-({3-[(2-cloro-1,3-tiazol-5-il)metoxi]bencil}-amino)-4-metil-2-oxo-1,2-dihidropiridin-3-il]acetil}amino)metil]-fenoxi}-*N*-etilacetamida;

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(12) *N*-[2-(aminometil)-5-fluorobencil]-2-(4-metil-1-{[(2-morfolin-4-ilpiridin-3-il)metil]amino}-2-oxo-1,2-dihidropiridin-3-il)acetamida;

(13) *N*-[2-(aminometil)-5-metilbenzoil]-2-(1-{[(5-cloro-1,3-dimetil-1*H*-pirazol-4-il)metil]amino}-4-metil-2-oxo-1,2-dihidropiridin-3-il)-acetamida;

(14) *N*-[2-(aminometil)-5-fluorobencil]-2-(4-metil-2-oxo-1-{[(1-fenil-1*H*-pirazol-5-il)metil]amino}-1,2-dihidropiridin-3-il) acetamida;

(15) *N*-[2-(aminometil)-5-fluorobencil]-2-(4-metil-1-{[(1-metil-1*H*-imidazol-2-il)metil]amino}-2-oxo-1,2-dihidropiridin-3-il)acetamida;

(16) *N*-[2-(aminometil)-5-fluorobencil]-2-{1-[(3-ciano-4-fluorobencil)-amino]-4-metil-2-oxo-1,2-dihidropiridin-3-il}acetamida;

(17) *N*-[2-(aminometil)-5-metilbencil]-2-(1-{[(1,3-dimetil-5-morfolin-4-il-1*H*-pirazol-4-il)metil]amino}-4-metil-2-oxo-1,2- dihidropiridin-3-il)acetamida;

(18) *N*-[(2-aminometil)-5-metilbencil]-2-[4-metil-2-oxo-1-({[5-(2-tienil)isoxazol-3-il]metil}amino)-1,2-dihidropiridin-3-il]acetamida;

(19) *N*-[2-(aminometil)-5-metilbencil]-2-{1-[(4-cianobencil)amino]-4-metil-2-oxo-1,2-dihidropiridin-3-il} acetamida;

(20) 2-[4-cloro-2-({[(1-{[(1,3-dimetil-5-morfolin-4-il-1*H*-pirazol-4-il)metil]amino}-4-metil-2-oxo-1,2-dihidropiridin-3-il)acetil]amino}-metil)fenoxi]-*N*-etilacetamida;

(21) *N*-[(6-amino-2,4-dimetilpiridin-3-il)metil]-2-(1-{[(1,3-dimetil-5-morfolin-4-il-1*H*-pirazol-4-il)metil]amino}-4-metil-2-oxo-1,2-dihidropiridin-3-il)acetamida;

(22) *N*-[2-(aminometil)-5-metilbenzoil]-2-(1-{[(1,5-dimetil-1*H*- pirazol-4-il)metil]amino}-4-metil-2-oxo-1,2-dihidropiridin-3-il)-acetamida;

(23) *N*-[(6-amino-2,4-dimetilpiridin-3-il)metil]-2-(1-{[(1,5-dimetil-1*H*-pirazol-4-il)metil]amino}-4-metil-2-oxo-1,2-dihidropiridin-3-il)-acetamida;

(24) *N*-[(6-amino-2-metilpiridin-3-il)metil]-2-(1-{[(1,5-dimetil-1*H*-pirazol-4-il)metil]amino}-4-metil-2-oxo-1,2-dihidropiridin-3-il)-acetamida;

(25) 2-[4-cloro-2-({[(1-{[(1-etil-3-metil-1*H*-pirazol-4-il)metil]-amino}-4-metil-2-oxo-1,2-dihidropiridin-3-il)acetil]amino}metil)-fenoxi]-*N*-etilacetamida;

(26) *N*-[2-(aminometil)-5-fluorobenzoil]-2-(1-{[(1-etil-3-metil-4*H*- pirazol-4-il)metil]amino}-4-metil-2-oxo-1,2-dihidropiridin-3-il)- acetamida;

(27) *N*-[(6-amino-2, 4-dimetilpiridin-3-il)metil]-2-(1-{[(1-etil-3- metil-1*H*-pirazol-4-il)metil]amino}-4-metil-2-oxo-1,2-dihidro- piridin-3-il)acetamida;

(28) *N*-[(6-amino-2-metilpiridin-3-il)metil]-2-(1-{[(1-etil-3-metil-1*H*-pirazol-4-il)metil]amino}-4-metil-2-oxo-1,2-dihidropiridin-3-il)acetamida;

(29) *N*-[2-(aminometil)-5-clorobencil]-2-(4-metil-1-{[(1-metil-1*H*-imidazol-2-il)metil]amino}-2-oxo-1,2-dihidropiridin-3-il)acetamida;

(30) *N*-[(6-amino-2-metilpiridin-3-il)metil]-2-(4-metil-1-{[(1-metil-1*H*-imidazol-2-il)metil]amino}-2-oxo-1,2-dihidropiridin-3-il)acetamida;

(31) *N*-[2-(aminometil)-5-clorobencil]-2-(4-metil-2-oxo-1-{[(1-fenil-1*H*-pirazol-5-il)metil]amino}-1,2-dihidropiridin-3-il)acetamida;

(32) *N*-[(6-amino-2, 4-dimetilpiridin-3-il) metil]-2-(4-metil-2-oxo-1- {[(1-fenil-1*H*-pirazol-5-il)metil]amino}-1,2-dihidropiridin-3-il)acetamida;

(33) *N*-[(6-amino-2-metilpiridin-3-il)metil]-2-(4-metil-2-oxo-1-{[(1- fenil-1*H*-pirazol-5-il)metil]amino}-1,2-dihidropiridin-3-il)acetamida;

(34) *N*-[2-(aminometil)-5-clorobenzoil]-2-{1-[(2,1,3-benzoxadiazol-5-il-metil)amino]-4-metil-2-oxo-1,2-dihidropiridin-3-il}acetamida;

(35) *N*-[2-(aminometil)-5-metilbencil]-2-{1-[(2,1,3-benzoxadiazol-5-il-metil)amino]-4-metil-2-oxo-1,2-dihdyropiridin-3-il}acetamida;

(36) *N*-[(6-amino-2,4-dimetilpiridin-3-il)metil]-2-{1-[(2,1,3-benzoxadiazol-5-ilmetil)amino]-4-metil-2-oxo-1,2-dihidropiridin-3-il}acetamida;

(37) *N*-[(6-amino-2-metilpiridin-3-il)metil]-2-{1-[(2,1,3-benzoxadiazol-5-il-metil)amino]-4-metil-2-oxo-1,2-dihidropiridin-3-il}acetamida;

(38) *N*-[2-(aminometil)-5-clorobenzoil]-2-(1-{[(2,4-dimetil-1,3-tiazol-5-il)metil]amino}-4-metil-2-oxo-1,2-dihidropiridin-3-il) acetamida;

(39) *N*-[2-(aminometil)-5-fluorobencil]-2-(1-{[(2, 4-dimetil-1,3-tiazol-5-il)metil]amino}-4-metil-2-oxo-1,2-dihidropiridin-3-il)acetamida;

(40) *N*-[(6-amino-2,4-dimetilpiridin-3-il)metil]-2-(1-{[(2,4-dimetil-1,3-tiazol-5-il)metil]amino}-4-metil-2-oxo-1,2-dihidropiridin-3-il)acetamida;

(41) *N*-[(6-amino-2-metilpiridin-3-il)metil]-2-(1-{[(2,4-dimetil-1,3- tiazol-5-il)metil]amino}-4-metil-2-oxo-1,2-dihidropiridin-3-il)acetamida;

(42) 2-(4-cloro-2-{[({1-[(2-cloro-5-fluorobencil)amino]-4-metil-2-oxo-1,2-dihidropiridin-3-il}acetil)amino]metil}fenoxi)-*N*-etilacetamida;

(43) *N*-[(6-amino-2,4-dimetilpiridin-3-il)metil]-2-{1-[(2-cloro-5-fluorobencil)amino]-4-metil-2-oxo-1,2-dihidropiridin-3-il}acetamida;

(44) *N*-[2-(aminometil)-5-fluorobenzoil]-2-{1-[(2-cloro-5-fluorobencil)-amino]-4-metil-2-oxo-1,2-dihidropiridin-3-il}acetamida;

(45) *N*-[(6-amino-2-metilpiridin-3-il)metil]-2-{1-[(2-cloro-5-fluoro-bencil)amino]-4-metil-2-oxo-1,2-dihidropiridin-3-il}acetamida;

(46) 2-(4-cloro-2-{[({1-[(2-fluoro-5-metoxibencil)amino]-4-metil-2- oxo-1,2-dihidropiridin-3-il}acetil)amino]metil}fenoxi)-*N*-etil- acetamida;

(47) *N*-[2-(aminometil)-5-metilbencil]-2-{1-[(2-fluoro-5-metoxi-bencil)amino]-4-metil-2-oxo-1,2-dihidropiridin-3-il}acetamida;

(48) *N*-[(6-amino-2,4-dimetilpiridin-3-il)metil]-2-{1-[(2-fluoro-5-metoxibencil)amino]-4-metil-2-oxo-1,2-dihidropiridin-3-il} acetamida;

(49) *N*-[(6-amino-2-metilpiridin-3-il)metil]-2-{1-[(2-fluoro-5-metoxi-bencil)amino]-4-metil-2-oxo-1,2-dihidropiridin-3-il}acetamida;

(50) *N*-[(6-amino-2-metilpiridin-3-il)metil]-2-(1-{[(2-metoxipiridin- 3-il)metil]amino}-4-metil-2-oxo-1,2-dihidropiridin-3-il) acetamida;

(51) 2-(1-{[(2-metoxipiridin-3-il)metil]amino}-4-metil-2-oxo-1,2-dihidropiridin-3-il)-*N*-[2-(1*H*-tetrazol-1-il)bencil]acetamida;

(52) *N*-[(6-amino-2,4-dimetilpiridin-3-il)metil]-2-(4-metil-1-{[(2- metil-1*H*-imidazol-5-il)metil]amino}-2-oxo-1,2-dihidropiridin-3-il)- acetamida;

(53) *N*-[(6-amino-2-metilpiridin-3-il)metil]-2-(4-metil-1-{[(2-metil-1*H*-imidazol-5-il)metil]amino}-2-oxo-1,2-dihidropiridin-3-il) acetamida;

(54) 2-[({4-metil-1-[(2-morfolin-4-ilbencil) amino]-2-oxo-1,2-dihdyropiridin-3-il}acetil)amino]metil}fenoxi)-*N*-etilacetamida;

(55) *N*-[(6-amino-2,4-dimetilpiridin-3-il)metil]-2-{4-metil-1-[(2- morfolin-4-ilbencil)amino]-2-oxo-1,2-dihidropiridin-3-il}acetamida;

(56) *N*-[(6-amino-2-metilpiridin-3-il)metil]-2-{4-metil-1-[(2- morfolin-4-ilbencil)amino]-2-oxo-1,2-dihidropiridin-3-il}acetamida;

(57) 2-[4-cloro-2-({[(4-metil-1-{[(2-morfolin-4-ilpiridin-3-il)metil]-amino}-2-oxo-1,2-dihidropiridin-3-il)acetil]amino}metil)fenoxi]-*N*-etilacetamida;

(58) *N*-[(6-amino-2,4-dimetilpiridin-3-il)metil]-2-(4-metil-1-{[(2- morfolin-4-ilpiridin-3-il)metil]amino}-2-oxo-1,2-dihidropiridin-3-il)- acetamida;

(59) *N*-[(6-amino-2-metilpiridin-3-il)metil]-2-(4-metil-1-{[(2-morfolin-4-ilpiridin-3-il)metil]amino}-2-oxo-1,2-dihidropiridin-3-il)acetamida;

(60) *N*-[2-(aminometil)-5-clorobencil]-2-{4-metil-2-oxo-1-[(2-fenoxibencil)amino]-1,2-dihidropiridin-3-il}acetamida;

(61) *N*-[(6-amino-2,4-dimetilpiridin-3-il)metil]-2-{4-metil-2-oxo-1- [(2-fenoxibencil)amino]-1,2-dihidropiridin-3-il}acetamida;

(62) *N*-[2-(aminometil)-5-metilbenzoil]-2-{4-metil-2-oxo-1-[(2-fenoxibencil)amino]-1,2-dihidropiridin-3-il}acetamida;

(63) *N*-[2-(aminometil)-5-clorobencil]-2-(1-{(3,5-dimetilisoxazol-4-il)metil]amino}-4-metil-2-oxo-1,2-dihidropiridin-3-il)acetamida;

(64) *N*-[2-(aminometil)-5-metilbencil]-2-(1-{[(3,5-dimetilisoxazol-4-il)metil]amino}-4-metil-2-oxo-1,2-dihidropiridin-3-il)acetamida;

(65) *N*-[(6-amino-2-metilpiridin-3-il)metil]-2-(1-{[(3,5-dimetil- isoxazol-4-il)metil]amino}-4-metil-2-oxo-1,2-dihidropiridin-3-il)acetamida;

(66) *N*-[2-(aminometil)-5-clorobencil]-2-{1-[(3-metoxibencil) amino]-4-metil-2-oxo-1,2-dihidropiridin-3-il}acetamida;

(67) *N*-[2-(aminometil)-5-metilbencil]-2-{1-[(3-metoxibencil) amino]-4-metil-2-oxo-1,2-dihidropiridin-3-il}acetamida;

(68) *N*-[(6-amino-2,4-dimetilpiridin-3-il)metil]-2-{1-[(3-metoxi-bencil)amino]-4-metil-2-oxo-1,2-dihidropiridin-3-il}acetamida;

(69) *N*-[(6-amino-2-metilpiridin-3-il)metil]-2-{1-[(3-metoxibencil)-amino]-4-metil-2-oxo-1,2-dihidropiridin-3-il}acetamida;

(70) *N*-[2-(aminometil)-5-clorobenzoil]-2-(4-metil-1-{[(3-metil-5-fenilisoxazol-4-il)metil]amino}-2-oxo-1,2-dihidropiridin-3-il)- acetamida;

(71) 2-[4-cloro-2-({[4-metil-1-{[(3-metil-5-fenilisoxazol-4-il)-metil]amino}-2-oxo-1,2-dihidropiridin-3-il)acetil]amino}metil)-fenoxi]-*N*-etilacetamida;

(72) *N*-[(6-amino-2,4-dimetilpiridin-3-il)metil]-2-(4-metil-1-{[(3-metil-5-fenilisoxazol-4-il)metil]amino}-2-oxo-1,2-dihidropiridin-3- il)acetamida;

(73) *N*-[(6-amino-2,4-dimetilpiridin-3-il)metil]-2-(4-metil-1-{[(4- metil-1*H*-imidazol-5-il)metil]amino}-2-oxo-1,2-dihidropiridin-3-il)- acetamida;

(74) *N*-[(6-amino-2-metilpiridin-3-il)metil]-2-(4-metil-1-{[(4-metil- 1*H*-imidazol-5-il)metil] amino}-2-oxo-1,2-dihidropiridin-3-il) acetamida;

(75) *N*-[(6-amino-2-metilpiridin-3-il)metil]-2-(4-metil-1-[(4-metil- 3,4-dihidro-2*H*-1,4-benzoxazin-7-il)metil]amino}-2-oxo-1,2-dihidro- piridin-3-il)-acetamida;

(76) 2-[4-cloro-2-({[(1-{[(5-cloro-1,3-dimetil-1*H*-pirazol-4-il)metil] - amino}-4-metil-2-oxo-1,2-dihidropiridin-3-il)acetil]amino}metil)- fenoxi]-*N*-etilacetamida;

(77) *N*-[(6-amino-2,4-dimetilpiridin-3-il)metil]-2-(1-{[(5-cloro-1,3- dimetil-1*H*-pirazol-4-il)metil]amino}-4-metil-2-oxo-1,2-dihidro- piridin-3-il)acetamida;

(78) *N*-[(6-amino-2-metilpiridin-3-il)metil]-2-(1-{[(5-cloro-1,3-dimetil-1*H*-pirazol-4-il)metil]amino}-4-metil-2-oxo-1,2-dihidro-piridin-3-il)acetamida;

(79) 2-[4-cloro-2-({[(1-{[(5-cloro-1-metil-3-fenil-1*H*-pirazol-4-il)-metil]amino}-4-metil-2-oxo-1,2-dihidropiridin-3-il)acetil]amino}-metil)fenoxi]-*N*-etilacetamida;

(80) *N*-[2-(aminometil)-5-fluorobencil]-2-(1-{[(5-cloro-1-metil-3-fenil-1*H*-pirazol-4-il)metil]amino}-4-metil-2-oxo-1,2-dihidro- piridin-3-il)acetamida;

(81) *N*-[(6-amino-2,4-dimetilpiridin-3-il)metil]-2-(1-{[(5-cloro-1- metil-3-fenil-1*H*-pirazol-4-il)metil]amino}-4-metil-2-oxo-1,2- dihidropiridin-3-il)acetamida;

(82) *N*-[(6-amino-2-metilpiridin-3-il)metil]-2-(1-{[(5-cloro-1-metil-3-fenil-1*H*-pirazol-4-il)metil]amino}-4-metil-2-oxo-1,2-dihidro- piridin-3-il)acetamida;

(83) 2-(4-cloro-2-{[({1-[(5-cloro-2-fluorobencil)amino]-4-metil-2-oxo- 1,2-dihidropiridin-3-il}acetil)amino]metil}fenoxi)-*N*-etilacetamida;

(84) *N*-[2-(aminometil)-5-metilbencil]-2-{1-[(5-cloro-2-fluorobencil)-amino]-4-metil-2-oxo-1,2-dihidropiridin-3-il}acetamida;

(85) *N*-[(6-amino-2,4-dimetilpiridin-3-il)metil]-2-{1-[(5-cloro-2-fluorobencil)amino]-4-metil-2-oxo-1,2-dihidropiridin-3-il}acetamida;

(86) *N*-[(6-amino-2-metilpiridin-3-il)metil]-2-{1-[(5-cloro-2-fluoro-bencil)amino]-4-metil-2-oxo-1,2-dihidropiridin-3-il}acetamida;

(87) *N*-[2-(aminometil)-5-metilbencil]-2-(1-{[(5-cloro-2-fenil-1*H*-imidazol-4-il)metil]amino}-4-metil-2-oxo-1,2-dihidropiridin-3-il) - acetamida;

(88) *N*-[(6-amino-2,4-dimetilpiridin-3-il)metil]-2-(1-{[(5-cloro-2-fenil-1*H*-imidazol-4-il)metil]amino}-4-metil-2-oxo-1,2-dihidro- piridin-3-il)acetamida;

(89) *N*-[(6-amino-2-metilpiridin-3-il)metil]-2-(1-{[(5-cloro-2-fenil- 1*H*-imidazol-4-il)metil]amino}-4-metil-2-oxo-1,2-dihidropiridin-3-il)-acetamida;

(90) 2-[4-cloro-2-({[(1-{[(5-cloro-2-tienil)metil]amino}-4-metil-2- oxo-1,2-dihidropiridin-3-il)acetil]amino}metil)fenoxi]-N-etil-acetamida;

(91) *N*-[(6-amino-2-metilpiridin-3-il)metil]-2-(1-{[(5-cloro-2-tienil)-metil]amino}-4-metil-2-oxo-1,2-dihidropiridin-3-il)acetamida;

(92) 2-[4-cloro-2-({[(4-metil-1-{[(5-metil-3-fenilisoxazol-4-il)-metil]amino}-2-oxo-1,2-dihidropiridin-3-il)acetil]amino}metil)- fenoxi]-*N*-etilacetamida;

(93) *N*-[(6-amino-2,4-dimetilpiridin-3-il)metil]-2-(4-metil-1-{[(5-metil-3-fenilisoxazol-4-il)metil]amino}-2-oxo-1,2-dihidropiridin-3- il)acetamida;

(94) *N*-[(6-amino-2-metilpiridin-3-il)metil]-2-(4-metil-1-[(5-metil-3-fenilisoxazol-4-il)metil]amino}-2-oxo-1,2-dihidropiridin-3-il)- acetamida;

(95) 2-[4-cloro-2-({[(4-metil-2-oxo-1-{[(5-piridin-2-il-2-tienil)-metil]amino}-1,2-dihidropiridin-3-il)acetil]amino}metil)fenoxi]-*N*-etilacetamida;

(96) *N*-[(6-amino-2,4-dimetilpiridin-3-il)metil]-2-(4-metil-2-oxo-1- {[(5-piridin-2-il-2-tienil)metil]amino}-1,2-dihidropiridin-3-il)- acetamida;

(97) *N*-[2-(aminometil)-5-fluorobencil]-2-(4-metil-2-oxo-1-{[(5- piridin-2-il-2-tienil)metil]amino}-1,2-dihidropiridin-3-il)acetamida;

(98) *N*-[(6-amino-2-metilpiridin-3-il)metil]-2-(4-metil-2-oxo-1-{[(5-piridin-2-il-2-tienil)metil]amino}-1,2-dihidropiridin-3-il)acetamida;

(99) *N*-[2-(aminometil)-5-fluorobencil]-2-(1-{[(6-cloro-1,3-benzo- dioxol-5-il)metil]amino}-4-metil-2-oxo-1,2-dihidropiridin-3-il)- acetamida;

(100) *N*-[(6-amino-2, 4-dimetilpiridin-3-il)metil]-2-(1-{[(6-cloro-1,3-benzodioxol-5-il)metil]amino}-4-metil-2-oxo-1,2-dihidropiridin-3-il)-acetamida;

(101) *N*-[(6-amino-2-metilpiridin-3-il)metil]-2-(1-{[(6-cloro-1,3-benzodioxol-5-il)metil]amino}-4-metil-2-oxo-1,2-dihidropiridin-3-il)-acetamida;

(102) 2-[4-cloro-2-({[(4-metil-2-oxo-1-{[3-(trifluorometoxi)bencil]-amino}-1,2-dihidropiridin-3-il)acetil]amino}metil)fenoxi]-*N*-etil-acetamida;

(103) *N*-[(6-amino-2,4-dimetilpiridin-3-il)metil]-2-(4-metil-2-oxo-1- {[3-(trifluorometoxi)bencil]amino}-1,2-dihidropiridin-3-il)acetamida;

(104) *N*-[2-(aminometil)-5-fluorobencil]-2-(4-metil-2-oxo-1-{[3-(trifluorometoxi)bencil]amino}-1,2-dihidropiridin-3-il)acetamida;

(105) *N*-[(6-amino-2-metilpiridin-3-il)metil]-2-(4-metil-2-oxo-1-{[3-(trifluorometoxi)bencil]amino}-1,2-dihidropiridin-3-il)acetamida;

(106) 2-{4-cloro-2-[({[4-metil-2-oxo-1-({[5-(2-tienil)isoxazol-3-il] -metil}amino)-1,2-dihidropiridin-3-il]acetil}amino)metil]fenoxi}-*N*-etilacetamida;

(107) *N*-[(6-amino-2,4-dimetilpiridin-3-il)metil]-2-[1-({3-[(2-cloro- 1,3-tiazol-5-il)metoxi]bencil}amino)-4-metil-2-oxo-1,2-dihidro-piridin-3-il]acetamida;

(108) *N*-[(6-amino-2-metilpiridin-3-il)metil]-2-[1-({3-[(2-cloro-1,3- tiazol-5-il)metoxi]bencil}amino)-4-metil-2-oxo-1,2-dihidropiridin-3-il]acetamida;

(109) *N*-[2-(aminometil)-5-clorobencil]-2-(1-{[(1R, 4S)-biciclo [2.2.1]-hept-5-en-2-ilmetil]amino}-4-metil-2-oxo-1,2-dihidropiridin-3-il)-acetamida;

(110) *N*-[(6-amino-2, 4-dimetilpiridin-3-il)metil]-2-(1-{[(1R, 4S)- biciclo [2.2.1]hept-5-en-2-ilmetil]amino}-4-metil-2-oxo-1,2-dihidro- piridin-3-il)acetamida;

(111) 2-(4-cloro-2-{[({1-[(ciclohexilmetil)amino]-4-metil-2-oxo-1,2-dihidropiridin-3-il}acetil)amino]metil}fenoxi)-*N*-etilacetamida;

(112) *N*-[2-(aminometil)-5-clorobencil]-2-{1-[(ciclohexilmetil)-amino]-4-metil-2-oxo-1,2-dihidropiridin-3-il}acetamida;

(113) *N*-[2-(aminometil)-5-fluorobencil]-2-{1-[(ciclohexilmetil)-amino]-4-metil-2-oxo-1,2-dihidropiridin-3-il}acetamida;

(114) *N*-[(6-amino-2-metilpiridin-3-il)metil]-2-{1-[(ciclohexilmetil)-amino]-4-metil-2-oxo-1,2-dihidropiridin-3-il} acetamida;

(115) *N*-[2-(aminometil)-5-metilbencil]-2-{1-[(ciclopentilmetil)-amino]-4-metil-2-oxo-1,2-dihidropiridin-3-il}acetamida;

(116) *N*-[(6-amino-2,4-dimetilpiridin-3-il)metil]-2-{1-[(ciclopentil-metil)amino]-4-metil-2-oxo-1,2-dihidropiridin-3-il}acetamida;

(117) *N*-[(6-amino-2-metilpiridin-3-il)metil]-2-{1-[(ciclopentil-metil)amino]-4-metil-2-oxo-1,2-dihidropiridin-3-il}acetamida;

(118) *N*-[(6-amino-2,4-dimetilpiridin-3-il)metil]-2-{4-metil-2-oxo-1-[(piridin-2-ilmetil)amino]-1,2-dihidropiridin-3-il}acetamida;

(119) *N*-[(6-amino-2-metilpiridin-3-il)metil]-2-{4-metil-2-oxo-1-[(piridin-2-ilmetil)amino]-1,2-dihidropiridin-3-il}acetamida;

(120) *N*-[2-(aminometil)-5-clorobencil]-2-{4-metil-2-oxo-1-[(piridin- 3-ilmetil)amino]-1,2-dihidropiridin-3-il}acetamida;

(121) 2-(4-cloro-2-{[({4-metil-2-oxo-1-[(piridin-3-ilmetil)amino]-1,2-dihidropiridin-3-il}acetil)amino]metil}fenoxi)-*N*-etilacetamida;

(122) *N*-[2-(aminometil)-5-metilbencil]-2-{4-metil-2-oxo-1-[(piridin-3-ilmetil)amino]-1,2-dihidropiridin-3-il}acetamida;

(123) *N*-[2-(aminometil)-5-fluorobencil]-2-{4-metil-2-oxo-1-[(piridin- 3-ilmetil)amino]-1,2-dihidropiridin-3-il}acetamida;

(124) *N*-[(6-amino-2,4-dimetilpiridin-3-il)metil]-2-{4-metil-2-oxo-1-[(piridin-3-ilmetil)amino]-1,2-dihidropiridin-3-il}acetamida;

(125) *N*-[(6-amino-2-metilpiridin-3-il)metil]-2-{4-metil-2-oxo-1- [(piridin-3-ilmetil)amino]-1,2-dihidropiridin-3-il}acetamida;

(126) *N*-[2-(aminometil)-5-metilbencil]-2-{4-metil-2-oxo-1-[(quinolin-8-ilmetil)amino]-1,2-dihidropiridin-3-il}acetamida;

(127) 2-(4-cloro-2-{[({4-metil-2-oxo-1-[(quinolin-8-ilmetil)amino]- 1,2-dihidropiridin-3-il}acetil)amino]metil}fenoxi)-*N*-etilacetamida;

(128) *N*-[(6-amino-2,4-dimetilpiridin-3-il)metil]-2-{4-metil-2-oxo-1-[(quinolin-8-ilmetil)amino]-1,2-dihidropiridin-3-il}acetamida;

(129) 2-[4-cloro-2-({[(1-{[2,2-difluoro-2-(1-oxidopiridin-2-il)etil]- amino}-4-metil-2-oxo-1,2-dihidropiridin-3-il)acetil]amino}metil)-fenoxi]-*N*-etilacetamida;

(130) 2-(4-cloro-2-{[({1-[(2,2-difluoro-2-piridin-2-iletil)amino]-4- metil-2-oxo-1,2-dihidropiridin-3-il}acetil)amino]metil}fenoxi)-*N*- etilacetamida;

(131) *N*-[(6-amino-2,4-dimetilpiridin-3-il)metil]-2-{1-[(2,2-difluoro-2-piridin-2-iletil)amino]-4-metil-2-oxo-1,2-dihidropiridin-3-il}- acetamida;

(132) *N*-[2-(aminometil)-5-metilbencil]-2-{4-metil-2-oxo-1-[(2-feniletil)amino]-1,2-dihidropiridin-3-il}acetamida;

(133) *N*-[2-(aminometil)-5-metoxibencil]-2-{4-metil-2-oxo-1-[(2-feniletil)amino]-1,2-dihidropiridin-3-il}acetamida;

(134) 2-(4-cloro-2-{[({4-metil-2-oxo-1-[(2-feniletil)amino]-1,2-dihidropiridin-3-il}acetil)amino]metil}fenoxi)-*N*-etilacetamida;

(135) *N*-[(6-amino-2,4-dimetilpiridin-3-il)metil]-2-{4-metil-2-oxo-1-[(2-feniletil) amino]-1,2-dihidropiridin-3-il}acetamida;

(136) *N*-[(6-amino-2-metilpiridin-3-il)metil]-2-{4-metil-2-oxo-1-[(2-feniletil)amino]-1,2-dihidropiridin-3-il}acetamida;

(137) *N*-[2-(aminometil)-5-clorobencil]-2-{4-metil-oxo-1-[(2-fenilpropil)amino]-1,2-dihidropiridin-3-il}acetamida;

(138) 2-(4-cloro-2-{[({4-metil-2-oxo-1-[(2-fenilpropil)amino]-1,2-dihidropiridin-3-il}acetil)amino]metil}fenoxi)-*N*-etilacetamida;

(139) *N*-[(6-amino-2, 4-dimetilpiridin-3-il)metil]-2-{4-metil-2-oxo-1- [(2-fenilpropil)amino]-1,2-dihidropiridin-3-il}acetamida; (140) *N*-[(6-amino-2-

metilpiridin-3-il)metil]-2-{4-metil-2-oxo-1-[(2-fenilpropil)amino]-1,2-dihidropiridin-3-il}acetamida;

(141) *N*-[(6-amino-2-metilpiridin-3-il)metil]-2-(4-metil-2-oxo-1-{[(2- oxo-1,2-dihidropiridin-3-il)metil]amino}-1,2-dihidropiridin-3-il) - acetamida;

(142) 2-(4-cloro-2-{[({1-[(3,3-dimetilbutil)amino]-4-metil-2-oxo-1,2-dihidropiridin-3-il}acetil)amino]metil}fenoxi)-*N*-etilacetamida;

(143) *N*-[(6-amino-2,4-dimetilpiridin-3-il)metil)-2-{1-[(3, 3-dimetil-butil)amino]-4-metil-2-oxo-1,2-dihidropiridin-3-il}acetamida;

(144) 2-(4-cloro-2-{[({1-[(4-cianobencil)amino]-4-metil-2-oxo-1,2-dihidropiridin-3-il}acetil)amino]metil}fenoxi)-*N*-etilacetamida;

(145) *N*-[2-(aminometil)-5-clorobencil]-2-{1-[(4-cianobencil)amino]-4-metil-2-oxo-1,2-dihidropiridin-3-il}acetamida;

(146) 2-(4-cloro-2-{ [({1-[(3-ciano-4-fluorobencil)amino]-4-metil-2-oxo-1,2-dihidropiridin-3-il}acetil)amino]metil}fenoxi)-*N*-etil- acetamida;

(147) *N*-[(6-amino-2,4-dimetilpiridin-3-il)metil]-2-{1-[(3-ciano-4-fluorobencil)amino]-4-metil-2-oxo-1,2-dihidropiridin-3-il}acetamida;

(148) *N*-[(6-amino-2-metilpiridin-3-il)metil]-2-{1-[(3-ciano-4-fluoro-bencil)amino]-4-metil-2-oxo-1,2-dihidropiridin-3-il}acetamida;

(149) 2-[1-(bencilamino)-4-metil-2-oxo-1,2-dihidropiridin-3-il]-*N*-{5-cloro-2-[2-(etilamino)-2-oxoetoxi]bencil}acetamida;

(150) *N*-[2-(aminometil)-5-fluorobencil]-2-[1-(bencilamino)-4-metil-2-oxo-1,2-dihidropiridin-3-il]acetamida;

(151) *N*-[(6-amino-2,4-dimetilpiridin-3-il)metil]-2-[1-(bencilamino)-4-metil-2-oxo-1,2-dihidropiridin-3-il]acetamida;

(152) *N*-[2-(aminometil)-5-clorobencil)-2-[1-(isobutilamino)-4-metil-2-oxo-1,2-dihidropiridin-3-il]acetamida;

(153) *N*-[2-(aminometil)-5-metilbencil]-2-[1-(isobutilamino)-4-metil-2-oxo-1,2-dihidropiridin-3-il]acetamida; y

(154) *N*-[(6-amino-2,4-dimetilpiridin-3-il)metil]-2-[1-(isobutilamino)- 4-metil-2-oxo-1,2-dihidropiridin-3-il]acetamida.

Ejemplo 6

Los Compuestos de los Ejemplos se examinaron en Prueba B más arriba y se encontró que exhibían valores $IC_{50}$TT menores de 50 μM. Por supuesto, se descubrió que los compuestos de Ejemplos 2(xi) y 2(xii) exhibían valores $IC_{50}$ de 92.2 nM y 0.62 μM, respectivamente.

**Abreviaturas**

| | | |
|---|---|---|
| aq. | = | acuoso |
| AUC | = | área bajo la curva |
| Boc | = | *terc*-butiloxicarbonilo |
| BSA | = | albúmina sérica bovina |
| d | = | (en relación con NMR) doblete |
| DCC | = | diciclohexil carbodiimida |
| DCE | = | 1,2-dicloroetano |
| DCM | = | diclorometano |
| DIPEA | = | diisopropiletilamina |
| DMAP | = | 4-(*N*,*N*-dimetilamino)piridina |
| DMF | = | dimetilformamida |
| DMSO | = | sulfóxido de dimetilo |
| DVT | = | trombosis de vena profunda |
| EDC | = | 1-(3-dimetilaminopropil)-3-etilcarbodiimida clorhidrato |
| Et | = | etilo |
| éter | = | éter dietílico |
| $Et_3N$ | = | trietilamino |
| EtOAc | = | acetato de etilo |
| EtOH | = | etanol |
| $Et_2O$ | = | éter dietílico |
| h | = | hora(s) |
| HATU | = | hexafluorofosfato de O-(azabenzotriazol-1-il)-*N*,*N*,*N*',*N*'-tetrametiluronio |

| | | |
|---|---|---|
| HBTU | = | [hexafluorofosfato de *N,N,N',N'*-tetrametil-*O*-(benzotriazol-1-il)uronio] |
| HCl | = | ácido clorhídrico, gas de cloruro de hidrógeno o sal clorhidrato (dependiendo del contexto) |
| HOAT | = | 1-hidroxi-7-azabenzotriazol |
| HOBT | = | 1-hidroxibenzotriazol |
| HPLC | = | cromatografía de líquidos de alta eficacia |
| LC | = | cromatografía de líquidos |
| *m*CPBA | = | ácido *meta*-cloroperbenzoico |
| Me | = | metilo |
| MeOH | = | metanol |
| min | = | minuto(s) |
| MS | = | espectroscopía de masas |
| NADH | = | nicotinamida adenina dinucleótido, forma reducida |
| NADPH | = | nicotinamida adenina dinucleótido fosfato, forma reducida |
| NBS | = | *N*-Bromosuccinimida |
| NIH | = | Instituto Nacional de la Salud (US) |
| NIHU | = | unidades del Instituto Nacional de la Salud |
| OAc | = | acetato |
| PCC | = | clorocromato de piridinio |
| Ph | = | fenilo |
| Pr | = | propilo |
| PyBOP | = | hexafluorofosfato de (benzotriazol-1-iloxi) tripirrolidinofosfonio |
| rt/RT | = | temperatura de la sala |
| SOPs | = | procedimientos estándar de operación |
| TBME | = | *terc*-butil metil éter |
| TBTU | = | [tetrafluoroborato de *N,N,N',N'*-tetrametil-*O*-(benzotriazol-1-il)uronio] |

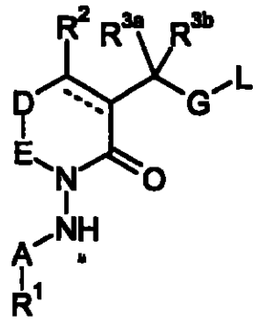
| | | |
|---|---|---|
| TEA | = | trietilamina |
| TFA | = | ácido trifluoroacético |
| THF | = | tetrahidrofurano |

Los prefijos *n*, *s*, *i* y *t* tienen sus significados usuales: normal, secundario, iso y terciario. El prefijo *c* significa ciclo.

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Reivindicaciones

1. Un compuesto de fórmula I



I

en donde

la línea discontinua está ausente o representa un enlace;

A representa C(O), $S(O)_2$, C(O)O (en cuyo último grupo la fracción O se une a $R^1$), C(O)NH, $S(O)_2NH$ (en cuyos últimos dos grupos la fracción NH se une a $R^1$) o $C_{1-6}$ alquileno;

$R^1$ representa

(a) $C_{1-10}$ alquilo, $C_{2-10}$ alquenilo, $C_{2-10}$ alquinilo (los cuales últimos tres grupos se sustituyen opcionalmente por uno o más sustituyentes seleccionados de halo, CN, $C_{3-10}$ cicloalquilo (sustituido opcionalmente por uno o más sustituyentes seleccionados de halo, OH, =O, $C_{1-6}$ alquilo, $C_{1-6}$ alcoxi y arilo), $OR^{4a}$, $S(O)_nR^{4b}$, $S(O)_2N(R^{4c})(R^{4d})$, $N(R^{4c})S(O)_2R^{4f}$, $N(R^{4g})(R^{4h})$, $B^1$-C(O)-$B^2$-$R^{4i}$, arilo y $Het^1$),

(b) $C_{3-10}$ cicloalquilo o $C_{4-10}$ cicloalquenilo, los cuales últimos dos grupos se sustituyen opcionalmente por uno o más sustituyentes seleccionados de halo, =O, CN, $C_{1-10}$ alquilo, $C_{3-10}$ cicloalquilo (sustituido opcionalmente por uno o más sustituyentes seleccionados de halo, OH, =O, $C_{1-6}$ alquilo, $C_{1-6}$ alcoxi y arilo),

$OR^{4a}$, $S(O)_nR^{4b}$, $S(O)_2N(R^{4c})(R^{4d})$, $N(R^{4c})S(O)_2R^{4f}$, $N(R^{4g})(R^{4h})$, $B^3$-$C(O)$-$B^4$-$R^{4i}$, arilo y $Het^2$,

(c) arilo, o

(d) $Het^3$;

$R^{4a}$ a $R^{4i}$ representan independientemente, en cada ocurrencia,

(a) H,

(b) $C_{1-10}$ alquilo, $C_{2-10}$ alquenilo, $C_{2-10}$ alquinilo (los cuales últimos tres grupos se sustituyen opcionalmente por uno o más sustituyentes seleccionados de halo, OH, $C_{1-6}$ alcoxi, arilo y $Het^4$),

(c) $C_{3-10}$ cicloalquilo, $C_{4-10}$ cicloalquenilo (los cuales últimos dos grupos se sustituyen opcionalmente por uno o más sustituyentes seleccionados de halo, OH, =O, $C_{1-6}$ alquilo, $C_{1-6}$ alcoxi, arilo y $Het^5$),

(d) arilo o

(e) $Het^6$,

siempre que $R^{4b}$ no represente H cuando n es 1 ó 2;

el grupo -D-E-

(a) cuando la línea discontinua representa un enlace, representa $-C(R^{5a})=C(R^{5b})-$, o

(b) cuando la línea discontinua está ausente, representa $-C(R^{6a})(R^{6b})-C(R^{7a})(R^{7b})-$; $R^{5a}$ y $R^{5b}$ representan independientemente H, halo, OH, $C_{1-4}$ alquilo, $(CH_2)_{0-4}O(C_{1-3}$ alquilo) (los cuales últimos dos grupos se sustituyen de manera opcional por un grupo OH o uno o más átomos F);

$R^{6a}$, $R^{6b}$, $R^{7a}$ y $R^{7b}$ representan independientemente H, F o metilo;

o $R^{5a}$ y $R^{5b}$ juntos representan 2-4 *n*-alquileno;

o uno de $R^{6a}$ y $R^{6b}$, junto con uno de $R^{7a}$ representa $C_{1-4}$ *n*- alquileno;

$R^2$ representa

(a) H,

(b) halo,

(c) $C_{1-6}$ alquilo, $C_{2-6}$ alquenilo, $C_{2-6}$ alquinilo, $C_{1-6}$ alcoxi (los cuales últimos cuatro grupos se sustituyen opcionalmente por uno o más sustituyentes seleccionados de halo, OH, CN, $C_{1-4}$ alcoxi, C(O)OH, C(O)O-$C_{1-4}$ alquilo y OC(O)-$C_{1-4}$ alquilo) o

(d) junto con $R^{3a}$, $R^2$ representa $C_{2-3}$ *n*-alquileno, $T^1$-($C_{1-2}$ *n*-alquileno) o ($C_{1-2}$ *n*-alquileno)-$T^1$, los cuales últimos tres grupos se sustituyen opcionalmente por halo, o

(e) junto con $R^{3a}$ y $R^{3b}$, $R^2$ representa $T^2$-[C(H)=], en donde $T^2$ se enlaza al átomo C al cual se une el grupo $R^2$;

$R^{3a}$ y $R^{3b}$ representan independientemente H, F o metilo (el cual último grupo se sustituye opcionalmente por uno o más átomos F), o

(a) junto con $R^2$, $R^{3a}$ representa $C_{2-3}$ *n*-alquileno, $T^1$-($C_{1-2}$ *n*-alquileno) o ($C_{1-2}$ *n*-alquileno)-$T^1$, los cuales últimos tres grupos se sustituyen opcionalmente por halo, o

(b) junto con $R^2$, $R^{3a}$ y $R^{3b}$ representa $T^2$-[C(H)=], en donde $T^2$ se enlaza al átomo C al cual se une el grupo $R^2$;

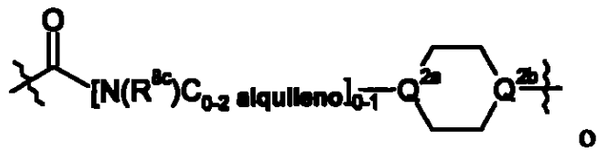
$T^1$ y $T^2$ representan independientemente O, S, N(H) o N($C_{1-4}$ alquilo);

G representa

(a) -C(O)N($R^{8a}$)-[CH($C(O)R^9$)]$_{0-1}$-$C_{0-3}$alquileno-($Q^1$)$_a$-,

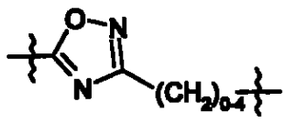
(b) -C(O)N($R^8$b)-$C_{2-3}$ alquenileno-($Q^1$)$_a$-,

(c)




o

(d)



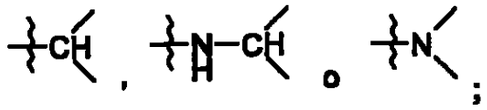

;

$R^9$ representa H o un grupo heterocíclico aromático de 5 a 10 miembros que comprende uno o dos anillos y contiene, como heteroátomo(s), un átomo de azufre u oxígeno y/o uno o más átomos de nitrógeno, grupo heterocíclico que se sustituye opcionalmente por uno o más sustituyentes seleccionados de halo y $C_{1-6}$ alquilo;

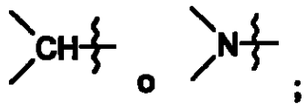
$Q^1$ representa O, $NR^{10a}$, $[N(H)]_{0-1}C(O)$-$C_{0-2}$ alquileno, C(O)NHNHC(O), o $N=C(R^{10b})$-;

a representa 0 ó 1;

$Q^{2a}$ representa



$Q^{2b}$ representa



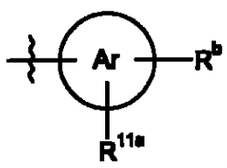
L representa

(a) $C_{0-6}$alquileno-$R^a$,

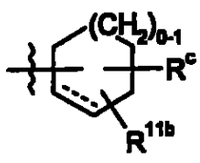
(b) $C_{0-2}$ alquileno-CH=CH-$C_{0-2}$ alquileno-$R^a$,

(c) $C_{0-2}$ alquileno-C≡$C_{0-2}$ alquileno-$R^a$,

(d)

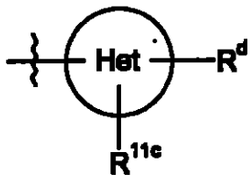


(e)



en donde la línea discontinua representa un doble enlace opcional, o

(f)




;

Ar representa fenilo o naftilo;

Het representa un grupo heterocíclico de 5 a 10 miembros que comprende uno o dos anillos y contiene, como heteroátomo(s), un átomo de azufre u oxígeno y/o uno o más átomos de nitrógeno;

$R^{11a}$ representa H o uno o más sustituyentes seleccionados de halo, OH, CN, $C_{1-6}$ alquilo, $C_{1-6}$ alcoxi (los cuales últimos dos grupos se sustituyen opcionalmente por uno o más sustituyentes seleccionados de halo, OH, $C_{1-4}$ alcoxi, $C(O)OR^{12a}$ y $C(O)N(R^{12b})R^{12c}$) y $S(O)_{0-2}R^{12d}$;

$R^{11b}$ y $R^{11c}$ representan independientemente H o uno o más sustituyentes seleccionados de halo, OH, CN, $C_{1-6}$ alquilo, $C_{1-6}$ alcoxi (los cuales últimos dos grupos se sustituyen opcionalmente por uno o más sustituyentes seleccionados de halo, OH, $C_{1-4}$ alcoxi, $C(O)OR^{12a}$ y $C(O)N(R^{12b})R^{12c}$), $S(O)_{0-2}R^{12d}$, =O, =NH, =NOH y =N-CN;

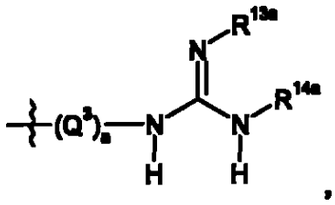
$R^{12a}$ a $R^{12c}$, representan independientemente H, $C_{1-6}$ alquilo o $C_{3-7}$ cicloalquilo (los cuales últimos dos grupos se sustituyen opcionalmente por un grupo OH ó $N(R^{12e})R^{12f}$ o por uno o más átomos halo);

$R^{12d}$ representa, independientemente en cada ocurrencia, $C_{1-6}$ alquilo sustituido opcionalmente por un grupo OH ó $N(R^{12e})R^{12f}$ o por uno o más átomos halo;

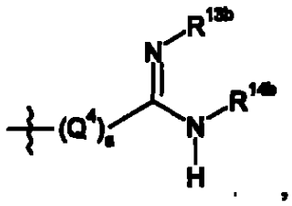
$R^{12e}$ y $R^{12f}$ representan, independientemente en cada ocurrencia, H o $C_{1-4}$ alquilo sustituido opcionalmente por uno o más átomos halo;

$R^a$ a $R^d$ representan independientemente (a)

(a)



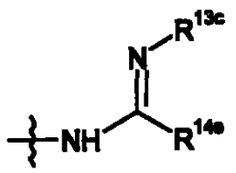
(b)



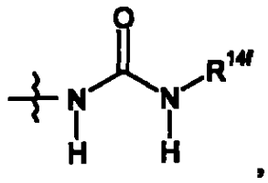
(c)



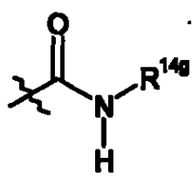
(d)



(e)



(f)



(g) $Het^x$

o $R^b$ a $R^d$ pueden representar también H;

$Q^3$ representa O, $N(R^{10c})$, $S(O)_2$, $S(O)_2NH$, C(O) o -CH=N-;

$Q^4$ representa O, S ó $CH_2$;

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a representa 0 ó 1;

$Het^x$ representa un grupo heterocíclico de a 5 ó 6 miembros que contiene uno a cuatro heteroátomos seleccionados de oxígeno, nitrógeno y/o azufre, el cual grupo heterocíclico puede sustituirse por uno o más sustituyentes seleccionados de halo, =O, $C_{1-6}$ alquilo y $C_{1-6}$ alcoxi (los cuales últimos dos grupos se sustituyen de manera opcional por uno o más átomos halo);

$R^{13a}$ a $R^{13c}$ representan independientemente

(a) H,

(b) CN,

(c) $NH_2$,

(d) $OR^{15}$ o

(e) $C(O)OR^{16}$

$R^{15}$ representa

(a) H,

(b) $C_{1-10}$ alquilo, $C_{3-10}$ alquenilo, $C_{3-10}$ alquinilo,

(c) $C_{3-10}$ cicloalquilo, $C_{4-10}$ cicloalquenilo, los cuales últimos dos grupos se sustituyen opcionalmente por uno o más sustituyentes seleccionados de halo y $C_{1-6}$ alquilo, o

(d) $C_{1-3}$ alquilo, el cual último grupo se interrumpe opcionalmente por oxígeno y se sustituye por arilo o -O-arilo;

$R^{16}$ representa

(a) $C_{1-10}$ alquilo, $C_{3-10}$ alquenilo, $C_{3-10}$ alquinilo, los cuales últimos tres grupos se interrumpen opcionalmente por uno o más átomos de oxígeno, o

(b) $C_{3-10}$ cicloalquilo, $C_{4-10}$ cicloalquenilo, los cuales últimos dos grupos se sustituyen opcionalmente por uno o más sustituyentes seleccionados de halo y $C_{1-6}$ alquilo, o

(c) $C_{1-3}$ alquilo, el cual último grupo se interrumpe opcionalmente por oxígeno y se sustituye por arilo o -O-arilo;

$R^{8a}$ a $R^{8c}$, $R^{10a}$ a $R^{10c}$ y $R^{14a}$ a $R^{14g}$ representan independientemente

(a) H o

(b) $C_{1-4}$ alquilo (el cual último grupo se sustituye opcionalmente por uno o más sustituyentes seleccionados de halo y OH),

o $R^{14a}$ y $R^{14b}$ representan independientemente $C(O)O-C_{1-6}$ alquilo (la parte alquilo de cuyo último grupo se sustituye opcionalmente por arilo y/o uno o más átomos halo),

o $R^{14c}$ representa

(a) $C_{1-4}$ alquilo sustituido por $C_{3-7}$ cicloalquilo o arilo,

(b) $C_{3-7}$ cicloalquilo,

(c) $C(O)O-C_{1-6}$ alquilo (la parte alquilo de cuyo último grupo se sustituye opcionalmente por arilo y/o uno o más átomos halo),

(d) $C(O)C_{1-6}$ alquilo,

(e) $C(O)N(H)-C_{1-6}$ alquilo (la parte alquilo de cuyo último grupo se sustituye opcionalmente por arilo y/o uno o más átomos halo) o

(f) $S(O)_2-C_{1-6}$ alquilo (la parte alquilo de cuyo último grupo se sustituye opcionalmente por arilo y/o uno o más átomos halo),

o $R^{14c}$ y $R^{14d}$ juntos representan $C_{3-6}$ *n*-alquileno interrumpido opcionalmente por O, S, N(H) o $N(C_{1-4}$ alquilo) y/o se sustituye por uno o más grupos $C_{1-4}$ alquilo;

cada arilo representa independientemente un grupo aromático carbocíclico $C_{6-10}$, grupo que puede comprender uno o dos anillos y puede sustituirse por uno o más sustituyentes seleccionados de

(a) halo,

(b) CN,

(c) $C_{1-10}$ alquilo, $C_{2-10}$ alquenilo, $C_{2-10}$ alquinilo (los cuales últimos tres grupos se sustituyen opcionalmente por uno o más sustituyentes seleccionados de halo, OH, $C_{1-6}$ alcoxi, C(O)OH, $C(O)O-C_{1-6}$ alquilo, fenilo (el cual último grupo se sustituye opcionalmente por halo) y $Het^7$),

(d) $C_{3-10}$ cicloalquilo, $C_{4-10}$ cicloalquenilo (los cuales últimos dos grupos se sustituyen opcionalmente por uno o más sustituyentes

seleccionados de halo, OH, =O, $C_{1-6}$ alquilo, $C_{1-6}$ alcoxi, fenilo (el cual último grupo se sustituye opcionalmente por halo) y $Het^8$),

(e) $OR^{17a}$

(f) $S(O)_pR^{17b}$,

(g) $S(O)_2N(R^{17c})(R^{17d})$,

(h) $N(R^{17e})S(O)_2R^{17f}$,

(i) $N(R^{17g})(R^{17h})$,

(j) $B^5$-C(O)-$B^6$-$R^{17i}$,

(k) fenilo (el cual último grupo se sustituye opcionalmente por halo),

(l) $Het^9$ y

(m) $Si(R^{18a})(R^{18b})(R^{18c})$;

$R^{17a}$ a $R^{17i}$ representan independientemente, en cada ocurrencia,

(a) H,

(b) $C_{1-10}$ alquilo, $C_{2-10}$ alquenilo, $C_{2-10}$ alquinilo (los cuales últimos tres grupos se sustituyen opcionalmente por uno o más sustituyentes seleccionados de halo, OH, $C_{1-6}$ alcoxi, fenilo (el cual último grupo se sustituye opcionalmente por halo) y $Het^{10}$),

(c) $C_{3-10}$ cicloalquilo, $C_{4-10}$ cicloalquenilo (los cuales últimos dos grupos se sustituyen opcionalmente por uno o más sustituyentes seleccionados de halo, OH, =O, $C_{1-6}$ alquilo, $C_{1-6}$ alcoxi, fenilo (el cual último grupo se sustituye opcionalmente por halo) y $Het^{11}$),

(d) fenilo (el cual último grupo se sustituye opcionalmente por halo) o

(e) $Het^{12}$,

siempre que $R^{17b}$ no represente H cuando p es 1 ó 2;

$Het^1$ a $Het^{12}$ representan independientemente grupos heterocíclicos de 4 a 14 miembros que contienen uno o más heteroátomos seleccionados de oxígeno, nitrógeno y/o azufre, los cuales grupos heterocíclicos pueden comprender uno, dos o tres anillos y pueden sustituirse por uno o más sustituyentes seleccionados de

(a) halo,

(b) CN,

(c) $C_{1-10}$ alquilo, $C_{2-10}$ alquenilo, $C_{2-10}$ alquinilo (los cuales últimos cuatro grupos se sustituyen opcionalmente por uno o más sustituyentes seleccionados de halo, OH, $C_{1-6}$ alcoxi, C(O)OH, $C(O)O-C_{1-6}$ alquilo, fenilo (el cual último grupo se sustituye opcionalmente por halo) y $Het^b$),

(d) $C_{3-10}$ ciclolquilo, $C_{4-10}$ cicloalquenilo (los cuales últimos dos grupos se sustituyen opcionalmente por uno o más sustituyentes seleccionados de halo, OH, =O, $C_{1-6}$ alquilo, $C_{1-6}$ alcoxi, fenilo (el cual último grupo se sustituye opcionalmente por halo) y $Het^b$),

(e) =O,

(f) $OR^{19a}$,

(g) $S(O)_qR^{19b}$,

(h) $S(O)_2N(R^{19c})(R^{19d})$,

(i) $N(R^{19e})S(O)_2R^{19f}$

(j) $N(R^{19g})(R^{19h})$,

(k) $B^7$-C(O)-$B^8$-$R^{19i}$,

(l) fenilo (el cual último grupo se sustituye opcionalmente por halo),

(m) $Het^c$ y

(n) $Si(R^{20a})(R^{20b})(R^{20c})$;

$R^{19a}$ a $R^{19i}$ representan independientemente, en cada ocurrencia,

(a) H,

(b) $C_{1-10}$ alquilo, $C_{2-10}$ alquenilo, $_{2-10}$ alquinilo (los cuales últimos tres grupos se sustituyen opcionalmente por uno o más sustituyentes seleccionados de halo, OH, $C_{1-6}$ alcoxi, fenilo (el cual último grupo se sustituye opcionalmente por halo) y $Het^d$),

(c) $C_{3-10}$ cicloalquilo, $C_{4-10}$ cicloalquenilo (los cuales últimos dos grupos se sustituyen opcionalmente por uno o más sustituyentes seleccionados de halo, OH, =O, $C_{1-6}$ alquilo, $C_{1-6}$ alcoxi, fenilo (el cual último grupo se sustituye opcionalmente por halo) y $Het^c$),

(d) fenilo (el cual último grupo se sustituye opcionalmente por halo) o

(e) $Het^f$,

siempre que $R^{19b}$ no represente H cuando q es 1 ó 2;

$Het^a$ a $Het^f$ representan independientemente grupos heterocíclicos de 5 o 6 miembros que contienen uno a cuatro heteroátomos seleccionados de oxígeno, nitrógeno y/o azufre, grupos heterocíclicos que pueden sustituirse por uno o más sustituyentes seleccionados de halo, =O y $C_{1-6}$ alquilo;

$B^1$ a $B^8$ representan independientemente un enlace directo, O, S ó NH;
n, p y q representan independientemente 0, 1 ó *2;*

$R^{18a}$, $R^{18b}$, $R^{18c}$, $R^{20a}$, $R^{20b}$ y $R^{20c}$ representan independientemente $C_{1-6}$ alquilo o fenilo (el cual último grupo se sustituye opcionalmente por halo o $C_{1-4}$ alquilo);

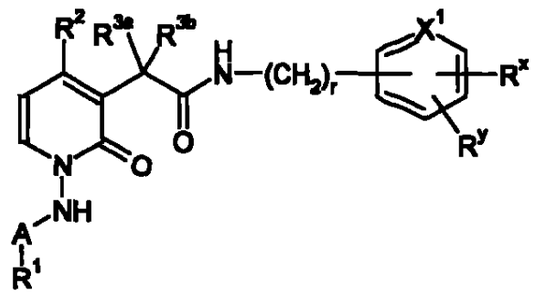
a menos que se especifique otra cosa

(i) grupos alquilo, alquenilo, alquinilo, cicloalquilo, cicloalquenilo, alquileno y alquenileno, así como la parte alquilo de grupos alcoxi, pueden sustituirse por uno o más átomos halo, y

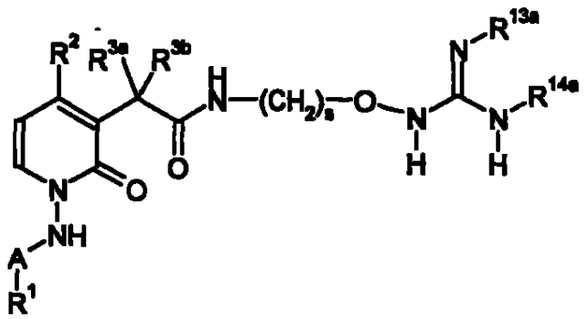
(ii) grupos cicloalquilo y cicloalquenilo pueden comprender uno o dos anillos y, adicionalmente, pueden fusionarse mediante anillo a uno o dos grupos fenilo;

o su derivado farmacéuticamente aceptable,

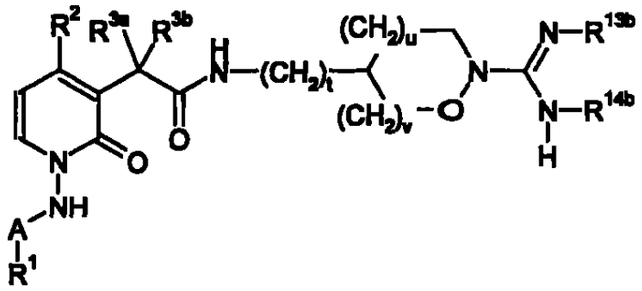
2. Un compuesto como se reivindica en la Reivindicación 1 que es un compuesto de fórmula Ic, Id o Ie,



Ic



Id



Ie

en donde $X^1$ representa CH ó N;

cuando $X^1$ representa CH

(a) $R^x$ representa $R^b$ como se define en la Reivindicación 1, y

(b) $R^y$ representa $R^{11a}$ como se define en la Reivindicación 1;

cuando $X^1$ representa N

(a) $R^x$ representa $R^d$ como se define en la Reivindicación 1, y

(b) $R^y$ representa $R^{11c}$ como se define en la Reivindicación 1;

r representa 1 a 3;

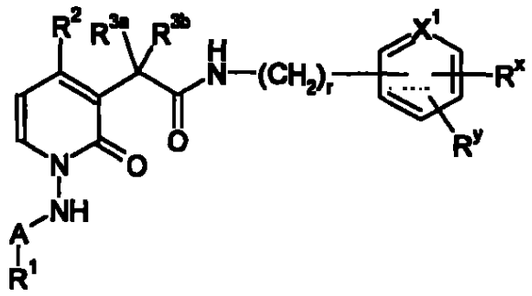
s representa 2 a 4; y

t representa1 a 3;

u y v representan independientemente 0 a 2, siendo la sumatoria de u y v 1 ó 2; y

$R^1$, $R^2$, $R^{3a}$, $R^{3b}$, $R^{11a}$, $R^{11c}$, $R^{13a}$, $R^{13b}$, $R^{14a}$, $R^{14b}$, $R^b$, $R^d$, y A son como se define en la Reivindicación 1.

3. Un compuesto como se reivindica en la Reivindicación 2 que es un compuesto de fórmula Ic,



Ic

en donde

A representa $CH(CH_3)CH_2$ (último grupo en el cual la unidad $CH(CH^3)$ se une a $R^1$) o $CH_2$, $(CH_2)_2$ o $CF_2CH_2$ (último grupo en el cual la unidad $CF_2$ se une a $R^1$) ;

$R^1$ representa

(a) isopropilo o *terc*-butilo,

(b) ciclopentilo, ciclohexilo o biciclo[2.2.1]hept-5-eno,

(c) fenilo sustituido opcionalmente por uno o dos sustituyentes seleccionados de halo, CN, metilo, $CF_3$, metoxi, $OCF_3$, fenoxi, morfolin-4-ilo o O-$CH_2$-(2-clorotiazol-5-ilo),

(d) imidazolilo sustituido de manera opcional por uno a tres sustituyentes seleccionados de Cl, metilo y fenilo,

(e) isoxazolilo sustituido de manera opcional por uno o dos sustituyentes seleccionados de metilo, fenilo y 2-tienilo,

(f) tiazolilo sustituido de manera opcional por uno o dos grupos metilo,

(g) tienilo sustituido de manera opcional por Cl o piridinilo,

(h) pirazolilo sustituido opcionalmente por uno a tres sustituyentes seleccionados de Cl, metilo, etilo, fenilo y morfolin-4-ilo,

(i) pirrolilo sustituido de manera opcional por uno a tres sustituyentes seleccionados de metil, $S(O)_2$-fenilo, C(O)-fenilo y 1,3,4-triazol-1-ilo,

(j) piridinilo sustituido de manera opcional por OH, metoxi o morfolin-4-ilo, y de manera opcional en la forma de un *N*-óxido,

(k) piridonilo,

(l) pirazinilo,

(m) benzodioxolilo opcionalmente sustituido por halo,

(n) benzomorfolinilo sustituido de manera opcional por metilo;

(o) 2,1,3-benzoxadiazolilo,

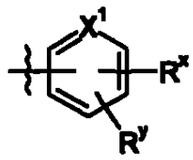
(p) 2,3-dihidrobenzofuranilo o

(q) quinolinilo;

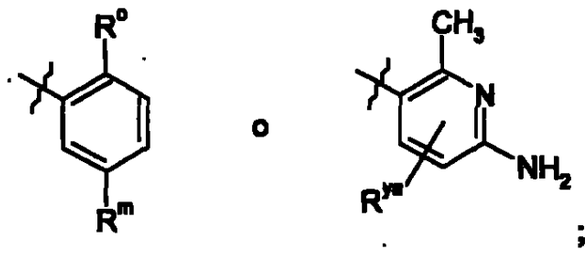
$R^5$ y $R^6$ ambos representan H;

r representa 1;

el grupo



representa



;

$R^o$ representa H, F, Cl, OH, metilo, tetrazol-1-ilo, $OCH_2C(O)N(H)R^{12b}$ ó $CH_2N(H)R^{14c}$;

$R^{12b}$ representa H o $C_{1-3}$ alquilo opcionalmente sustituido por $N(CH_3)_2$;

$R^{14c}$ representa C(O)O-*terc*-butilo, H, etilo, $CH_2CF_3$ o ciclopentilo;

$R^m$ representa H, metilo, $CF_3$, metoxi, F ó Cl; y

$R^{ya}$ representa H ó metilo.

4. Una formulación farmacéutica que incluye un compuesto como se define en una cualquiera de las Reivindicaciones 1 a 3, o su derivado

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farmacéuticamente aceptable, en mezcla con un coadyuvante, diluyente o excipiente farmacéuticamente aceptable.

5. Un compuesto como se define en una cualquiera de las Reivindicaciones 1 a 3, o su derivado farmacéuticamente aceptable, para uso como un producto farmacéutico.

6. El uso de un compuesto como se define en una cualquiera de las Reivindicaciones 1 a 3, o su derivado farmacéuticamente aceptable, como un ingrediente activo para la manufactura de un medicamento para el tratamiento de una enfermedad donde es benéfica la inhibición de trombina.

7. Un método de tratamiento de una enfermedad donde es benéfica la inhibición de trombina, método que comprende la administración de una cantidad terapéuticamente efectiva de un compuesto como se define en una cualquiera de las Reivindicaciones 1 a 3, o su derivado farmacéuticamente aceptable, a una persona que sufre de, o susceptible a, tal enfermedad.

8. Un proceso para la preparación de un compuesto de fórmula I como se define en la Reivindicación 1, que comprende:

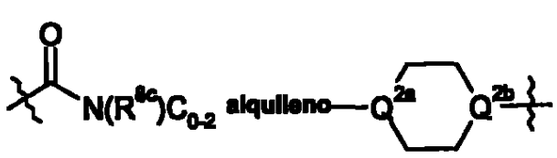
(a) para compuestos de fórmula I en la cual el grupo G representa

(i) $C(O)N(R^{8a})$-$[CH(C(O)R^{9})]_{0-1}$-$C_{0-3}$alquileno-$(Q^{1})_{a}$-,

(ii) $C(O)N(R^{8b})$-$C_{2-3}$ alquenileno-$(Q^{1})_{a}$-,

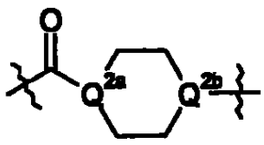
(iii) $C(O)N(R^{8b})$-$C_{2-3}$ alquinileno-$(Q^{1})_{a}$-,

(iv)




o

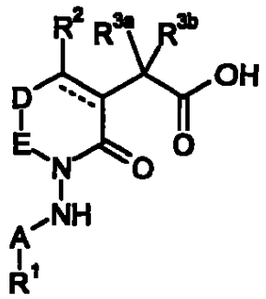
(v)



,

en donde $Q^{2a}$ representa N o NHCH,

acoplamiento de un compuesto de fórmula II,



II

en donde la línea discontinua, $R^1$, $R^2$, $R^{3a}$, $R^{3b}$, A, D y E son como se define en la Reivindicación 1, con un compuesto de fórmula III,

$$H\text{-}G^a\text{-}L \qquad III$$

en donde L es como ya se definió en reivindicación 1 $G^a$ representa

(i) $-N(R^{8a})-[CH(C(O)R^9)]_{0-1}-C_{0-3}$ alquileno-$(Q^1)_a$-,

(ii) $-N(R^{8b})-C_{2-3}$ alquenileno-$(Q^1)_a$-,

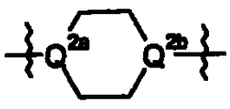
(iii) $-N(R^{8b})-C_{2-3}$ alquinileno-$(Q^1)_a$-,

(iv)




o

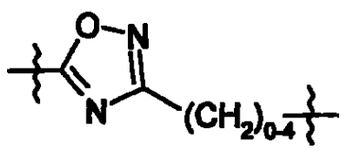
(v)



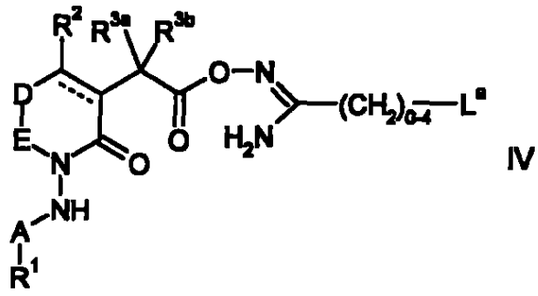
,

en donde $Q^{2a}$ representa N o NHCH y $R^{8a}$, $R^{8b}$, $R^{8c}$, $R^9$, $Q^1$, $Q^{2b}$ y a son como se define en la Reivindicación 1;

(b) para compuestos de fórmula I en la cual G representa



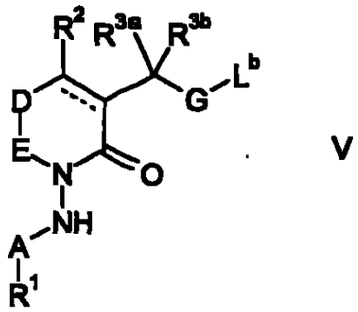
y L representa $L^a$, el cual último grupo representa L como se define en la Reivindicación 1, excepto que no represente $C_0$ alquileno-$R^a$, ciclación de un compuesto de fórmula IV,



IV

en donde $L^a$ es como se define más arriba y la línea discontinua, $R^1$, $R^2$, $R^{3a}$, $R^{3b}$, A, D y E son como se define en la Reivindicación 1;

(c) para compuestos de fórmula I en la cual $R^a$, $R^b$, $R^c$ o $R^d$ representa -C(=NH)$NH_2$, -C(=$NNH_2$)$NH_2$ o -C(=NOH)$NH_2$, la reacción de un compuesto de fórmula V,



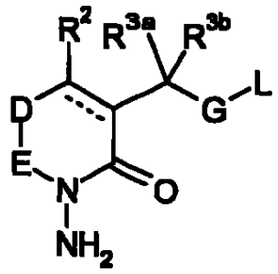
V

en donde $L^b$ representa L como se define en la Reivindicación 1, excepto que $R^a$, $R^b$, $R^c$ o $R^d$ (según lo apropiado) se reemplaza por un grupo ciano o -C(=NH)O-$C_{1-4}$ alquilo, y la línea discontinua, $R^1$, $R^2$, $R^{3a}$, $R^{3b}$, A, D, E y G son como se define en la Reivindicación 1, con una fuente adecuada de amoníaco, hidrazina o hidroxilamina;

(d) para compuestos de fórmula I en la cual $R^{13a}$, $R^{13b}$ o $R^{13c}$ representa H, desprotección de un compuesto correspondiente de fórmula I en la cual $R^{13a}$, $R^{13b}$ o $R^{13c}$, (según lo apropiado) representa C(O)O-$CH_2$arilo;

(e) para compuestos de fórmula I en la cual $R^{14c}$ representa H, desprotección de un compuesto correspondiente de fórmula I en la cual $R^{14c}$ representa $C(O)O\text{-}C_{1\text{-}6}$ alquilo;

(f) reacción de un compuesto de fórmula VI,



VI

en donde la línea discontinua, $R^2$, $R^{3a}$, $R^{3b}$, A, D, E, G y L son como se define en la Reivindicación 1, con un compuesto de fórmula VII,

$$R^1\text{-}A\text{-}Lg^1 \qquad \text{VII}$$

en donde $Lg^1$ representa un grupo saliente y $R^1$ y A son como se define en la Reivindicación 1;

(g) para compuestos de fórmula I en la cual A representa C(O)NH, reacción de un compuesto de fórmula VI, como se define más arriba, con un compuesto de fórmula VIII,

$$R^1\text{-}N{=}C{=}O \qquad \text{VIII}$$

en donde $R^1$ como se define en la Reivindicación 1;

(h) para compuestos de fórmula I en la cual A representa $C_{1\text{-}6}$ alquileno, reacción de un compuesto de fórmula VI, como se define más arriba, con un compuesto de fórmula IX,

$$R^1\text{-}C_{0\text{-}5}\text{ alquileno-CHO} \qquad \text{IX}$$

en donde $R^1$ es como se define en la Reivindicación 1, seguida por reducción en la presencia de un agente reductor; o

(i) para compuestos de fórmula I en la cual $R^a$, $R^b$, $R^c$ o $R^d$ representa-C $(=NCN)NH_2$, reacción de un compuesto correspondiente de fórmula I en la cual $R^a$, $R^b$, $R^c$ o $R^d$, respectivamente, representa-$C(=NH)NH_2$ con bromuro de cianógeno.

9. Un compuesto de fórmula II, como se define en la Reivindicación 8, o su derivado protegido.

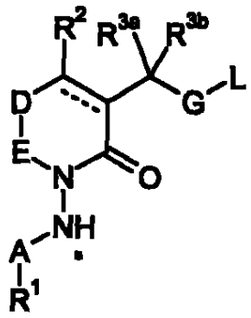
10. Un compuesto de fórmula IV, como se define en la Reivindicación 8, o su derivado protegido.

11. Un compuesto de fórmula VI, como se define en la Reivindicación 8, o su derivado protegido.

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## EXTRACTO

Se provee un compuesto de fórmula I



I

en donde la línea discontinua, $R^1$, $R^2$, $R^{3a}$, $R^{3b}$, A, D, E, G y L tienen los significados dados en la descripción, compuestos que son útiles como, o son útiles como profármacos de, inhibidores competitivos de proteasas tipo tripsina, tales como trombina y, por consiguiente, en particular, en el tratamiento de afecciones donde es benéfica la inhibición de trombina (verbigracia, trastornos tales como tromboembolismos, donde se requiere o desea la inhibición de trombina, y/o enfermedades donde es indicada una terapia anticoagulante).

2869 283

PCT/SE2005/000124

# PATENT COOPERATION TREATY

JBR

From the INTERNATIONAL BUREAU

## PCT

## NOTIFICATION OF THE RECORDING OF A CHANGE

(PCT Rule 92bis.1 and Administrative Instructions, Section 422)

| CODE | DATE |
|---|---|
| | |

To:

ASTRAZENECA
Global Intellectual Property
S-151 85 Södertälje
Sweden

| | |
|---|---|
| Date of mailing (day/month/year): 21 June 2006 (21.06.2006) | ANKOM 28 JUN 2006 GIPS |
| Applicant's or agent's file reference: 101215-1 WO | DATA ENTERED / FINAL CHECK |
| International application No.: PCT/SE2005/000124 | International filing date (day/month/year): 02 February 2005 (02.02.2005) |

**IMPORTANT NOTIFICATION**

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 |
|---|---|---|
| THERRIEN, Eric<br>University of Montreal<br>Dep of Chemistry<br>C.P. 6128, Succursale Centre-Ville<br>Montreal, Québec H3C 1J7<br>Canada | CA | CA |
| | Telephone No. | |
| | Facsimile No. | |
| | Teleprinter No. | |

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

[ ] the person [ ] the name [X] the address [ ] the nationality [ ] the residence

| Name and Address | State of Nationality | State of Residence |
|---|---|---|
| THERRIEN, Eric<br>969 Marc-Aurele Fortin<br>Laval, Quebec H7L 6H9<br>Canada | CA | CA |
| | Telephone No. | |
| | Facsimile No. | |
| | Teleprinter No. | |

3. Further observations, if necessary:

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>Sudha GAUTAM |
|---|---|
| Facsimile No. +41 22 338 7080 | Telephone No. (41-22) 338 8517 |

Form PCT/IB/308 (March 1994) 000858878

GLBX 284

**PCT REQUEST**

Original (for SUBMISSION)

| | | |
|---|---|---|
| 0 | For receiving Office use only | |
| 0-1 | International Application No. | |
| 0-2 | International Filing Date | |
| 0-3 | Name of receiving Office and "PCT International Application" | |

| | | |
|---|---|---|
| 0-4 | Form PCT/RO/101 PCT Request | |
| 0-4-1 | Prepared Using | PCT-SAFE [EASY mode]<br>Version 3.50 (Build 0002.169) |
| 0-5 | Petition<br>The undersigned requests that the present international application be processed according to the Patent Cooperation Treaty | |
| 0-6 | Receiving Office (specified by the applicant) | Swedish Patent Office (RO/SE) |
| 0-7 | Applicant's or agent's file reference | 101215-1 WO |
| I | Title of invention | NEW PYRIDIN-2-ONE COMPOUNDS USEFUL AS INHIBITORS OF THROMBIN |
| II | Applicant | |
| II-1 | This person is | applicant only |
| II-2 | Applicant for | all designated States except US |
| II-4 | Name | ASTRAZENECA AB |
| II-5 | Address | 151 85 Södertälje<br>Sweden |
| II-6 | State of nationality | SE |
| II-7 | State of residence | SE |
| II-8 | Telephone No. | +46 8 553 260 00 |
| II-9 | Facsimile No. | +46 8 553 288 20 |
| III-1 | Applicant and/or Inventor | |
| III-1-1 | This person is | applicant and inventor |
| III-1-2 | Applicant for | US only |
| III-1-4 | Name (LAST, First) | BAYRAKDARIAN, Malkan |
| III-1-5 | Address | AstraZeneca R&D Montreal<br>7171 Frederick-Banting<br>St. Laurent<br>Montreal, Québec H4S 1Z9<br>Canada |
| III-1-6 | State of nationality | CA |
| III-1-7 | State of residence | CA |

| | | |
|---|---|---|
| III-2 | Applicant and/or inventor | |
| III-2-1 | This person is | applicant and inventor |
| III-2-2 | Applicant for | US only |
| III-2-4 | Name (LAST, First) | BERGGREN, Kristina |
| III-2-5 | Address | AstraZeneca R&D Mölndal<br>431 83 Mölndal<br>Sweden |
| III-2-6 | State of nationality | SE |
| III-2-7 | State of residence | SE |
| III-3 | Applicant and/or inventor | |
| III-3-1 | This person is | applicant and inventor |
| III-3-2 | Applicant for | US only |
| III-3-4 | Name (LAST, First) | DAVIDSSON, Öjvind |
| III-3-5 | Address | AstraZeneca R&D Mölndal<br>431 83 Mölndal<br>Sweden |
| III-3-6 | State of nationality | SE |
| III-3-7 | State of residence | SE |
| III-4 | Applicant and/or inventor | |
| III-4-1 | This person is | applicant and inventor |
| III-4-2 | Applicant for | US only |
| III-4-4 | Name (LAST, First) | FJELLSTRÖM, Ola |
| III-4-5 | Address | AstraZeneca R&D Mölndal<br>431 83 Mölndal<br>Sweden |
| III-4-6 | State of nationality | SE |
| III-4-7 | State of residence | SE |
| III-5 | Applicant and/or inventor | |
| III-5-1 | This person is | applicant and inventor |
| III-5-2 | Applicant for | US only |
| III-5-4 | Name (LAST, First) | GUSTAFSSON, David |
| III-5-5 | Address | AstraZeneca R&D Mölndal<br>431 83 Mölndal<br>Sweden |
| III-5-6 | State of nationality | SE |
| III-5-7 | State of residence | SE |

| | | |
|---|---|---|
| III-6 | Applicant and/or inventor | |
| III-6-1 | This person is | applicant and inventor |
| III-6-2 | Applicant for | US only |
| III-6-4 | Name (LAST, First) | HANESSIAN, Stephen |
| III-6-5 | Address | University of Montreal<br>Dep of Chemistry<br>C.P. 6128, Succursale Centre-Ville<br>Montreal, Québec H3C 1J7<br>Canada |
| III-6-6 | State of nationality | CA |
| III-6-7 | State of residence | CA |
| III-7 | Applicant and/or inventor | |
| III-7-1 | This person is | applicant and inventor |
| III-7-2 | Applicant for | US only |
| III-7-4 | Name (LAST, First) | INGEMARDT, Tord |
| III-7-5 | Address | AstraZeneca R&D Mölndal<br>431 83 Mölndal<br>Sweden |
| III-7-6 | State of nationality | SE |
| III-7-7 | State of residence | SE |
| III-8 | Applicant and/or inventor | |
| III-8-1 | This person is | applicant and inventor |
| III-8-2 | Applicant for | US only |
| III-8-4 | Name (LAST, First) | NILSSON, Ingemar |
| III-8-5 | Address | AstraZeneca R&D Mölndal<br>431 83 Mölndal<br>Sweden |
| III-8-6 | State of nationality | SE |
| III-8-7 | State of residence | SE |
| III-9 | Applicant and/or inventor | |
| III-9-1 | This person is | applicant and inventor |
| III-9-2 | Applicant for | US only |
| III-9-4 | Name (LAST, First) | HÄGÅRD, Mats |
| III-9-5 | Address | AstraZeneca R&D Mölndal<br>431 83 Mölndal<br>Sweden |
| III-9-6 | State of nationality | SE |
| III-9-7 | State of residence | SE |

| | | |
|---|---|---|
| III-10 | Applicant and/or Inventor | |
| III-10-1 | This person is | applicant and inventor |
| III-10-2 | Applicant for | US only |
| III-10-4 | Name (LAST, First) | SIMARD, Daniel |
| III-10-5 | Address | University of Montreal<br>Dep of Chemistry<br>C.P. 6128, Succursale Centre-Ville<br>Montreal, Québec H3C 1J7<br>Canada |
| III-10-6 | State of nationality | CA |
| III-10-7 | State of residence | CA |
| III-11 | Applicant and/or Inventor | |
| III-11-1 | This person is | applicant and inventor |
| III-11-2 | Applicant for | US only |
| III-11-4 | Name (LAST, First) | THERRIEN, Eric |
| III-11-5 | Address | University of Montreal<br>Dep of Chemistry<br>C.P. 6128, Succursale Centre-Ville<br>Montreal, Québec H3C 1J7<br>Canada |
| III-11-6 | State of nationality | CA |
| III-11-7 | State of residence | CA |
| IV-1 | Agent or common representative; or address for correspondence<br>The person identified below is hereby/ has been appointed to act on behalf of the applicant(s) before the competent International Authorities as: | agent |
| IV-1-1 | Name | ASTRAZENECA |
| IV-1-2 | Address | Global Intellectual Property<br>151 85 Södertälje<br>Sweden |
| IV-1-3 | Telephone No. | +46 8 553 260 00 |
| IV-1-4 | Facsimile No. | +46 8 553 288 20 |
| V | DESIGNATIONS | |
| V-1 | The filing of this request constitutes under Rule 4.9(a), the designation of all Contracting States bound by the PCT on the international filing date, for the grant of every kind of protection available and, where applicable, for the grant of both regional and national patents. | |

| | | | |
|---|---|---|---|
| VI-1 | Priority claim of earlier national application | | |
| VI-1-1 | Filing date | 06 February 2004 (06.02.2004) | |
| VI-1-2 | Number | 0400254-9 | |
| VI-1-3 | Country | SE | |
| VI-2 | Priority claim of earlier national application | | |
| VI-2-1 | Filing date | 24 June 2004 (24.06.2004) | |
| VI-2-2 | Number | 0401658-0 | |
| VI-2-3 | Country | SE | |
| VII-1 | International Searching Authority Chosen | Swedish Patent Office (ISA/SE) | |
| VII-2 | Request to use results of earlier search; reference to that search | | |
| VII-2-1 | Date | 06 February 2004 (06.02.2004) | |
| VII-2-2 | Number | SE 04/00064 | |
| VII-2-3 | Country (or regional Office) | SE | |
| VIII | Declarations | Number of declarations | |
| VIII-1 | Declaration as to the identity of the inventor | - | |
| VIII-2 | Declaration as to the applicant's entitlement, as at the international filing date, to apply for and be granted a patent | - | |
| VIII-3 | Declaration as to the applicant's entitlement, as at the international filing date, to claim the priority of the earlier application | - | |
| VIII-4 | Declaration of inventorship (only for the purposes of the designation of the United States of America) | - | |
| VIII-5 | Declaration as to non-prejudicial disclosures or exceptions to lack of novelty | - | |
| IX | Check list | number of sheets | electronic file(s) attached |
| IX-1 | Request (including declaration sheets) | 6 | ✓ |
| IX-2 | Description | 170 | - |
| IX-3 | Claims | 19 | - |
| IX-4 | Abstract | 1 | ✓ |
| IX-5 | Drawings | 0 | - |
| IX-7 | TOTAL | 196 | |

101215-1 WO

6/6

**PCT REQUEST**

Original (for SUBMISSION )

| | Accompanying items | paper document(s) attached | electronic file(s) attached |
|---|---|---|---|
| IX-8 | Fee calculation sheet | ✓ | - |
| IX-9 | Original separate power of attorney | ✓ | - |
| IX-11 | Copy of general power of attorney | reference no. GF 5069/04 | - |
| IX-13 | Priority document(s) | Item(s) VI-1 VI-2 | - |
| IX-17 | PCT-SAFE physical media | - | ✓ |
| IX-18 | other | ITS Report SE 04/00064 | |
| IX-19 | Figure of the drawings which should accompany the abstract | | |
| IX-20 | Language of filing of the international application | English | |
| X-1 | Signature of applicant, agent or common representative | Christer Wahlström | |
| X-1-1 | Name | ASTRAZENECA | |
| X-1-2 | Name of signatory | Christer Wahlström | |
| X-1-3 | Capacity | | |

**FOR RECEIVING OFFICE USE ONLY**

| | | |
|---|---|---|
| 10-1 | Date of actual receipt of the purported international application | |
| 10-2 | Drawings: | |
| 10-2-1 | Received | |
| 10-2-2 | Not received | |
| 10-3 | Corrected date of actual receipt due to later but timely received papers or drawings completing the purported international application | |
| 10-4 | Date of timely receipt of the required corrections under PCT Article 11(2) | |
| 10-5 | International Searching Authority | ISA/SE |
| 10-6 | Transmittal of search copy delayed until search fee is paid | |

**FOR INTERNATIONAL BUREAU USE ONLY**

| | | |
|---|---|---|
| 11-1 | Date of receipt of the record copy by the International Bureau | |

# Brigard & Castro

BOGOTA - COLOMBIA

## PODER

Yo (nosotros)

domiciliado(s) en

Nombro(amos) a: **RAMIRO CASTRO DUQUE y/o JUAN PABLO CADENA SARMIENTO y/o BEATRIZ JARAMILLO S.**
de Bogotá, Colombia, apoderados verdaderos y legales con poder especial, amplio y suficiente, para recabar de las oficinas y autoridades colombianas administrativas, judiciales y de policía, en cualquier instancia o recurso, la obtención de patentes de invención, registros de marcas, diseños industriales, modelos de utilidad, depósitos de nombres comerciales y enseñas, registros de derechos de autor y contratos sobre los mismos, obtención de certificados de obtentor de variedades vegetales, así como sus prórrogas, renovaciones, anotaciones de traspaso, cambios de nombre y/o domicilio; elaborar, tramitar y registrar contratos de licencia y licencias de cualesquiera clases; intervenir como demandante o como demandado en cualquier instancia y recurso ante cualquier juez, corporación, funcionario público o autoridad en acciones judiciales, administrativas y de policía tales como: oposiciones al registro de marcas; acciones de caducidad, cancelación y nulidad; acciones reivindicatorias, acciones derivadas de la obtención o explotación de licencias; acciones de competencia desleal; demandas penales; acciones de indemnización de perjuicios, reclamos y observaciones a solicitudes de patentes, diseños industriales, modelos de utilidad, en el ejercicio de medidas cautelares y en otras acciones o medidas similares.

A este efecto, lo(a) faculto(amos) para elevar solicitudes, formular descripciones, enmiendas, protestas, declaraciones, oposiciones, cancelaciones, nulidades, apelaciones y reclamos; pagar impuestos, cuotas y gravámenes prescritos por la ley; renunciar o desistir a derechos concedidos o en curso de concesión; recibir toda clase de documentos y valores, dando el descargo respectivo, y, en general, para dar ante dichas autoridades todos los pasos necesarios al efecto indicado y tomar todas las medidas que creyeren conducentes al resguardo de mis (nuestros intereses), con todas las demás facultades legales necesarias.

Este poder comprende la facultad de ratificar o confirmar en mi (nuestro) nombre lo actuado así como la facultad de desistir, transigir, comprometer, y la de sustituirlo en todo o en parte y revocar sustituciones. Asimismo nombro(amos) a: **RAMIRO CASTRO DUQUE y/o JUAN PABLO CADENA SARMIENTO y/o BEATRIZ JARAMILLO S.**
domiciliado(s) en la Carrera 7 No. 16-56 Piso 9, mis (nuestros) apoderados en Colombia, con facultades para recibir notificaciones y designar apoderados judiciales o extrajudiciales.

Otorgado y firmado en

hoy de de 200_

Firma

Nombre
Cargo

## POWER OF ATTORNEY

I (We) **ASTRAZENECA AB**

domiciled in SE-151-Sodertalje, Sweden

Hereby appoint **RAMIRO CASTRO DUQUE** and/or **JUAN PABLO CADENA SARMIENTO** and/or **BEATRIZ JARAMILLO S.**
of Bogotá, Colombia, my (our) true and lawful attorneys with special, ample and sufficient power to obtain from the Colombian administrative, judicial and police offices and authorities, in any instance, privileges of patents of invention, registration of trademarks, industrial designs and utility models; registration of commercial names and emblems, registration of copyright and contracts related thereto, certificates of obtainers of vegetables varieties, as well as extensions, renewals and recordal of assignments and changes of name and domicile related to the above; to prepare, prosecute and register licenses of any kind; to act as plaintiff or defendant in any instance or recourse, and before any judge, corporation, public official or authority in judicial, administrative and police actions, such as: oppositions to the registration of trademarks; caducity, cancellation and nullity actions; claim actions derived from the obtaining or explotation of licenses, action of unfair competition; penal demands, actions of indemnities for damages: claims or observations on patent applications, models, industrial designs and utility models; in the exercise of preventive measures: and in other actions or similar proceedings.

To that effect they are hereby empowered to file applications, formulate descriptions, amendments, protests, declarations, oppositions, cancellations, nullities, appeals and claims; to pay taxes, quotas and assessments prescribed by law, renounce or waive the rights granted or in the process of granting; to receive all kind of documents and valuables, giving the respective release of receipt, and, in general, to take before said authorities the necessary steps to such effect, and any measures that they may deem pertinent to the safeguard of my (our) interest(s) with all the other necessary legal powers.

This power includes the faculty to ratify or confirm desist, settle and compromise on my (our) behalf, and to substitute this power in whole or in part and to revoke substitutions. At the same time I (We) hereby appoint **RAMIRO CASTRO DUQUE** and/or **JUAN PABLO CADENA SARMIENTO** and/or **BEATRIZ JARAMILLO S.**
domiciled in Carrera 7 No. 16-56, Piso [illegible] attorney(s) in fact, with powers to [illegible] and to designate judicial and extra[illegible]

Granted and signed in Macclesfield, Cheshire, England

this 18th day of MARCH 2008

Signature

Name KEVIN BILL
Title Director, IP Services

CONSULADO NOTARIAL - SECCIÓN FOTOCOPIAS - LA FOTOCOPIA QUE SE TIENE A LA VISTA ES FIEL COPIA DEL QUE REPOSA EN ESTA NOTARÍA - REPÚBLICA DE COLOMBIA
18 MAR 2008
OSCAR ALARCÓN NUÑEZ
NOTARIO CUARENTA Y SEIS

## CERTIFICADO NOTARIAL (SOCIEDAD)

Hoy de de
personalmente compareció ante mí

a quien conozco, y de quien me consta que firmó el anterior documento, debidamente juramentado declaró y dijo que él es

de

Sociedad legalmente constituida para un período de duración que aún no ha terminado; que el declarante está autorizado por dicha compañía para conferir este poder; que el sello estampado por él al pie de tal poder, en nombre y representación de la expresada compañía, es el sello oficial de ella; y que el objeto para el cual se confiere este instrumento está comprendido dentro del de la sociedad.

El suscrito Notario hace constar que tuvo a la vista las pruebas de la existencia de la sociedad.

Estado de
con fecha

y que quien confiere el presente poder es su representante.

Notario Público (sello)

## NOTARIAL CERTIFICATE (CORPORATION)

On this 18th day of July 2003 of
personally appeared before me
KEVIN BILL
to me known, and known to me to be the person who signed the foregoing instrument who being by me duly sworn did depose and say that he (she) is the
ATTORNEY
of
ASTRAZENECA AB

Which is legally constituted for a term not yet expired, that deponent is authorized by said Company to conf -this Power of Attorney: that the seal affixed hereunto by the deponent in the name and on behalf of said Corporation is the corporate seal thereof; and that purpose for which this instrument is granted included within the corporate purpose of company.

The undersigned Notary Public attests that he has seen the documents that prove the existence of the company.

State of Sweden
under date of 1st January 2003

and that he (she) who grants the present power of attorney is its Representative.

Notary Public (Seal)

## CERTIFICADO NOTARIAL PERSONA NATURAL

Hoy de de , compareció(eron)
ante mí

a quien (es) conozco y me consta que es(son) la(s) persona(s) firmante(s) del documento que precede y quien(es) declara(n) que otorgan el mismo para los fines y propósitos que en él se expresan.

Notario Público (sello)

## NOTARIAL CERTIFICATE NATURAL PERSON

On this day of of
personally appeared before me

who is(are) known to me and [illegible] attest executed the foregoing document and he (they) declared he (they) grant(s) the document for the uses and purposes therein expressed.

26 MAR 2003
OSCAR ALARCON NUÑEZ
NOTARIO CUARENTA Y OCHO

Notary Public (Seal)

LEGALIZACION POR APOSTILLA ES REQUERIDA.

LEGALIZATION BY APOSTILLE IS REQUIRED.

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**APOSTILLE**
(Hague Convention of 5 October 1961 / Convention de La Haye du 5 octobre 1961)

**UNITED KINGDOM OF GREAT BRITAIN AND NORTHERN IRELAND**

1. Country: United Kingdom of Great Britain and Northern Ireland
   Pays: Royaume-Uni de Grande-Bretagne et d'Irlande du Nord

   This public document / Le présent acte public

2. Has been signed by — J B Hodgson
   a été signé par

3. Acting in the capacity of — Notary Public
   agissant en qualité de

4. Bears the seal/stamp of — The Said Notary Public
   est revêtu du sceau/timbre de

Certified/Attesté

5. at London/à Londres — 6. the/le 17 February 2004

7. by Her Majesty's Principal Secretary of State for Foreign and Commonwealth Affairs /
   par le Secrétaire d'Etat Principal de Sa Majesté aux Affaires Etrangères et du Commonwealth.

8. Number/sous No **G348987**

9. Stamp:
   timbre:

10. Signature: J. Ireland

*For the Secretary of State / Pour le Secrétaire d'Etat*

If this document is to be used in a country which is not party to the Hague Convention of 5 October 1961, it should be presented to the consular section of the mission representing that country.

CONSULADO NOTARIO CUARENTA Y SEIS BOGOTA
CIRCULO DE BOGOTA
COPIA FOTOSTATICA
06 MAR 2006
OSCAR ALARCON NUÑEZ
NOTARIO CUARENTA Y SEIS

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**TRADUCCIÓN SIMPLE AL ESPAÑOL del la Apostilla que vienen junto con el Certificado Notarial (Sociedad) y el Poder concedido por ASTRAZENECA AB, domiciliada en SE - 151 Sodertalje, Suecia a Ramiro Castro Duque y/o Juan Pablo Cadena Sarmiento y/o Beatriz Jaramillo S, domiciliados en la Carrera 7 #16-56, P. 9, Bogotá D.C., Colombia.**

AUTENTICACIÓN

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

**REINO UNIDO DE GRAN BRETAÑA E IRLANDA DEL NORTE**

1. País: Reino Unido de Gran Bretaña e Irlanda del Norte
2. Este documento público
   ha sido firmado por **J. B. Hodgson**
3. actuando en capacidad de **Notario Público**
4. lleva el sello de: **Dicho Notario Público**

**CERTIFICADO**

5. en Londres **6. el 17 de Febrero de 2004**
7. por El secretario de Estado Principal de Su Majestad para Asuntos Exteriores y de la Comunidad
8. No. **G348987**
9. Sello **10. Firma**

**J. Ireland (Firma)**

Si este documento va a ser utilizado en un país que no es parte de la Convención de La Haya del 5 de Octubre de 1961, debe ser presentado a la sección consular de la misión que representa a ese país.

COMO NOTARIO CUARENTA Y SEIS DEL CIRCULO DE BOGOTÁ, HAGO CONSTAR QUE LA FOTOSTÁTICA QUE ME HA SIDO PRESENTADA ES FIEL COPIA DE LA QUE HE TENIDO A LA VISTA

06 MAR 2006

NOTARIO CUARENTA Y SEIS

REPÚBLICA DE COLOMBIA

ORGANIZACION ELECTORAL
REGISTRADURÍA NACIONAL DEL ESTADO CIVIL

293

GAVIRI A

# REGISTRO CIVIL DE DEFUNCIÓN

Indicativo Serial 5562241

**Datos de la oficina de registro**

| Clase de oficina: Registraduría | | Notaría | X | Consulado | | Corregimiento | | Insp. de Policía | | Código | 9795 |
|---|---|---|---|---|---|---|---|---|---|---|---|

País - Departamento - Municipio - Corregimiento o/o Inspección de Policía

COLOMBIA CUNDINAMARCA BOGOTA D..C NOTARIA 32.

**Datos del inscrito**

Apellidos y nombres completos

CASTRO DUQUE RAMIRO

| Documento de identificación (Clase y número) | Sexo (en Letras) |
|---|---|
| C.C. No. 170322 DE BOGOTA ---------- | MASCULINO |

**Datos de la defunción**

Lugar de la Defunción: País - Departamento - Municipio - Corregimiento o/o Inspección de Policía

COLOMBIA CUNDINAMARCA BOGOTA D.C.

| Fecha de la defunción | Hora | Número de certificado de defunción |
|---|---|---|
| Año 2004 Mes 10 Día 30 | 04:10 PM | A- 2094375. |

Presunción de muerte

| Juzgado que profiere la sentencia | Fecha de la sentencia |
|---|---|
| ------------------ | Año Mes Día |

| Documento presentado | | Nombre y cargo del funcionario |
|---|---|---|
| Autorización judicial | Certificado Médico X | ANDRES DIAZ CAMPOS.-<br>R.M. No. 79982662 |

**Datos del denunciante**

Apellidos y nombres completos

EDGAR DAVID REGINO H.

| Documentos de identificación (Clase y número) | Firma |
|---|---|
| C.C.No. 15.030.154 DE LORICA CORDOBA | [firma] |

**Primer testigo**

Apellidos y nombres completos

------------------

| Documentos de identificación (Clase y número) | Firma |
|---|---|
| ------------------ | ---------- |

**Segundo testigo**

Apellidos y nombres completos

------------------

| Documentos de identificación (Clase y número) | Firma |
|---|---|
| ------------------ | ---------- |

| Fecha de inscripción | Nombre y firma del funcionario que autoriza |
|---|---|
| Año 2004 Mes 11 Día 02 | BLANCA LUCIA ... RESTREPO<br>NOTARIA ... |

ESPACIO PARA NOTAS

PADRES: ALFONSO CASTRO
MERCEDES DUQUE.

ORIGINAL PARA LA OFICINA DE REGISTRO

**NOTARIA 32**
DEL CIRCULO DE SANTA FE DE BOGOTA, D.C.

Germán Eleázar Moreno L.
Notario

COMO SECRETARIO DELEGADO DE LA NOTARIA TREINTA Y DOS (32) DEL CIRCULO DE BOGOTA

**CERTIFICO ; QUE:**

La presente acta es fiel copia del original tomada del registro civil de defunciones serial indicativo número: 5T6220[illegible]
que expido en la ciudad de Bogotá D.C., hoy: 05 NOV. 2004

[illegible]
SECRETARIO DELEGADO

NOTARIA 32 DEL
DE BOGOTA D.C.
NELSON FLOREZ G.
SECRETARIO DELEGADO PARA COPIAS
DECRETO 1334 DE 1989

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
Rad: 06-075897- -00000-0000
Fec: 2006-08-02 16:52:54 Dep: 2020 NUECREACIONES
Tra: 11 PATENTEIYII
Cva: 376 FASCNACIONALI
Act 411 PRESENTACION Folios: 276

277
294

# REQUISITOS MINIMOS PARA ADMISION A TRAMITE PCT

PATENTE DE INVENCION [ ] MODELO DE UTILIDAD [ ]

- Indicación de que se solicita la concesión de una patente [ ]
- Datos de identificación del solicitante o de la persona que presenta la solicitud [ ]
- Descripción de la invención [ ]
- Dibujos de ser estos pertinentes [ ]
- Comprobante de pago de las tasas establecidas [ ]

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 se solicita el registro de un Esquema de Trazado [ ]
- Datos de identificación del solicitante o de la persona que presenta la solicitud [ ]
- Representación gráfica del esquema trazado [ ]
- Comprobante de pago de las tasas establecidas [ ]

COMPLETA [ ] INCOMPLETA [ ]

Firma Responsable

Fecha 02 AGO. 2006

Carrera 13 No. 27-00 Piso 5, 7 y 10
Conmutador: 3 82 08 40
Fax: 350 52 20
E-mail: info@sic.gov.co
www.sic.gov.co
Bogotá, D.C., Colombia

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**REPUBLICA DE COLOMBIA**

**SUPERINTENDENCIA DE INDUSTRIA Y COMERCI**

Bogotá,
2020

Doctor(a)
CADENA SARMIENTO JUAN PABLO
Apoderado(a) y/o Representante de
ASTRAZENECA AB

| | | |
|---|---|---|
| REFERENCIA | Radicación No. | 6 75897 |
| | Solicitud internacional | SE2005/000124 |
| | Fecha inicio fase nacional | 06/09/2006 |
| | Trámite | 11 |
| | Evento | 378 |
| | Actuación | 430 |
| | Oficio No. | 10489 |

Como resultado del examen de forma, realizado con fundamento en el artículo 38 de la Decisión 486 de la Comisión de la Comunidad Andina, artículo 27 del Tratado de Cooperación en Materia de Patentes (PCT), regla 51 bis del Reglamento y Circular Única de la Superintendencia de Industria y Comercio, se le comunica que:

1. La solicitud no contiene la copia del documento en que consta la cesión del derecho a la patente del inventor al solicitante o a su causante. (Art. 26-k) Decisión 486.

En cumplimiento de lo dispuesto por el artículo 39 de la Decisión 486, se le requiere para que dentro del término de dos meses siguientes a la fecha de notificación del presente oficio, complete los requisitos anteriormente enunciados. En caso de no dar cumplimiento al presente requerimiento, la solicitud se considerará abandonada y perderá su prelación.

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo quinto del título primero de la Circular Unica No.10 de 2001.

ALIX CARMENZA CESPEDES DE VERGEL
Jefe de la división de Nuevas Creaciones

El anterior requerimiento fue notificado por fijación en lista de fecha 15 SET. 2006
adpal