SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 11-156143- -00000-0000
Fecha: 2011-11-16 16:58:27 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 218

Industria y Comercio
SUPERINTENDENCIA

DELEGATURA DE PROPIEDAD INDUSTRIAL
DIRECCIÓN DE NUEVAS CREACIONES

SOLICITUD DE PATENTE DE INVENCIÓN

TITULO: INHIBIDORES DE LA REPLICACIÓN DEL VIRUS DE LA INMUNODEFICIENCIA HUMANA.

SOLICITANTE: GILEAD SCIENCES LIMITED

DIRECCIÓN: IDA Business & Technology Park Carrigtohill, Co. Cork

APODERADO: CARLOS R. OLARTE

BOGOTÁ 16 de Noviembre de 2011

P2011/000184

OLARTEMOURE

OLARTE MOURE & ASOCIADOS

Industria y Comercio
SUPERINTENDENCIA

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No. 11-156143- -00000-0000
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Act. 411 PRESENTACION Folios: 218

PETITORIO - FORMULARIO ÚNICO
PATENTE PCT
ENTRADA EN FASE NACIONAL **P2011/000184**

SOLICITUD DE:

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

[X] Capítulo I. [ ] Capítulo II.

(2) SOLICITANTE (71)

Nombre: GILEAD SCIENCES LIMITED
Dirección: IDA Business & Technology Park Carrigtohill, Co. Cork
Nacionalidad o Domicilio: Irlanda
Lugar de Constitución: Irlanda
Teléfono: **Fax:**
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IDENTIFICACIÓN
C.C. [ ] **NIT** [ ]
C.E. [ ] **Otro** [ ]
Cual
Número

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C.E. [ ] **Otro** [ ]
Cual
Número 79.782.747Bta
TP 74.295

INVENTOR (ES) (72)

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(5) PCT (86)

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Publicación Internacional No. WO 2010/130034 Fecha Noviembre 18, 2010

(6) Título (54) INHIBIDORES DE LA REPLICACIÓN DEL VIRUS DE LA INMUNODEFICIENCIA HUMANA.

Clasificación Internacional (51) C07D 213/55; A61K 31/44; A61K 31/5375; A61K 31/54; A61P 31/18; C07D 213/60; C07D 401/00; C07D 405/00; C07D 413/00; C07D 417/00; C07D 471/04; C07D 491/06; C07D 498/06.

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US	Diciembre 11, 2009	61/285,766

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

(10) **ANEXOS**

- [x] Comprobante de pago de la tasa de presentación de la solicitud.
- [ ] Documento que acredita la existencia y representación legal cuando el solicitante sea persona jurídica.
- [ ] Poderes, si fuere el caso.
- [x] Documento de cesión del inventor al solicitante o a su causante. Declaración bajo la regla 4.17 del PCT.
- [ ] Declaraciones.
- [x] Copia de la solicitud internacional. (Resumen, descripción, reivindicaciones, dibujos).
- [x] Traducción de la solicitud internacional al castellano. (Resumen, descripción, reivindicaciones, dibujos).
- [x] Copia del examen preliminar internacional efectuado por la Autoridad Internacional de Examen Preliminar (IPEA).
- [ ] Traducción del examen preliminar internacional efectuado por la IPEA.
- [ ] De ser el caso, copia del contrato de acceso.
- [ ] De ser el caso, documento que acredite la licencia o autorización de uso de conocimientos tradicionales de las comunidades indígenas.
- [ ] De ser el caso, certificado de depósito del material biológico.
- [ ] Arte final 12 x 12.
- [ ] De ser el caso, información sobre otras solicitudes de patente o títulos obtenidos en el extranjero por el mismo titular o su causante, relacionadas parcial o totalmente con la invención de esta solicitud.
- [x] De ser el caso, modificaciones efectuadas a la solicitud internacional.
- [x] Otros. Búsqueda Internacional

(11) **FIGURA CARACTERÍSTICA:**

(12) Solicito la concesión de la patente,

NOMBRE: CARLOS R. OLARTE FIRMA:

C.C. 79.782.747 Btá T.P. 74.295

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NIT : 800.176.089-2
- / -

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SUPERINTENDENCIA

RECIBO DE CAJA

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RECIBIDO DE : OLARTE MOURE & ASOCIADOS NI 830.122.870

*** Soporte del Pago ***

TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PAGO	VR.PAGO
CONSIGNACION	BANCO DE BOGOTA	062754387	408398712	10/11/2011	11.097.000.00

*** Conceptos Pagados ***

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

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

Responsable: _____
***

Recibo de Caja Aplicado al Expediente No. _____

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
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Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
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PCT REQUEST

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VIII-2-1	**Declaration: Entitlement to apply for and be granted a patent** Declaration as to the applicant's entitlement, as at the international filing date, to apply for and be granted a patent (Rules 4.17(ii) and 51bis.1(a)(ii)), in a case where the declaration under Rule 4.17(iv) is not appropriate: Name (LAST, First)	In relation to this international application BOEHRINGER INGELHEIM INTERNATIONAL GmbH is entitled to apply for and be granted a patent by virtue of the following:
VIII-2-1(i)		YOAKIM, Christiane of 2100 Cunard Street Laval, Québec H7S 2G5 Canada is the inventor of the subject matter for which protection is sought by way of this international application
VIII-2-1(ii)		BOEHRINGER INGELHEIM (CANADA) LTD is entitled as employer of the inventor, YOAKIM, Christiane
VIII-2-1(i)		BAILEY, Murray D. of 2100 Cunard Street Laval, Québec H7S 2G5 Canada is the inventor of the subject matter for which protection is sought by way of this international application
VIII-2-1(ii)		BOEHRINGER INGELHEIM (CANADA) LTD is entitled as employer of the inventor, BAILEY, Murray D.
VIII-2-1(i)		BILODEAU, François of 2100 Cunard Street Laval, Québec H7S 2G5 Canada is the inventor of the subject matter for which protection is sought by way of this international application
VIII-2-1(ii)		BOEHRINGER INGELHEIM (CANADA) LTD is entitled as employer of the inventor, BILODEAU, François
VIII-2-1(i)		CARSON, Rebekah J. of 2100 Cunard Street Laval, Québec H7S 2G5 Canada is the inventor of the subject matter for which protection is sought by way of this international application
VIII-2-1(ii)		BOEHRINGER INGELHEIM (CANADA) LTD is entitled as employer of the inventor, CARSON, Rebekah J.
VIII-2-1(i)		FADER, Lee of 2100 Cunard Street Laval, Québec H7S 2G5 Canada is the inventor of the subject matter for which protection is sought by way of this international application

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VIII-2-1(ii)		BOEHRINGER INGELHEIM (CANADA) LTD is entitled as employer of the inventor, FADER, Lee
VIII-2-1(i)		KAWAI, Stephen of 2100 Cunard Street Laval, Québec H7S 2G5 Canada is the inventor of the subject matter for which protection is sought by way of this international application
VIII-2-1(ii)		BOEHRINGER INGELHEIM (CANADA) LTD is entitled as employer of the inventor, KAWAI, Stephen
VIII-2-1(i)		LAPLANTE, Steven of 2100 Cunard Street Laval, Québec H7S 2G5 Canada is the inventor of the subject matter for which protection is sought by way of this international application
VIII-2-1(ii)		BOEHRINGER INGELHEIM (CANADA) LTD is entitled as employer of the inventor, LAPLANTE, Steven
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VIII-2-1(ii)		BOEHRINGER INGELHEIM (CANADA) LTD is entitled as employer of the inventor, SURPRENANT, Simon
VIII-2-1(i)		THIBEAULT, Carl of 2100 Cunard Street Laval, Québec H7S 2G5 Canada is the inventor of the subject matter for which protection is sought by way of this international application
VIII-2-1(ii)		BOEHRINGER INGELHEIM (CANADA) LTD is entitled as employer of the inventor, THIBEAULT, Carl

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VIII-2-1(i)		TSANTRIZOS, Youla S. of 2100 Cunard Street Laval, Québec H7S 2G5 Canada is the inventor of the subject matter for which protection is sought by way of this international application
VIII-2-1(ii)		BOEHRINGER INGELHEIM (CANADA) LTD is entitled as employer of the inventor, TSANTRIZOS, Youla S.
VIII-2-1(iii)		an agreement between BOEHRINGER INGELHEIM CANADA LTD and BOEHRINGER INGELHEIM INTERNATIONAL GmbH, dated 01 January 2001 (01.01.2001)

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

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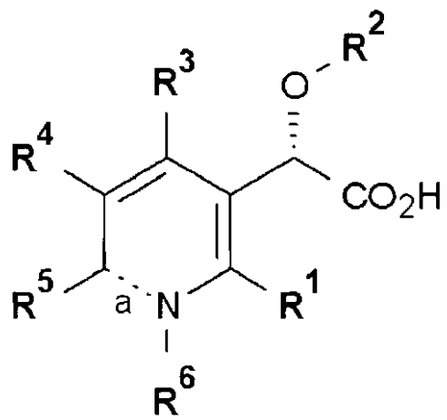
(74) Agent: **LOOPER, Ywe, J.**; c/o Boehringer Ingelheim (Canada) Ltd ., 2100 Cunard Street, Laval, Québec H7S 2G5 (CA).

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

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

[Continued on next page]

(54) Title: INHIBITORS OF HUMAN IMMUNODEFICIENCY VIRUS REPLICATION



(I)

(57) Abstract: Compounds of formula I wherein a, R^1, R^2, R^3, R^4, R^5 and R^6 are defined herein, are useful as inhibitors of HIV replication.

WO 2010/130034 A1

SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:

— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*

Published:

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

INHIBITORS OF HUMAN IMMUNODEFICIENCY VIRUS REPLICATION

RELATED APPLICATIONS

This application claims benefit of U.S. Serial No. 61/178551, filed May 15, 2009, and U.S. Serial No. 61/285766, filed December 11, 2009, which are herein incorporated by reference.

FIELD OF THE INVENTION

The present invention relates to compounds, compositions and methods for the treatment of human immunodeficiency virus (HIV) infection. In particular, the present invention provides novel inhibitors of the HIV integrase enzyme, pharmaceutical compositions containing such compounds and methods for using these compounds to reduce HIV replication and in the treatment of HIV infection.

BACKGROUND OF THE INVENTION

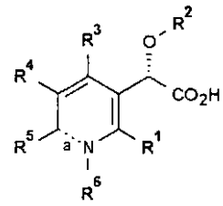
Acquired immune deficiency syndrome (AIDS) is caused by the human immunodeficiency virus (HIV), particularly the HIV-1 strain. Most currently approved therapies for HIV infection target the viral reverse transcriptase and protease enzymes. There are also two approved drugs targeting HIV entry and one approved drug targeting the integrase enzyme. Within the reverse transcriptase inhibitor and protease inhibitor classes, resistance of HIV to existing drugs is a problem. Therefore, it is important to discover and develop new antiretroviral compounds.

International patent application WO 2007/131350 and United States published patent application US 2006/0106070 describe compounds which are active against HIV replication.

SUMMARY OF THE INVENTION

The present invention provides a novel series of compounds having inhibitory activity against HIV replication. Therefore, the compounds of the invention may be used to inhibit the activity of HIV integrase and may be used to reduce HIV replication.

One aspect of the invention provides a compound of Formula I and a racemate, enantiomer or diastereomer of a compound of formula (I):



(I)

wherein

R^1 is (C_{1-6})alkyl, (C_{2-6})alkenyl or (C_{3-6})cycloalkyl, wherein the (C_{1-6})alkyl is optionally substituted with $-O(C_{1-6})$alkyl or $-S(C_{1-6})$alkyl;

R^2 is (C_{1-8})alkyl or (C_{3-8})cycloalkyl, wherein the (C_{3-8})cycloalkyl is optionally substituted with (C_{1-6})alkyl;

R^3 is aryl, wherein the aryl is optionally fused to one or more cycles, at least one of which is a heterocycle, to form a heteropolycycle, and wherein the aryl or heteropolycycle is optionally substituted with 1 to 4 substituents each independently selected from (C_{1-6})alkyl, halo and $-O(C_{1-6})$alkyl;

R^4 is (C_{1-6})alkyl, -CN, halo, (C_{1-6})haloalkyl, (C_{3-5})cycloalkyl, or $-O(C_{1-6})$alkyl; and

a is a double bond, R^6 is absent and R^5 is R^{51} or $-(C_{1-3})$alkyl-R^{51}; or

a is a single bond and R^5 and R^6 are joined, together with the atoms to which they are bonded, to form a 5-membered ring optionally having 1 to 3 further heteroatoms each independently selected from O, N and S, wherein the 5-membered ring is optionally substituted with 1 to 3 R^{51} substituents;

wherein R^{51} is in each case independently selected from R^{52}, $-OR^{53}$, $-N(R^{54})R^{53}$, $-C(=O)R^{52}$, $-C(=O)OR^{53}$, $-C(=O)N(R^{54})R^{53}$, $-OC(=O)N(R^{54})R^{53}$, $-N(R^{54})C(=O)R^{52}$, $-N(R^{54})C(=O)N(R^{54})R^{53}$ and $-N(R^{54})C(=O)OR^{53}$; wherein

R^{52} is in each case independently selected from R^{53}, (C_{2-8})alkenyl and (C_{2-8})alkynyl,

R^{53} is in each case independently selected from (C_{1-8})alkyl, (C_{3-8})cycloalkyl, (C_{3-8})cycloalkyl-(C_{1-6})alkyl-, aryl, aryl-(C_{1-6})alkyl-, **Het**, and **Het**-(C_{1-6})alkyl-, and

R^{54} is in each case independently selected from H and (C_{1-3})alkyl;

wherein each of R^{52} and R^{53} is optionally substituted with 1 to 3 substituents each independently selected from R^{55}, halo, -CN, $-OR^{56}$, $-SR^{56}$, $-SOR^{56}$, $-SO_2R^{56}$, $-N(R^{54})R^{56}$, $-N(R^{54})C(=O)R^{55}$, $-N(R^{54})C(=O)N(R^{54})R^{56}$, $-N(R^{54})C(=O)OR^{56}$, $-OC(=O)N(R^{54})R^{56}$, $-C(=O)R^{55}$, $-C(=O)OR^{56}$, and $-CON(R^{54})R^{56}$, wherein

R^{55} is in each case independently selected from R^{56}, (C_{2-8})alkenyl and (C_{2-8})alkynyl, and

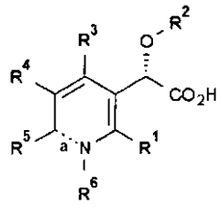
R^{56} is in each case independently selected from H, (C_{1-8})alkyl, (C_{3-8})cycloalkyl, (C_{3-8})cycloalkyl-(C_{1-6})alkyl-, aryl, aryl-(C_{1-6})alkyl-, **Het**, and **Het**-(C_{1-6})alkyl-,

wherein each of R^{55} and R^{56} is, where possible, in each case independently optionally substituted with 1 to 3 substituents each independently selected from (C_{1-6})alkyl, (C_{1-6})haloalkyl, halo, -OH, -O(C_{1-6})alkyl, $-NH_2$, -NH(C_{1-6})alkyl, -N$((C_{1-6})alkyl)_2$ and -NH(C=O)(C_{1-6})alkyl;

wherein **Het** is a 4- to 7-membered saturated, unsaturated or aromatic heterocycle having 1 to 4 heteroatoms each independently selected from O, N and S, or a 7- to 14-membered saturated, unsaturated or aromatic heteropolycycle having wherever possible 1 to 5 heteroatoms, each independently selected from O, N and S;

or a salt thereof.

Another aspect of Formula (I) provides a compound of Formula II and a racemate, enantiomer or diastereomer of a compound of formula (II):



(II)

wherein

R^1 is (C_{1-6})alkyl, (C_{2-6})alkenyl or (C_{3-6})cycloalkyl, wherein the (C_{1-6})alkyl is optionally substituted with –O(C_{1-6})alkyl or -S(C_{1-6})alkyl;

R^2 is (C_{1-8})alkyl or (C_{3-8})cycloalkyl, wherein the (C_{3-8})cycloalkyl is optionally substituted with (C_{1-6})alkyl;

R^3 is aryl, wherein the aryl is optionally fused to one or more cycles, at least one of which is a heterocycle, to form a heteropolycycle, and wherein the aryl or heteropolycycle is optionally substituted with 1 to 4 substituents each independently selected from (C_{1-6})alkyl, halo and -O(C_{1-6})alkyl;

R^4 is (C_{1-6})alkyl, -CN, halo, (C_{1-6})haloalkyl, (C_{3-5})cycloalkyl, or –O(C_{1-6})alkyl; and

a is a double bond, R^6 is absent and R^5 is R^{51} or -(C_{1-3})alkyl-R^{51}; or

a is a single bond and R^5 and R^6 are joined, together with the atoms to which they are bonded, to form a 5-membered ring optionally having 1 to 3 further heteroatoms each independently selected from O, N and S, wherein the 5-membered ring is optionally substituted with 1 to 3 R^{51} substituents;

wherein R^{51} is in each case independently selected from R^{52}, $-OR^{53}$, $-N(R^{54})R^{53}$, $-C(=O)R^{52}$, $-C(=O)OR^{53}$, $-C(=O)N(R^{54})R^{53}$, $-OC(=O)N(R^{54})R^{53}$, $-N(R^{54})C(=O)R^{52}$, $-N(R^{54})C(=O)N(R^{54})R^{53}$ and $-N(R^{54})C(=O)OR^{53}$; wherein

R^{52} is in each case independently selected from R^{53}, (C_{2-8})alkenyl and (C_{2-8})alkynyl,

R^{53} is in each case independently selected from (C_{1-8})alkyl, (C_{3-8})cycloalkyl, (C_{5-14})spirocycloalkyl, (C_{3-8})cycloalkyl-(C_{1-6})alkyl-, aryl, aryl-(C_{1-6})alkyl-, **Het**, and **Het**-(C_{1-6})alkyl-, and

R^{54} is in each case independently selected from H and (C_{1-3})alkyl;

wherein each of R^{52} and R^{53} is optionally substituted with 1 to 3 substituents each independently selected from R^{55}, halo, -CN, $-OR^{56}$, $-SR^{56}$, $-SOR^{56}$, $-SO_2R^{56}$, $-N(R^{54})R^{56}$, $-N(R^{54})C(=O)R^{55}$, $-N(R^{54})C(=O)N(R^{54})R^{56}$, $-N(R^{54})C(=O)OR^{56}$, $-OC(=O)N(R^{54})R^{56}$, $-C(=O)R^{55}$, $-C(=O)OR^{56}$, and $-CON(R^{54})R^{56}$, wherein

R^{55} is in each case independently selected from R^{56}, (C_{2-8})alkenyl and (C_{2-8})alkynyl, and

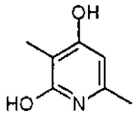
R^{56} is in each case independently selected from H, (C_{1-8})alkyl, (C_{3-8})cycloalkyl, (C_{3-8})cycloalkyl-(C_{1-6})alkyl-, aryl, aryl-(C_{1-6})alkyl-, **Het**, and **Het**-(C_{1-6})alkyl-,

wherein each of R^{55} and R^{56} is, where possible, in each case independently optionally substituted with 1 to 3 substituents each independently selected from (C_{1-6})alkyl, (C_{1-6})haloalkyl, halo, -OH, $-O(C_{1-6})$alkyl, $-NH_2$, $-NH(C_{1-6})$alkyl, $-N((C_{1-6})alkyl)_2$ and $-NH(C=O)(C_{1-6})$alkyl;

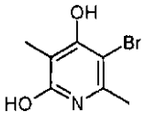
wherein **Het** is a 4- to 7-membered saturated, unsaturated or aromatic heterocycle having 1 to 4 heteroatoms each independently selected from O, N and S, or a 7- to 14-membered saturated, unsaturated or aromatic heteropolycycle having wherever possible 1 to 5 heteroatoms, each independently selected from O, N and S;

or a salt thereof.

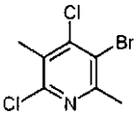
Another aspect of the invention provides one or more intermediates selected from the formulas:



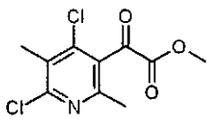
2c



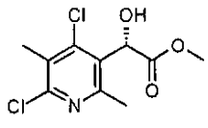
2d



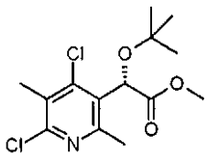
2e



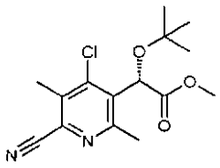
2f



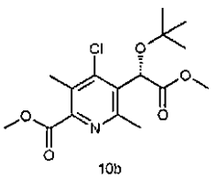
2g



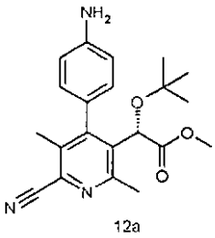
2h



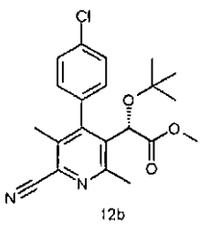
10a



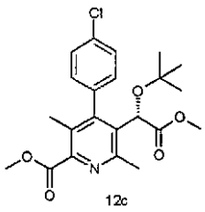
10b



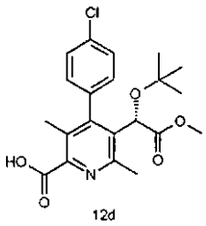
12a



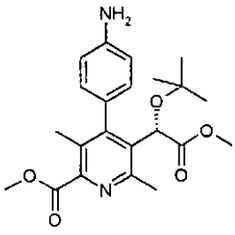
12b



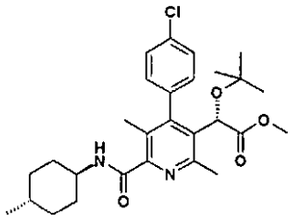
12c



12d



36a



37a

or

Another aspect of this invention provides a compound of formula (I) or a pharmaceutically acceptable salt thereof, as a medicament.

Still another aspect of this invention provides a pharmaceutical composition comprising a therapeutically effective amount of a compound of formula (I) or a

pharmaceutically acceptable salt thereof; and one or more pharmaceutically acceptable carriers.

According to an embodiment of this aspect, the pharmaceutical composition according to this invention additionally comprises at least one other antiviral agent.

The invention also provides the use of a pharmaceutical composition as described hereinabove for the treatment of an HIV infection in a human being having or at risk of having the infection.

A further aspect of the invention involves a method of treating an HIV infection in a human being having or at risk of having the infection, the method comprising administering to the human being a therapeutically effective amount of a compound of formula (I), a pharmaceutically acceptable salt thereof, or a composition thereof as described hereinabove.

Another aspect of the invention involves a method of treating an HIV infection in a human being having or at risk of having the infection, the method comprising administering to the human being a therapeutically effective amount of a combination of a compound of formula (I) or a pharmaceutically acceptable salt thereof, and at least one other antiviral agent; or a composition thereof.

Also within the scope of this invention is the use of a compound of formula (I) as described herein, or a pharmaceutically acceptable salt thereof, for the treatment of an HIV infection in a human being having or at risk of having the infection.

Another aspect of this invention provides the use of a compound of formula (I) as described herein, or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for the treatment of an HIV infection in a human being having or at risk of having the infection.

An additional aspect of this invention refers to an article of manufacture comprising a composition effective to treat an HIV infection; and packaging material comprising a label which indicates that the composition can be used to treat infection by HIV;

wherein the composition comprises a compound of formula (I) according to this invention or a pharmaceutically acceptable salt thereof.

Still another aspect of this invention relates to a method of inhibiting the replication of HIV comprising exposing the virus to an effective amount of the compound of formula (I), or a salt thereof, under conditions where replication of HIV is inhibited.

Further included in the scope of the invention is the use of a compound of formula (I) to inhibit the activity of the HIV integrase enzyme.

Further included in the scope of the invention is the use of a compound of formula (I), or a salt thereof, to inhibit the replication of HIV.

DETAILED DESCRIPTION OF THE INVENTION

DEFINITIONS

As used herein, the following definitions apply unless otherwise noted:

The term "substituent", as used herein and unless specified otherwise, is intended to mean an atom, radical or group which may be bonded to a carbon atom, a heteroatom or any other atom which may form part of a molecule or fragment thereof, which would otherwise be bonded to at least one hydrogen atom. Substituents contemplated in the context of a specific molecule or fragment thereof are those which give rise to chemically stable compounds, such as are recognized by those skilled in the art.

Unless specifically indicated, throughout the specification and the appended claims, a given chemical formula or name shall encompass salts, including pharmaceutically acceptable salts thereof and solvates thereof, such as for instance hydrates, including solvates of the free compounds or solvates of a salt of the compound. For example, the compounds of the present invention can exist in unsolvated as well as solvated forms with pharmaceutically acceptable solvents such as water, ethanol and the like. In general, the solvated forms are considered equivalent to the unsolvated forms for the purpose of the present invention.

In one aspect the present invention also provides all pharmaceutically-acceptable isotopically labeled compounds of the present invention wherein one or more atoms are replaced by atoms having the same atomic number, but an atomic mass or mass number different from the atomic mass or mass number predominantly found in nature. Examples of isotopes suitable for inclusion in the compounds of the present invention include isotopes of hydrogen, for example 2H or 3H. Isotopically labeled compounds of the present invention, for example deuterated versions of the compounds, can be prepared by conventional techniques known to those skilled in the art or by synthetic processes analogous to those described in the present application using appropriate isotopically labeled reagents in place of the non-labeled reagent mentioned therein.

The term "(C_{1-n})alkyl" as used herein, wherein n is an integer, either alone or in combination with another radical, is intended to mean acyclic, straight or branched chain alkyl radicals containing from 1 to n carbon atoms. "(C_{1-6})alkyl" includes, but is not limited to, methyl, ethyl, propyl (*n*-propyl), butyl (*n*-butyl), 1-methylethyl (*iso*-propyl), 1-methylpropyl (*sec*-butyl), 2-methylpropyl (*iso*-butyl), 1,1-dimethylethyl (*tert*-butyl), pentyl and hexyl. The abbreviation Me denotes a methyl group; Et denotes an ethyl group, Pr denotes a propyl group, iPr denotes a 1-methylethyl group, Bu denotes a butyl group and tBu denotes a 1,1-dimethylethyl group.

The term "(C_{2-n})alkenyl", as used herein, wherein n is an integer, either alone or in combination with another radical, is intended to mean an unsaturated, acyclic straight or branched chain radical containing two to n carbon atoms, at least two of which are bonded to each other by a double bond. Examples of (C_{2-6})alkenyl radicals include, but are not limited to, ethenyl (vinyl), 1-propenyl, 2-propenyl, and 1-butenyl. Unless specified otherwise, the term "(C_{2-n})alkenyl" is understood to encompass individual stereoisomers where possible, including but not limited to (*E*) and (*Z*) isomers, and mixtures thereof. When a (C_{2-n})alkenyl group is substituted, it is understood to be substituted on any carbon atom thereof which would otherwise bear a hydrogen atom, unless specified otherwise, such that the substitution would give rise to a chemically stable compound, such as are recognized by those skilled in the art.

The term "(C_{2-n})alkynyl", as used herein, wherein n is an integer, either alone or in combination with another radical, is intended to mean an unsaturated, acyclic straight or branched chain radical containing two to n carbon atoms, at least two of which are bonded to each other by a triple bond. Examples of (C_{2-6})alkynyl radicals include, but are not limited to, ethynyl, 1-propynyl, 2-propynyl, and 1-butynyl. When a (C_{2-n})alkynyl group is substituted, it is understood to be substituted on any carbon atom thereof which would otherwise bear a hydrogen atom, unless specified otherwise, such that the substitution would give rise to a chemically stable compound, such as are recognized by those skilled in the art.

The term "(C_{3-m})cycloalkyl" as used herein, wherein m is an integer, either alone or in combination with another radical, is intended to mean a cycloalkyl substituent containing from 3 to m carbon atoms. Examples of (C_{3-7})cycloalkyl radicals include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl.

The term "(C_{5-n})spirocycloalkyl", wherein n is an integer, either alone or in combination with another radical, denotes a cycloalkyl multi-ring system having two rings linked by one common atom. Examples of (C_{5-14})spirocycloalkyl radicals include, but are not limited to,  and  .

The term "(C_{3-m})cycloalkyl-(C_{1-n})alkyl-" as used herein, wherein n and m are both integers, either alone or in combination with another radical, is intended to mean an alkyl radical having 1 to n carbon atoms as defined above which is itself substituted with a cycloalkyl radical containing from 3 to m carbon atoms as defined above. Examples of (C_{3-7})cycloalkyl-(C_{1-6})alkyl- include, but are not limited to, cyclopropylmethyl, cyclobutylmethyl, cyclopentylmethyl, cyclohexylmethyl, 1-cyclopropylethyl, 2-cyclopropylethyl, 1-cyclobutylethyl, 2-cyclobutylethyl, 1-cyclopentylethyl, 2-cyclopentylethyl, 1-cyclohexylethyl and 2-cyclohexylethyl. When a (C_{3-m})cycloalkyl-(C_{1-n})alkyl- group is substituted, it is understood that substituents may be attached to either the cycloalkyl or the alkyl portion thereof or both, unless specified otherwise, such that the substitution would give rise to a chemically stable compound, such as are recognized by those skilled in the art.

The term "aryl" as used herein, either alone or in combination with another radical, is intended to mean a carbocyclic aromatic monocyclic group containing 6 carbon atoms which may be further fused to a second 5- or 6-membered carbocyclic group which may be aromatic, saturated or unsaturated. Aryl includes, but is not limited to, phenyl, indanyl, indenyl, 1-naphthyl, 2-naphthyl, tetrahydronaphthyl and dihydronaphthyl.

The term "aryl-(C_{1-n})alkyl-" as used herein, wherein n is an integer, either alone or in combination with another radical, is intended to mean an alkyl radical having 1 to n carbon atoms as defined above which is itself substituted with an aryl radical as defined above. Examples of aryl-(C_{1-6})alkyl- include, but are not limited to, phenylmethyl (benzyl), 1-phenylethyl, 2-phenylethyl and phenylpropyl. When an aryl-(C_{1-n})alkyl- group is substituted, it is understood that substituents may be attached to either the aryl or the alkyl portion thereof or both, unless specified otherwise, such that the substitution would give rise to a chemically stable compound, such as are recognized by those skilled in the art.

The term "**Het**" as used herein, either alone or in combination with another radical, is intended to mean a 4- to 7-membered saturated, unsaturated or aromatic heterocycle having 1 to 4 heteroatoms each independently selected from O, N and S, or a 7- to 14-membered saturated, unsaturated or aromatic heteropolycycle having wherever possible 1 to 5 heteroatoms, each independently selected from O, N and S, unless specified otherwise. When a **Het** group is substituted, it is understood that substituents may be attached to any carbon atom or heteroatom thereof which would otherwise bear a hydrogen atom, unless specified otherwise, such that the substitution would give rise to a chemically stable compound, such as are recognized by those skilled in the art.

The term "**Het**-(C_{1-n})alkyl-" as used herein and unless specified otherwise, wherein n is an integer, either alone or in combination with another radical, is intended to mean an alkyl radical having 1 to n carbon atoms as defined above which is itself substituted with a **Het** substituent as defined above. Examples of **Het**-(C_{1-6})alkyl- include, but are not limited to, thienylmethyl, furylmethyl, piperidinylethyl, 2-

pyridinylmethyl, 3-pyridinylmethyl, 4-pyridinylmethyl, quinolinylpropyl, and the like. When an **Het**-(C_{1-n})alkyl- group is substituted, it is understood that substituents may be attached to either the **Het** or the alkyl portion thereof or both, unless specified otherwise, such that the substitution would give rise to a chemically stable compound, such as are recognized by those skilled in the art.

The term "heteroatom" as used herein is intended to mean O, S or N.

The term "carbocycle" as used herein, either alone or in combination with another radical, is intended to mean a 3- to 8-membered saturated, unsaturated or aromatic cyclic radical in which all of the ring members are carbon atoms, and which may be fused to one or more 3- to 8-membered saturated, unsaturated or aromatic carbocyclic groups. When a carbocycle is substituted, it is understood that substituents may be attached to any carbon atom which would otherwise bear a hydrogen atom, unless specified otherwise, such that the substitution would give rise to a chemically stable compound, such as are recognized by those skilled in the art.

The term "heterocycle" as used herein and unless specified otherwise, either alone or in combination with another radical, is intended to mean a 3- to 7-membered saturated, unsaturated or aromatic heterocycle containing from 1 to 4 heteroatoms each independently selected from O, N and S; or a monovalent radical derived by removal of a hydrogen atom therefrom. Examples of such heterocycles include, but are not limited to, azetidine, pyrrolidine, tetrahydrofuran, tetrahydrothiophene, thiazolidine, oxazolidine, pyrrole, thiophene, furan, pyrazole, imidazole, isoxazole, oxazole, isothiazole, thiazole, triazole, tetrazole, piperidine, piperazine, azepine, diazepine, pyran, 1,4-dioxane, 4-morpholine, 4-thiomorpholine, pyridine, pyridine-N-oxide, pyridazine, pyrazine and pyrimidine, and saturated, unsaturated and aromatic derivatives thereof.

The term "heteropolycycle" as used herein and unless specified otherwise, either alone or in combination with another radical, is intended to mean a heterocycle as defined above fused to one or more other cycle, including a carbocycle, a heterocycle or any other cycle; or a monovalent radical derived by removal of a

hydrogen atom therefrom. Examples of such heteropolycycles include, but are not limited to, indole, isoindole, benzimidazole, benzothiophene, benzofuran, benzopyran, benzodioxole, benzodioxane, benzothiazole, quinoline, isoquinoline, and naphthyridine, and saturated, unsaturated and aromatic derivatives thereof.

The term "halo" as used herein is intended to mean a halogen substituent selected from fluoro, chloro, bromo or iodo.

The term "(C_{1-n})haloalkyl" as used herein, wherein n is an integer, either alone or in combination with another radical, is intended to mean an alkyl radical having 1 to n carbon atoms as defined above wherein one or more hydrogen atoms are each replaced by a halo substituent. When two or more hydrogen atoms are replaced by halo substituents, the halo substituents may be the same or different. Examples of (C_{1-6})haloalkyl include but are not limited to chloromethyl, chloroethyl, dichloroethyl, bromomethyl, bromoethyl, dibromoethyl, chlorobromoethyl, fluoromethyl, difluoromethyl, trifluoromethyl, fluoroethyl and difluoroethyl.

The terms "-O-(C_{1-n})alkyl" as used herein interchangeably, wherein n is an integer, either alone or in combination with another radical, is intended to mean an oxygen atom further bonded to an alkyl radical having 1 to n carbon atoms as defined above. Examples of -O-(C_{1-n})alkyl include but are not limited to methoxy (CH_3O-), ethoxy (CH_3CH_2O-), propoxy ($CH_3CH_2CH_2O$-), 1-methylethoxy (*iso*-propoxy; $(CH_3)_2CH$-O-) and 1,1-dimethylethoxy (*tert*-butoxy; $(CH_3)_3C$-O-). When an -O-(C_{1-n})alkyl radical is substituted, it is understood to be substituted on the (C_{1-n})alkyl portion thereof, such that the substitution would give rise to a chemically stable compound, such as are recognized by those skilled in the art.

The terms "-S-(C_{1-n})alkyl" as used herein interchangeably, wherein n is an integer, either alone or in combination with another radical, is intended to mean an sulfur atom further bonded to an alkyl radical having 1 to n carbon atoms as defined above. Examples of -S-(C_{1-n})alkyl include but are not limited to methylthio (CH_3S-), ethylthio (CH_3CH_2S-), propylthio ($CH_3CH_2CH_2S$-), 1-methylethylthio (*iso*propylthio; $(CH_3)_2CH$-S-) and 1,1-dimethylethylthio (*tert*-butylthio; $(CH_3)_3C$-S-). When -S-(C_{1-n})alkyl radical, or an oxidized derivative thereof, such as an -SO-(C_{1-n})alkyl

radical or an -SO_2-(C_{1-n})alkyl radical, is substituted, each is understood to be substituted on the (C_{1-n})alkyl portion thereof, such that the substitution would give rise to a chemically stable compound, such as are recognized by those skilled in the art.

The term "protecting group" as used herein is intended to mean protecting groups that can be used during synthetic transformation, including but not limited to examples which are listed in Greene, "Protective Groups in Organic Chemistry", John Wiley & Sons, New York (1981), and more recent editions thereof, herein incorporated by reference.

The following designations ---- and  are used interchangeably in sub-formulas to indicate the bond which is connected to the rest of the molecule as defined.

The term "salt thereof" as used herein is intended to mean any acid and/or base addition salt of a compound according to the invention, including but not limited to a pharmaceutically acceptable salt thereof.

The phrase "pharmaceutically acceptable" is employed herein to refer to those compounds, materials, compositions, and/or dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of human beings and animals without excessive toxicity, irritation, allergic response, or other problem or complication, commensurate with a reasonable benefit/risk ratio.

As used herein, "pharmaceutically acceptable salts" refer to derivatives of the disclosed compounds wherein the parent compound is modified by making acid or base salts thereof. Examples of pharmaceutically acceptable salts include, but are not limited to, mineral or organic acid salts of basic residues such as amines; alkali or organic salts of acidic residues such as carboxylic acids; and the like. For example, such salts include acetates, ascorbates, aspartates, benzenesulfonates, benzoates, besylates, bicarbonates, bitartrates, bromides/hydrobromides, Ca-edetates/edetates, camsylates, carbonates, chlorides/hydrochlorides, citrates, cyclamates, edisylates, ethane disulfonates, estolates, esylates, fumarates,

gentisates (salt of 2,5-dihydroxy benzoic acid), gluceptates, gluconates, glutamates, glycinates, glycolates, glycollylarsnilates, hexylresorcinates, hydrabamines, hydroxymaleates, hydroxynaphthoates, iodides, isethionates, lactates, lactobionates, malates, maleates, malonates, mandelates, methanesulfonates, mesylates, methylbromides, methylnitrates, methylsulfates, mucates, napsylates, nitrates, oxalates, pamoates, pantothenates, phenylacetates, phosphates/diphosphates, polygalacturonates, propionates, saccharinates, salicylates, stearates subacetates, succinates, sulfamides, sulfates, tannates, tartrates, teoclates, toluenesulfonates, triethiodides, xinafoates (salt of 1-hydroxy-2-naphthoicacid) , ammonium, arginine, benzathines, chloroprocaines, cholines, diethanolamines, ethylenediamines, lysine, meglumines, TRIS (*C,C,C*-tris(hydroxymethyl)-aminomethan or Trometamol) and procaines. Further pharmaceutically acceptable salts can be formed with cations from metals like aluminium, calcium, lithium, magnesium, potassium, sodium, zinc and the like. (also see Pharmaceutical salts, Berge, S.M. et al., J. Pharm. Sci., (1977), 66, 1-19 and Handbook of Pharmaceutical Salts, P.Heinrich Stahl, Camille G. Wermuth (Eds.), Wiley-VCH, 2002, both of which are herein incorporated by reference).

The pharmaceutically acceptable salts of the present invention can be synthesized from the parent compound which contains a basic or acidic moiety by conventional chemical methods. Generally, such salts can be prepared by reacting the free acid or base forms of these compounds with a sufficient amount of the appropriate base or acid in water or in an organic diluent like ether, ethyl acetate, ethanol, isopropanol, or acetonitrile, or a mixture thereof.

Salts of other acids than those mentioned above which for example are useful for purifying or isolating the compounds of the present invention also comprise a part of the invention.

The term "treatment" as used herein is intended to mean the administration of a compound or composition according to the present invention to alleviate or eliminate symptoms of HIV infection and/or to reduce viral load in a patient. The term "treatment" also encompasses the administration of a compound or composition according to the present invention post-exposure of the individual to the virus but

before the appearance of symptoms of the disease, and/or prior to the detection of the virus in the blood, to prevent the appearance of symptoms of the disease and/or to prevent the virus from reaching detectible levels in the blood, and the administration of a compound or composition according to the present invention to prevent perinatal transmission of HIV from mother to baby, by administration to the mother before giving birth and to the child within the first days of life.

The term "antiviral agent" as used herein is intended to mean an agent (compound or biological) that is effective to inhibit the formation and/or replication of a virus in a human being, including but not limited to agents that interfere with either host or viral mechanisms necessary for the formation and/or replication of a virus in a human being.

The term "inhibitor of HIV replication" as used herein is intended to mean an agent capable of reducing or eliminating the ability of HIV to replicate in a host cell, whether *in vitro, ex vivo* or *in vivo*.

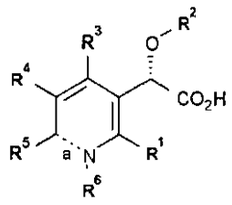
The term "HIV integrase" or "integrase", used herein interchangeably, means the integrase enzyme encoded by the human immunodeficiency virus type 1. The polypeptide sequence of the integrase enzyme of NL4.3 strain of HIV-1 is provided as SEQ ID NO: 1.

The term "therapeutically effective amount" means an amount of a compound according to the invention, which when administered to a patient in need thereof, is sufficient to effect treatment for disease-states, conditions, or disorders for which the compounds have utility. Such an amount would be sufficient to elicit the biological or medical response of a tissue system, or patient that is sought by a researcher or clinician. The amount of a compound according to the invention which constitutes a therapeutically effective amount will vary depending on such factors as the compound and its biological activity, the composition used for administration, the time of administration, the route of administration, the rate of excretion of the compound, the duration of the treatment, the type of disease-state or disorder being treated and its severity, drugs used in combination with or coincidentally with the compounds of the invention, and the age, body weight, general health, sex and diet

of the patient. Such a therapeutically effective amount can be determined routinely by one of ordinary skill in the art having regard to their own knowledge, the state of the art, and this disclosure.

PREFERRED EMBODIMENTS

In the following preferred embodiments, groups and substituents of the compounds of formula (I):



(I)

according to this invention are described in detail. Any and each individual definition as set out herein may be combined with any and each individual definition as set out herein.

R^1:

R^1-A:

In at least one embodiment, **R^1** is (C_{1-4})alkyl, (C_{2-4})alkenyl or (C_{3-5})cycloalkyl, wherein the (C_{1-4})alkyl is optionally substituted with $-O(C_{1-3})$alkyl or $-S(C_{1-3})$alkyl.

R^1-B:

In at least one embodiment, **R^1** is selected from:

$-CH_3$, $-CH_2OMe$, $-CH_2OEt$, $-CH_2SMe$, $-CH=CH_2$ and  .

R^1-C:

In at least one embodiment, **R^1** is (C_{1-4})alkyl.

R^1-D:

In at least one embodiment, **R^1** is $-CH_3$.

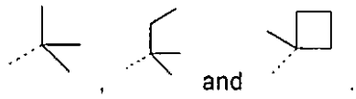
R^2:

R^2-A:

In at least one embodiment, R^2 is (C_{3-8})alkyl or (C_{3-8})cycloalkyl wherein the (C_{3-8})cycloalkyl is optionally substituted with (C_{1-6})alkyl.

R^2-B:

In at least one embodiment, R^2 is selected from:



R^2-C:

In at least one embodiment, R^2 is (C_{3-8})alkyl.

R^2-D:

In at least one embodiment, R^2 is  or  .

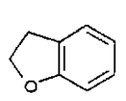
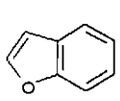
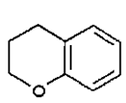
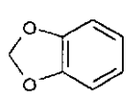
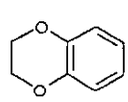
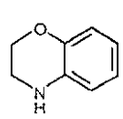
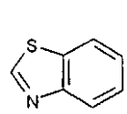
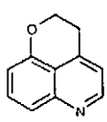
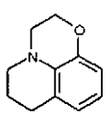
R^3:

R^3-A:

In at least one embodiment, R^3 is phenyl or R^3 is phenyl fused to one or more cycles, at least one of which is a heterocycle, to form a 9- to 13-membered heteropolycycle having 1 or 2 heteroatoms, each independently selected from N, O and S; wherein the phenyl or heteropolycycle is optionally substituted with 1 to 4 substituents each independently selected from (C_{1-6})alkyl, halo and $-O(C_{1-6})$alkyl.

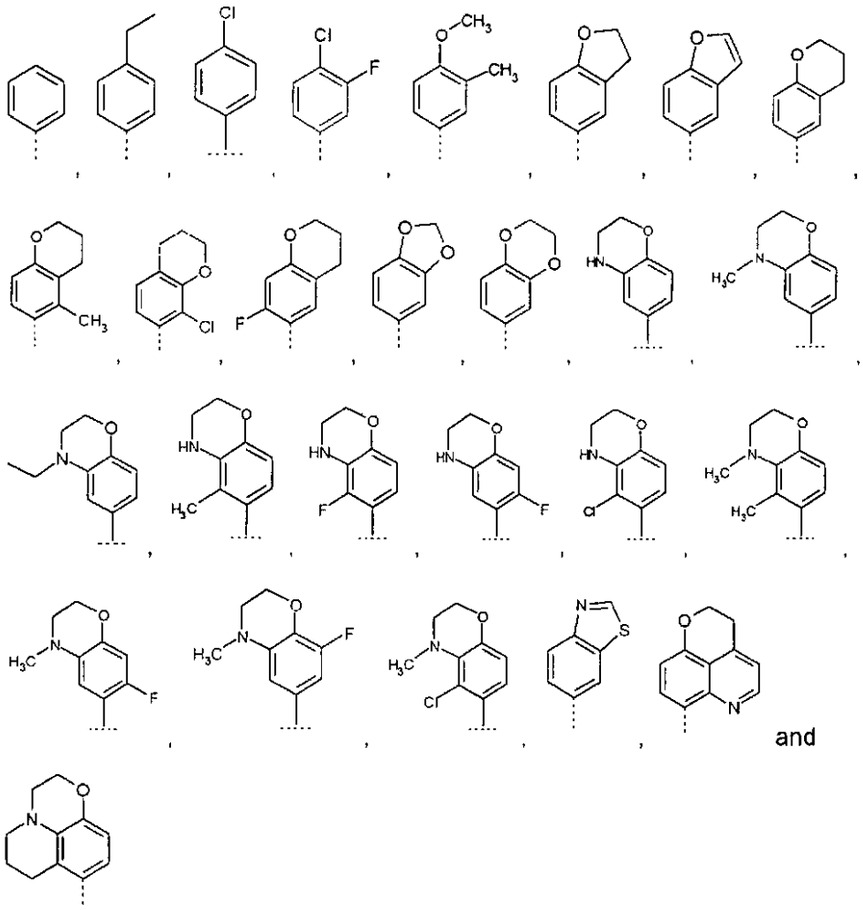
R^3-B:

In at least one embodiment, R^3 is phenyl or a heteropolycycle selected from:

 ,  ,  ,  ,  ,  ,  ,  and  ; wherein the phenyl or heteropolycycle is optionally substituted with 1 to 4 substituents each independently selected from (C_{1-6})alkyl, halo and $-O(C_{1-6})$alkyl.

R^3-C:

In at least one embodiment, R^3 is selected from:

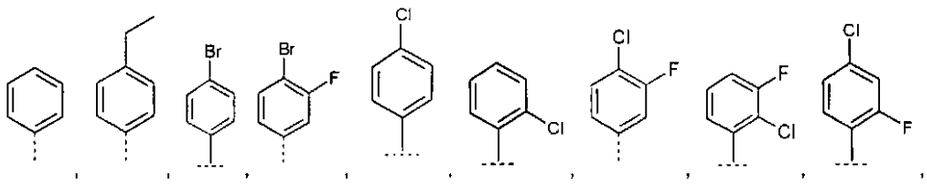


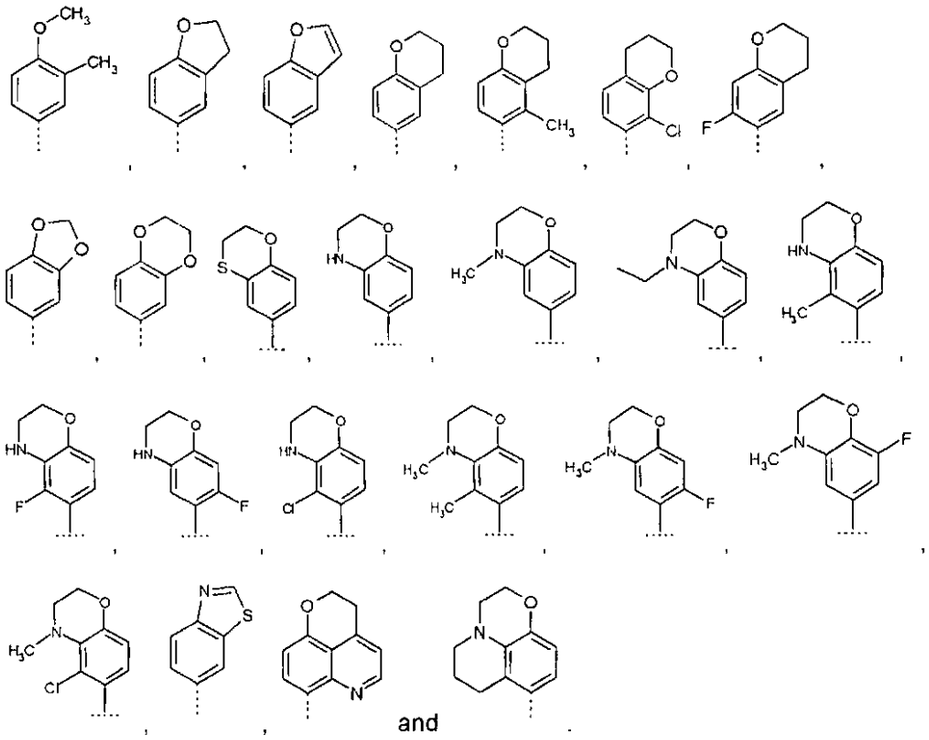
and

.

R^3-D:

In at least one embodiment, R^3 is selected from:



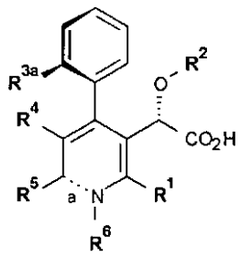


and

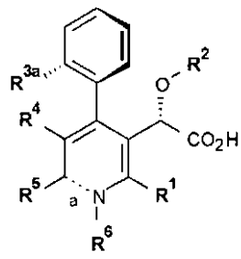
One skilled in the art will recognize that when the R^3 substituent is not symmetrically substituted about the axis of rotation of the bond attaching R^3 to **Core**, the compounds of the invention will have a rotational axis of asymmetry and thus rotational isomers are possible. When the energy barrier to rotation is relatively low, the rotational isomers rapidly interconvert at room temperature and are considered to be conformers. In contrast, when the energy barrier to rotation is relatively high, the rotational isomers interconvert so slowly at room temperature that they may be isolated and are considered to be atropisomers.

Because the compounds of the invention also posess at least one other chiral center, namely, the chiral carbon atom bonded to $-OR^2$, the rotational isomers will exist as diastereomers. For example, when the unsymmetrically substituted R^3 substituent bears a substituent R^{3a} at a position *ortho* to the bond attaching R^3 to **Core**, wherein R^{3a} is any atom or group other than hydrogen which is a substituent of R^3 by any definition of R^3 set forth herein, the following atropisomeric formulas A-

1 and **A-2** are possible, where, in conformance with accepted stereochemical notation, the darkened and/or solid wedge bonds indicate the side or edge of the R^3 substituent that is projecting towards the viewer:



A-1



A-2

Although for purposes of illustration, R^3 is shown as phenyl unsymmetrically substituted at the ortho position with a substituent R^{3a} in formulas **A-1** and **A-2**, it will be clear to the person skilled in the art that analogous atropisomers exist for other unsymmetrically substituted R^3 substituents.

It has been found that, when it is possible to separate the individual diastereomeric atropisomers so that their individual activities against HIV can be measured, the atropisomer with the formula similar to **A-1** above, where the substituent on the R^3 group is on the opposite side of the plane of the pyridine ring from the $-OR^2$ group, is in some cases more active against HIV, when measured, for example, by the procedure of Example 48 below, than the atropisomer with the formula similar to **A-2** above, where the substituent on the R^3 group is on the same side of the plane of the pyridine ring as the $-OR^2$ group.

R^4:

R^4-A:

In at least one embodiment, R^4 is (C_{1-6})alkyl, -CN, halo or (C_{1-6})haloalkyl.

R^4-B:

In at least one embodiment, R^4 is (C_{1-6})alkyl, -CN or halo.

R^4-C:

In at least one embodiment, R^4 is selected from $-CH_3$, –CN and -F.

R^4-D:

In at least one embodiment, R^4 is (C_{1-6})alkyl.

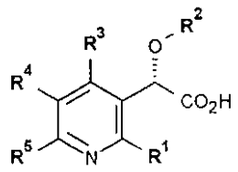
R^4-E:

In at least one embodiment, R^4 is $-CH_3$.

Core and R^5/R^6:

Core-A:

In at least one embodiment, **a** is a double bond and R^6 is absent such that the compound of the invention is a compound of formula (Ia):



(Ia)

wherein R^1, R^2, R^3, R^4 and R^5 are as defined herein.

R^5/R^6-A:

In at least one embodiment, **a** is a double bond, R^6 is absent and R^5 is R^{51} or $-(C_{1-3})$alkyl-R^{51};

wherein R^{51} is selected from R^{52}, $-OR^{53}$, $-N(R^{54})R^{53}$, $-C(=O)R^{52}$, $-C(=O)OR^{53}$, $-C(=O)N(R^{54})R^{53}$, $-N(R^{54})C(=O)R^{52}$, $-N(R^{54})C(=O)N(R^{54})R^{53}$ and $-N(R^{54})C(=O)OR^{53}$; wherein

R^{52} is selected from R^{53} and (C_{2-8})alkenyl, and

R^{53} is selected from (C_{1-8})alkyl, (C_{3-8})cycloalkyl, (C_{3-8})cycloalkyl-(C_{1-6})alkyl-, aryl, aryl-(C_{1-6})alkyl-, **Het**, and **Het**-(C_{1-6})alkyl-, and

R^{54} is in each case independently selected from H and (C_{1-3})alkyl;

wherein each of R^{52} and R^{53} is optionally substituted with 1 to 3 substituents each independently selected from R^{56}, halo, -CN, $-OR^{56}$, $-SR^{56}$, $-SO_2R^{56}$, $-N(R^{54})R^{56}$ and $-CON(R^{54})R^{56}$, wherein

R^{56} is in each case independently selected from H, (C_{1-8})alkyl, (C_{3-8})cycloalkyl, (C_{3-8})cycloalkyl-(C_{1-6})alkyl-, aryl, aryl-(C_{1-6})alkyl-, **Het**, and **Het**-(C_{1-6})alkyl-,

wherein R^{56} is, where possible, in each case independently optionally substituted with 1 to 3 substituents each independently selected from (C_{1-6})alkyl, (C_{1-6})haloalkyl, halo, $-O(C_{1-6})$alkyl, $-N((C_{1-6})\text{alkyl})_2$ and $-NH(C=O)(C_{1-6})$alkyl;

wherein **Het** is a 4- to 7-membered saturated, unsaturated or aromatic heterocycle having 1 to 4 heteroatoms each independently selected from O, N and S, or a 7- to 14-membered saturated, unsaturated or aromatic

heteropolycycle having wherever possible 1 to 5 heteroatoms, each independently selected from O, N and S.

R^5/R^6-B:

In at least one embodiment, a is a double bond, R^6 is absent and R^5 is R^{51} or $-(C_{1-3})alkyl-R^{51}$;

wherein R^{51} is selected from R^{52}, $-OR^{53}$, $-N(R^{54})R^{53}$, $-C(=O)R^{52}$, $--C(=O)OR^{53}$, $-C(=O)N(R^{54})R^{53}$, $-N(R^{54})C(=O)R^{52}$, $-N(R^{54})C(=O)N(R^{54})R^{53}$ and $-N(R^{54})C(=O)OR^{53}$; wherein

R^{52} is selected from R^{53} and (C_{2-8})alkenyl, and

R^{53} is selected from (C_{1-8})alkyl, (C_{3-8})cycloalkyl, (C_{3-8})cycloalkyl-(C_{1-6})alkyl-, aryl, aryl-(C_{1-6})alkyl-, **Het**, and **Het**-(C_{1-6})alkyl-,
wherein **Het** and the **Het** portion of **Het**-(C_{1-6})alkyl- are in each case independently selected from a 5- or 6-membered saturated, unsaturated or aromatic heterocycle having 1 to 3 heteroatoms each independently selected from O, N and S, and an 8- 9- or 10-membered saturated, unsaturated or aromatic heteropolycycle having 1 to 3 heteroatoms each independently selected from O, N and S; and

R^{54} is in each case independently selected from H and (C_{1-3})alkyl;

wherein each of R^{52} and R^{53} is optionally substituted with 1 to 3 substituents each independently selected from R^{56}, halo, -CN, $-OR^{56}$, $-SR^{56}$, $-SO_2R^{56}$, $-N(R^{54})R^{56}$, and $-CON(R^{54})R^{56}$, wherein

R^{56} is in each case independently selected from H, (C_{1-8})alkyl, (C_{3-8})cycloalkyl, (C_{3-8})cycloalkyl-(C_{1-6})alkyl-, aryl, aryl-(C_{1-6})alkyl-, **Het**, and **Het**-(C_{1-6})alkyl-,
wherein **Het** and the **Het** portion of **Het**-(C_{1-6})alkyl- are in each case independently selected from a 5- or 6-membered saturated, unsaturated or aromatic heterocycle having 1 to 3 heteroatoms each independently selected from O, N and S;

wherein R^{56} is, where possible, in each case independently optionally substituted with 1 to 3 substituents each independently selected from (C_{1-6})alkyl, (C_{1-6})haloalkyl, halo, $-O(C_{1-6})$alkyl, $-N((C_{1-6})alkyl)_2$ and $-NH(C=O)(C_{1-6})$alkyl.

R^5/R^6-C:

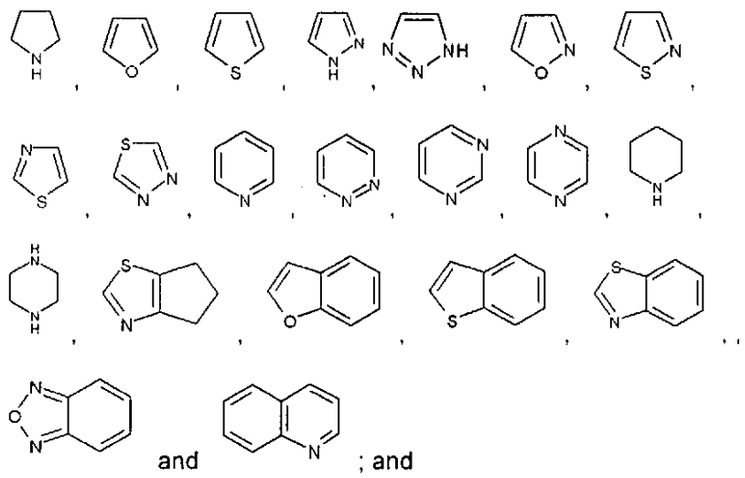
In at least one embodiment, a is a double bond, R^6 is absent and R^5 is R^{51} or $-(C_{1-3})alkyl-R^{51}$;

wherein R^{51} is selected from R^{52}, $-OR^{53}$, $-N(R^{54})R^{53}$, $-C(=O)R^{52}$, $--C(=O)OR^{53}$, $-C(=O)N(R^{54})R^{53}$, $-N(R^{54})C(=O)R^{52}$, $-N(R^{54})C(=O)N(R^{54})R^{53}$ and $-N(R^{64})C(=O)OR^{53}$; wherein

R^{52} is selected from R^{53} and (C_{2-8})alkenyl, and

R^{53} is selected from (C_{1-8})alkyl, (C_{3-8})cycloalkyl, (C_{3-8})cycloalkyl-(C_{1-6})alkyl-, aryl, aryl-(C_{1-6})alkyl-, **Het**, and **Het**-(C_{1-6})alkyl-,

wherein **Het** and the **Het** portion of **Het**-(C_{1-6})alkyl- are in each case independently selected from:



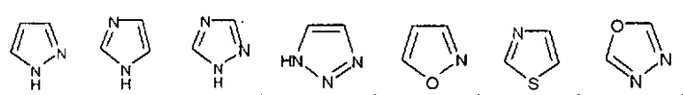
and ; and

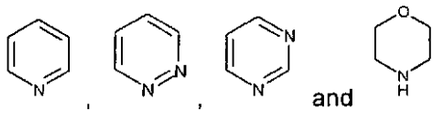
R^{54} is in each case independently selected from H and (C_{1-3})alkyl;

wherein each of R^{52} and R^{53} is optionally substituted with 1 to 3 substituents each independently selected from R^{56}, halo, -CN, $-OR^{56}$, $-SR^{56}$, $-SO_2R^{56}$, $-N(R^{54})R^{56}$ and $-CON(R^{54})R^{56}$, wherein

R^{56} is in each case independently selected from H, (C_{1-8})alkyl, (C_{3-8})cycloalkyl, (C_{3-8})cycloalkyl-(C_{1-6})alkyl-, aryl, aryl-(C_{1-6})alkyl-, **Het**, and **Het**-(C_{1-6})alkyl-,

wherein **Het** and the **Het** portion of **Het**-(C_{1-6})alkyl- are in each case independently selected from:

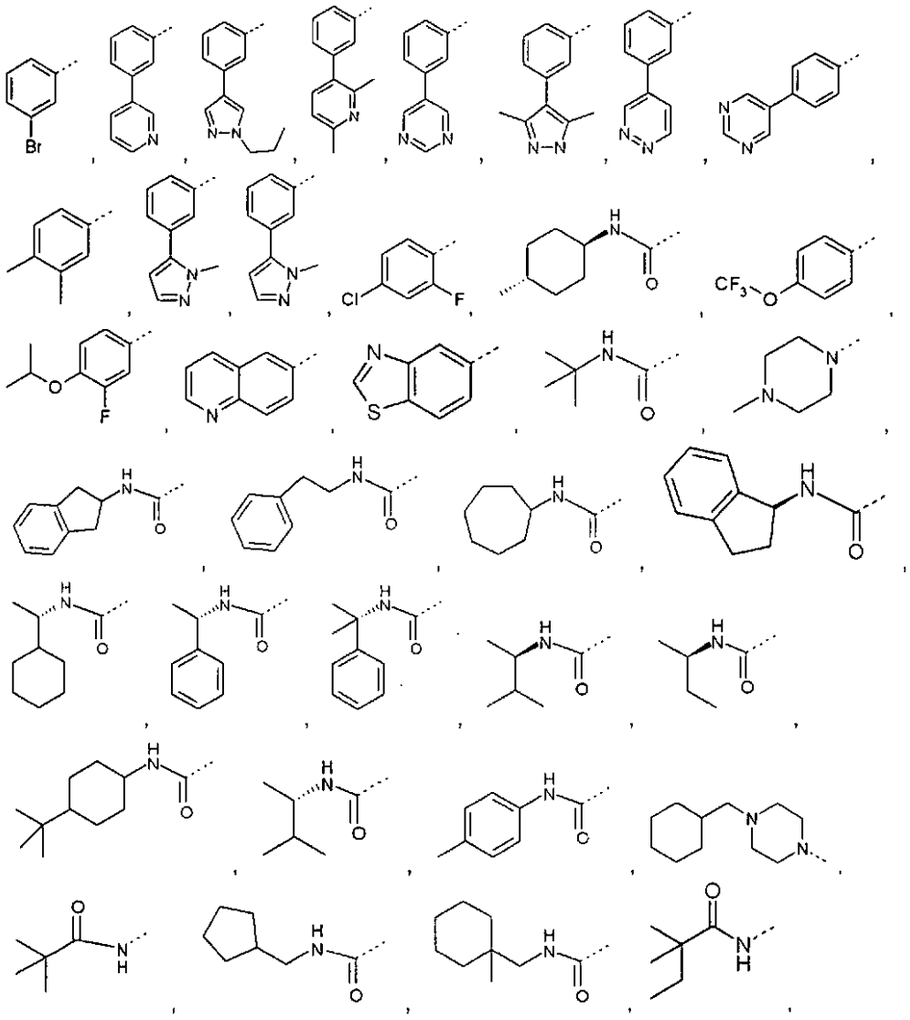


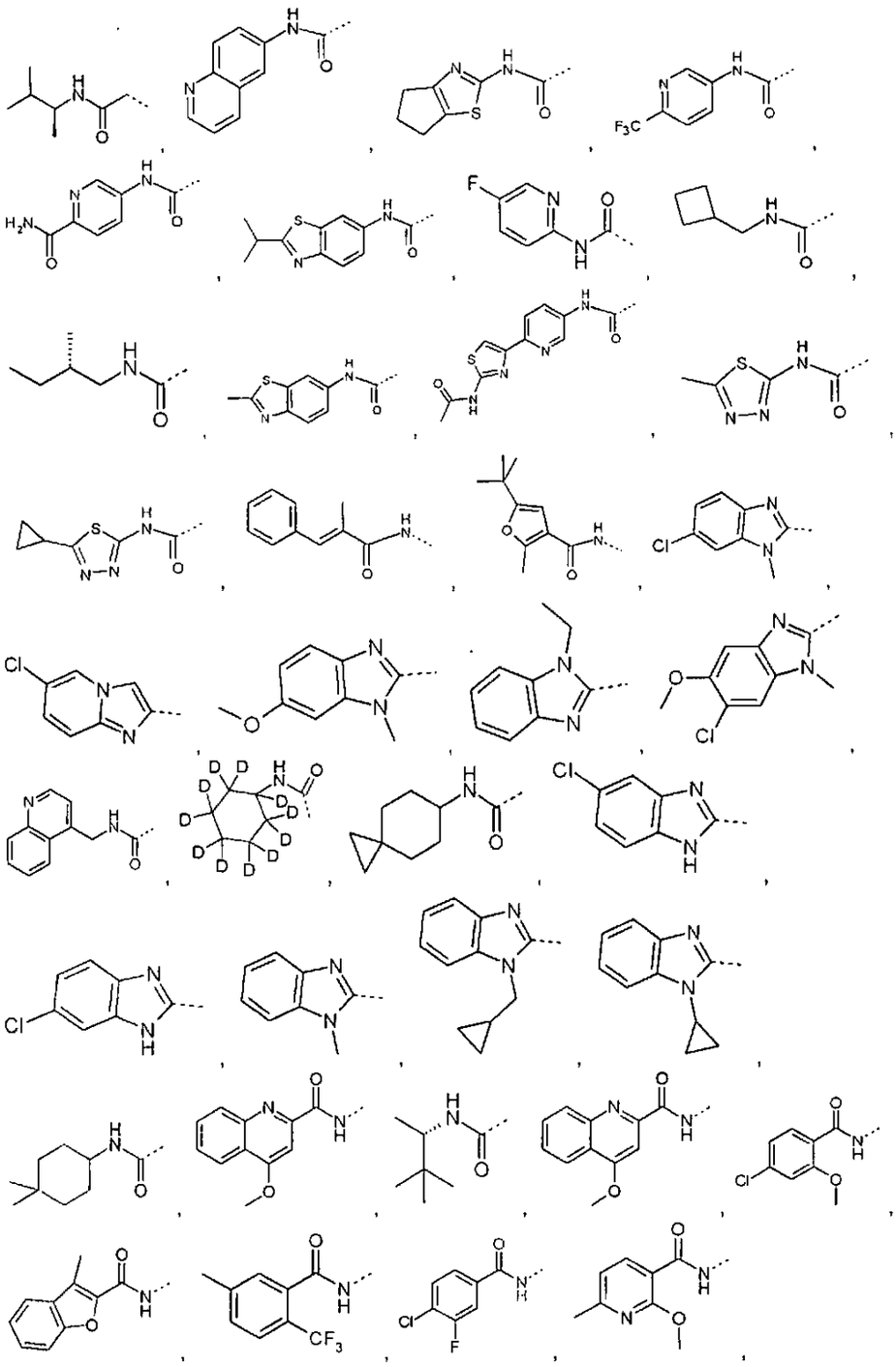

and ;

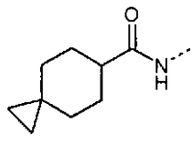
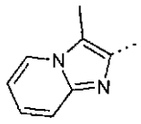
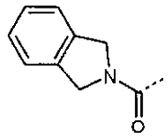
wherein R^{56} is, where possible, in each case independently optionally substituted with 1 to 3 substituents each independently selected from (C_{1-6})alkyl, (C_{1-6})haloalkyl, halo, $-O(C_{1-6})$alkyl, $-N((C_{1-6})alkyl)_2$ and $-NH(C=O)(C_{1-6})$alkyl.

R^5/R^6-D:

In at least one embodiment, **a** is a double bond, R^6 is absent and R^5 is selected from:







and


R^5/R^6-E:

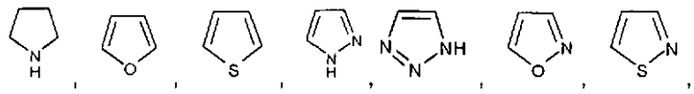
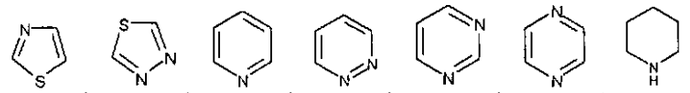
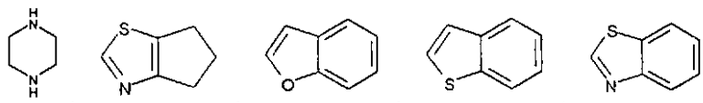
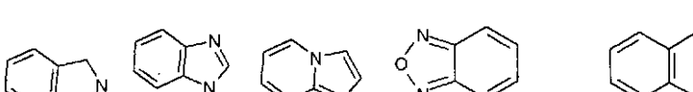
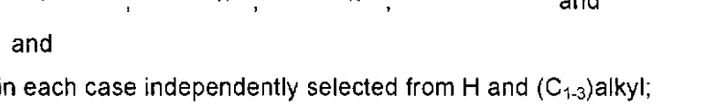
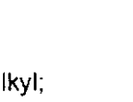
In at least one embodiment, a is a double bond, R^6 is absent and R^5 is R^{51} or -(C_{1-3})alkyl-R^{51};

wherein R^{51} is selected from R^{52}, -OR^{53}, -C(=O)R^{52}, --C(=O)OR^{53}, -C(=O)N(R^{54})R^{53}, -N(R^{54})C(=O)R^{52}, -N(R^{54})C(=O)N(R^{54})R^{53} and -N(R^{54})C(=O)OR^{53}; wherein

R^{52} is selected from R^{53} and (C_{2-8})alkenyl, and

R^{53} is selected from (C_{1-8})alkyl, (C_{3-8})cycloalkyl, (C_{3-8})cycloalkyl-(C_{1-6})alkyl-, aryl, aryl-(C_{1-6})alkyl-, **Het**, and **Het**-(C_{1-6})alkyl-,

wherein **Het** and the **Het** portion of **Het**-(C_{1-6})alkyl- are in each case independently selected from:






and

;

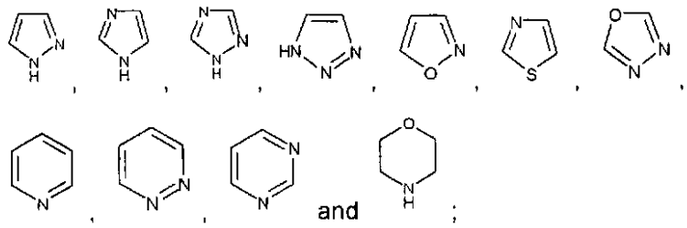
and

R^{54} is in each case independently selected from H and (C_{1-3})alkyl;

wherein each of R^{52} and R^{53} is optionally substituted with 1 to 3 substituents each independently selected from R^{56}, halo, -CN, -OR^{56}, -SR^{56}, -SO_2R^{56}, -N(R^{54})R^{56} and -CON(R^{54})R^{56}, wherein

R^{56} is in each case independently selected from H, (C_{1-8})alkyl, (C_{3-8})cycloalkyl, (C_{3-8})cycloalkyl-(C_{1-6})alkyl-, aryl, aryl-(C_{1-6})alkyl-, **Het**, and **Het**-(C_{1-6})alkyl-,

wherein **Het** and the **Het** portion of **Het**-(C_{1-6})alkyl- are in each case independently selected from:



and ;

wherein R^{56} is, where possible, in each case independently optionally substituted with 1 to 3 substituents each independently selected from (C_{1-6})alkyl, (C_{1-6})haloalkyl, halo, -O(C_{1-6})alkyl, -N((C_{1-6})alkyl)$_2$ and -NH(C=O)(C_{1-6})alkyl.

R^5/R^6-F:

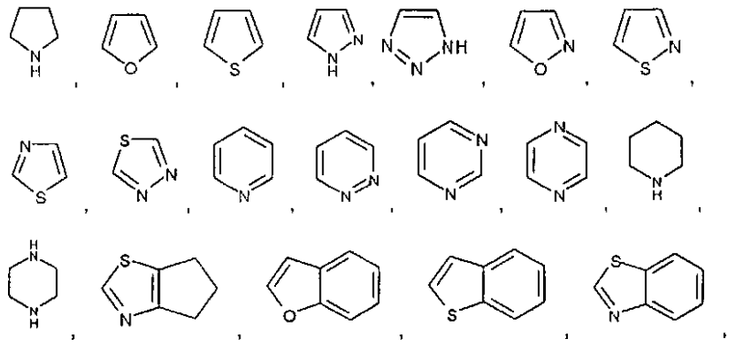
In at least one embodiment, **a** is a double bond, R^6 is absent and R^5 is R^{51} or -(C_{1-3})alkyl-R^{51};

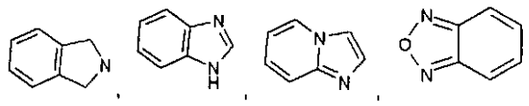
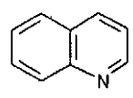
wherein R^{51} is selected from R^{52}, -OR^{53}, -C(=O)R^{52}, --C(=O)OR^{53}, -C(=O)N(R^{54})R^{53}, -N(R^{54})C(=O)R^{52}, -N(R^{54})C(=O)N(R^{54})R^{53} and -N(R^{54})C(=O)OR^{53}; wherein

R^{52} is selected from R^{53} and (C_{2-8})alkenyl, and

R^{53} is selected from (C_{1-8})alkyl, (C_{3-8})cycloalkyl, (C_{7-12})spirocycloalkyl, (C_{3-8})cycloalkyl-(C_{1-6})alkyl-, aryl, aryl-(C_{1-6})alkyl-, **Het**, and **Het**-(C_{1-6})alkyl-,

wherein **Het** and the **Het** portion of **Het**-(C_{1-6})alkyl- are in each case independently selected from:



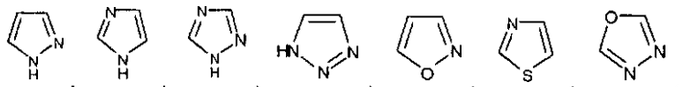
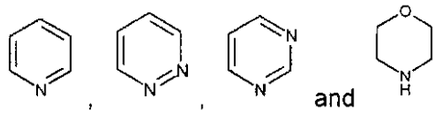

and

;

and

R^{54} is in each case independently selected from H and (C_{1-3})alkyl;

wherein each of R^{52} and R^{53} is optionally substituted with 1 to 3 substituents each independently selected from R^{56}, halo, -CN, $-OR^{56}$, $-SR^{56}$, $-SO_2R^{56}$, $-N(R^{54})R^{56}$ and $-CON(R^{54})R^{56}$, wherein

R^{56} is in each case independently selected from H, (C_{1-8})alkyl, (C_{3-8})cycloalkyl, (C_{3-8})cycloalkyl-(C_{1-6})alkyl-, aryl, aryl-(C_{1-6})alkyl-, **Het**, and **Het**-(C_{1-6})alkyl-, wherein **Het** and the **Het** portion of **Het**-(C_{1-6})alkyl- are in each case independently selected from:



and

;

wherein R^{56} is, where possible, in each case independently optionally substituted with 1 to 3 substituents each independently selected from (C_{1-6})alkyl, (C_{1-6})haloalkyl, halo, -O(C_{1-6})alkyl, -N$((C_{1-6})\text{alkyl})_2$ and -NH(C=O)(C_{1-6})alkyl.

Examples of preferred subgeneric embodiments of the present invention are set forth in the following table, wherein each substituent group of each embodiment is defined according to the definitions set forth above:

Embodiment	R^1	R^2	R^3	R^4	Core	R^5/R^6
E-1	R^1-A	R^2-A	R^3-A	R^4-A	Core-A	R^5/R^6-A
E-2	R^1-A	R^2-A	R^3-A	R^4-A	Core-A	R^5/R^6-B
E-3	R^1-A	R^2-A	R^3-A	R^4-B	Core-A	R^5/R^6-A
E-4	R^1-A	R^2-A	R^3-A	R^4-B	Core-A	R^5/R^6-B
E-5	R^1-A	R^2-A	R^3-A	R^4-D	Core-A	R^5/R^6-A
E-6	R^1-A	R^2-A	R^3-A	R^4-D	Core-A	R^5/R^6-B

Embodiment	R^1	R^2	R^3	R^4	Core	R^5/R^6
E-7	R^1-A	R^2-C	R^3-A	R^4-A	Core-A	R^5/R^6-A
E-8	R^1-A	R^2-C	R^3-A	R^4-A	Core-A	R^5/R^6-B
E-9	R^1-A	R^2-C	R^3-A	R^4-B	Core-A	R^5/R^6-A
E-10	R^1-A	R^2-C	R^3-A	R^4-B	Core-A	R^5/R^6-B
E-11	R^1-A	R^2-C	R^3-A	R^4-D	Core-A	R^5/R^6-A
E-12	R^1-A	R^2-C	R^3-A	R^4-D	Core-A	R^5/R^6-B
E-13	R^1-B	R^2-B	R^3-D	R^4-E	Core-A	R^6/R^6-C
E-14	R^1-B	R^2-B	R^3-D	R^4-E	Core-A	R^5/R^6-E
E-15	R^1-B	R^2-D	R^3-B	R^4-B	Core-A	R^5/R^6-D
E-16	R^1-B	R^2-A	R^3-B	R^4-D	Core-A	R^5/R^6-D
E-17	R^1-B	R^2-D	R^3-D	R^4-D	Core-A	R^6/R^6-A
E-18	R^1-C	R^2-A	R^3-A	R^4-A	Core-A	R^5/R^6-A
E-19	R^1-C	R^2-A	R^3-A	R^4-A	Core-A	R^6/R^6-B
E-20	R^1-C	R^2-A	R^3-A	R^4-B	Core-A	R^5/R^6-A
E-21	R^1-C	R^2-A	R^3-A	R^4-B	Core-A	R^5/R^6-B
E-22	R^1-C	R^2-A	R^3-A	R^4-D	Core-A	R^5/R^6-A
E-23	R^1-C	R^2-A	R^3-A	R^4-D	Core-A	R^5/R^6-B
E-24	R^1-C	R^2-C	R^3-A	R^4-A	Core-A	R^5/R^6-A
E-25	R^1-C	R^2-C	R^3-A	R^4-A	Core-A	R^5/R^6-B
E-26	R^1-C	R^2-C	R^3-A	R^4-B	Core-A	R^5/R^6-A
E-27	R^1-C	R^2-C	R^3-A	R^4-B	Core-A	R^5/R^6-B
E-28	R^1-C	R^2-C	R^3-A	R^4-D	Core-A	R^5/R^6-A
E-29	R^1-C	R^2-C	R^3-A	R^4-D	Core-A	R^5/R^6-B
E-30	R^1-C	R^2-B	R^3-B	R^4-A	Core-A	R^5/R^6-C
E-31	R^1-C	R^2-A	R^3-A	R^4-B	Core-A	R^5/R^6-F
E-32	R^1-D	R^2-B	R^3-B	R^4-E	Core-A	R^5/R^6-C
E-33	R^1-D	R^2-D	R^3-C	R^4-E	Core-A	R^5/R^6-E
E-34	R^1-D	R^2-D	R^3-C	R^4-B	Core-A	R^5/R^6-E
E-35	R^1-D	R^2-B	R^3-C	R^4-B	Core-A	R^6/R^6-B
E-36	R^1-D	R^2-D	R^3-C	R^4-E	Core-A	R^5/R^6-F
E-37	R^1-D	R^2-D	R^3-C	R^4-B	Core-A	R^5/R^6-F

Examples of most preferred compounds according to this invention are each single

compound listed in the following Tables 1 to 6.

Unless specifically indicated, throughout the specification and the appended claims, a given chemical formula or name shall encompass tautomers, and all stereo, optical and geometrical isomers (e.g. enantiomers, diastereomers, E/Z isomers, atropisomers) resulting from all possible steriochemistry at a chiral center for which specific steriochemistry is not otherwise decsribed, and racemates thereof, as well as mixtures in different proportions of the separate enantiomers, mixtures of diastereomers, or mixtures of any of the foregoing forms where such isomers and enantiomers exist.

It is well-known in the art that the biological and pharmacological activity of a compound is sensitive to the stereochemistry of the compound. Thus, for example, enantiomers often exhibit strikingly different biological activity including but not limited to differences in pharmacokinetic properties, including but not limited to metabolism, protein binding, and the like, and pharmacological properties, including but not limited to the type of activity displayed, the degree of activity, toxicity, and the like. Thus, one skilled in the art will appreciate that one enantiomer may be more active or may exhibit beneficial effects when enriched relative to the other enantiomer or when separated from the other enantiomer. Additionally, one skilled in the art would know how to separate, enrich, or selectively prepare the enantiomers of the compounds of the present invention from this disclosure and the knowledge in the art.

Preparation of pure stereoisomers, e.g. enantiomers and diastereomers, or mixtures of desired enantiomeric excess (ee) or enantiomeric purity, are accomplished by one or more of the many methods of (a) separation or resolution of enantiomers, or (b) enantioselective synthesis known to those of skill in the art, or a combination thereof. These resolution methods generally rely on chiral recognition and include but are not limited to chromatography using chiral stationary phases, enantioselective host-guest complexation, resolution or synthesis using chiral auxiliaries, enantioselective synthesis, enzymatic and nonenzymatic kinetic resolution, or spontaneous enantioselective crystallization. Such methods are disclosed generally in Chiral Separation Techniques: A Practical Approach (2nd

Ed.), G. Subramanian (ed.), Wiley-VCH, 2000; T.E. Beesley and R.P.W. Scott, Chiral Chromatography, John Wiley & Sons, 1999; and Satinder Ahuja, Chiral Separations by Chromatography, Am. Chem. Soc., 2000. Furthermore, there are equally well-known methods for the quantitation of enantiomeric excess or purity, including but not limited to GC, HPLC, CE, or NMR, and assignment of absolute configuration and conformation, including but not limited to CD, ORD, X-ray crystallography, or NMR.

PHARMACEUTICAL COMPOSITION

Suitable preparations for administering the compounds of the invention will be apparent to those with ordinary skill in the art and include for example tablets, pills, capsules, suppositories, lozenges, troches, solutions, syrups, elixirs, sachets, injectables, inhalatives and powders. The content of the pharmaceutically active compound(s) should be in the range from 0.05 to 90 wt.-%, preferably 0.1 to 50 wt.-% of the composition as a whole.

Suitable tablets may be obtained, for example, by mixing one or more compounds according to the invention with known excipients, for example inert diluents, carriers, disintegrants, adjuvants, surfactants, binders and/or lubricants. The tablets may also consist of several layers.

When one enantiomer of a chiral active ingredient has a different biological activity than the other, it is contemplated that the pharmaceutical composition according to the invention may comprise a racemic mixture of the active ingredient, a mixture enriched in one enantiomer of the active ingredient or a pure enantiomer of the active ingredient. The mixture enriched in one enantiomer of the active ingredient is contemplated to contain from more than 50% to about 100% of one enantiomer of the active ingredient and from about 0% to less than 50% of the other enantiomer of the active ingredient. Preferably, when the composition comprises a mixture enriched in one enantiomer of the active ingredient or a pure enantiomer of the active ingredient, the composition comprises from more than 50% to about 100% of, or only, the more physiologically active enantiomer and/or the less toxic enantiomer. It is well known that one enantiomer of an active ingredient may be the more physiologically active for one therapeutic indication while the other enantiomer of the

active ingredient may be the more physiologically active for a different therapeutic indication; therefore the preferred enantiomeric makeup of the pharmaceutical composition may differ for use of the composition in treating different therapeutic indications.

Therefore, according to one embodiment, the pharmaceutical composition according to the invention comprises a racemic mixture of the compound of formula (I), or a pharmaceutically acceptable salt thereof.

An alternative embodiment provides a pharmaceutical composition comprising a mixture enriched in one enantiomer of the compound of formula (I), or a pharmaceutically acceptable salt thereof.

A further embodiment provides a pharmaceutical composition comprising a pure enantiomer of the compound of formula (I), or a pharmaceutically acceptable salt thereof.

The dose range of the compounds of the invention applicable per day is usually from 0.001 to 100 mg/kg of body weight, preferably from 0.01 to 50 mg/kg of body weight. Each dosage unit may conveniently contain from 5% to 95% active compound (w/w). Preferably such preparations contain from 20% to 80% active compound.

The actual pharmaceutically effective amount or therapeutic dosage will of course depend on factors known by those skilled in the art such as age and weight of the patient, route of administration and severity of disease. In any case the combination will be administered at dosages and in a manner which allows a pharmaceutically effective amount to be delivered based upon patient's unique condition.

When the composition of this invention comprises a combination of a compound of the invention and one or more additional therapeutic or prophylactic agent, both the compound and the additional agent should be present at dosage levels of between about 10 to 100%, and more preferably between about 10 and 80% of the dosage normally administered in a monotherapy regimen.

COMBINATION THERAPY

Combination therapy is contemplated wherein a compound according to the invention, or a pharmaceutically acceptable salt thereof, is co-administered with at least one additional antiviral agent. The additional agents may be combined with compounds of this invention to create a single dosage form. Alternatively these additional agents may be separately administered, concurrently or sequentially, as part of a multiple dosage form.

When the pharmaceutical composition of this invention comprises a combination of a compound according to the invention, or a pharmaceutically acceptable salt thereof, and one or more additional antiviral agent, both the compound and the additional agent should be present at dosage levels of between about 10 to 100%, and more preferably between about 10 and 80% of the dosage normally administered in a monotherapy regimen. In the case of a synergistic interaction between the compound of the invention and the additional antiviral agent or agents, the dosage of any or all of the active agents in the combination may be reduced compared to the dosage normally administered in a monotherapy regimen.

Antiviral agents contemplated for use in such combination therapy include agents (compounds or biologicals) that are effective to inhibit the formation and/or replication of a virus in a human being, including but not limited to agents that interfere with either host or viral mechanisms necessary for the formation and/or replication of a virus in a human being. Such agents can be selected from:

- NRTIs (nucleoside or nucleotide reverse transcriptase inhibitors) including but not limited to zidovudine/RETROVIR® (GSK), didanosine/VIDEX® (BMS), stavudine/ZERIT® (BMS), lamivudine/EPIVIR® (GSK/Shire), emtricitabine/EMTRIVA® (Gilead Sciences), abacavir/ZIAGEN® (GSK), and tenofovir/VIREAD® (Gilead Sciences), apricitabine (Avexa), elvucitabine (Achillion) and OBP-601 (Oncolys), amdoxovir (RFS Pharma);
- NNRTIs (non-nucleoside reverse transcriptase inhibitors) including but not limited to nevirapine/VIRAMUNE® (Boehringer Ingelheim), delavirdine/RESCRIPTOR® (Pfizer), efavirenz/SUSTIVA® (BMS), etravirine/INTELENCE® (Johnson & Johnson), rilpivirine (Johnson & Johnson), UK-453,061 (Pfizer) and RDEA806 (Ardea Biosciences), IDX-899 (GSK);

- protease inhibitors including but not limited to ritonavir/NORVIR® (Abbott), tipranavir/APTIVUS® (Boehringer Ingelheim), saquinavir/INVIRASE® (Hoffmann LaRoche), nelfinavir/VIRACEPT® (Pfizer), indinavir/CRIXIVAN® (Merck), fosamprenavir/LEXIVA® (GSK/Vertex), atazanavir/REYATAZ® (BMS), lopinavir/KALETRA® (Abbott), and darunavir/PREZISTA® (Johnson & Johnson);
- entry inhibitors including but not limited to
  - CCR5 antagonists including but not limited to maraviroc/SELZENTRY® (Pfizer), vicriviroc (Schering-Plough), INCB9471 (Incyte), PF-232798 (Pfizer), PRO-140 (Progenics Pharm), GSK706769 (GSK), PF-232798 (Pfizer), TBR-220 and TBR-652 (Tovira Therapeutics);
  - CXCR4 antagonists including but not limited to AMD-11070 (Genzyme),
  - fusion inhibitors including but not limited to enfuvirtide/FUZEON® (Trimeris), sifuvirtide (Fasogen), albuvirtide (Frontier Bio), FRI-1144 (Trimeris); and
  - others including but not limited to BMS-488043 (BMS);
- integrase inhibitors including but not limited to raltegravir/ISENTRESS® (Merck), elvitegravir (Gilead Sciences), GSK1349572 and GSK1265744 (GSK), JTK-656 (Japan Tobacco);
- TAT inhibitors;
- maturation inhibitors including but not limited to bevirimat (Myriad Genetics), vivecon (Myriad Genetics); and
- immunomodulating agents including but not limited to levamisole/ERGAMISOL® (Janssen-Ortho); and
- other antiviral agents including hydroxyurea, ribavirin, IL-2, IL-12 and pensafuside.

Furthermore, a compound according to the invention can be used with at least one other compound according to the invention or with one or more antifungal or antibacterial agents (including but not limited to fluconazole).

Therefore, according to one embodiment, the pharmaceutical composition of this invention additionally comprises one or more antiviral agents.

A further embodiment provides the pharmaceutical composition of this invention wherein the one or more antiviral agent comprises at least one NNRTI.

According to another embodiment of the pharmaceutical composition of this invention, the one or more antiviral agent comprises at least one NRTI.

According to yet another embodiment of the pharmaceutical composition of this invention, the one or more antiviral agent comprises at least one protease inhibitor.

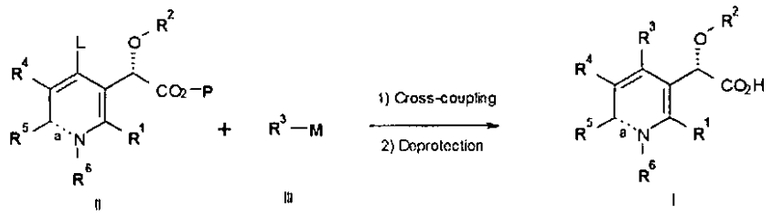
According to still another embodiment of the pharmaceutical composition of this invention, the one or more antiviral agent comprises at least one entry inhibitor.

According to a further embodiment of the pharmaceutical composition of this invention, the one or more antiviral agent comprises at least one integrase inhibitor.

METHODOLOGY AND SYNTHESIS

The synthesis of compounds of formula (I) according to this invention is conveniently accomplished following the general procedures outlined in the schemes below wherein **a**, R^1, R^2, R^3, R^4, R^5 and R^6 are as defined herein. Other procedures by which compounds of the invention may be prepared are well known in the art or are set forth in the examples below.

Scheme 1



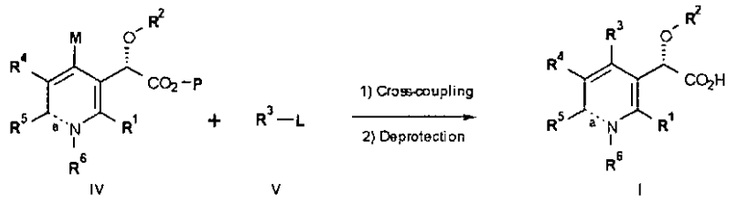
II III I

Intermediates II, wherein **a**, R^1, R^2, R^4, R^5 and R^6 are as defined herein, **L** is a leaving group including but not limited to iodo, bromo, chloro or -OTf, and **P** is a protecting group chosen from commonly used protecting groups for carboxylic acids, including but not limited to a methyl or ethyl ester, and intermediates **III**, wherein R^3 is as defined herein and **M** is a group suitable for reacting with group **L** in a coupling reaction, such as are well known in the art, including but not limited to $-B(OH)_2$ or a boronate ester incuding but not limited to $-B(OCH_3)_2$ and $-B(OC(CH_3)_2C(CH_3)_2O)$; -I; $-SnR_3$ wherein **R** is (C_{1-6})alkyl; or -Zn**X** wherein **X** is halo, are commercially available

or are prepared by reactions well known in the art or as set forth in the examples below. Protected derivatives of compounds of formula (I) can be prepared by well known coupling reactions of intermediates **II** and **III**, including but not limited to Suzuki cross-coupling between a boronic acid or boronate ester derivative **III** and a halo or triflate derivative **II**; copper catalyzed Ullmann cross-coupling between iodo derivatives **II** and **III**; Negishi cross-coupling between an arylzinc reagent **III** and an iodo or triflate derivative **II**; and Stille coupling between an arylltin reagent **III** and a bromo or iodo derivative **II**. The protected products of the coupling reaction are then deprotected, for example by saponification, to provide compounds of formula (I).

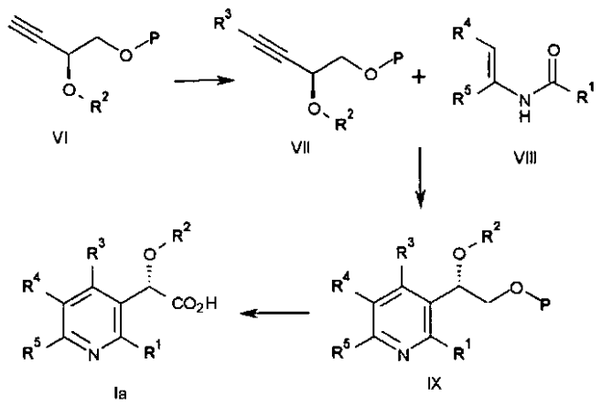
Alternatively, as shown in Scheme 2 below, intermediates **IV** and **V**, wherein **a**, R^1, R^2, R^3, R^4, R^5, R^6, **L**, **M** and **P** are as defined herein, may be coupled using the cross-coupling methods described above, followed by deprotection, to provide compounds of formula (I).

Scheme 2



Furthermore, compounds of formula (Ia) wherein **a** is a single bond, R^6 is absent and R^1, R^2, R^3, R^4 and R^5 are as defined herein are conveniently prepared using the general procedure illustrated in Scheme 3 below.

Scheme 3



Intermediates **VI** and **VIII**, wherein R^1, R^2, R^3, R^4 and R^5 are as defined herein and **P** is a suitable protecting group, well known in the art, are commercially available or are prepared by reactions well known in the art or as set forth in the examples below. Intermediates **VI** are conveniently transformed to intermediates **VII** using conditions well-known to those skilled in the art, including but not limited to a Sonogashira coupling between intermediates **VI** and R^3-I. Intermediates **VII** and **VIII** undergo a cyclocondensation reaction under well known conditions, including but not limited to reaction with $(CF_3SO_2)_2O$ (triflic anhydride) in the presence of 2-chloropyridine to give intermediates **IX**. Deprotection of intermediate **IX**, followed by oxidation of the primary alcohol using conditions well known in the art, including but not limited to oxidation with Dess-Martin periodinane followed by sodium chlorite oxidation, provides compounds of formula (Ia).

It will be apparent to one skilled in the art that a compound of formula (I), or any of the intermediates **II** to **XI** involved in its preparation, wherein any of the substituents **a**, R^1, R^2, R^3, R^4, R^5 and R^6 has one meaning as defined herein, may be transformed to another compound of formula (I), or to any of the intermediates **II** to **XI** involved in its preparation as appropriate, wherein any of the substituents **a**, R^1, R^2, R^3, R^4, R^5 and R^6 has a different meaning as defined herein, at any chemically convenient step in the preparation. Examples of such transformations include but are not limited to alkylation, conversion of an aromatic primary amino group to a chloro or bromo substituent using a Sandmeyer reaction, and reductive dehalogenation. In addition, the substituents R^1, R^2, R^3, R^4, R^5 and R^6 may be protected and/or deprotected at intermediate steps in the preparation of a compound of formula (I), as will be

recognized by the skilled person.

Examples

Other features of the present invention will become apparent from the following non-limiting examples which illustrate, by way of example, the principles of the invention. It will be apparent to a skilled person that the procedures exemplified below may be used, with appropriate modifications, to prepare other compounds of the invention as described herein.

As is well known to a person skilled in the art, reactions are performed in an inert atmosphere (including but not limited to nitrogen or argon) where necessary to protect reaction components from air or moisture. Temperatures are given in degrees Celsius (°C). Solution percentages and ratios express a volume to volume relationship, unless stated otherwise. Flash chromatography is carried out on silica gel (SiO2) according to the procedure of W.C. Still et al., J. Org. Chem., (1978), 43, 2923. Mass spectral analyses are recorded using electrospray mass spectrometry. A number of intermediate and final products are purified using CombiFlash® Companion or RF apparatus, purchased from Teledyne Isco Inc, employing pre-packed silica gel cartridges and EtOAc and hexanes as solvents. These cartridges are available either from Silicycle Inc (SiliaFlash, 40-63 µm silica) or from Teledyne Isco (RediSep, 40-63 µm silica). Preparative HPLC is carried out under standard conditions using a SunFire™ Prep C18 OBD 5 µm reverse phase column, 19 x 50 mm and a linear gradient employing 0.1%TFA/acetonitrile and 0.1%TFA/water as solvents. Compounds are isolated as TFA salts when applicable.

Alternatively, preparative HPLC is carried out under standard conditions using a SunFire™ Prep C18 OBD 5 µm reverse phase column, 19 x 50 mm and a linear gradient employing 10 mM ammonium formate in H_2O (pH = 3.8); and MeOH. Alternatively, preparative HPLC is carried out under standard conditions using a XBridge™ Prep C18 OBD 5 µm reverse phase column, 19 x 50 mm and a linear gradient employing 10 mM ammonium bicarbonate in H_2O (pH = 10.0); and MeOH.

Analytical HPLC is carried out under standard conditions using a SunFire™ C18 (3.5 µm, 4.6x30 mm) reverse phase column at 220 nm, elution with a linear gradient

as described in the following table (Solvent A is 0.06% TFA in H_2O; solvent B is 0.06% TFA in CH_3CN):

Time (min)	Flow (mL/min)	Solvent A (%)	Solvent B (%)
0	2.5	98	2
0.5	2.5	98	2
6.0	2.5	50	50
10.5	3.0	0	100
11.5	3.0	0	100

Alternatively, analytical HPLC is carried out under standard conditions using a SunFire™ C18 (3.5 µm, 4.6x30 mm) reverse phase column at 220 nm, elution with a linear gradient as described in the following table (Solvent A is 0.06% TFA in H_2O; solvent B is 0.06% TFA in CH_3CN):

Time (min)	Flow (mL/min)	Solvent A (%)	Solvent B (%)
0	2.5	98	2
0.6	2.5	98	2
5.5	2.5	50	50
7.3	3.0	0	100
7.9	3.0	0	100

Alternatively, analytical HPLC is carried out under standard conditions using a SunFire™ C18 (3.5 µm, 4.6x30 mm) reverse phase column at 220 nm, elution with a linear gradient as described in the following table (Solvent A is 0.06% TFA in H_2O; solvent B is 0.06% TFA in CH_3CN):

Time (min)	Flow (mL/min)	Solvent A (%)	Solvent B (%)
0	2.5	98	2
0.6	2.5	98	2
3.4	2.5	50	50
4.5	3.0	0	100
4.9	3.0	0	100

Alternatively, analytical HPLC is carried out under standard conditions using a SunFire™ C18 (3.5 µm, 4.6x30 mm) reverse phase column at 220 nm, elution with a linear gradient as described in the following table (Solvent A 10 mM Ammonium Formate in H_2O (pH = 3.8); solvent B MeOH):

Time (min)	Flow (mL/min)	Solvent A (%)	Solvent B (%)
0	4.0	98	2
2.85	4.0	0	100
2.86	5.0	0	100
3.60	5.0	0	100

Alternatively, analytical UPLC is carried out using a shorter run time using an Aquity™ HSST3 (1.8 µm, 2.1x50 mm) reverse phase column at 220 nm, elution with a linear gradient as described in the following table (Solvent A is 0.06% TFA in H_2O; solvent B is 0.06% TFA in CH_3CN):

Time (min)	Flow (mL/min)	Solvent A (%)	Solvent B (%)
0	0.9	98	2
1.5	0.9	50	50
2.6	0.9	0	100

Alternatively, analytical UPLC is carried out using a shorter run time using an Aquity™ HSST3 (1.8 µm, 2.1x50 mm) reverse phase column at 220 nm, elution with a linear gradient as described in the following table (Solvent A 10 mM Ammonium Formate in H_2O (pH = 3.8); solvent B MeOH):

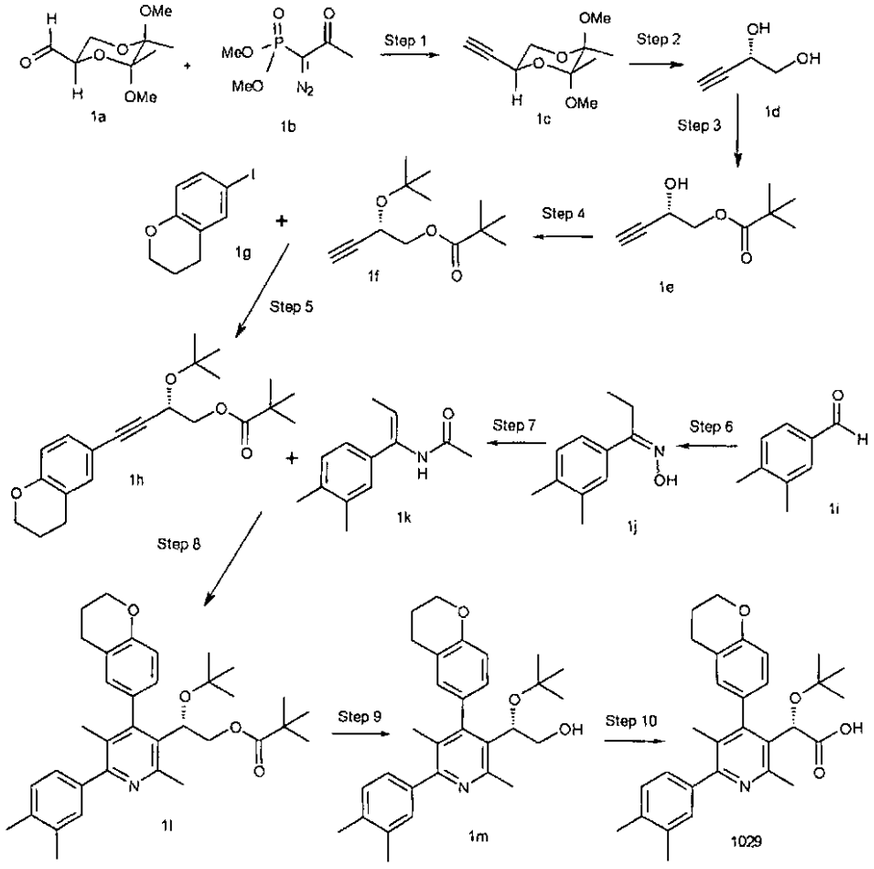
Time (min)	Flow (mL/min)	Solvent A (%)	Solvent B (%)
0	0.8	95	5
2.30	0.9	0	100
2.32	1.0	0	100
3.00	1.0	0	100

Abbreviations or symbols used herein include:

Ac: acetyl; **AcOH**: acetic acid; **Ac_2O**: acetic anhydride; **BOC** or **Boc**: *tert*-butyloxycarbonyl; **BSA**: bovine serum albumin; **Bu**: butyl; **DABCO**: 1,4-diazabicyclo[2.2.2]octane; **DBU**: 1,8-diazabicyclo[5.4.0]undec-7-ene; **DCE**: dichloroethane; **DEAD**: diethyl azodicarboxylate; **DCM**: dichloromethane; **DIAD**: diisopropyl azodicarboxylate; **DIBAL**: diisobutyl aluminum hydride; **DMA**: dimethyl acetamide; **DMAP**: N,N-dimethyl-4-aminopyridine; **DME**: 1,2-dimethoxyethane; **DMF**: *N,N*-dimethylformamide; **DMSO**: dimethylsulfoxide; **DPPA**: diphenylphosphoryl azide; **Dppf**: 1,1'-Bis(diphenylphosphino)ferrocene; **EC_{50}**: 50% effective concentration;**eq**: equivalent; **Et**: ethyl; **Et_3N** : triethylamine; **Et_2O**: diethyl ether; **EtOAc**: ethyl acetate; **EtOH**: ethanol; **HPLC**: high performance liquid chromatography; **IC_{50}**: 50% inhibitory concentration; **^{i}Pr** or **i-Pr**: 1-methylethyl (*iso*-propyl); **LiHMDS**: lithium hexamethyldisilazide; **Me**: methyl; **MeCN**: acetonitrile; **MeOH**: methanol; **MOI**: multiplicity of infection; **MS**: mass spectrometry (ES: electrospray); **n-BuONa**: sodium n-butoxide; **n-BuOH**: n-butanol; **n-BuLi**: n-butyl lithium; **NMP**: N-methylpyrrolidone; **NMR**: nuclear magnetic resonance spectroscopy; **Ph**: phenyl; **PhMe**: toluene; **PG**: protecting group; **Pr**: propyl; **RPMI**: Roswell Park Memorial Institute (cell culture medium); **RT**: room temperature (approximately 18°C to 25°C); **SM**: starting material; **TBTU**: 2-(1H-Benzotriazole-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate; ***tert*-butyl** or **t-butyl**: 1,1-dimethylethyl; **Tf**: trifluoromethanesulfonyl; **Tf_2O**: trifluoromethanesulfonic anhydride; **TFA**: trifluoroacetic acid; **THF**: tetrahydrofuran; **TLC**: thin layer chromatography; and **UPLC**: ultra high performance liquid chromatography.

EXAMPLE 1

SYNTHESIS OF COMPOUND 1029 (TABLE 1)



Step 1:

A mixture of aldehyde **1a** (5.85 g, 28.6 mmol; prepared according to Michel, P. and Ley, S. V. *Synthesis* **2003**, *10*, 1598-1602), phoshonate **1b** (6.6 g, 34 mmol) and K_2CO_3 (8.8 g, 64 mmol) in MeOH (125 mL) is stirred overnight at RT. The mixture is concentrated nearly to dryness and the residue is partitioned between H_2O (250 mL) and EtOAc (500 mL). The aqueous layer is washed with EtOAc (2 x 250 mL), and the combined organic layers are dried over anhydrous Na_2SO_4 and concentrated to give alkyne **1c**.

Step 2:

A mixture of alkyne **1c** (5.0 g, 25 mmol) in TFA (35 mL) and water (3.6 mL) is stirred at RT for about 30 min. The mixture is concentrated under reduced pressure and the

residue is purified by CombiFlash® Companion to give diol **1d**.

Step 3:

A solution of diol **1d** (1.2 g, 14 mmol) and Et_3N (1.7 mL, 12 mmol) in DCM (80 mL) is cooled to 0°C under N_2. Trimethylacetyl chloride is added dropwise and the resulting mixture is allowed to stir overnight at RT. The reaction is quenched with MeOH (100 mL) and stirring is continued for about 20 min. The mixture is concentrated under reduced pressure and the residue is purified by CombiFlash® Companion to give the desired mono ester **1e**.

Step 4:

In a sealable reaction flask, a solution of the propargylic alcohol **1e** (375 mg, 2.20 mmol) and Amberlyst® H-15 resin (150 mg) in hexane (3 mL) is cooled to -78°C. Isobutene is then bubbled through the solution until the volume approximately doubles. The tube is then sealed, brought to RT and is stirred overnight. The tube is then cooled to -78°C, is opened and brought back to RT. The mixture is then filtered through a plug of SiO_2 (EtOAc wash) and concentrated under reduced pressure to provide pure *tert*-butyl ether **1f**.

Step 5:

Solid $Pd(PPh_3)_4$ (444 mg, 0.385 mmol) and CuI (146 mg, 0.769 mmol) are added successively to a mixture of **1g** (10 g, 34 mmol) and alkyne **1f** (11 g, 55 mmol) in DMF (23 mL) and Et_2NH (115 mL). The reaction mixture is stirred overnight at RT and then concentrated, diluted with EtOAc (300 mL) and washed successively with brine, 1 N aqueous HCl and water. The organic layer is dried over Na_2SO_4 and the residue purified by CombiFlash® Companion to give alkyne **1h**.

Step 6:

To a mixture of 3,4-dimethylbenzaldehyde (**1i**; 500 mg, 3.73 mmol) and Et_2O (12 mL) is added ethylmagnesium bromide (3M, 1.4 mL, 1.2 mmol) dropwise. After 15 min, the reaction is quenched with saturated aqueous NH_4Cl (50 mL) and the layers are separated. The organic layer is washed with saturated aqueous NH_4Cl (50 mL), dried over Na_2SO_4 and concentrated to give the intermediate benzyl alcohol. To a mixture of this material and DCM (28 mL) is added silica gel (2.2 g) followed by pyridinium chlorochromate (1.5 g, 7.2 mmol). The mixture is stirred for 45 min and the mixture is filtered through a plug of silica (3 x 1.5 cm) which is then washed with DCM (total of 50 mL). The filtrate is evaporated to dryness to give the intermediate ketone. This material is combined with sodium acetate (102 mg, 1.25 mmol) and

hydroxylamine hydrochloride (87 mg, 1.25 mmol) in MeOH (0.8 mL) and is heated to 85°C in a sealed tube. After 1 h, the reaction is allowed to cool to room temperature and concentrated onto silica gel (2 g). The product is purified by CombiFlash® Companion to give the oxime **1j** as a mixture of *cis*- and *trans*- isomers.

Step 7:

A mixture of oxime **1j** (130 mg, 0.73 mmol) and PhMe (1.7 mL) is degassed by bubbling N_2 gas through the solution for 30 min. Ph_3P (0.23 g, 0.88 mmol) is added and the mixture stirred for 10 min at RT. Ac_2O (84 µL, 0.89 mmol) is added and the mixture is stirred at reflux for 16 h, cooled to room temperature and concentrated *in vacuo*. A mixture of the residue, MeOH (3 mL) and excess K_2CO_3 (200 mg) is stirred for 1 h and the methanol is removed *in vacuo*. The residue is dissolved in EtOAc (10 mL) and water (5 mL). The organic layer is washed with water, concentrated and purified by CombiFlash® Companion to give amide **1k** as a mixture of *cis*- and *trans*- isomers.

Step 8:

Tf_2O (48 µL, 0.29 mmol) is added via syringe over 1 min to a stirred mixture of amide **1k** (55 mg, 0.27 mmol) and 2-chloropyridine (34 µL, 0.36 mmol) in DCM (0.7 mL) at -78°C. After 5 min, the reaction flask is placed in an ice-water bath and warmed to 0°C. Alkyne **1h** (69 mg, 0.19 mmol) in DCM (0.7 mL) is added *via* syringe and the mixture is allowed to warm to RT. After stirring for 30 min, Et_3N (1 mL) is added and the mixture is evaporated to dryness. The residue is dissolved in EtOAc (10 mL) and washed with water. The organic layer is dried over Na_2SO_4 and concentrated and the residue is purified by CombiFlash® Companion giving pyridine **1l**.

Step 9:

$LiBH_4$ in THF (2 M, 470 µL, 0.940 mmol) is added to a solution of ester **1l** (51 mg, 0.094 mmol) dissolved in THF (0.85 mL) and the reaction mixture is heated to 85°C and stirred for 30 min. Excess reagent is quenched with HCl (2 mL) and the mixture neutralized with $NaHCO_3$ (10 mL) and extracted with EtOAc (3 x 10 mL). The combined organic layers are dried over Na_2SO_4 and concentrated to give alcohol **1m**.

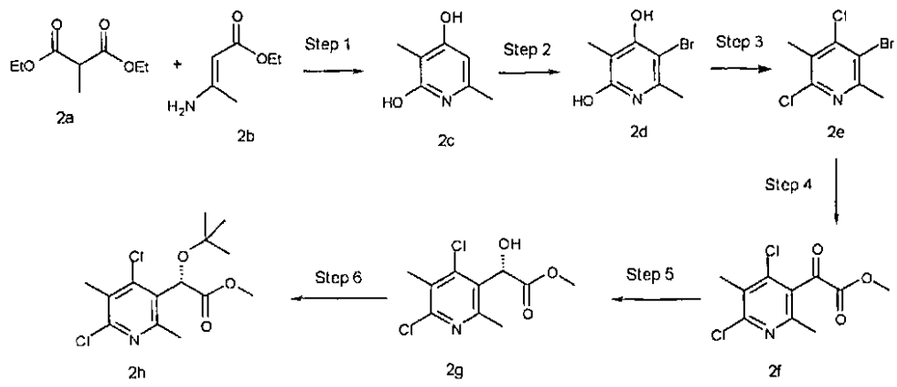
Step 10:

Dess-Martin periodinane (71 mg, 0.17 mmol) is added to a mixture of alcohol **1m** (43 mg, 0.094 mmol) and DCM (1.7 mL). After 2 h, the reaction mixture is

concentrated, the residue is dissolved in 1:1 THF/tBuOH (2 mL), and 2,3-dimethyl-2-butene (1M in THF, 0.75 mL, 0.75 mmol) is added. A separate mixture of $NaClO_2$ (71 mg, 0.79 mmol) and NaH_2PO_4 (71 mg, 0.59 mmol) in water (1 mL) is added to the first mixture and the mixture is stirred at RT. After 30 min, the mixture is diluted with water (5 mL) and extracted with EtOAc (3 x 10 mL). The organic layer is dried over Na_2SO_4 and concentrated. The residue is purified by preparative HPLC to give compound **1029** (Table 1).

EXAMPLE 2

SYNTHESIS OF INTERMEDIATE 2H



Step 1:

To a solution of sodium ethoxide (1.48 L, 3.74 mol, 21% w/w in EtOH) at RT is added a solution of diethyl methylmalonate **2a** (645 mL, 3.72 mol) in anhydrous PhMe (330 mL). The resulting solution is stirred for 30 min and a solution of ethyl 3-aminocrotonate **2b** (485 mL, 3.71 mol) in anhydrous PhMe (490 mL) is added. The mixture is stirred at reflux for 39 h, EtOH (1-1.5 L) is removed by vacuum distillation, the mixture is cooled and water (1.6 L) is added. The mixture is stirred at 40°C for ~2 h, then is cooled and the phases are separated. The aqueous phase is washed with PhMe (2 x 50 mL) and then adjusted to pH 5-6 with conc. HCl. The solid is filtered and dried to afford dihydroxypyridine **2c**.

Step 2:

To a mixture of dihydroxypyridine **2c** (100 g, 0.718 mol) and DCM (800 mL) at ambient temperature is added dropwise Br_2 (37 mL, 150 g, 0.72 mol) in DCM (550 mL) over 16 min. The resulting mixture is stirred at RT for 1 h and intermediate **2d** is collected by filtration (HBr salt).

Step 3:

The bromopyridine **2d** (191 g, HBr salt) is heated at reflux in $POCl_3$ (850 mL) for 18 h and cooled to RT. The excess $POCl_3$ is removed by evaporation and the residue is poured onto ice. The mixture is adjusted to basic pH using 10 N NaOH and solid $NaHCO_3$. The mixture is filtered and the filtrate extracted with DCM (3 x 800 mL) and dried over Na_2SO_4. The solution is passed through a SiO_2 (600 g) column and concentrated to afford **2e**.

Alternative procedure for step 3:

Bromopyridine **2d** (370 g, HBr salt) is heated at reflux in $POCl_3$ (1.25 L) for 18 h. The mixture is cooled and excess $POCl_3$ is evaporated. To the residue is added $PhPOCl_2$ (1.2 L) and the mixture is heated at 150°C for 28 h. The mixture is allowed to cool to RT and poured onto ice, then adjusted to basic pH with solid Na_2CO_3. The mixture is filtered and the filtrate is extracted with EtOAc (3 x 1500 mL), dried over Na_2SO_4 and filtered. The filtrate is passed through a SiO_2 (600 g) column and concentrated, and the residue is triturated with EtOAc to give **2e** (196 g). The filtrate is concentrated and purified by CombiFlash® Companion to give a second crop of **2e**.

Step 4:

To a solution of bromide **2e** (105 g, 0.411 mol) in anhydrous THF (1.14 L) is added Cu(I)Br (15 g, 0.1 mol). To the resulting mixture at RT is added iPrMgCl-LiCl (400 mL, 0.52 mol, 1.3 M in THF) over 30 min. The mixture is allowed to stir for 1 h, methyl chlorooxoacetate (80 mL, 0.87 mol) is added and stirring is continued for 1 h. The reaction is quenched with saturated $NaHCO_3$ and solid $NaHCO_3$ and the mixture extracted with EtOAc (3 x 1.2 L). The organic extract is dried over Na_2SO_4, and filtered. The extract is passed through a SiO_2 (300 g) column, concentrated and the residue is purified by CombiFlash® Companion (EtOAc/ hexanes) to afford **2f**.

Step 5:

To a mixture of ester **2f** (65 g, 0.248 mol) in anhydrous PhMe (400 mL) in a 3 necked 5 L round bottom flask equipped with a magnetic stir bar, addition funnel, thermometer and gas-inlet is added (R)-2-methyl-CBS-oxazoborolidine (1 M solution in toluene, 50 mL, 50 mmol) with stirring. The mixture is cooled to -35°C and a solution of catecholoborane (36 mL, 40.5 g, 338 mmol) in toluene (240 mL) is added over a 2 h period. Stirring is continued at -35°C for 30 min. The mixture is allowed to warm to -15°C and is diluted with EtOAc (400 mL) and aqueous Na_2CO_3 (15 wt %,

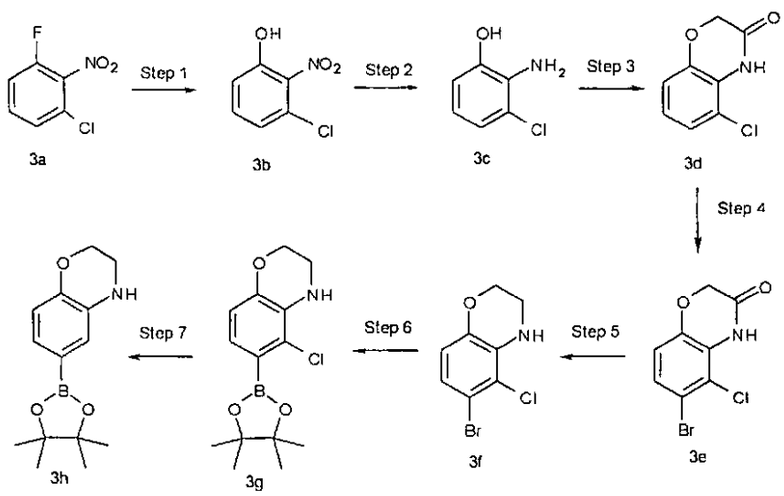
800 mL). The mixture is stirred vigorously for 30 min, and the organic phase is separated and washed with aqueous Na_2CO_3 (15 wt %, 2 x 200 mL; vigorous stirring for 30 min each time) and aqueous NH_4Cl (15 wt %, 2 x 300 mL; vigorous stirring for 30 min each time). The organic layer is separated, passed through SiO_2 (300 g) eluting with EtOAc, and concentrated *in vacuo*. The residue is purified by CombiFlash® Companion to afford **2g**.

Step 6:

A mixture of **2g** (33.8 g, 0.128 mol) and t-butyl acetate (2.4 L) is cooled in an ice bath, and perchloric acid (70% aq) (300 mL) is added quickly. The flask is sealed and allowed to stir for 6 h at ~0-5°C. The reaction is quenched with a saturated solution of Na_2CO_3 (850 mL) and the mixture is adjusted to pH 8 -9 with solid Na_2CO_3. The mixture is filtered, the organic layer is separated and the aqueous layer extracted with EtOAc (3 x 750 mL), dried over Na_2SO_4, filtered and concentrated. DCM is added to the residue and the mixture is filtered. The organic phase is concentrated and purified using the CombiFlash® Companion (hexane/EtOAc: 1% to 30%) to afford **2h** (>98% ee by chiral HPLC) and recovered starting material **2g**.

EXAMPLE 3

SYNTHESIS OF INTERMEDIATES 3G AND 3H



Step 1:

To a mixture of 2-chloro-6-fluoronitrobenzene **3a** (6.62 g, 37.7 mmol) and $LiOH \cdot H_2O$

(6.33 g, 151 mmol) in THF (45 mL) and water (65 mL) is added aqueous H_2O_2 (30%, 8.6 mL, 80.0 mmol). The mixture is sealed and is heated to 60°C with rapid stirring. After 3 days, the mixture is cooled, added to half-saturated aqueous sodium thiosulfate (200 mL) and shaken vigorously in a separatory funnel. The mixture is acidified to pH < 3 with 1 N HCl, extracted with EtOAc (500 mL) and washed with brine (400 mL). The combined extracts are dried over magnesium sulfate, filtered and evaporated to give phenol **3b**.

Step 2:

To a mixture of phenol **3b** (6.37 g, 36.7 mmol) and THF (100 mL) is added tin powder (17.4 g, 147 mmol) followed by 1 N HCl (220 mL, 220 mmol) and the mixture is stirred vigorously at RT for 16 h. The mixture is cooled to 0°C and neutralized with 10 N NaOH (22 mL), and stirred vigorously for about 15 min. The mixture is filtered through a pad of Celite® and the solids are washed thoroughly with EtOAc (4 x 200 mL). The filtrate is acidified with 1 N HCl (4 mL) and diluted with brine (400 mL) and the organic phase is washed with brine (400 mL). The extract is dried over sodium sulfate, filtered and concentrated to afford aminophenol **3c**.

Step 3:

Chloroacetyl chloride (1.94 mL, 24.3 mmol) is added to an ice-cold mixture of aminophenol **3c** (2.91 g, 20.3 mmol) and K_2CO_3 (8.40 g, 60.8 mmol) in anhydrous DMF (200 mL) under a N_2 atmosphere. After 5 min, the reaction is allowed to warm to RT and, after a further 45 min, is heated to 50°C. After 15 h, the reaction is cooled and extracted with EtOAc (600 mL), and washed with water/brine (1 L), half-saturated sodium bicarbonate (1 L) and brine (600 mL). The organic phase is then dried over $MgSO_4$, filtered and concentrated to afford lactam **3d**.

Step 4:

Bromine (1.8 mL, 35 mmol) is slowly added dropwise to a stirred mixture of lactam **3d** (3.15 g; 17.1 mmol) in anhydrous DCM (40 mL) at RT. After 3 h, the mixture is slowly added to saturated aqueous sodium thiosulfate (200 mL) and extracted with DCM (4 x 100 mL). The combined extracts are washed with brine (200 mL), dried over $MgSO_4$, filtered and evaporated to afford the bromide **3e**.

Step 5:

A solution of borane in THF (1.0 M, 18.5 mL, 18.5 mmol) is added dropwise to an ice-cold mixture of lactam **3e** (4.00 g, 15.2 mmol) in anhydrous THF (75 mL), and the reaction is allowed to warm to RT. After about 30 min, the solution is heated to

gentle reflux under a N_2 atmosphere. After 2 h, the mixture is cooled to 0°C, carefully quenched with 1N NaOH (19 mL) and stirred for about 15 min. The mixture is diluted with water (30 mL) and the THF is evaporated. The aqueous residue is extracted with EtOAc (400 mL + 50 mL) and washed with water/brine (200 mL), 0.5 N NaOH (200 mL) and brine (100 mL). The combined extracts are dried over magnesium sulfate, filtered and evaporated to afford the morpholine derivative **3f**.

Step 6:

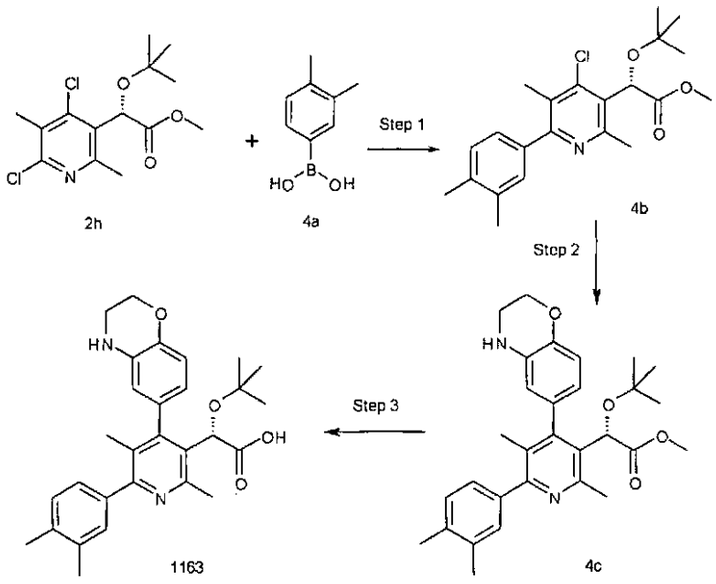
Anhydrous DMF (30 mL) is added to a flask charged with aryl bromide **3f** (1.84 g, 7.42 mmol), *bis*(pinacolato)diborane (2.83 g, 11.1 mmol) and potassium acetate (2.47 g, 26.0 mmol) and the mixture is deoxygenated by bubbling a stream of N_2 gas through the mixture for about 15 min. 1,1'-bis(diphenylphosphino)ferrocene (909 mg, 1.11 mmol) is added, and the mixture is deoxygenated for about a further 5 min and then heated to 95°C. After about 16 h, the reaction mixture is cooled, extracted with EtOAc (300 mL) and the extract is washed with 1:1 water/brine (500 mL) and brine (200 mL), dried over $MgSO_4$, filtered and concentrated. The residue is purified by chromatography over silica gel (EtOAc/hexanes) to afford the boronate **3g** contaminated with 0.8 eq of the diboron reagent.

Step 7:

Palladium on activated charcoal (10% Pd by weight, 1.08 g) is added to a mixture of aryl chloride **3g** (3.0 g, 10 mmol) and ammonium formate (6.4 g, 0.10 mol) in MeOH (75 mL). The mixture is heated at reflux for 30 min, cooled to RT and filtered through Celite®. The filter cake is rinsed with MeOH, the filtrate is concentrated to dryness and the residue is partitioned between water (50 mL) and EtOAc (100 mL). The organic layer is washed with brine (20 mL), dried over anhydrous $MgSO_4$ and concentrated to obtain boronic ester **3h**.

EXAMPLE 4

SYNTHESIS OF COMPOUND 1163 (TABLE 1)



Step 1:

To a solution of the dichloropyridine **2h** (Example 2) (2.0 g, 6.25 mmol) and 3,4-dimethylphenylboronic acid **4a** (1.12 g, 7.5 mmol) in DMF (20 mL) is added 2M Na_2CO_3 (7.8 mL, 16 mmol) followed by $PdCl_2(PPh_3)_2$ (440 mg, 0.62 mmol). The reaction mixture is degassed by bubbling with argon (10 min), the reaction vessel is sealed and the mixture is heated at 110°C for 16 h. The cooled mixture is diluted with EtOAc, washed with water and brine, dried over $MgSO_4$ and filtered. The residue is purified by CombiFlash® Companion (Hexanes/EtOAc) to give **4b**.

Step 2:

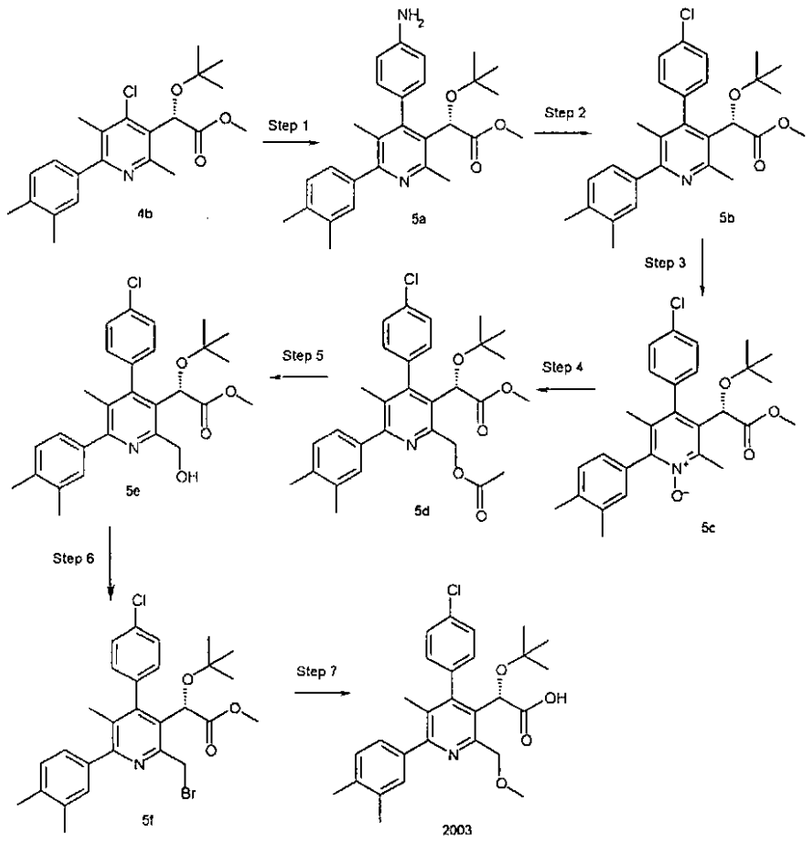
To a mixture of chloropyridine **4b** (250 mg, 0.64 mmol) in DMA (5.6 mL) is added boronate ester **3h** (Example 3) (218 mg, 0.83 mmol), $Pd([P(t\text{-}Bu)_3]_2$ (33 mg, 0.064 mmol), and $NaHCO_3$ (269 mg, 3.2 mmol), followed by water (565 µL). The mixture is degassed by bubbling with argon under sonication for 10 min, the reaction vessel is sealed and the mixture is heated at 130°C for 16 h. The reaction mixture is diluted with EtOAc (30 mL) and washed with brine (2x), water, and brine, dried over $MgSO_4$, filtered and concentrated and the residue is purified by CombiFlash® Companion (30% EtOAc/hexanes) to afford **4c**.

Step 3:

To a mixture of ester **4c** (191 mg, 0.39 mmol) and THF (8 mL)/MeOH (4 mL) is added 1.0N NaOH (4 mL, 4.0 mmol) at RT. The mixture is stirred at 50°C for 18 h, cooled to RT, quenched with AcOH and diluted with EtOAc. The mixture is washed with water and brine, dried ($MgSO_4$), filtered and concentrated under vacuum. The residue is purified by CombiFlash® Companion (DCM/MeOH, 0-5%) and the product is diluted with MeCN/H_2O, frozen and lyophilized to give compound **1163** (Table 1).

EXAMPLE 5

SYNTHESIS OF COMPOUND 2003 (TABLE 2)



Step 1:

To a solution of chloropyridine **4b** (Example 4) (2.0 g, 5.1 mmol) in DMA (40 mL) is added 4-(4,4,5,5-tetramethyl-1,2,3-dioxaborolan-2-yl)aniline (1.6 g; 7.2 mmol)

followed by $NaHCO_3$ (2.2 g, 26 mmol) and distilled water (3 mL). The mixture is split into two microwave flasks and streams of argon gas are bubbled through the vigorously stirred mixtures for 30 min. *bis*-(Tri-*tert*-butylphosphine) palladium(0) catalyst (131 mg; 0.256 mmol) is added to each flask and the argon bubbling is continued for 10 min. The flasks are sealed and heated at 130°C for 16 h. The two reaction mixtures are pooled together, diluted with EtOAc (300 mL), and washed with water/brine (1:1 v/v; 5 x 100 mL) and brine (2 x 100 mL). The organic phase is dried over $MgSO_4$, filtered and concentrated. The residue is purified with CombiFlash® Companion to yield intermediate **5a**.

Step 2:

To a mixture of copper (II) chloride (558 mg, 4.15 mmol) and dry MeCN (20 mL) at 0°C under nitrogen atmosphere is added, dropwise, *t*-butyl nitrite (0.55 mL; 4.17 mmol). A solution of aniline **5a** (1.3 g, 2.9 mmol) in dry MeCN (20 mL) is added dropwise over 5 min and the ice bath removed after 15 min. After 16 h, the solvent is evaporated and the residue is adsorbed onto silica gel, purified by CombiFlash® Companion and dried under high vacuum to afford intermediate **5b**.

Step 3:

Meta-chloroperbenzoic acid (80%, 455 mg, 2.11 mmol) is added to a stirred mixture of pyridine **5b** (546 mg, 1.17 mmol) in anhydrous DCM (10 mL) and the reaction is allowed to stir at ambient temperature. After 2 days, additional *meta*-chloroperbenzoic acid (200 mg) and DCM (2 mL) are added and the stirring continued. After an additional day, the mixture is extracted with EtOAc (2 x 50 mL), and washed with saturated $NaHCO_3$ and brine. The combined organic phases are dried over $MgSO_4$ and concentrated to afford the N-oxide **5c**.

Step 4:

Pyridine N-oxide **5c** (1.17 mmol) is dissolved in Ac_2O (7.5 mL, 79 mmol) and the resulting solution is heated to 60°C under a nitrogen atmosphere. After 2 h, the solution is concentrated under high vacuum and the residue is dried under high vacuum for 1 h. The residue is extracted with EtOAc (100 mL) and washed with saturated $NaHCO_3$ and brine. The extract is dried over $MgSO_4$ and concentrated to afford intermediate **5d**.

Step 5:

HCl in dioxane (4N; 1.0 mL, 4.0 mmol) is added to a stirred mixture of **5d** (1.17 mmol) and dry MeOH (4.2 mL) cooled to 0°C, and the mixture is allowed to warm to

ambient temperature. After 21 h, the mixture is extracted with EtOAc (80 + 20 mL) and washed with saturated $NaHCO_3$ and brine. The combined extracts are dried over $MgSO_4$ and evaporated to afford alcohol **5e**.

Step 6:

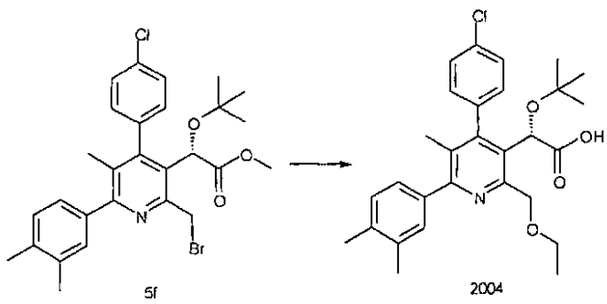
To a stirred mixture of alcohol **5e** (1.17 mmol) and anhydrous DCM (8 mL) at ambient temperature is added CBr_4 (427 mg, 1.3 mmol) followed by triphenylphosphine (339 mg; 1.3 mmol). The mixture is stirred at ambient temperature for 16 h, then diluted with DCM, absorbed onto silica gel and purified by CombiFlash® Companion to afford bromide **5f**.

Step 7:

NaH (60 % oil dispersion; *ca.* 2 mg) is added to a mixture of bromide **5f** (30 mg, 0.055 mmol), anhydrous THF (0.5 mL) and anhydrous MeOH (50 µL, 1.2 mmol) and the mixture is stirred in a sealed vial at ambient temperature. After 2 h, additional NaH (*ca.* 2 mg) is added and the stirring continued. After 17 h, the reaction mixture is acidified with acetic acid, diluted with water, filtered through a Millex filter, divided into two portions and purified by preparatory HPLC. The relevant fractions are pooled and lyophilized to afford compound **2003** (Table 2, TFA salt).

EXAMPLE 6

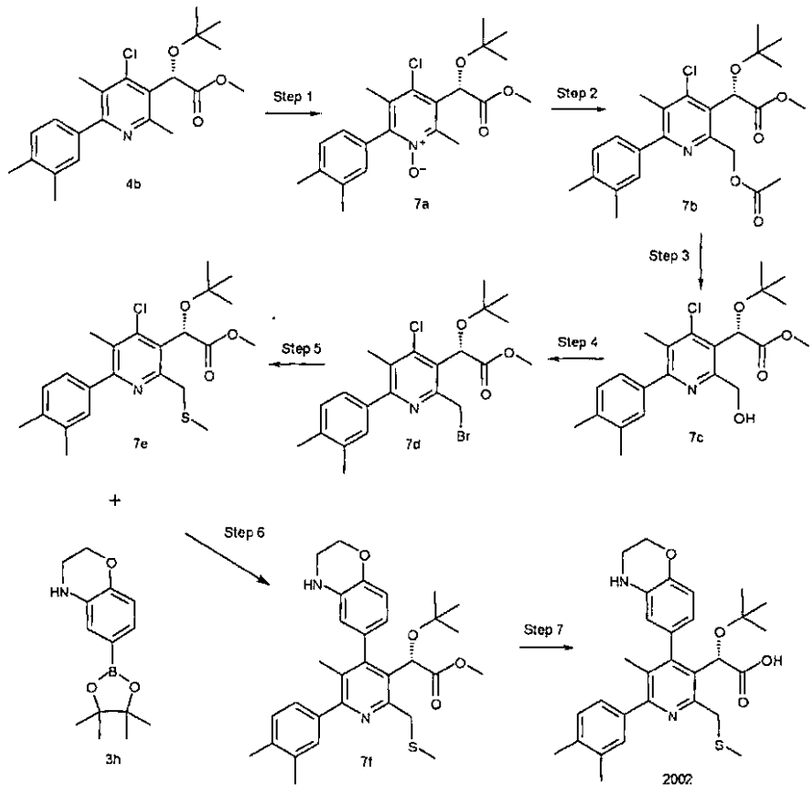
SYNTHESIS OF COMPOUND 2004 (TABLE 2)



Intermediate **5f** (Example 5) is transformed to compound **2004** (Table 2) using the procedure described in step 7 of Example 5, except that MeOH is replaced with absolute EtOH.

EXAMPLE 7

SYNTHESIS OF COMPOUND 2002 (TABLE 2)



Step 1 to Step 4:

Intermediate **4b** (Example 4) is transformed to intermediate **7d** using the procedures described in steps 3 to 6 of Example 5.

Step 5:

To a stirred solution of bromide **7d** (314 mg, 0.67 mmol) in anhydrous DMF (2.0 mL) at ambient temperature is added sodium thiomethoxide (57 mg, 0.81 mmol). Stirring is continued for 1 h and the solution is extracted with EtOAc (75 mL) and washed with saturated $NaHCO_3$ and brine. The extract is dried over $MgSO_4$ and concentrated and the residue is purified by CombiFlash®Companion to afford the thioether **7e**.

Step 6:

To a mixture of chloropyridine **7e** (63 mg, 0.14 mmol), boronate ester **3h** (Example 3) (53 mg, 0.20 mmol), *bis*-(tri-*tert*-butylphosphine) palladium(0) catalyst (16 mg;

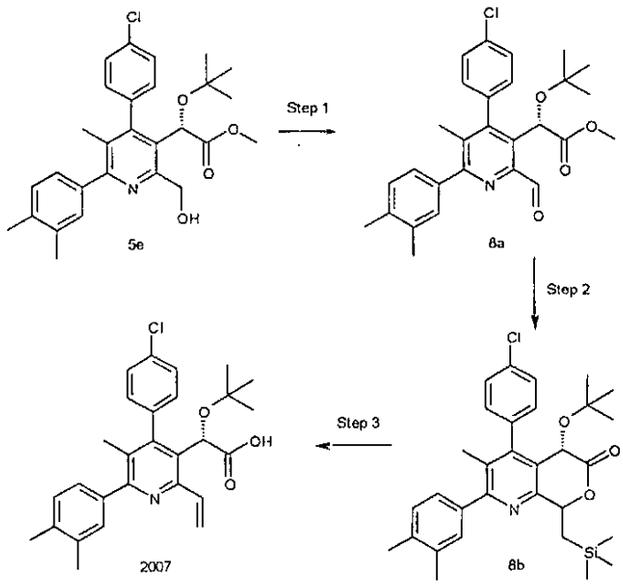
0.031 mmol), Dave-Phos ligand (24 mg, 0.061 mmol) and $NaHCO_3$ (60 mg, 0.71 mmol) in DMA (1.3 mL) in a microwave vial is added distilled water (0.13 mL), and the mixture is deoxygenated by bubbling argon for 15 min. The vial is sealed and heated to 130°C. After 16 h, the mixture is extracted with EtOAc (40 mL) and washed with water and brine. The extract is dried over $MgSO_4$ and concentrated, and the residue is purified by CombiFlash®Companion to afford intermediate **7f**.

Step 7:

To a mixture of ester **7f** (15 mg, 0.028 mmol) and $LiOH \cdot H_2O$ (10 mg, 0.24 mmol) is added THF (0.70 mL) followed by distilled water (0.15 mL) and MeOH (0.1 mL), and the mixture is heated to 45°C. After 16 h, the mixture is acidified with AcOH, diluted with MeCN / water, split into two portions and purified by preparatory HPLC. The relevant fractions are pooled and lyophilized to yield compound **2002** (Table 2) (TFA salt).

EXAMPLE 8

SYNTHESIS OF COMPOUND 2007 (TABLE 2)



Step 1:

A mixture of alcohol **5e** (Example 5) (200 mg, 0.49 mmol), Dess-Martin periodinane (251 mg; 0.59 mmol) and anhydrous DCM (6 mL) is stirred at RT under a nitrogen atmosphere for 18 h. The reaction mixture is vigorously stirred with saturated

$NaHCO_3$ / $Na_2S_2O_3$ (1:1, v/v, 12 mL) for 20 min and is extracted with DCM. The combined extracts are washed with saturated $NaHCO_3$, dried over $MgSO_4$ and concentrated to afford the aldehyde **8a**.

Step 2:

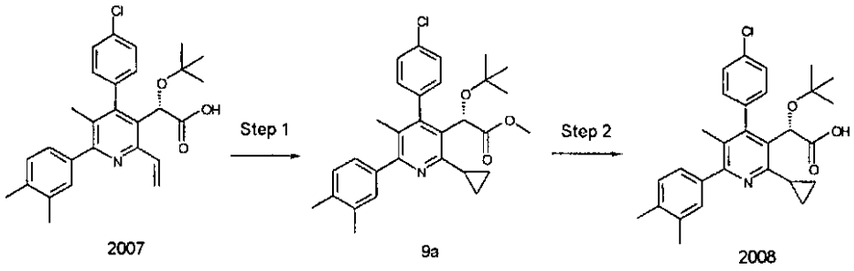
Trimethylsilylmethylmagnesium bromide (90%, 1M solution in Et_2O, 0.34 mL, 0.31 mmol) is added dropwise to a stirred solution of aldehyde **8a** (125 mg, 0.26 mmol) in anhydrous THF (2.0 mL) cooled to -35°C under a nitrogen atmosphere. After 1 h, additional trimethylsilylmethyl magnesium bromide solution (0.26 mL; 0.23 mmol) is added. After a further 2 h, the reaction is quenched with saturated NH_4Cl (1 mL) and the mixture is extracted with EtOAc (20 mL), and washed with 5% $NaHCO_3$ and brine. The extract is dried over $MgSO_4$, filtered and evaporated and the residue is purified by CombiFlash® Companion to afford lactone **8b**.

Step 3:

To a stirred mixture of lactone **8b** (98 mg; 0.183 mmol) and anhydrous THF (3.0 mL) under a nitrogen atmosphere is added dropwise tetrabutylammonium fluoride solution (1 M solution in THF; 0.27 mL; 0.27 mmol). The mixture is allowed to stir at 0°C for 30 min, then is allowed to warm to ambient temperature. After 1 h, the reaction is concentrated to dryness and the residue is dissolved in MeCN (10 mL). An aliquot (1 mL) is set aside and the remaining solution is adsorbed onto silica gel and purified by CombiFlash® to afford compound **2007** (Table 2). The 1 ml aliquot is purified by preparatory HPLC to yield compound **2007** (TFA salt).

EXAMPLE 9

SYNTHESIS OF COMPOUND 2008 (TABLE 2)



2007 9a 2008

Step 1:

To a stirred, ice cold solution of compound **2007** (Example 8) (12 mg, 0.026 mmol) is added dropwise a solution of diazomethane in Et_2O (ca. 0.7 M, 2 mL) *via* a plastic pipette. After 5 min, palladium(II) acetate (5 mg, 0.02 mmol) is added and the

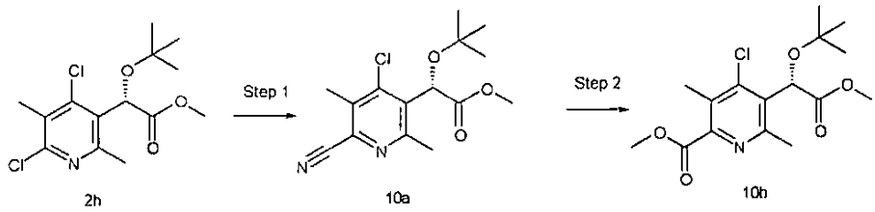
mixture is stirred for 15 min. Nitrogen gas is bubbled through the solution to remove excess diazomethane and the residue is dried under high vacuum for 10 min to yield intermediate **9a**.

Step 2:

Intermediate **9a** is converted to compound **2008** using the procedure described in step 7 of Example 7.

EXAMPLE 10

SYNTHESIS OF INTERMEDIATE 10B



2h 10a 10b

Step 1:

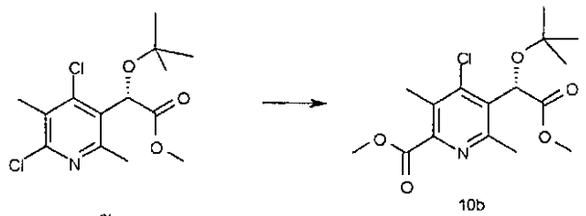
Dichloropyridine **2h** (Example 2) (11 g, 33 mmol), $Zn(CN)_2$ (7.8 g, 66 mmol) and $Pd[PPh_3]_4$ (1.9 g, 1.6 mmol) are combined in DMA (100 mL) and heated in a sealed tube to 115°C. After 6 h, the reaction is cooled to RT, $Pd[PPh_3]_4$ (1.9 g, 1.6 mmol) is added and the reaction allowed to continue for 1 h. The mixture is cooled to RT, diluted with EtOAc (250 mL) and washed with water (250 mL). The aqueous layer is washed with EtOAc (100 mL) and the combined organic layers are washed with water (250 mL). The organic layer is dried over Na_2SO_4 and concentrated. The residue is purified by CombiFlash® Companion to give **10a**.

Step 2:

A mixture of nitrile **10a** (1.0 g, 3.2 mmol), aqueous NaOH (10 N, 3.4 mL, 32 mmol) and EtOH (3.2 mL) is heated at 90°C in a sealed tube for 16 h. The mixture is cooled to RT and diluted with concentrated aqueous HCl (12N, 4 mL, 48 mmol) and water (50 mL). The mixture is extracted with EtOAc (3 x 50 mL) and the combined organic layers are dried over Na_2SO_4 and concentrated to dryness. The residue is taken up in MeOH (1 mL) and Et_2O (10 mL) and treated slowly with a hexane solution of $TMSCH_2N_2$ (2M, 3.5 mL, 7.0 mmol), and the mixture stirred for 10 min. The mixture is evaporated to dryness and the product is purified by CombiFlash® Companion to give the diester **10b**.

EXAMPLE 11

ALTERNATIVE SYNTHESIS OF INTERMEDIATE 10B

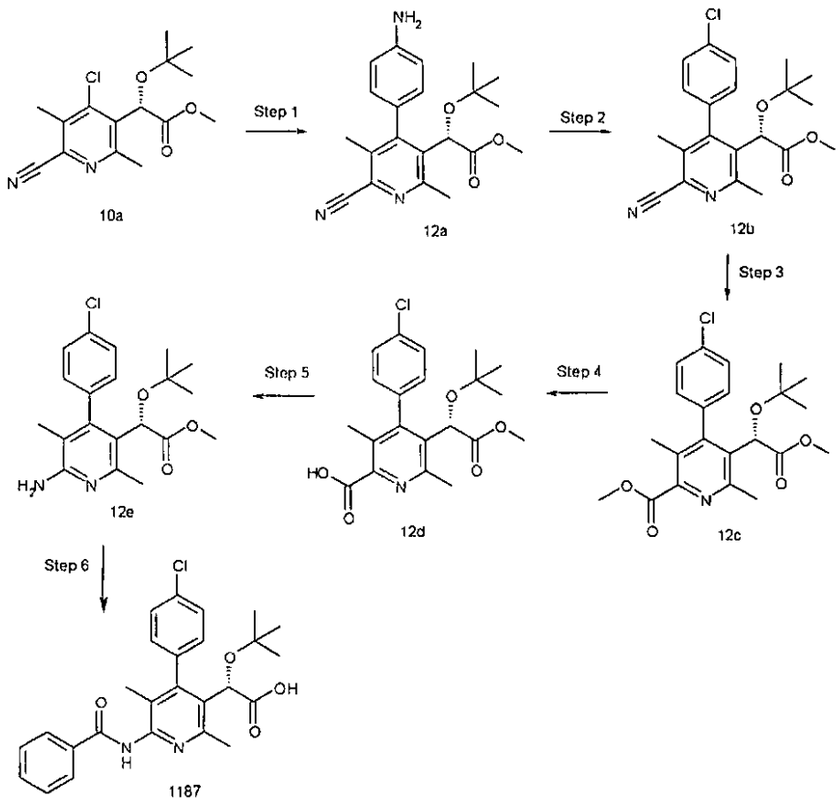


2h 10b

A mixture of $Pd(OAc)_2$ (70 mg, 0.31 mmol), 1,3- propylene bis(dicyclohexylphosphonium tetrafluoroborate (0.38 g, 0.63 mmol), dichloropyridine **2h** (Example 2) (2.0 g, 6.2 mmol) and potassium carbonate (1.3 g, 9.4 mmol) is added to dried 4Å molecular sieves (3.0 g) in an oven-dried round bottom flask (100 mL) equipped with Teflon® coated magnetic stir bar, sealed with a rubber septum and cooled under vacuum. The rubber septum is secured by wrapping with electrical tape and DMF (20 mL) and MeOH (2.5 mL, 62 mmol) are added via syringe. A balloon of CO is connected to the reaction vessel using a short length of rubber tubing (~ 1 in.), a needle adapter and a 20 G needle. The inert atmosphere is then exchanged for carbon monoxide by briefly exposing the reaction vessel to vacuum (1-2 sec) and backfilling with carbon monoxide (3 times). The reaction mixture is heated at 120°C and stirred vigorously for 16 h, then is allowed to cool to room temperature, and is diluted with EtOAc (20 mL), combined and filtered through a plug of Celite (eluting with EtOAc). The filtrate is washed with water and brine, dried over $MgSO_4$, filtered and concentrated. The residue is purified by CombiFlash® Companion (EtOAc/hexanes) to give the diester **10b**.

EXAMPLE 12

SYNTHESIS OF COMPOUND 1187 (TABLE 1)



Step 1:

A mixture of nitrile **10a** (Example 10) (1.7 g, 5.4 mmol), 2-aminophenylboronic acid (1.0 g, 7.3 mmol), *bis*[tri-*t*-butylphosphine]palladium(0) (276 mg, 0.54 mmol), $NaHCO_3$ (2.25 g, 26.7 mmol), DMA (50 mL) and water (5 mL) is degassed by bubbling Ar(g) under sonication for 5 min. The mixture is heated to 130°C and stirred for 15 h, then cooled to RT and partitioned between EtOAc (225 mL) and water (200 mL). The aqueous layer is extracted with EtOAc (2 x 100 mL) and the combined organic layers are washed with water, dried over Na_2SO_4 and concentrated. The residue is purified by CombiFlash® Companion to give the aniline **12a**.

Step 2:

Aniline **12a** is converted to intermediate **12b** using the procedure described in step 2 of Example 5.

Step 3:

A mixture of **12b** (3.8 g, 9.8 mmol), aqueous NaOH (10N, 9.8 mL, 98 mmol) and EtOH (10 mL) is heated at 90 °C in a sealed tube for 16 h. The mixture is cooled to RT and diluted with concentrated HCl (12N, 10 mL, 120 mmol) and water (500 mL). The mixture is extracted with EtOAc (3 x 500 mL) and the combined organic layers are dried over Na_2SO_4 and concentrated to dryness. The residue is taken up in MeOH (5 mL) and Et_2O (50 mL) and treated slowly with a hexane solution of $TMSCH_2N_2$ (2M, 3.5 mL, 15.0 mmol), and the mixture is stirred for 10 min, then evaporated to dryness. The residue is purified by CombiFlash® Companion to give the diester **12c**.

Step 4:

A mixture of diester **12c** (2.9 g, 6.9 mmol), THF (9 mL) and MeOH (3 mL) is treated with LiOH (1N, 9.7 mL, 9.7 mmol). The mixture is stirred for 10 min, then is acidified with aqueous HCl (1N, 15 mL, 15 mmol), diluted with brine and extracted with EtOAc (3 x 50 mL). The combined organic layers are dried over Na_2SO_4 and concentrated to give carboxylic acid **12d**.

Step 5:

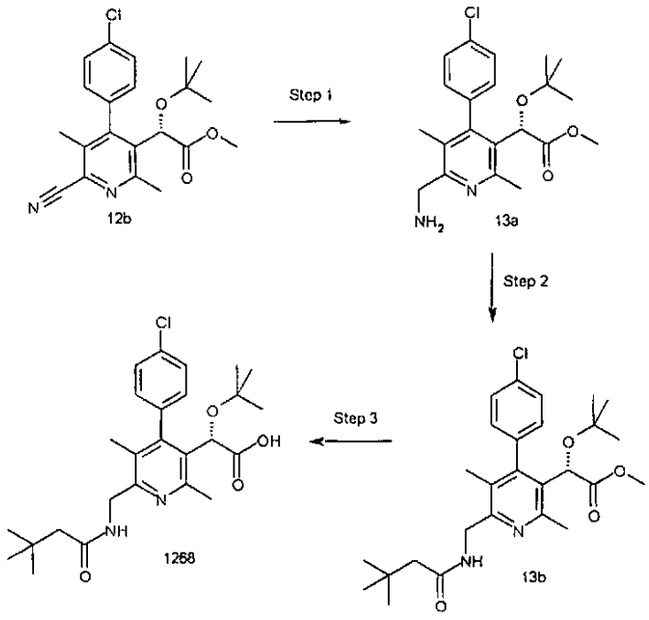
To a mixture of **12d** (1.9 g, 4.6 mmol) and Et_3N (1.3 mL, 9.3 mmol) in PhMe (63 mL) is added water (0.4 mL, 23 mmol) followed by DPPA (2.0 mL, 9.3 mmol). The mixture is heated at 90°C for 30 min, and then a further portion of DPPA (500 µL, 2.3 mmol) is added. Stirring is continued for 40 min and the mixture is cooled to RT, diluted with EtOAc (100 mL), and washed with saturated aqueous $NaHCO_3$, water and brine. The organic layer is dried over Na_2SO_4 and concentrated and the residue is purified by CombiFlash® Companion to give intermediate **12e**.

Step 6:

A mixture of aminopyridine **12e** (30 mg, 0.08 mmol) in THF (2 mL) is treated with Et_3N (22 µL, 0.16 mmol) followed by benzoyl chloride (12 µL, 0.10 mmol) and the mixture is heated at 50°C for 2 h. The mixture is diluted with MeOH (0.5 mL), aqueous NaOH (5N, 80 µL, 0.40 mmol) is added, and the mixture is stirred at 55°C for 2 h. The mixture is concentrated nearly to dryness and diluted with AcOH (1.5 mL) and DMF (0.5 mL), and purified by preparative HPLC to give compound **1187** (Table 1).

EXAMPLE 13

SYNTHESIS OF COMPOUND 1268 (TABLE 1)



Step 1:

A mixture of nitrile **12b** (Example 12) (6 g, 15.4 mmol) and AcOH (100 mL) is treated with 10% Pd/C (1.64 g, 1.54 mmol). The mixture is purged with hydrogen gas and stirred at RT for 1.5 h. The flask is evacuated several times and the catalyst is removed by filtration through Celite® with EtOAc washes. The mixture is concentrated *in vacuo* and the residue is taken up in EtOAc, washed with saturated $NaHCO_3$ and saturated brine, dried over $MgSO_4$, and concentrated. The residue is purified by CombiFlash® Companion (1-10% MeOH/DCM gradient with 1% Et_3N) to afford after concentration, amine **13a**.

Step 2:

To a solution of amine **13a** (85 mg, 0.22 mmol) in DCM (2 mL) is added Et_3N (61 µL, 0.44 mmol) followed by t-butylacetyl chloride (34 µL, 0.24 mmol). The mixture is stirred at RT for 2 h and concentrated to dryness. The crude material containing amide **13b** is used in the following step.

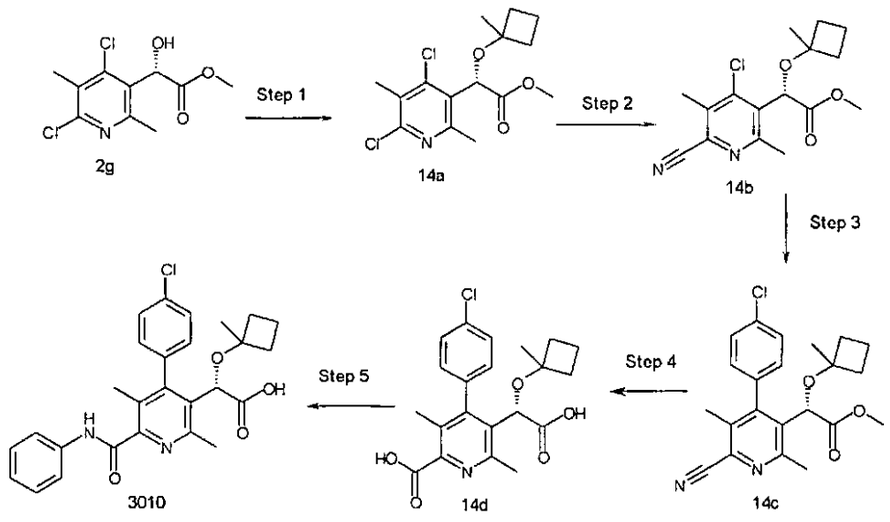
Step 3:

A mixture of **13b** (106 mg, 0.22 mmol), MeOH (0.5 mL) and THF (1.5 mL) is treated with 5N NaOH (217 µL, 1.08 mmol). The mixture is stirred at 50°C for 16 h and

concentrated to dryness. The residue is dissolved in AcOH/DMSO (1 mL each) and purified by preparative HPLC to afford after freezing and lyophilization, compound **1268** (Table 1).

EXAMPLE 14

SYNTHESIS OF COMPOUND 3010 (TABLE 3)



Step 1:

To solid P_2O_5 (652 mg, 4.6 mmol) in a dry RB flask is slowly added 85% H_3PO_4 (503 µL, 7.34 mmol) via syringe. This mixture is allowed to stir a few minutes; DCM (20 mL) is then added followed by alcohol **2g** (Example 2) (970 mg, 3.67 mmol). To this mixture is added $BF_3{\cdot}Et_2O$ (931 µL, 7.34 mmol) and methylenecyclobutane (3.4 mL, 37 mmol). The mixture is stirred at RT for 2 h then is quenched rapidly with aqueous $NaHCO_3$. The reaction mixture is diluted with EtOAc, washed with saturated brine, dried ($MgSO_4$), filtered and concentrated. The residue is purified using the Combi-Flash® Companion (hexanes/EtOAc) to give ether **14a** and recovered starting alcohol **1g**.

Step 2:

A mixture of **14a** (825 mg, 2.48 mmol), $Zn(CN)_2$ (583 mg, 5 mmol), $Pd(PPh_3)_4$ (430 mg, 0.37 mmol) and DMA (12 mL) is sealed in a microwave vessel and heated in the microwave at 125°C (10 min) using a Biotage Initiator Sixty. The reaction mixture is cooled, poured into EtOAc and washed with saturated brine. The organic phase is dried over $MgSO_4$, filtered and concentrated and the residue is purified by

Combi-Flash® Companion (hexanes/EtOAc) to give nitrile **14b**.

Step 3:

Intermediate **14b** is transformed to intermediate **14c** using the procedure described in steps 1 and 2 of Example 12.

Step 4:

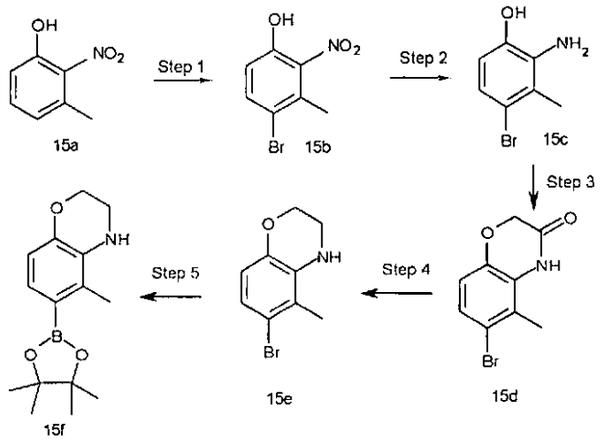
To nitrile **14c** (176 mg, 0.44 mmol) in MeOH (4 mL) is added 5 N NaOH (441 µL, 4.4 mmol). The mixture is heated at 65°C (24 h), cooled to RT, acidified with 1N HCl (pH ~1-2) and extracted with EtOAc (3x). The combined organic phases are dried ($MgSO_4$), filtered and concentrated to give diacid **14d**.

Step 5:

To a solution of diacid **14d** (181 mg, 0.45 mmol) in anhydrous THF (8 mL) is added Et_3N (263 µL, 1.9 mmol) and pivaloyl chloride (116 µL, 0.94 mmol) at RT and the mixture is stirred for 1 h. To a portion of this stock solution (2 mL, 0.11 mmol) is added aniline (11.3 µL, 0.12 mmol) and the mixture is allowed to stir at RT for 16 h. The reaction mixture is treated with 10 N NaOH (112 µL, 1.12 mmol) for 4 h and concentrated to dryness, purified by preparative HPLC and lyophilized to give compound **3010** (Table 3).

EXAMPLE 15

SYNTHESIS OF INTERMEDIATE 15F



Step 1:

A mixture of nitrophenol **15a** (5.23 g, 34.1 mmol) and AcOH (20 mL) is cooled in an ice bath and bromine (1.75 mL, 34.15 mmol, dissolved in 5 mL AcOH) is added

dropwise with stirring. The mixture is stirred for about 1 h at 0°C and poured into ice water (250 mL). The mixture is extracted with EtOAc (2 X 100 mL), washed with 5% $NaHCO_3$, dried over anhydrous $MgSO_4$, filtered and concentrated to give **15b**. This material is used in the next step without further purification.

Step 2:

To a well stirred ethanol solution (75 mL) of **15b** (8.1 g, 34.9 mmol) is added $SnCl_2$ (20 g, 105 mmol) and the reaction mixture is stirred at reflux for 2.5 h. A further portion of $SnCl_2$ (2g, 10 mmol) is added and heating at reflux is continued for 1 h. The mixture is cooled to RT and poured onto ice (250 g), and the pH is adjusted to approximately 7.5 with aqueous 5% $NaHCO_3$. The mixture is extracted with EtOAc (3 X 100 mL) and the organic extract is washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated to dryness to give the aniline intermediate **15c**.

Step 3:

To a stirred, ice cold, mixture of K_2CO_3 (2.05 g, 14.8 mmol), aniline **15c** (750 mg, 3.71 mmol) and DMF (5 mL) under nitrogen, is added chloroacetyl chloride (355 µL, 4.45 mmol) dropwise. The mixture is allowed to warm to RT over a period of about 15 min and is then heated to 60°C for 1 h. The mixture is allowed to cool to RT, is poured into a mixture of ice/water (250 mL) and is stirred for approximately 15 min. The suspension is centrifuged, and the supernatant is discarded. The solid material is left drying under suction overnight to give intermediate **15d**.

Step 4:

To an ice cold mixture of the cyclic amide **15d** (280 mg, 1.16 mmol) and THF (6 mL) under nitrogen is slowly added a borane-THF solution (1M in THF, 1.74 mL, 1.74 mmol). The reaction mixture is slowly allowed to warm to RT, then is stirred at RT for 1.5 h and then gently heated to reflux for 1 h. The mixture is cooled in an ice bath and is carefully quenched with aqueous 1 M NaOH (4 mL) over about 10 min. The reaction mixture is partitioned between EtOAc (150 mL) and water (25 mL). The organic layer is washed with aqueous 1 N NaOH (20 mL) and saturated aqueous NaCl, and dried over anhydrous $MgSO_4$, filtered and concentrated to give **15e**.

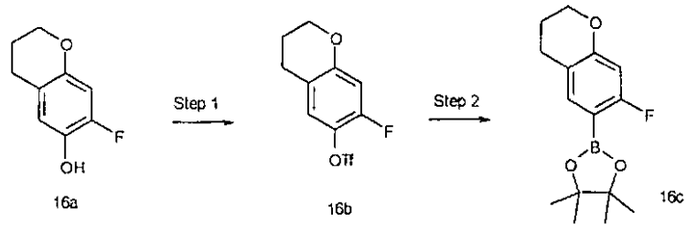
Step 5:

A well stirred mixture of the arylbromide **15e** (0.50 g, 2.2 mmol), potassium acetate (728 mg, 7.7 mmol) and bis(pinacolato)diborane (0.83 g, 3.3 mmol) in DMF (15 mL) is degassed by bubbling Ar through the solution for about 20 min. $PdCl_2$(dppf)-DCM (320 mg, 0.44 mmol) is added and degassing is continued for about 15 min. The

system is sealed (teflon screw cap vessel) under Ar and heated to 90°C for 5 h. The reaction mixture is allowed to cool to RT, diluted with EtOAc (150 mL), washed with brine and water, dried over anhydrous $MgSO_4$, filtered and concentrated to dryness. The residue is purified by CombiFlash® Companion (EtOAc/hexanes) to give the desired boronate **15f**.

EXAMPLE 16

SYNTHESIS OF INTERMEDIATE 16C



16a 16b 16c

Step 1:

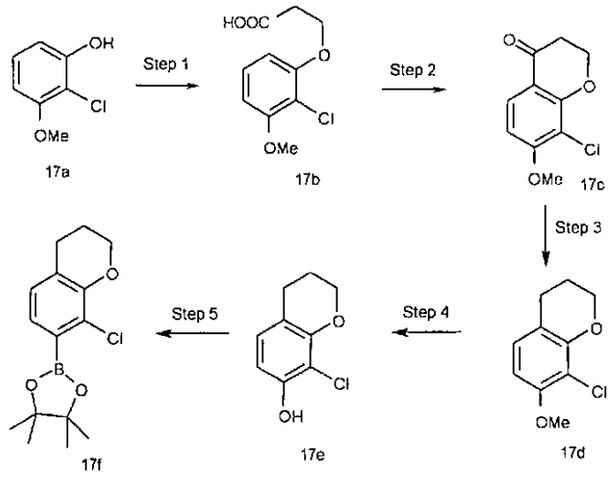
Neat Tf_2O (0.56 mL, 3.3 mmol) is added dropwise to a cooled (0°C) mixture of phenol **16a** (350 mg, 2.1 mmol; prepared according to Doi *et al Bull. Chem. Soc. Jpn.* **2004** *77*, 2257-2263) and pyridine (0.91 mL, 11 mmol) in DCM (10 mL) under an Ar atmosphere. The mixture is allowed to warm to RT and is stirred for 2 h. The reaction is quenched by the addition of a 10% citric acid solution (20 mL) and the mixture is extracted with DCM (3 x 20 mL). The combined organic layers are washed with water, dried over $MgSO_4$, filtered and concentrated to dryness. The residue is purified by CombiFlash® Companion to provide triflate **16b**.

Step 2:

A mixture of the triflate **16b** (510 mg, 1.7 mmol), bis[pinacolato]diborane (560 mg, 2.2 mmol) and potassium acetate (500 mg, 5.1 mmol) in DMF (18 mL) is degassed with Ar for 5 min, and $PdCl_2$dppf-DCM complex (140 mg, 0.17 mmol) is added. The reaction mixture is degassed for an additional 5 min and heated to 100°C by microwave irradiation for 10 min, then cooled to RT. The mixture is diluted with EtOAc (60 mL) and washed with brine, dried over $MgSO_4$, filtered and concentrated. The residue is further purified by CombiFlash® Companion to afford boronic ester **16c**.

EXAMPLE 17

SYNTHESIS OF INTERMEDIATE 17F



Step 1:

A solution of phenol **17a** (0.91 g, 5.74 mmol) in dry DMF (1 mL) is added dropwise to a mixture of NaH (60% in oil, 0.60 g, 15 mmol) in dry DMF (1 mL) cooled to 15°C and the mixture is stirred for 20 min. A solution of 3-bromopropionic acid (1.1 g, 6.9 mmol) in dry DMF (0.5 mL) is added dropwise and the mixture is stirred at RT overnight. After 16 h, MeOH (1.2 mL) is added and the reaction mixture is added to dilute HCl (12 mL of 1 N HCl in 100 mL water) and extracted with EtOAc (80 mL; the pH of the aqueous phase is adjusted to pH <3). The organic layer is dried over anhydrous Na_2SO_4, filtered and concentrated to give **17b** contaminated with some unreacted starting material.

Step 2:

A mixture of **17b** (1.53 g, 6.63 mmol) and polyphosphoric acid (7 g) is heated to 75°C. After 4 h, the reaction is cooled, and ice and water are slowly added with rapid stirring. The mixture is extracted with EtOAc (100 mL) and the organic extract is washed with water, saturated $NaHCO_3$ and brine, dried over anhydrous $MgSO_4$ and concentrated to give **17c** (crude).

Step 3:

AcOH (80 mL) is added to a mixture of chromanone **17c** (6.2 g, 29 mmol) and freshly activated zinc powder (38 g, 580 mmol). The mixture is stirred at 100°C for15 h and filtered through Celite, and the Celite pad is rinsed repeatedly with EtOAc (4 x 25 mL). The filtrate is concentrated and extracted with EtOAc (400 mL)

and the organic extract is washed with saturated $NaHCO_3$ (2 x 400 mL) and brine (200 mL). The organic phase is dried over $MgSO_4$ and evaporated to provide crude chromane **17d**.

Step 4:

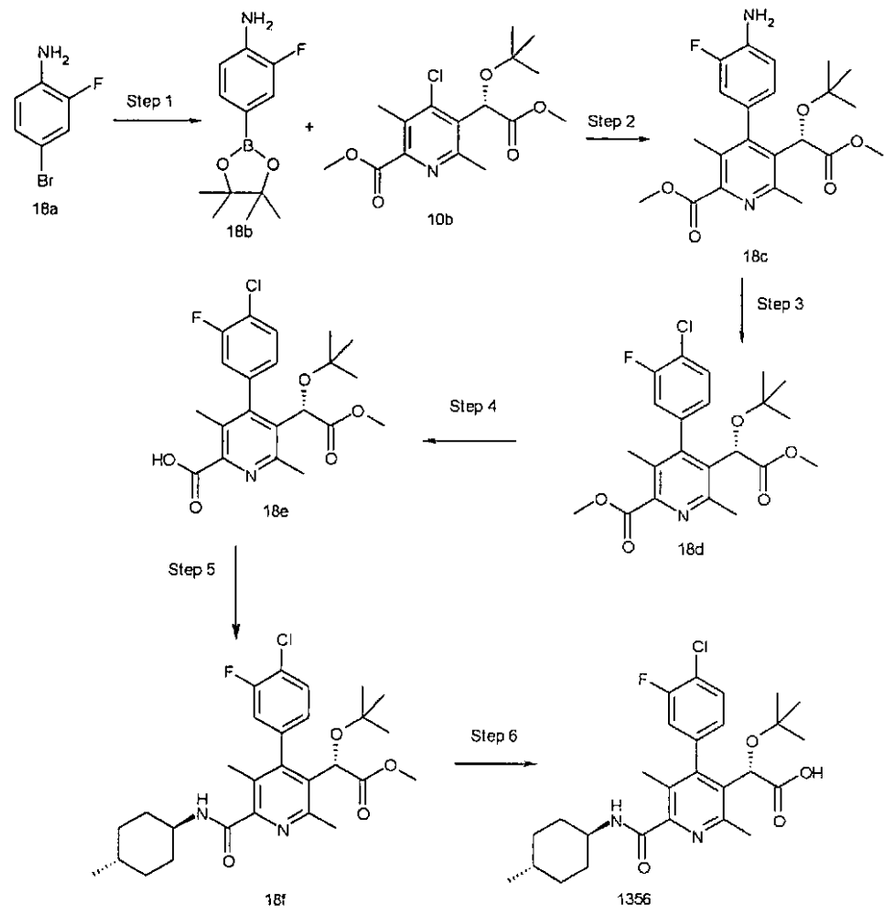
A mixture of anisole **17d** (4.0 g, 20 mmol) and dry dichloromethane (40 mL) is cooled to -78°C. A BBr_3 solution (1M in DCM, 44 mL, 44 mmol) is added dropwise and then the reaction mixture is removed from the dry ice bath. After 45 min, the mixture is cooled (ca. 0°C) and the reaction is quenched with water (25 mL) added dropwise. The mixture is diluted with water (400 mL) and is carefully neutralized with saturated aqueous $NaHCO_3$ (final pH ca 8). This mixture is then extracted with DCM (300 mL and then 100 mL) and the combined organic layers are dried over Na_2SO_4 and evaporated to dryness. The product is purified by CombiFlash® Companion to provide phenol **17e**.

Step 5:

Compound **17e** is transformed to compound **17f** using the procedure described in steps 1 and 2 of Example 16.

EXAMPLE 18

SYNTHESIS OF COMPOUND 1356 (TABLE 1)



Step 1:

To a mixture of bromide **18a** (1.0 g, 5.3 mmol), *bis*-(pinacolato)diboron (1.9 g, 7.4 mmol) and potassium acetate (1.6 g, 16 mmol) is added anhydrous DMF (20 mL) and the mixture is deoxygenated by bubbling a stream of N_2 gas through the mixture for about 25 min. 1,1'-Bis(diphenylphosphino)ferrocene (0.58 mg, 0.79 mmol) is added and the mixture is deoxygenated for approximately a further 5 min, then heated to 95°C. After 5 h, the reaction mixture is cooled, diluted with EtOAc (200 mL) and washed with brine (2 x 100 mL). The layers are filtered through a pad of Celite and reseparated. The organic phase is dried over anhydrous $MgSO_4$, filtered and concentrated and the residue is purified by CombiFlash® Companion

(EtOAc/hexanes) to afford the boronate **18b**.

Step 2:

Intermediate **18b** is coupled to intermediate **10b** (Example 10) using the procedure described in step 1 of Example 12 to give intermediate **18c**.

Step 3:

Intermediate **18c** is transformed to intermediate **18d** using the procedure described in step 2 of Example 5.

Step 4:

Intermediate **18d** is transformed to intermediate **18e** using procedure described in step 4 of Example 12.

Step 5:

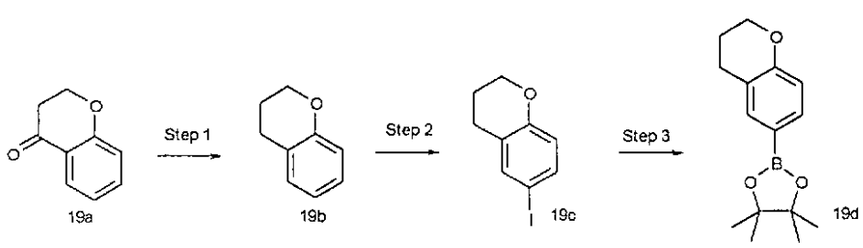
A mixture of carboxylic acid **18e** (44 mg, 0.10 mmol) in NMP is treated with Et_3N (58 µL, 0.42 mmol) and TBTU (67 mg, 0.21 mmol). The mixture is stirred for 5 min and *trans*-4-methylcyclohexylamine (35 µL, 0.31 mmol) is added. The mixture is stirred for 1 h, diluted with EtOAc (40 mL), washed with water and brine, dried over $MgSO_4$, filtered and concentrated. The crude mixture is purified by CombiFlash® Companion using a gradient of EtOAc/hexanes to afford the desired amide **18f**.

Step 6:

A mixture of amide **18f** (42 mg, 0.080 mmol), THF (1.5 mL) and MeOH (0.75 mL) is treated with 1.0 N LiOH (0.75 mL, 0.75 mmol). The mixture is stirred at 55°C for 1 h, neutralized with AcOH and purified by preparative HPLC. A mixture of the product and DCM (3 mL) is adjusted to pH > 10 with 1N NaOH and neutralized with AcOH. The mixture is passed through a phase separator filter and the organic layer is concentrated *in vacuo*, diluted with a mixture of MeCN / water and lyophilized to give compound **1356**.

EXAMPLE 19

SYNTHESIS OF INTERMEDIATE 19D



Step 1:

A mixture of chromanone **19a** (9.78 g, 66.0 mmol) and AcOH (20 mL) is added to a mixture of zinc dust (108 g, 1.65 mol) in AcOH (150 mL). The mixture is heated to 100°C and is stirred overnight, then filtered through Celite® (washed with EtOAc, 100mL), diluted with PhMe (300 mL) and concentrated to give intermediate **19b**.

Step 2:

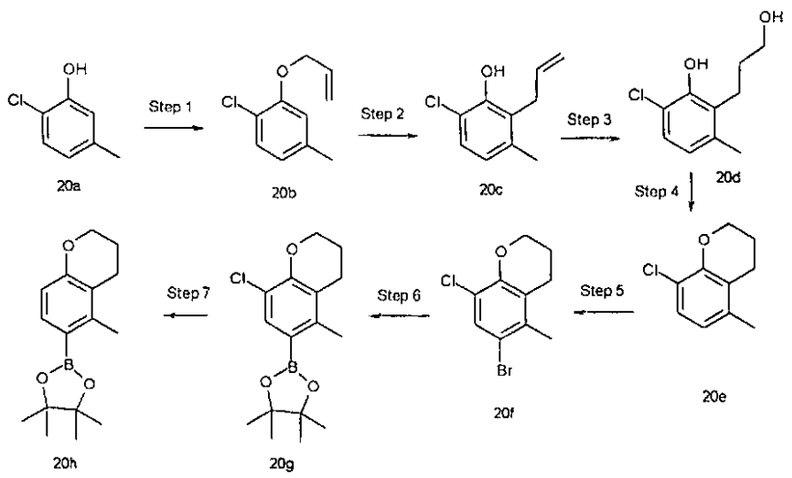
$AgNO_3$ (12.0 g, 70.6 mmol) and I_2 (15.8 g, 62.3 mmol) are added sequentially to a mixture of **19b** (8.45 g, 63.0 mmol) and MeOH (225 mL). The mixture is allowed to stir for about 1 h and filtered through Celite®, and the filtrate is concentrated under reduced pressure. The residue is diluted with EtOAc (250 mL) and washed with saturated sodium thiosulfate (250 mL). The organic layer is washed with water (200 mL), dried over Na_2SO_4, filtered and concentrated. The residue is further purified by CombiFlash® Companion to give 6-iodochroman **19c**.

Step 3:

A mixture of the 6-iodochroman **19c** (1.0 g, 3.85 mmol), bis[pinacolato]diborane (1.22 g, 4.81 mmol) and potassium acetate (1.10 g, 11.5 mmol) in DMF (36 mL) is degassed with Ar for about 5 min followed by the addition of the $PdCl_2$dppf-DCM complex (314 mg, 0.38 mmol). The reaction mixture is then degassed for about an additional 5 min and heated to 95°C for 5 h. The mixture is then cooled to RT, diluted with water and extracted with EtOAc (3 x 100 mL). The combined organic extracts are washed with water (100 mL) and brine (100 mL), dried over $MgSO_4$, filtered and concentrated. The residue is further purified by CombiFlash® Companion using a gradient of EtOAc/hexanes to afford intermediate **19d**.

EXAMPLE 20

SYNTHESIS OF INTERMEDIATE 20H



Step 1:

A mixture of phenol **20a** (6.75 g, 47.3 mmol) and DMF (270 mL) is treated with allyl bromide (6.55 mL, 75.7 mmol). To this mixture, NaH (60%, 4 g, 99.4 mmol) is added portionwise and stirring is continued overnight. The reaction mixture is diluted with EtOAc (500 mL) and washed with H_2O. The organic layer is dried over $MgSO_4$, filtered and concentrated to dryness to obtain the desired product **20b**.

Step 2:

The ether **20b** (8.6 g) is stirred and heated at 240°C for 20 min in a microwave vial to provide **20c**.

Step 3:

To a mixture of the allyl intermediate **20c** (9.3 g, 45.8 mmol) in anhydrous THF (300 mL) at 0°C is added borane (1 M in THF, 96 mL, 96 mmol, 2.1 eq). The mixture is allowed to warm to RT and then is stirred for 2.5 h. The mixture is then cooled to 0°C and treated with 10 N NaOH dropwise, followed by slow addition of 30% H_2O_2 (104 ml, 916 mmol). The resulting mixture is allowed to warm to RT and is stirred at RT for 1 h. The reaction mixture is diluted with HCl (10%, 100 mL) and extracted with EtOAc (3 x 200 mL). The combined organic phases are dried over $MgSO_4$ and concentrated. The residue is purified by CombiFlash® Companion to give **20d**.

Step 4:

To a mixture of the diol **20d** (7.1 g, 35.3 mmol) in THF (500 mL) are added PPh_3 (12 g, 45.9 mmol), followed by DEAD (7.2 mL, 45.9 mmol). The mixture is stirred at RT

for 4 h. The reaction mixture is concentrated under reduced pressure and purified by CombiFlash® Companion to obtain the desired product **20e**.

Step 5:

A mixture of the chroman derivative **20e** (5.26 g, 28.8 mmol) and AcOH (70 mL) is treated with Br_2 (19.2 mL, 37.4 mmol) in AcOH (40 mL). The mixture is stirred at RT for 15 min, then diluted with toluene and concentrated to dryness. The residue is taken up in EtOAc (25 mL) and washed with saturated $Na_2S_2O_3$ (25 mL) and saturated $NaHCO_3$ (25 mL). The organic layer is dried over $MgSO_4$, concentrated and purified by CombiFlash® Companion to obtain the desired product **20f**.

Step 6:

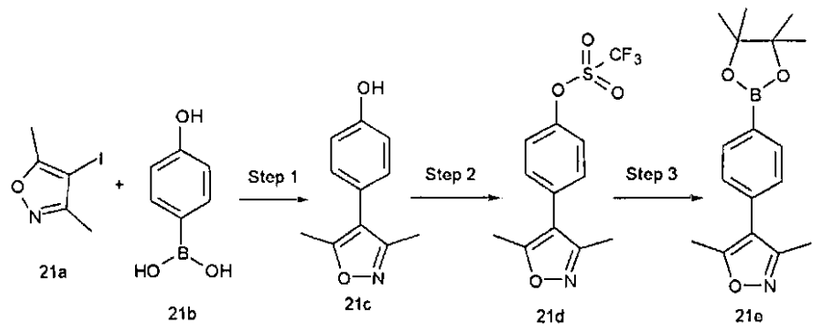
A mixture of bromide **20f** (2.71 g, 10.4 mmol) and DMF (120 mL) is treated with bispinacolatoborane (4 g, 15.5 mmol) and potassium acetate (3.45 g, 36.3 mmol). The mixture is degassed (using an Ar balloon) and $PdCl_2$dppf (845 mg, 1.04 mmol) is added. The mixture is degassed again (using an Ar balloon) and heated at 95°C for 16 h. The mixture is cooled to RT, diluted with H_2O (300 mL) and extracted with EtOAc (2 x 300 mL). The combined organic layers are washed with water, dried over $MgSO_4$, filtered and concentrated. The residue is purified by CombiFlash® Companion and is triturated with hexanes to provide intermediate **20g**.

Step 7:

Palladium on activated charcoal (10% Pd by weight, 0.63 mg, 0.59 mmol) is added to a solution of aryl chloride **20g** (0.91 g, 2.95 mmol) and ammonium formate (1.92 g, 30.4 mmol) dissolved in MeOH and the mixture is heated to reflux. After 15 min, the reaction is cooled to RT and filtered through Celite®, and the Celite® pad is rinsed with MeOH. The filtrate is concentrated to dryness and the residue partitioned between water and EtOAc (10 mL each). The organic layer is dried over anhydrous $MgSO_4$ and concentrated to obtain boronic ester **20h**.

EXAMPLE 21

SYNTHESIS OF INTERMEDIATE 21E



Step 1:

A mixture of **21a** (1.0 g, 4.5 mmol), **21b** (0.72 g, 5.2 mmol), potassium carbonate (1.6 g, 12 mmol) and *trans*-dichlorobis(triphenylphosphine)palladium (II) (0.36 g, 0.62 mmol) in DMF (8.3 mL) and water (0.88 mL) is heated under microwave for 15 min at 130°C. The mixture is partitioned between EtOAc (25 mL) and water (25 mL) and the organic layer is washed with water, dried over Na_2SO_4, filtered and concentrated. The residue is purified by CombiFlash® Companion using a gradient of EtOAc/hexanes to afford the desired alcohol **21c**.

Step 2:

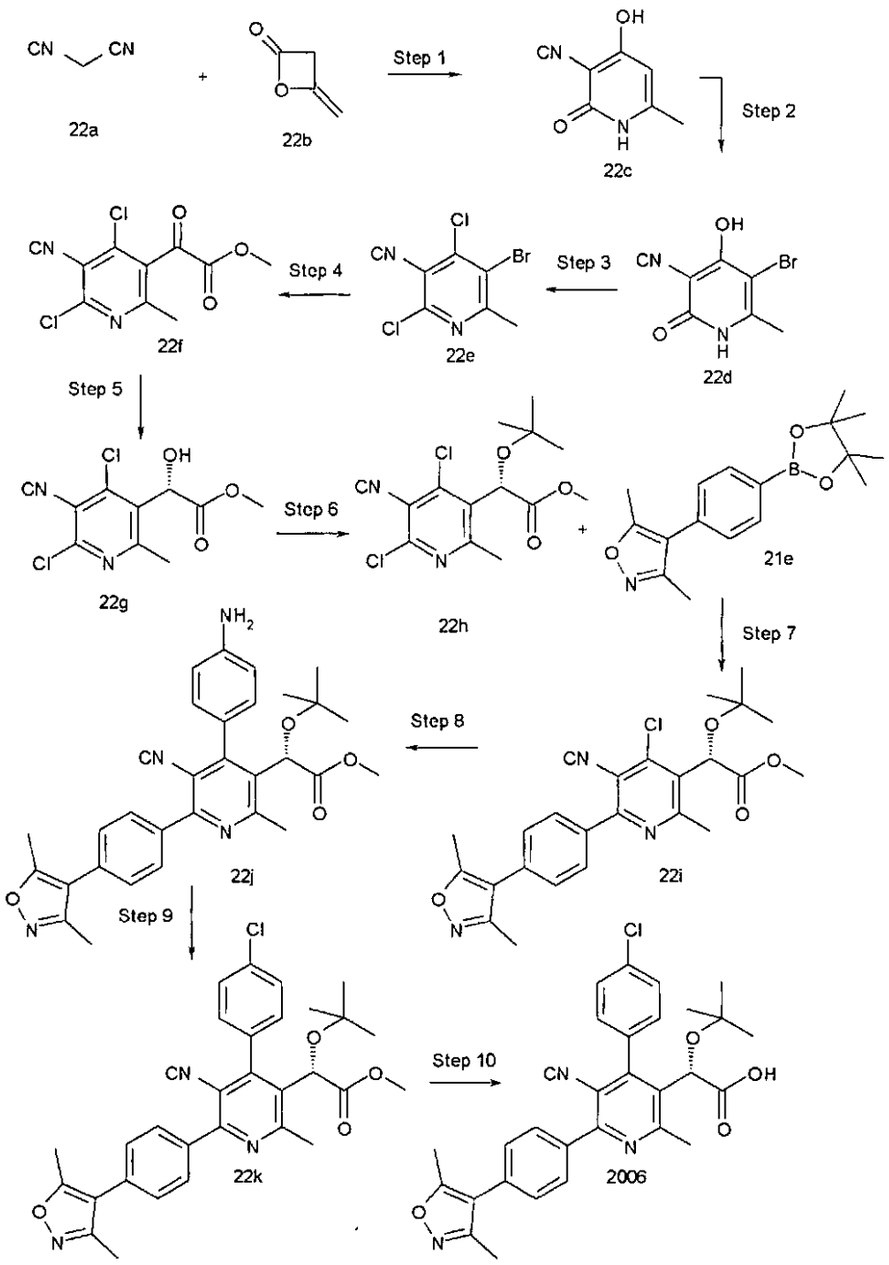
A mixture of alcohol **21c** (0.70 g, 3.7 mmol) in pyridine (15 mL) is treated with Tf_2O (0.95 mL, 5.6 mmol) and stirred at 23°C for 30 min. The mixture is concentrated and the residue is partitioned between DCM (50 mL) and 10% HCl (50 mL). The organic layer is washed with 10% HCl and saturated $NaHCO_3$ solution and passed through a phase separator. Evaporation of the organic layer gives the triflate **21d**.

Step 3:

A solution of the triflate **21d** (1.2 g, 3.7 mmol), bis(pinacolato)diborane (1.4 g, 5.5 mmol) and potassium acetate (1.2 g, 13 mmol) in DMF (50 mL) is degassed with Ar for about 5 min followed by the addition of the $PdCl_2$dppf-DCM complex (0.39 mg, 0.48 mmol). The reaction mixture is then degassed for about an additional 5 min before being heated to 95°C overnight. The reaction mixture is then cooled to RT, diluted with water (150 mL) and extracted with EtOAc (3 x 100 mL). The combined organic extracts are washed with water, dried over Na_2SO_4, filtered and concentrated. The residue is purified by CombiFlash® Companion using a gradient of EtOAc/hexanes to give borane **21e**.

EXAMPLE 22

SYNTHESIS OF COMPOUND 2006 (TABLE 2)



Step 1:

4-Hydroxypyridone **22c** is synthesized using the procedure described by T. Kato; Y. Kubota; M. Tanaka; H. Takahashi and T. Chiba; *Heterocycles* **1978**, *9*, 811.

Step 2:

Intermediate **22c** is transformed to intermediate **22d** using procedures described in step 2 of Example 2.

Step 3:

Intermediate **22d** is transformed to intermediate **22e** using procedures described in step 3 of Example 2.

Step 4:

Intermediate **22e** is transformed to intermediate **22f** using procedures described in step 4 of Example 2.

Step 5:

Intermediate **22f** is transformed to intermediate **22g** using procedures described in step 5 of Example 2.

Step 6:

Intermediate **22g** is transformed to intermediate **22h** using procedures described in step 6 of Example 2.

Step 7:

Intermediate **22h** is transformed to intermediate **22i** using procedures described in step 1 of Example 4.

Step 8:

Intermediate **22i** is transformed to intermediate **22j** using procedures described in step 1 of Example 5.

Step 9:

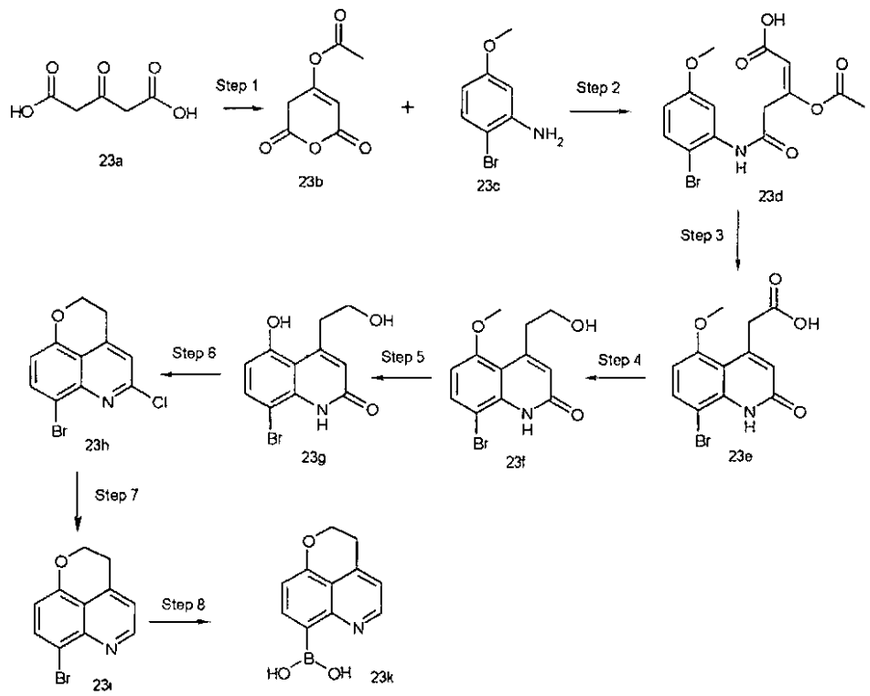
Intermediate **22j** is transformed to intermediate **22k** using procedures described in step 2 of Example 5.

Step 10:

Intermediate **22j** is transformed to compound **2006** using procedures described in step 3 of Example 4.

EXAMPLE 23

SYNTHESIS OF INTERMEDIATE 23K



Step 1:

1,3-acetonedicarboxylic acid **23a** (30 g; 205.3 mmol) is added in portions to Ac_2O (55 g; 587.7 mmol) and the mixture is stirred at 35°C for 23 h, then filtered. The filtrate is diluted with benzene (200 mL) and the solution stored at 5°C for 3 h. The precipitate is filtered and dried under vacuum to give intermediate **23b**.

Step 2:

To a stirred solution of aniline **23c** (7.5 g, 44 mmol) in AcOH (50 mL) is added **23b** (8.0 g, 40 mmol) portionwise. The reaction mixture is warmed to 35°C for 2 h, then cooled to room temperature and poured in ice/water (600 mL). The resulting precipitate is isolated by filtration, rinsed with water (100 mL) and dried under vacuum to give **23d**.

Step 3:

Intermediate **23d** (5.7 g, 15.4 mmol) is added portionwise to concentrated sulfuric acid (20 mL) at RT, so that the temperature of the reaction mixture is kept below 30°C during addition. The mixture is stirred at RT for 30 min and poured in ice/water (400 mL). The resulting precipitate is isolated by filtration, rinsed with water and

dried under vacuum to give **23e**.

Step 4:

A solution of borane (1.0 M in THF, 10.5 ml, 10.5 mmol) is added dropwise to an ice cold solution of quinolone **23e** (1.5 g, 4.8 mmol) in dry THF (40 mL) under a N_2 atmosphere. The mixture is allowed to warm to RT and stirred for 22 h. An additional equivalent of BH_3 is added at 0°C and the reaction mixture is heated to 45°C for 2 h. The reaction is carefully quenched witn 1.0 N NaOH (10 mL) and THF is removed under vacuum. The mixture is poured in EtOAc (100 mL) and the precipitate is collected by filtration and dried under vacuum to provide **23f**.

Step 5:

To a mixture of **23f** (1.1 g, 3.8 mmol) and DCM (60 mL) at -78°C is added dropwise a 1.0 M BBr_3 solution (23 mL, 23 mmol). The cooling bath is removed after 1 h and the mixture is stirred at RT for 16 h. The mixture is poured in ice/water (100 mL) and the precipitate is collected by filtration and dried under vacuum to give **23g**.

Step 6:

To a solution of intermediate **23g** (773 mg, 2.27 mmol) in THF (30 mL) is added PPh_3 (928 mg, 3.5 mmol) followed by DIAD (0.69 ml, 3.5 mmol) (dropwise), and the solution is stirred at RT for 2 h. The reaction mixture is concentrated under vacuum and the crude product is directly added portionwise to $POCl_3$ (2 mL) at RT. The reaction mixture is stirred at 100°C for 45 min and then cooled to room temperature. The mixture is concentrated under vacuum and the crude product is diluted with DCM. The organic phase is washed with 1.0 N NaOH, water, and brine, dried ($MgSO_4$), filtered and concentrated under vacuum. The crude product is purified by combiFlash® (Hex/EtOAc 9/1 to 1/1) to give **23h**.

Step 7:

To a solution of chloroquinoline **23h** (300 mg, 1 mmol) in TFA (10 mL) is added zinc (340 mg, 5 mmol) and the mixture is stirred at RT for 16 h. The mixture is filtered and concentrated under vacuum, and the residue is diluted with 1.0 N NaOH (50 mL) and extracted with DCM (3x). The combined organic extracts are washed with water and brine, dried ($MgSO_4$), filtered and concentrated under vacuum. The residue is purified by combiFlash® (Hex/EtOAc 6/4 to 4/6) to give **23i**.

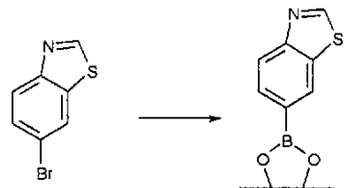
Step 8:

A mixture of aryl halide **23i** (5 g, 20 mmol) Et_2O (400 mL) under a nitrogen atmosphere is heated to 43°C then cooled to -75°C in a dry ice/acetone bath. n-

Butyllithium solution (1.38 M in hexanes, 21.7 mL, 30 mmol) is added dropwise (4 min addition time, internal temp below 70°C). The mixture is stirred for an additional 5 min and n-butyllithium solution (880 µL, 1.2 mmol) is added. After 5 min, triisopropyl borate (16.9 mL, 72 mmoles) is added while the temperature is held at -74°C. The reaction mixture is allowed to warm to -42°C and 5 mL (21 mmol) of triisopropylborate are added. The mixture is stirred for 10 min at -18°C,and 2.5 mL (11 mmol) of triisopropylborate followed by aqueous 2 N HCl (200 mL, 400 mmol) are added. The mixture is allowed to stir at room temperature for 2.5 h, then is diluted with Et_2O (50 mL) and 2N HCl (50 mL). (The layers are separated and the aqueous layer is adjusted to pH = 7 with 10N NaOH (45 mL) and 1N NaOH (20 mL). The precipitate is filtered and dried for 16 h at high vacuum affording the desired compound **23k**.

EXAMPLE 24

SYNTHESIS OF INTERMEDIATE 24B

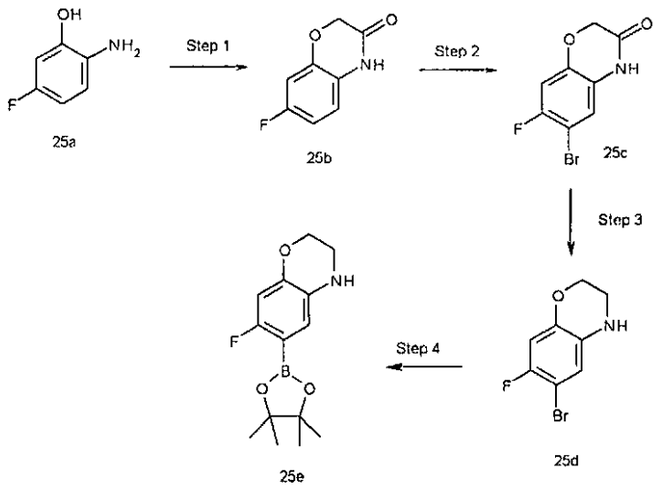


24a 24b

To a mixture of the bromide **24a** (152 mg, 0.71 mmol) and DMF (5 mL) is added bis(pinacolato)diboron (234 mg, 0.92 mmol) and KOAc (210 mg, 2.13 mmol). The solution is degassed with argon gas under sonication (10 min) and dichloro[1,1'-bis(diphenylphosphino)ferrocene]palladium (II) DCM adduct (87 mg, 0.10 mmol) is added. The mixture is heated at 90°C for 16 h and cooled to RT. The mixture is diluted with EtOAc, washed with saturated brine, dried ($MgSO_4$), filtered and concentrated. The residue is purified using the CombiFlash® Companion (hexanes/EtOAc) to give the boronate **24b**.

EXAMPLE 25

SYNTHESIS OF INTERMEDIATE 25E



Step 1:

To a cold (0°C) mixture of **25a** (15.0 g, 118 mmol) and DMF (180 mL) is added K_2CO_3 (48.9 g, 354 mmol) followed by dropwise addition of chloroacetyl chloride (9.40 mL, 118 mmol). The reaction mixture is allowed to warm to RT and then heated to 60°C for 2 h. The reaction mixture is cooled to RT, poured into ice-water (2.0 L) and stirred for 30 min. The mixture is filtered and the solid rinsed with water and dried under reduced pressure to provide **25b**.

Step 2:

To a cooled (10°C) mixture of **25b** (12.4 g, 74.4 mmol), DCM (150 mL) and glacial Ac_2O (150 mL) is added dropwise over 1.5 hours, a solution of Br_2 (4.6 mL, 89 mmol) in DCM (75 mL). After 2 hours at 10°C, an additional amount of Br_2 (2.30 mL, 44.6 mmol) in DCM (40 mL) is added over 1 h with stirring at 10°C. Stirring is continued for 1 h and the reaction mixture is concentrated under reduced pressure. The residue is triturated with Et_2O (500 mL) to provide bromide **25c**.

Step 3:

To a solution of **25c** (13.4 g, 54.5 mmol) in THF (300 mL) is added slowly borane-methyl sulfide complex (55.0 mL, 2.0 M solution in THF, 110 mmol) at 0°C. The mixture is allowed to warm to room temperature and then stirred at reflux for 1 h. The reaction mixture is cooled to 0°C, quenched slowly with 1 M aqueous HCl (27 mL), and then refluxed for 1 h. The mixture is diluted with Et_2O, neutralized with 1 M aqueous NaOH and after further extraction is concentrated. The residue is purified

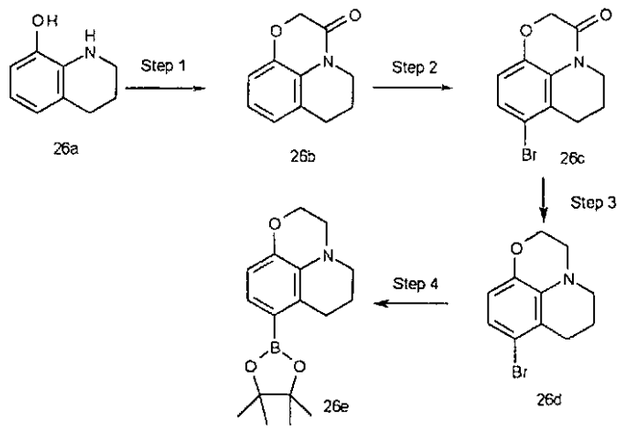
by flash column chromatography (15 to 30% EtOAc/hexanes) to provide intermediate **25d**.

Step 4:

A mixture of **25d** (10.0 g, 43.1 mmol), bis(pinacolato)diboron (16.4 g, 64.7 mmol) and KOAc (12.7 g, 129 mmol) in 1,4-dioxane (430 mL) is degassed with nitrogen for 30 min at RT and heated at 100°C under a nitrogen atmosphere. After 30 min, dichloro[1,1'-bis(diphenylphosphino)ferrocene]palladium (II) DCM adduct (3.5 g, 4.3 mmol) is added and stirring is continued at 100°C (15 h). The reaction mixture is cooled to RT and filtered through a pad of Celite®. The Celite® pad is rinsed with EtOAc and the combined filtrate is concentrated under reduced pressure. The residue is purified by flash column chromatography (twice with 25% EtOAc/hexanes followed by 5 % EtOAc/DCM) to provide **25e**.

EXAMPLE 26

SYNTHESIS OF INTERMEDIATE 26E



Step 1:

To a cold (0°C) solution of 1,2,3,4-tetrahydroquinolin-8-ol **26a** (6.00 g, 40 mmol) in DMF (60 mL) is added K_2CO_3 (16.7 g, 121 mmol) followed by dropwise addition of chloroacetyl chloride (4.25 mL, 53.6 mmol). The reaction mixture is warmed to RT and heated at 60°C for 2 h. The reaction mixture is cooled to RT, poured into ice-water (1.5 L) and stirred for 30 min. The resulting mixture is filtered and the solid rinsed with water and dried under reduced pressure (16 h) to provide amide **26b**.

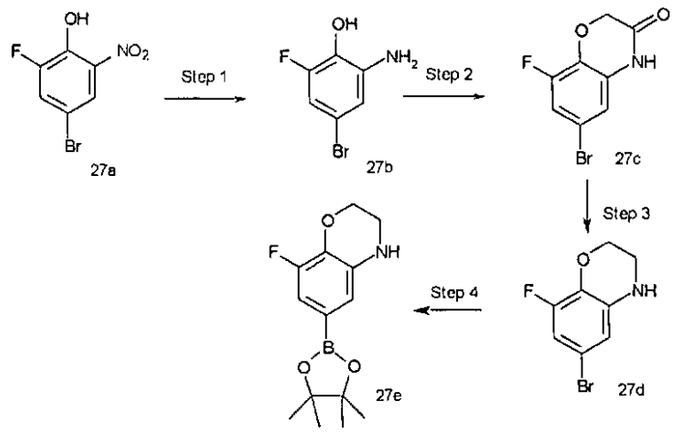
Steps 2, 3, and 4:

Intermediate **26b** is transformed to intermediate **26e** using procedures described in

steps 2 to 4 of Example 25.

EXAMPLE 27

SYNTHESIS OF INTERMEDIATE 27E



Step 1:

To a mixture of 4-bromo-2-fluoro-6-nitrophenol **27a** (12.0 g, 51 mmol) and EtOH (375 mL) is added a solution of sodium dithionite (35.4 g, 203 mmol) in water (125 mL). The mixture is heated at reflux for 1 h, then cooled to 0°C and slowly neutralized with saturated aqueous $NaHCO_3$ (150 mL). The mixture is concentrated and the residue is triturated with 10% MeOH/EtOAc (1.0 L) and filtered through a pad of Celite®. Concentration of the filtrate under reduced pressure provides aniline **27b**.

Step 2:

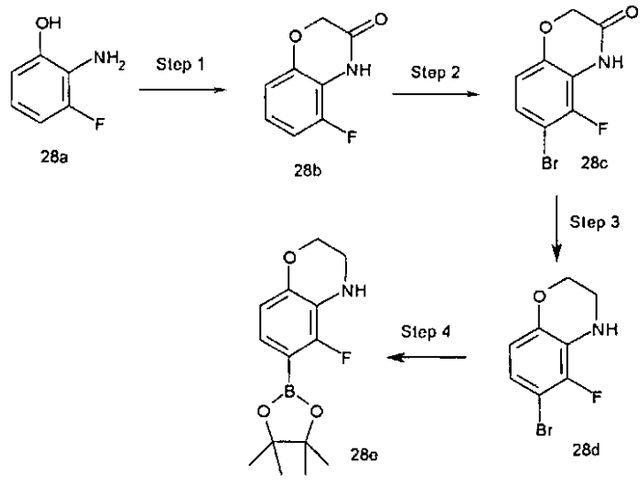
Intermediate **27b** is transformed to intermediate **27c** using the procedure described in step 1 of Example 25.

Steps 3 and 4:

Intermediate **27c** is transformed to intermediate **27e** using the procedures described in steps 3 and 4 of Example 25.

EXAMPLE 28

SYNTHESIS OF INTERMEDIATE 28E

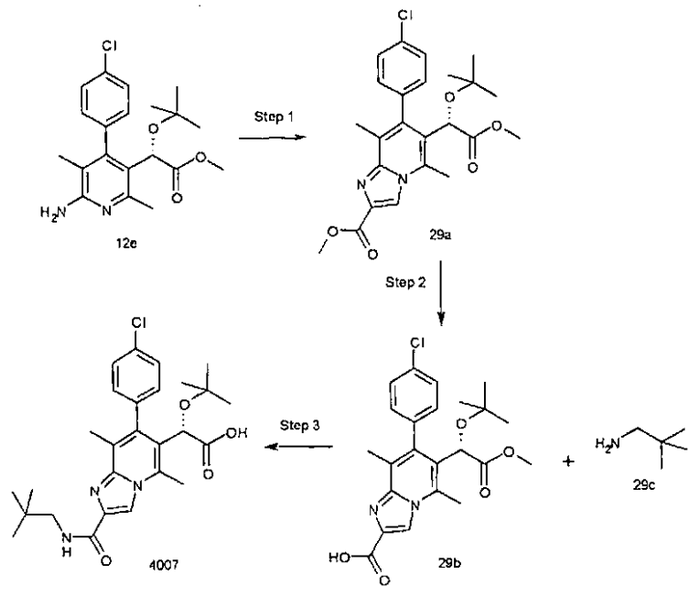


Steps 1 to 4:

Intermediate **28a** is transformed to intermediate **28e** using procedures described in steps 1 through 4 of Example 25.

EXAMPLE 29

SYNTHESIS OF COMPOUND 4007 (TABLE 4)



Step 1:

To a mixture of **12e** (Example 12) (570 mg, 1.5 mmol), EtOH (11 mL) and acetone (2.2 mL) is added $NaHCO_3$ (197 mg, 1.6 mmol) and methyl bromopyruvate (177 µL, 1.7 mmol). The mixture is heated at 85°C for 16 h and solvents are evaporated *in vacuo*. The residue is dissolved in DCM (20 mL), washed twice with water, dried over $MgSO_4$ and concentrated *in vacuo* giving **29a**.

Step 2:

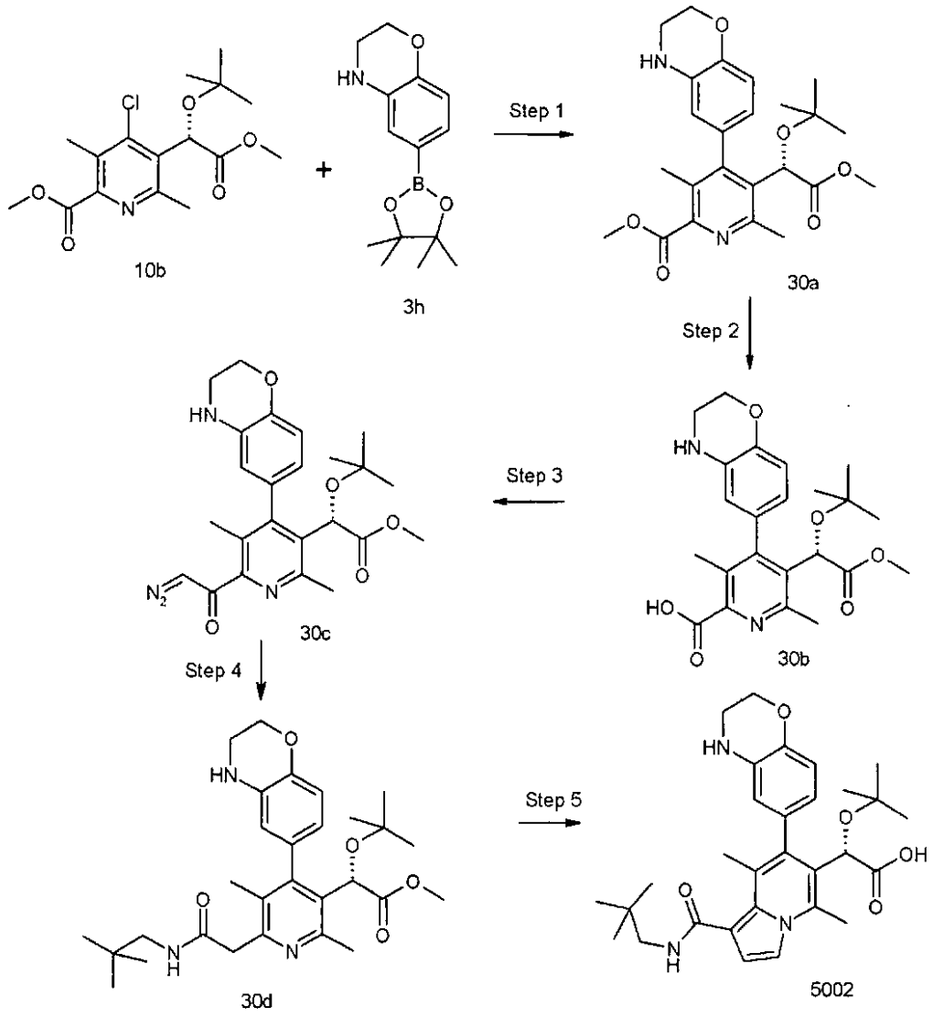
A mixture of **29a** (620 mg, 1.4 mmol), THF (18.7 mL) and MeOH (6.2 mL) is treated with LiOH (1N, 1.4 mL, 1.4 mmol) at 23°C for 15 h. A further portion of 1N LiOH (1.4 mL, 1.4 mmol) is added and the mixture is stirred for 4 h at 23°C. 1N NaOH (0.1 mL, 0.1 mmol) is then added and reaction is continued until complete conversion to product is detected by UPLC-MS. The mixture is adjusted to pH 1 with 1N HCl and extracted with DCM (3x), and the organic extract is dried over $MgSO_4$. The residue is purified by CombiFlash® (5% MeOH / 94 % DCM / 1% AcOH) affording pure **29b**.

Step 3:

To a mixture of **29b** (50 mg, 0.11 mmol) and NMP (1 mL) is added Et_3N (63 µL, 0.45 mmol), followed by N,N,N',N'-tetramethyl-O-(benzotriazol-1-yl)uronium tetrafluoroborate (72 mg, 0.22 mmol). The mixture is stirred for 10 min, treated with neopentylamine **29c** (30 mg, 0.34 mmol) and stirred 16 h at 23°C. 1N NaOH (0.5 mL, 0.5 mmol) is added to the reaction mixture and stirring is continued for 2 h at 60°C. The solution is neutralized with AcOH and EtOAc (75 mL) is added. The organic layer is washed with water and brine, dried over $MgSO_4$, filtered and concenrated *in vacuo* and the residue is purified by prep HPLC. A mixture of the product and DCM (3 mL) is treated with 1N NaOH (pH > 10) and neutralized with AcOH. The mixture is passed through a phase separator filter and the organic layer is concentrated *in vacuo*. The residue is diluted with a mixture of MeCN / water and lyophilized to give compound **4007**.

EXAMPLE 30

SYNTHESIS OF COMPOUND 5002 (TABLE 5)



Step 1:

Intermediates **10b** (Example 10) and **3h** (Example 3) are transformed to intermediate **30a** using the procedure described in step 2 of Example 4.

Step 2:

Intermediate **30a** is transformed to intermediate **30b** using the procedure described in step 4 of Example 12.

Step 3:

To a mixture of **30b** (700 mg, 1.5 mmol), Et_3N (420 µL, 3.0 mmoles) and THF (15 mL) at 0°C is added isobutyl chloroformate (205 µL, 1.6 mmol) dropwise. The

mixture is stirred at 0°C for 30 min, and diazomethane (0.67 M in Et_2O, 11.2 mL, 7.5 mmol) is added. The mixture is allowed to reach 23°C and stirred for 2 h, then is concentrated *in vacuo*. A mixture of EtOAc and water is added to the residue, the layers are separated and the organic layer is washed with saturated $NaHCO_3$, water and brine, dried over Na_2SO_4, filtered and concentrated *in vacuo* affording **30c**.

Step 4:

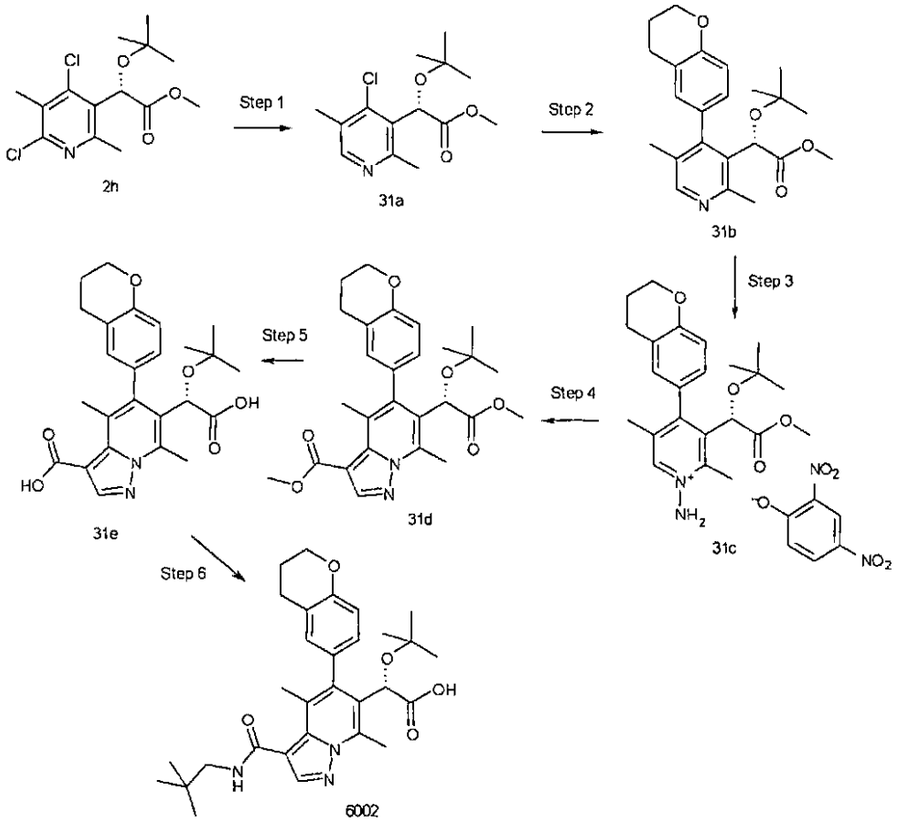
A mixture of **30c** (125 mg, 0.28 mmol) and DCM (1 mL) is treated with neopentylamine **29c** (Example 29) (65 µL, 0.55 mmol) and Et_3N (47 µL, 0.34 mmol), followed by addition of silver benzoate (16 mg, 0.07 mmol). The mixture is stirred at 23°C for 16 h. The mixture is diluted with DCM, washed with saturated NH_4Cl, saturated $NaHCO_3$ and water, dried over Na_2SO_4, filtered and concentrated *in vacuo* providing **30d**.

Step 5:

A mixture of **30d** (40 mg, 0.08 mmol), chloroacetaldehyde (50% in water, 15 µL, 0.12 mmol) and $NaHCO_3$ (19.7 mg, 0.23 mmol) in EtOH (0.5 mL) is heated at reflux for 16 h. The mixture is cooled to 23°C and filtered, and the solvent is evaporated *in vacuo*. The residue is mixed with THF (1 mL) and MeOH (0.3 mL), and 1N NaOH (0.3 mL, 0.3 mmol) is added. The mixture is stirred at 45°C until the reaction is complete, then cooled to 23°C, adjusted to pH 5 with AcOH and purified by prep. HPLC to give compound **5002**.

EXAMPLE 31

SYNTHESIS OF COMPOUND 6002 (TABLE 6)



Step 1:

To a mixture of intermediate **2h** (Example 2) (5 g, 15.6 mmol) in AcOH (100 mL) is added zinc (15.3 g, 234 mmoles). The mixture is stirred at 60°C for 120 min, then is cooled to 23°C and filtered through a Celite® pad, and the filtrate is concentrated *in vacuo*. The residue is slowly neutralized with saturated $NaHCO_3$ and extracted twice with EtOAc. The organic layers are combined, washed with water and brine, dried over $MgSO_4$, filtered and concentrated *in vacuo* to give the desired intermediate **31a**.

Step 2:

A mixture of DMA (15.8 mL) and distilled water (1.58 mL) is degassed for 10 min with nitrogen and added by syringe to a mixture of the intermediate **31a** (1 g, 3.5 mmol), 6-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-chroman **19d** (Example 19)

(1 g, 3.85 mmol) and $NaHCO_3$ (1.47 gr, 17.5 mmol) under nitrogen atmosphere in a 48 mL resealeable vessel equipped with a magnetic stirring bar and fixed with a rubber septum. Bis(tri-*t*-butylphosphine)palladium (179 mg, 0.35 mmol) is added to the reaction mixture and the vessel is placed in a sonicator for 10 min while being purged with nitrogen. The vessel is sealed with a Teflon cap and heated at 130°C for 4 h. The mixture is diluted with EtOAc and filtered through Celite®, and the organic extract is washed with water and brine, dried over $MgSO_4$ and concentrated *in vacuo*. The residue is purified by flash chromatography (10-25-100% ethyl acetate: hexanes) affording **31b**.

Step 3:

To a 15 mL resealable vessel equipped with a magnetic stirring bar is added intermediate **31b** (500 mg, 1.3 mmol), *O*-(2,4-dinitrophenyl)hydroxylamine (300mg, 1.5 mmol; prepared as described in *Tet.Lett.* **1972**, *28*, 3833-3843) and MeCN (1.7 mL). The reaction vessel is sealed with Teflon cap and the mixture is stirred at 40°C for 24 h, then is cooled to 23°C and concentrated in vacuo affording **31c**.

Step 4:

To a mixture of **31c** (521 mg, 1.3 mmol) and DMF (17.4 mL) is added K_2CO_3 (198 mg, 1.43 mmol). The reaction mixture is stirred for 5 min at 23°C (exposed to air), then methyl proprionate (132 mg, 1.56 mmol) is added and stirring is continued for 18 h. The mixture is diluted with EtOAC and washed with saturated $NaHCO_3$, water and brine. The organic layer is dried over$MgSO_4$, filtered and concentrated *in vacuo* and the residue is purified by flash chromatography (10-100% ethyl acetate: hexanes) affording **31d**.

Step 5:

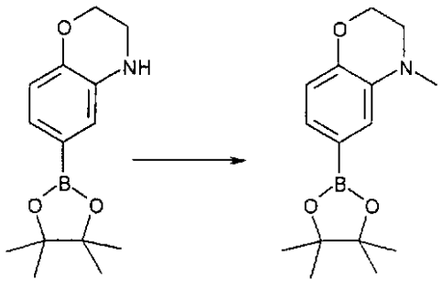
A mixture of **31d** (250 mg, 0.52 mmol), THF (2.5 mL) and MeOH (0.83 mL) is treated with a solution of 10 N NaOH (0.42 mL, 4.2 mmol) at 60°C for 18 h. The mixture is adjusted to pH 1 with 1N HCl and extracted with DCM (3x). The combined organic layers are dried over $MgSO_4$, filtered and concentrated *in vacuo* affording intermediate **31e**.

Step 6:

Intermediate **31e** is transformed to compound **6002** using the procedure described in step 3 of Example 29.

EXAMPLE 32

SYNTHESIS OF INTERMEDIATE 32A

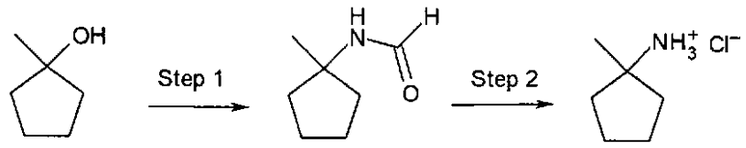


3h 32a

To a mixture of boronate **3h** (Example 3) (0.80 g, 3.1 mmol) and acetone (20 mL) is added K_2CO_3 (5.23 g, 38 mmol) followed by methyl iodide (2.9 mL, 39 mmol). The reaction vessel is sealed and the reaction mixture stirred at RT (24 h). The mixture is diluted with EtOAc and saturated brine. The aqueous phase is extracted with EtOAc (2x) and the combined organic phases are dried ($MgSO_4$), filtered and concentrated to dryness to afford the desired boronate **32a**.

EXAMPLE 33

SYNTHESIS OF INTERMEDIATE 33C



33a 33b 33c

Step 1:

To a mixture of methylcyclopentanol **33a** (2.0 g, 20 mmol) and AcOH (2.0 mL) is added KCN (1.43 g, 22 mmol) portionwise, followed by conc. H_2SO_4 (3.0 mL) added dropwise at a rate to keep the temperature at 30-35°C. The mixture is heated to 60°C for 30 min and is then stirred at RT (16 h). Ice water (35 mL) is added, and the mixture is adjusted to basic pH with solid K_2CO_3 and extracted with Et_2O (5x). The combined organic phases are dried over $MgSO_4$, filtered and concentrated to give **33b**.

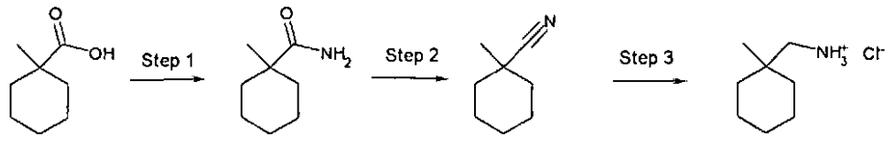
Step 2:

A mixture of derivative **33b** (1.5 g, 11.8 mmol) and dioxane (8 mL) is treated with 5N

HCl (8.0 mL) and EtOH (4 mL). The mixture is heated at gentle reflux for 4 h, then ethanol and dioxane are removed under vacuum. The aqueous phase is washed with hexanes and then concentrated. Traces of water are removed by azeotropic removal with EtOH. The resulting solid is dried under high vacuum to give the amine hydrochloride salt **33c**.

EXAMPLE 34

SYNTHESIS OF INTERMEDIATE 34D



34a 34b 34c 34d

Step 1:

A mixture of 1-methylcyclohexane carboxylic acid **34a** (25 g, 176 mmol) in DCM (125 mL) is cooled to 0°C and a catalytic amount of DMF (250 µL) is added. Oxalyl chloride (20 mL, 228 mmol) is then added dropwise over 30 min and the mixture is allowed to stir for 45 min. The reaction mixture is then warmed to RT and stirred an additional 2.5 h. The mixture is concentrated to dryness and dried and the residue is mixed with 1,4-dioxane (125 mL). To this mixture is added portionwise a solution of 20% ammonium hydroxide (125 mL) at RT (1 h). The mixture is diluted with water (200 mL) and extracted with EtOAc (3x). The combined organic extracts are washed with saturated brine, dried ($MgSO_4$), filtered and concentrated to give a crude solid. This material is dissolved in hot hexanes (125 mL) and left at 4°C (18 h). The solid formed is filtered and washed with cold hexanes to afford amide **34b**.

Step 2:

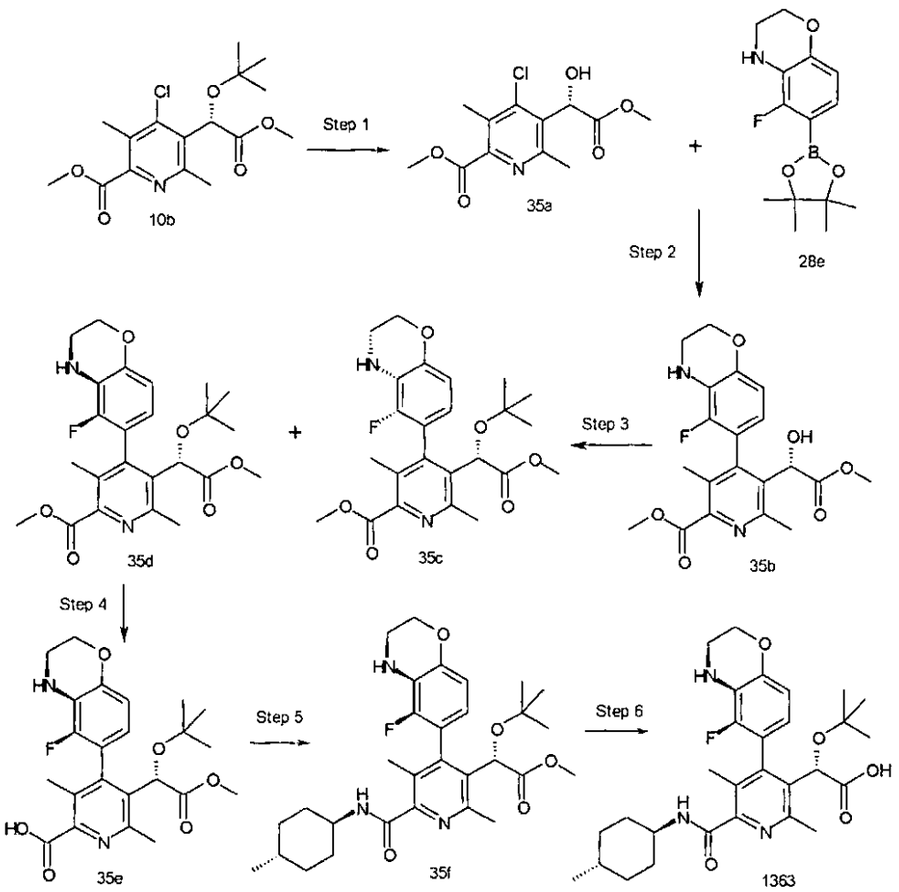
In a 2 necked round bottomed flask equipped with a condenser is added **34b** (18.0 g, 128 mmol) in thionyl chloride (12 mL, 106 mmol). The mixture is heated to reflux for 2 h until gas evolution ceases, then cooled to RT and diluted with Et_2O (125 mL) with careful addition of water (75 mL). The mixture is vigorously stirred for 5 min and then adjusted to basic pH with solid Na_2CO_3. The organic phase is separated and washed with saturated Na_2CO_3 and saturated brine, dried over $MgSO_4$, treated with charcoal and filtered through Celite®. The filtrate is concentrated under vacuum at RT to give **34c**.

Step 3:

To a mixture of EtOH (50 mL) and HCl (g) (8.3 g, 0.23 mmol) at 0°C is added **34c** (14.7 g, 119 mmol) followed by platinum oxide (400 mg). The mixture is placed in a Parr shaker and treated with H_2(g) at 40 psi for 48 h. The atmosphere is flushed and the mixture filtered through Celite® and washed with EtOH. The filtrate is concentrated to dryness and the residue is washed with ether, filtered and dried to give the intermediate **34d** as the hydrochloride salt.

EXAMPLE 35

SYNTHESIS OF COMPOUND 1363 (TABLE 1) INCLUDING SEPARATION OF ATROPISOMERS



Step 1:

To a mixture of the diester **10b** (1.0g, 2.91 mmol), DCM (7 mL) and MeOH (0.25 mL) is added TFA (8 mL). The mixture is allowed to stir at RT for 2 h and is

concentrated to dryness. The residue is taken up in EtOAc and washed with saturated $NaHCO_3$, dried (Na_2SO_4), filtered and concentrated to give alcohol **35a**.

Step 2:

A mixture of boronate **28e** (400 mg, 1.43 mmol), alcohol **35a** (420 mg, 1.46 mmol), 2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl (S-Phos, 59 mg, 0.1 mmol), tris(dibenzylideneacetone)dipalladium(0) (39 mg, 0.04 mmol) and Na_2CO_3 (607 mg, 5.7 mmol) in 2-methyl tetrahydrofuran (5.6 mL) and water (1.4 mL) is placed in a sealable vessel. The mixture is degassed by bubbling argon through the solution (10 min) and the vessel is sealed and heated at 75°C (20 h). Further portions of the catalyst and ligand are added and the mixture is again heated at 75°C (20 h). The cooled mixture is filtered, diluted with EtOAc, washed with brine, dried over Na_2SO_4, filtered and concentrated. The residue is purified by CombiFlash® Companion to give a mixture of isomers **35b**.

Step 3:

The mixture of alcohols **35b** (362 mg, 0.90 mmol) in tert-butyl acetate (7.1 mL, 53 mmol) is cooled to 0°C in an ice bath and treated portionwise with perchloric acid (70% w/w in water, 1.2 mL, 13.4 mmol). The vessel is capped and the reaction mixture stirred at 0°C until about 50% completion. The reaction is quenched with 1N NaOH (pH~9) and the mixture is extracted with EtOAc. The organic phase is washed with water and brine, dried over Na_2SO_4 and concentrated. The residue is purified by CombiFlash® Companion (20 to 100% EtOAc/hexanes) to give the separated isomers **35c** and **35d** plus unreacted starting alcohols **35b**.

Step 4:

To a mixture of diester **35d** (87 mg, 0.19 mmol), MeOH (0.4 mL) and THF (1.2 mL) is added 1N LiOH (0.21 mL, 0.21 mmol). The mixture is allowed to stir at RT (16 h) then is acidified with 1N HCl and extracted with EtOAc (2x). The organic extract is dried over Na_2SO_4, filtered and concentrated to give acid **35e**.

Step 5:

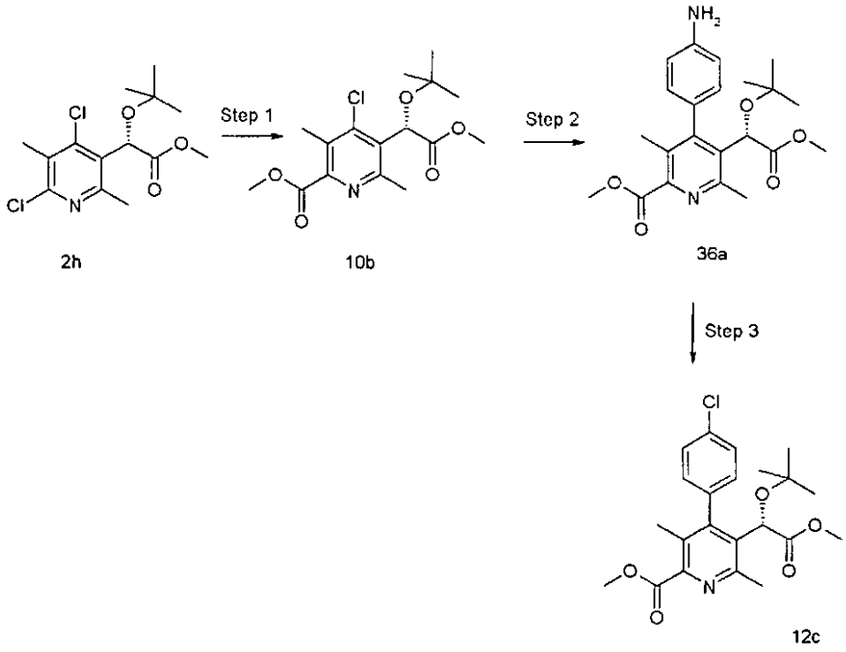
A mixture of acid **35e** (30 mg, 0.06 mmol) and NMP (1 mL) is treated with TBTU (40 mg, 0.12 mmol) and Et_3N (35 µL, 0.25 mmol). The mixture is allowed to stir at RT for 5 min then trans-4-methylcyclohexyl amine (25 µL, 0.19 mmol) is added. The reaction is allowed to stir at RT (2 h) and is then diluted with EtOAc. The organic phase is washed with saturated NH_4Cl, H_2O, and brine, dried over $MgSO_4$, filtered and concentrated to dryness to afford the amide **35f**.

Step 6:

A mixture of amide **35f**, THF (0.9 mL) and MeOH (0.3 mL) is treated with 1N NaOH (0.29 ml, 0.29 mmol) at 50°C (1 h). The solution is acidified with AcOH and purified by preparative HPLC. The pure fractions are combined, concentrated to remove MeCN and then extracted into DCM. The organic phase is dried over Na_2SO_4, filtered and concentrated. This solid is re-dissolved in DCM and treated with 10 drops of 1N NaOH and then neutralized with AcOH. The phases are separated and the aqueous layer is extracted with DCM. The combined organic phases are concentrated and lyophilized to give compound **1363**.

EXAMPLE 36

ALTERNATIVE SYNTHESIS OF INTERMEDIATE 12C



2h 10b 36a 12c

Step 1:

A steel bomb is charged with the compound **2h** (11 g, 34.3 mmol), $Pd(OAc)_2$ (0.17 mg, 0.68 mmol) , bis(diphenylphosphino)ferrocene (0.42 g, 0.76 mmol) and 2,6-lutidine (8.0 mL, 68.7 mmol). Degassed MeOH (50 mL) is added and the system is sealed. The system is purged with N_2 (2x) and CO (3x). The mixture is stirred at 110°C under 200 psi of CO for 48 h. The reaction mixture is filtered, concentrated and purified by Combiflash® Companion to give **10b**.

Step 2:

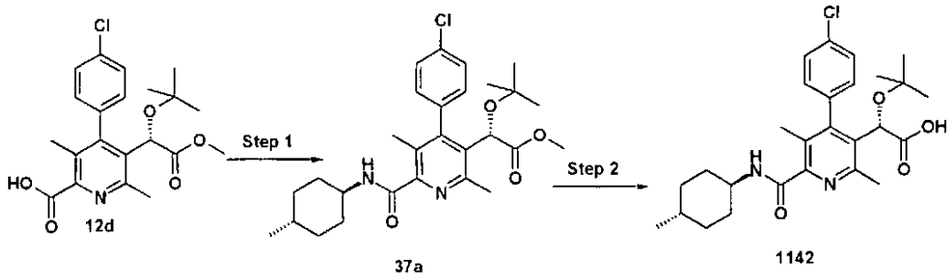
Intermediate **10b** is transformed to intermediate **36a** using the procedure described in step 1 of Example 12.

Step 3:

Intermediate **36a** is transformed to intermediate **12c** using the procedure described in step 2 of Example 5.

EXAMPLE 37

SYNTHESIS OF COMPOUND 1142 (TABLE 1)



Step 1:

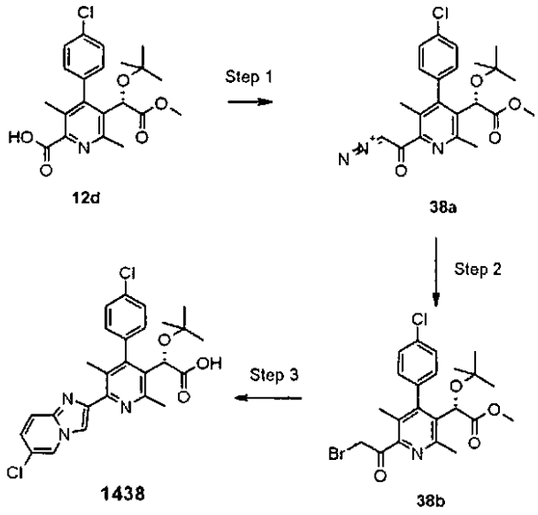
Intermediate **12d** is transformed to intermediate **37a** using the procedure described in step 5 of Example 35.

Step 2:

A mixture of amide **37a**, (30 mg, 0.06 mmol), THF (2.5 mL) and MeOH (0.75 mL) is treated with 5N NaOH (65 µL, 0.33 mmol) at 60°C (1 h). The solution is neutralized with AcOH (19 µL, 0.33 mmol) and evaporated to dryness. The residue is then purified by CombiFlash® Companion to give compound **1142**.

EXAMPLE 38

SYNTHESIS OF COMPOUND 1438 (TABLE 1)



Step 1:

To **12d** (1 g, 2.5 mmol) and Et_3N (481 µL, 3.5 mmol) in THF (13 mL) at 0°C is added isobutyl chloroformate (448 µL, 3.5 mmol) dropwise. The mixture is stirred at 0°C for 1 h. A diazomethane solution (0.67 M in diethyl ether, 37 mL, 25 mmol) is added slowly and the mixture is allowed to reach 23°C. After 1 h, the mixture is concentrated *in vacuo* and then EtOAc and water are added. The organic layer is washed with a saturated aqueous solution of $NaHCO_3$, water, brine, dried over Na_2SO_4, filtered and concentrated *in vacuo*. Crude product is is purified by CombiFlash® Companion to give **38a**.

Step 2:

To a solution of **38a** (828 mg, 2.5 mmol) in THF (16 mL) at 0°C is added dropwise an HBr solution (48% aq, 1.09 mL, 9.6 mmol). The mixture is stirred for 1 h at 0°C.The solution is diluted with EtOAc, washed with $NaHCO_3$ (sat), water, brine, dried over Na_2SO_4, filtered and concentrated *in vacuo* to provide **38b**.

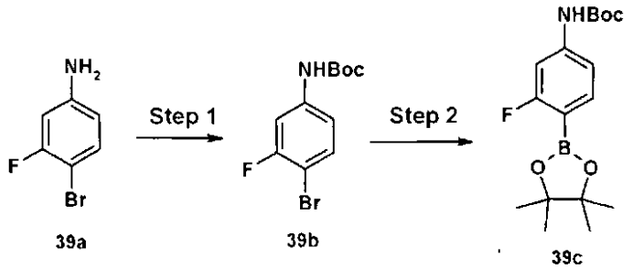
Step 3:

To **38b** (50 mg, 0.1 mmol) in a mixture of EtOH (750 µL) and acetone (150 µL) is added $NaHCO_3$ (8.1 mg, 0.11 mmol) and 2-amino-5-chloropyridine (14.7 mg, 0.11 mmol) in a sealed tube. The mixture is heated at 85°C for 30 min then concentrated *in vacuo*. The residue is diluted with THF (1 mL), MeOH (300 µL) and a NaOH solution (5 N, 103 µL, 0.52 mmol) and the resulting mixture is then stirred for 15 min

at 60°C. The mixture is cooled to 23°C and the pH is adjusted to ~5-6 with AcOH. The crude mixture is purified by prep HPLC (MeOH/water containing 10mM ammonium bicarbonate (pH10)). The desired fractions are collected and concentrated under reduced pressure. The residue is dissolved in MeCN (1.5 mL) and freeze-dried to give **1438**.

EXAMPLE 39

SYNTHESIS OF INTERMEDIATE 39C



39a 39b 39c

Step 1:

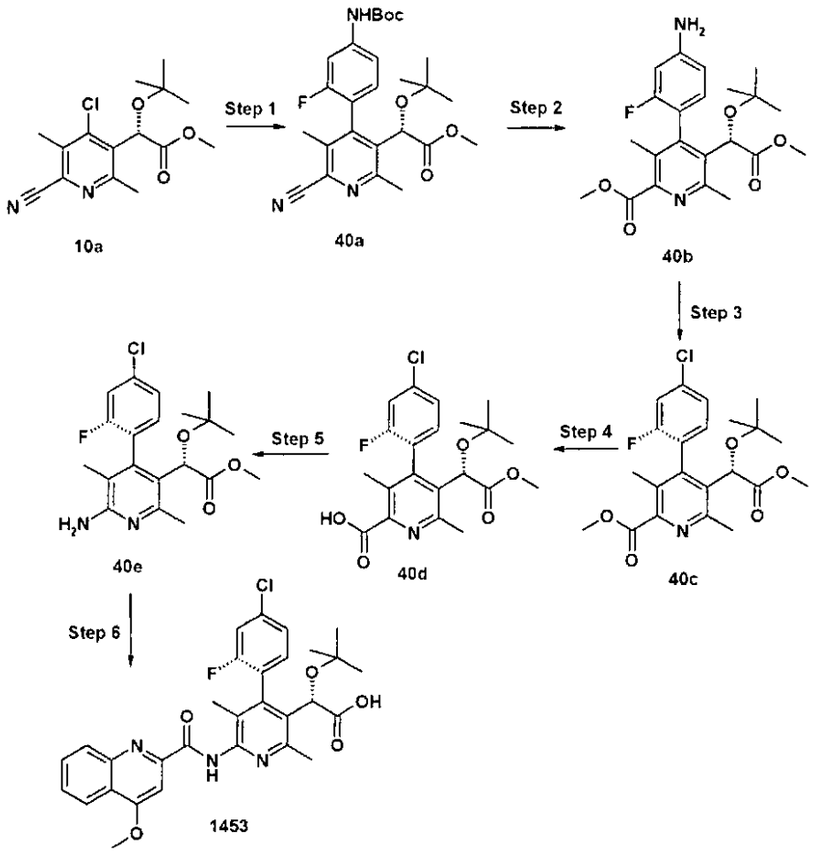
To a THF solution (90 mL) of **39a** (7.2 g, 38 mmol) is added solid $NaHCO_3$ (16 g, 190 mmol) and water (9 mL) at RT. This mixture is stirred for 10 min before the portionwise addition of solid di-t-butyl dicarbonate (16.5 g, 76 mmol). The mixture is stirred at 55°C for 16 h or until completion. The mixture is filtered and then partitioned between EtOAc and water. The aqueous phase is extracted with EtOAc and the combined organic phases are washed with brine, dried ($MgSO_4$) filtered and concentrated. The crude product is purified by CombiFlash® Companion to give **39b**.

Step 2:

To **39b** (11 g, 37.8 mmol) dissolved in dry 1,4-dioxane (120 mL) is added bis(pinacolato)diboron (13.7 g, 54 mmol) and potassium acetate (9.9 g, 101 mmol) before being deoxygenated by bubbling a stream of argon for 15 min. To this mixture is added 1,1'-bis(diphenylphosphino)ferrocene (2.75 g, 3.4 mmol). This mixture is degassed a further 5 min before being refluxed at 100°C for 16 h. The cooled mixture is diluted with EtOAc and water and then filtered through Celite. The phases are separated and the organic layer is washed with water, brine, dried ($MgSO_4$), filtered and concentrated. The resulting residue is purified by CombiFlash® Companion to give intermediate **39c**.

EXAMPLE 40

SYNTHESIS OF COMPOUND 1453 (TABLE 1)



Step 1:

Intermediate **10a** (4.0 g, 12.9 mmol) is treated with boronate **39c** (5.2 g, 15.5 mmol) using the procedure described in step 1 of Example 12 to afford **40a**.

Step 2:

Intermediate **40a** is transformed to diester **40b** using the procedure described in step 3 of Example 12.

Step 3:

Aniline **40b** (2.86 g, 6.84 mmol) is converted to intermediate **40c** using the procedure described in step 2 of Example 5. The atropisomers are separated at this stage by CombiFlash® Companion to give **40c**.

Step 4:

Diester **40c** is converted to mono-acid **40d** using the procedure described in step 4 of Example 12.

Step 5:

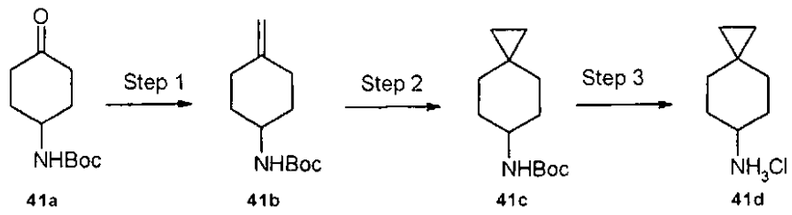
Intermediate **40d** is transformed to intermediate **40e** using the procedure described in step 5 of Example 12.

Step 6:

To a solution of 4-methoxy-2-quinoline carboxylic acid (302 mg, 1.5 mmol) and DMF (15 µL) in DCM (7 mL) is added oxalyl chloride as a 2M solution in DCM (968 µL, 1.94 mmol) dropwise at RT (with evolution of gas). After 20 min, the solution is concentrated to dryness and then dissolved in THF (2 mL). To this solution is added intermediate **40e** (294 mg, 0.74 mmol) and DIPEA (650 µL, 3.72 mmol) then heated at 50°C for 2h. The cooled reaction mixture is diluted with EtOAC and washed consecutively with a NH_4Cl solution (sat), a $NaHCO_3$ solution (sat) and brine. The organic phase is dried ($MgSO_4$), filtered and concentrated to dryness. The solution of the crude ester (431 mg, 0.74 mmol) in THF (4 mL) and MeOH (2 mL) is heated at 50°C before being treated with 5 N NaOH (743 µL, 3.72 mmol). The reaction is stopped after 1 h by quenching with AcOH (500 µL) and the mixture is concentrated to dryness. The residue is taken up into MeOH and purified by preparative HPLC to give, after lyophilization, compound **1453**.

EXAMPLE 41

SYNTHESIS OF INTERMEDIATE 41D



Step 1:

Compound **41a** is converted to **41b** using dimsyl sodium and methyl-triphenylphosphoium bromide as described in J. Am. Chem. Soc., **1980**, *102*, 1404-1408.

Step 2:

Intermediate **41b** (250 mg, 1.18 mmol) is dissolved in diethyl ether (5 mL) and cooled to 0°C before being treated with diazomethane in ether (40 mL, 2.8 mmol). To this cooled solution is added portionwise palladium (II) acetate (5 x 5 mg). This sequence is repeated until the reaction is complete by NMR analysis. The solution is

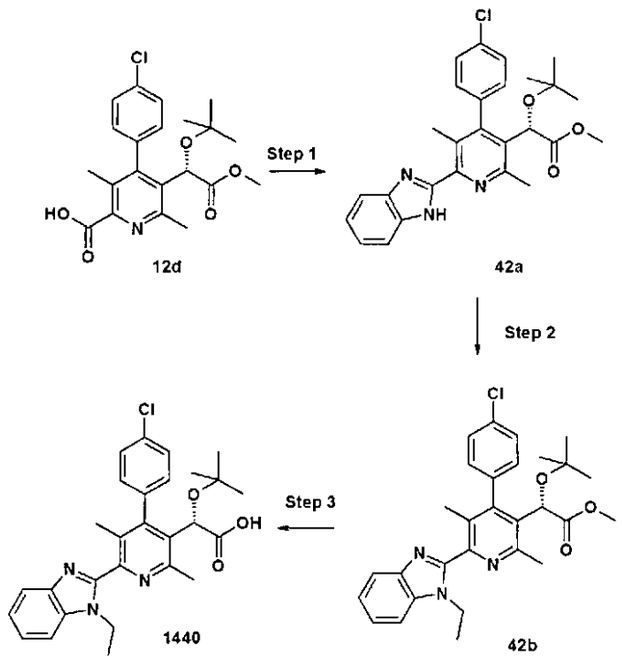
filtered and concentrated to give **41c**.

Step 3:

To **41c** (261 mg, 1.16 mmol) is added 4M HCl/dioxane (5 mL, 20 mmol) and the mixture is allowed to stir at RT for 2 h. The solution is concentrated and then treated with diethyl ether. This mixture is sonicated to afford a solid which is filtered and dried to give **41d** as the HCl salt.

EXAMPLE 42

SYNTHESIS OF COMPOUND 1440 (TABLE 1)



Step 1:

A solution of 2-aminoaniline (27 mg, 0.25 mmol), HATU (110 mg, 0.30 mmol) and **12d** (0.10 g, 0.25 mmol) in DMF (3 mL) at RT is treated with Et_3N (0.10 mL, 0.74 mmol). This mixture is stirred at RT for 1 h. EtOAc (10 mL) is added and the solution is washed with brine, dried ($MgSO_4$), filtered and the solvent evaporated. The crude amide is dissolved in AcOH (4 mL) and heated at 80^0C (1 h). The solution is concentrated, EtOAc (10 mL) is added and the solution is washed with saturated $NaHCO_3$ and brine. The layers are separated and the organic layer is evaporated to give the crude benzimidazole. The product is purified by CombiFlash® Companion to afford **42a**.

Step 2:

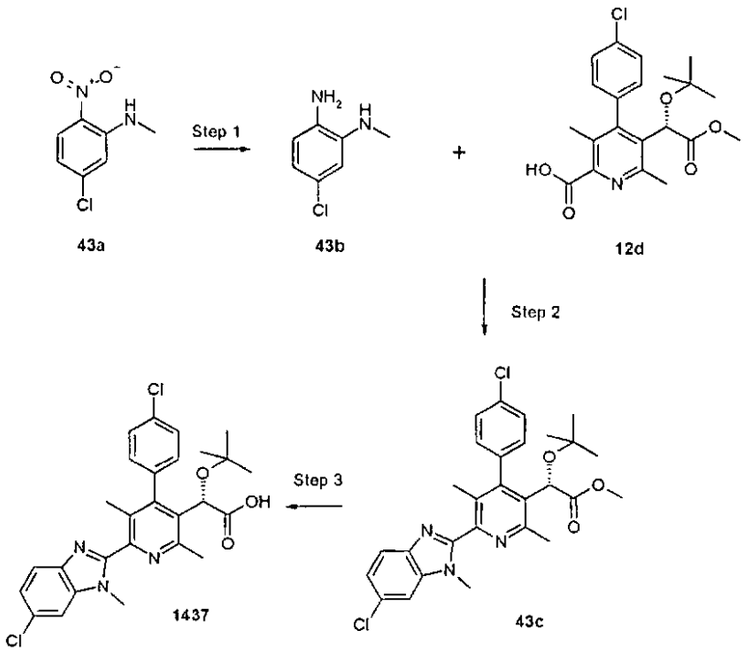
A solution of benzimidazole **42a** (120 mg, 0.25 mmol) in DMF (1.5 mL) is treated with NaH (60% dispersion in mineral oil, 11 mg, 0.27 mmol) and the mixture is stirred for 15 min. Iodoethane (30 µL, 0.37 mmol) is added and the reaction is stirred for 1 h. The reaction is diluted with water (15 mL) and extracted with EtOAc (15 mL). The organic layer is dried ($MgSO_4$) and evaporated to dryness to give compound **42b**.

Step 3:

A mixture of amide **42b** (125 mg, 0.25 mmol) in THF (3.5 mL) and MeOH (0.5 mL) is treated with 5N NaOH (250 µL, 1.5 mmol) at 50°C (3 h). The solution is acidified with AcOH and evaporated to dryness. The residue is then dissolved in MeOH (1 mL) and purified by preparative HPLC. The fractions containing pure compound are pooled, evaporated to dryness, redissolved in 1:1 MeCN / water (50 mL), frozen and lyophilized to give compound **1440**.

EXAMPLE 43

SYNTHESIS OF COMPOUND 1437 (TABLE 1)



Step 1:

To a solution of compound **43a** (1.9 g, 10 mmol) in THF is added tin powder and 1N

HCl (50 mL, 50 mmol). After 1 h of vigorous stirring, 1 N NaOH (50 mL) is added slowly to the reaction. The mixture is filtered on Celite and the filter cake is washed with EtOAc (200 mL). The filtrate is extracted with EtOAc and the combined organic layers are dried (Na_2SO_4) and concentrated to dryness to give compound **43b**.

Step 2:

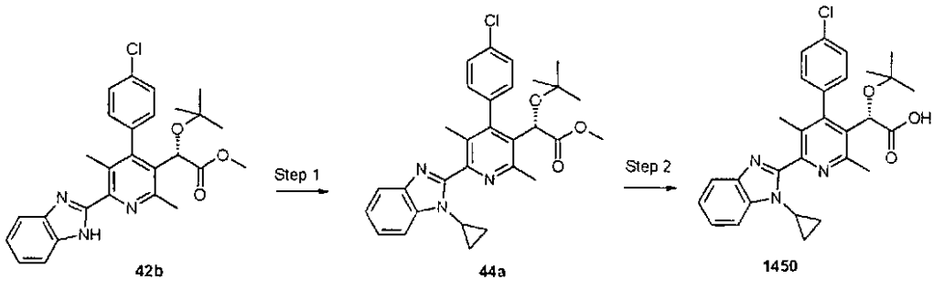
Intermediates **43b** and **12d** are coupled to give intermediate **43c** using the procedure described in step 1 of Example 42.

Step 3:

Intermediate **43c** is transformed to compound **1437** using the procedure described in step 3 of Example 42.

EXAMPLE 44

SYNTHESIS OF COMPOUND 1450 (TABLE 1)



42b 44a 1450

Step 1:

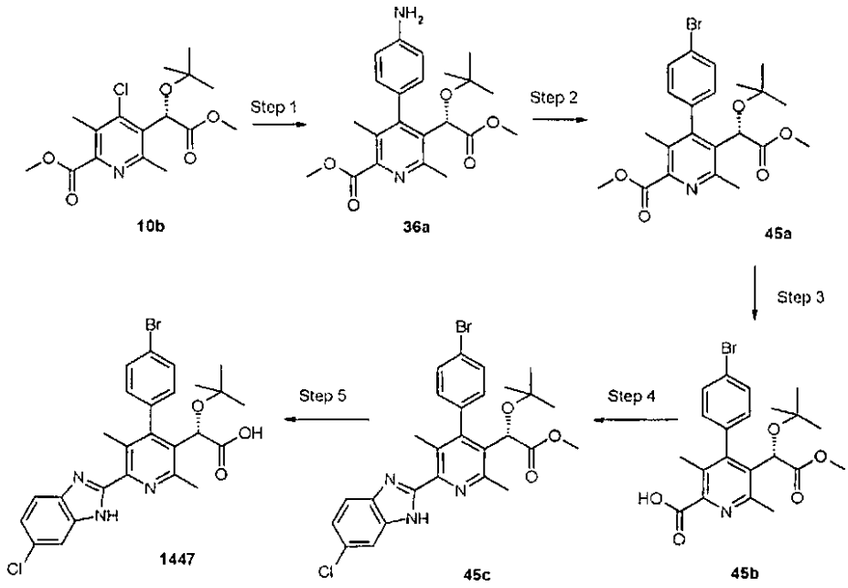
A mixture of benzimidazole **42b** (88 mg, 0.19 mmol), cyclopropyl boronic acid (32 mg, 0.37 mmol), copper acetate (34 mg, 0.19 mmol) 2,2-bipyridyl (29 mg, 0.19 mmol) and Na_2CO_3 (39 mg, 0.37 mmol) in DCE (3 ml) is heated to 70 °C for 18 h. The mixture is cooled to RT and washed with a mixture of water / saturated NH_4Cl (15 mL each). The water layer is extracted with DCM, and the organic layer is washed with brine, dried ($MgSO_4$), filtered and concentrated to give compound **44a**.

Step 2:

Intermediate **44a** is transformed to compound **1450** using the procedure described in step 3 of Example 42.

EXAMPLE 45

SYNTHESIS OF COMPOUND 1447 (TABLE 1)



Step 1:

Intermediate **10b** is transformed to intermediate **36a** using the procedure described in step 1 of Example 12

Step 2:

t-Butyl nitrite (90% w/w, 1.0 mL, 7.9 mmol) is added to a stirred suspension of $CuBr_2$ (1.6 g, 7.3 mmol) in anhydrous, deoxygenated MeCN (12 mL) cooled to 0°C under a nitrogen atmosphere. A solution of compound **36a** in dry, deoxygenated MeCN (15 mL + 5 mL rinse) is added dropwise and the reaction is allowed to warm to RT. After 4 h, additional t-butyl nitrite (0.3 mL, 2.4 mmol) is added and the stirring is continued. After 16 h, silica gel is added (30 g) and the solvent is evaporated. The product is purified by CombiFlash® Companion to afford intermediate **45a**.

Step 3:

Intermediate **45a** is transformed to intermediate **45b** using the procedure described in step 4 of Example 12.

Step 4:

Intermediate **45c** is transformed to intermediate **45c** using the procedure described in step 1 of Example 42.

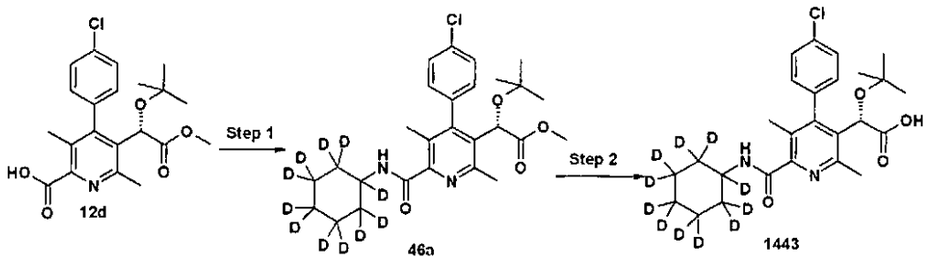
Step 5:

Intermediate **45c** is transformed to intermediate **1447** using the procedure described

in step 3 of Example 42.

EXAMPLE 46

SYNTHESIS OF COMPOUND 1443 (TABLE 1)



Step 1:

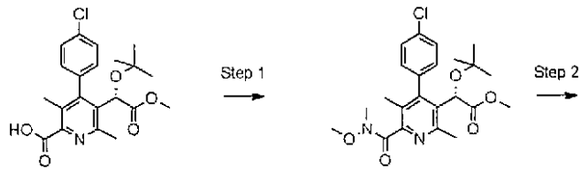
Intermediate **12d** and commercially available D-11 cyclohexylamine (CDN Isotopes) are coupled to give intermediate **46a** using the procedure described in step 5 of Example 35.

Step 2:

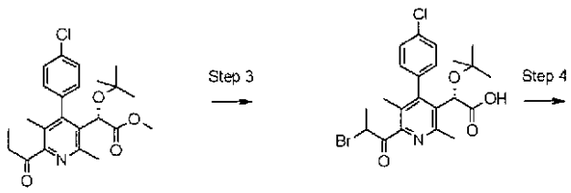
Intermediate **46a** is transformed to compound **1443** using the procedure described in step 2 of Example 37.

EXAMPLE 47

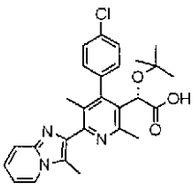
SYNTHESIS OF COMPOUND 1470 (TABLE 1)



12d 47a



47b 47c



1470

Step 1:

To **12d** (200 mg, 0.49 mmol) in *N*-methylpyrrolidinone (2.5 mL) is added Et_3N (137 µL, 0.99 mmol) followed by N,N,N',N'-tetramethyl-O-(benzotriazol-1-yl)uronium tetrafluoroborate (320 mg, 0.99 mmol). The mixture is stirred for 10 min, treated with *N,O*-dimethylhydroxylamine hydrochloride (96 mg, 0.99 mmol) and then stirred for 60 h at 23°C. A saturated, aqueous solution of ammonium chloride is added to the mixture. The solution is diluted with water and extracted with EtOAc (2x). The combined organic layers are washed with water (2x), brine, dried over $MgSO_4$, filtered and evaporated *in vacuo*. The crude product is purified by CombiFlash® Companion with an eluting gradient of 20 to 100% EtOAc / hexanes to afford **47a**.

Step 2:

To a solution of **47a** (163 mg, 0.36 mmol) in THF (3.6 mL) at -78°C is added dropwise an ethyl magnesium bromide solution (2.2 M in THF, 198 µL, 0.44 mmol). The mixture is stirred for 30 min at -40°C. A 1N HCl solution (~10-15 mL) is added to the reaction mixture and then the mixture is extracted with diethyl ether (2x). The combined organic layers are washed with brine, dried over Na_2SO_4, filtered and

concentrated *in vacuo*. The crude product is purified by CombiFlash® Companion with an eluting gradient of 5 to 20% EtOAc / hexanes affording pure **47b**.

Step 3:

To **47b** (100 mg, 0.24 mmol) in THF (1 mL) is added phenyl trimethylammonium tribromide (94.5 mg, 0.25 mmol). The reaction mixture is stirred at reflux for 20 h. The solution is taken up in EtOAc, washed with $NaHCO_3$ (sat), brine, dried over Na_2SO_4, filtered and concentrated *in vacuo* to give **47c**.

Step 4:

To **47c** (50 mg, 0.1 mmol) in a mixture of EtOH (729 µL) and acetone (145 µL) is added $NaHCO_3$ (8.8 mg, 0.11 mmol) and 2-aminopyridine (14.2 mg, 0.11 mmol) in a resealable tube. The mixture is heated at 85°C for 2 h then concentrated *in vacuo*. The residue is diluted with THF (1 mL), MeOH (300 µL), aqueous NaOH solution (5N, 140 µL, 0.70 mmol) and stirred for 60 h at 23°C. The pH of the mixture is adjusted to approximately 5-6 with AcOH. The crude mixture is purified by prep HPLC (MeOH: water containing 10mM ammonium formate (pH 3.8)). The desired fractions are collected and concentrated under reduced pressure. The residues are dissolved in AcCN (1.5 mL) and freeze-dried to afford **1470**.

EXAMPLE 48

C8166 HIV-1 LUCIFERASE ASSAY (EC_{50})

C8166 cells are derived from a human T-lymphotrophic virus type 1 immortalized but nonexpressing line of cord blood lymphocytes (obtained from J. Sullivan and originally produced in the laboratory of R. Gallo, Virology 1983; 129: 51-64) and are highly permissive to HIV-1 infection. The pGL3 Basic LTR/TAR plasmid is made by introducing the HIV-1 HxB2 LTR sequence from nucleotide -138 to +80 (Sca1-HindIII) upstream of the luciferase gene in the pGL3 Basic Vector (a promoterless luciferase expression vector from Promega catalogue # E1751) with the gene for blasticidine resistance cloned in. The reporter cells are made by electroporating C8166 cells with pGL3 Basic LTR/TAR and selecting positive clones with blasticidine. Clone C8166-LTRluc #A8-F5-G7 is selected by 3 consecutive rounds of limiting dilution under blasticidine selection. Cultures are maintained in complete media (consisting of: Roswell Park Memorial Institute medium (RPMI) 1640 + 10% FBS + 10^{-5} M β-mercaptoethanol + 10 µg/ml gentamycin) with 5 µg/ml blasticidine, however, blasticidine selection is removed from the cells before performing the viral

replication assay.

LUCIFERASE ASSAY PROTOCOL

Preparation of Compounds

Serial dilutions of HIV-1 inhibitor compounds are prepared in complete media from 10 mM DMSO stock solutions. Eleven serial dilutions of 2.5X are made at 8X desired final concentration in a 1 mL deep well titer plate (96 wells). The 12th well contains complete media with no inhibitor and serves as the positive control. All samples contain the same concentration of DMSO (≤ 0.1% DMSO). A 25 µL aliquot of inhibitor is added, to triplicate wells, of a 96 well tissue culture treated clear view black microtiter plate (Corning Costar catalogue # 3904). The total volume per well is 200 µL of media containing cells and inhibitor. The last row is reserved for uninfected C8166 LTRluc cells to serve as the background blank control and the first row is media alone.

Infection of Cells

C8166 LTRluc cells are counted and placed in a minimal volume of complete RPMI 1640 in a tissue culture flask (ex. 30 X 10^6 cells in 10 mL media/25 cm^2 flask). Cells are infected with HIV-1 or virus with variant integrase generated as described below at a molecules of infection (moi) of 0.005. Cells are incubated for 1.5 hours at 37°C on a rotating rack in a 5% CO_2 incubator and re-suspended in complete RPMI to give a final concentration of 25,000-cells/175 µL. 175 µL of cell mix is added to wells of a 96 well microtiter plate containing 25 µL 8X inhibitors. 25,000 uninfected C8166-LTRluc cells/well in 200 µL complete RPMI are added to the last row for background control. Cells are incubated at 37 °C in 5% CO_2 incubator for 3 days.

Luciferase Assay

50 µL Steady Glo (luciferase substrate $T_{1/2}$=5 hours Promega catalogue # E2520) is added to each well of the 96 well plate. The relative light units (RLU) of luciferase is determined using the LUMIstar Galaxy luminometer (BMG LabTechnologies). Plates are read from the bottom for 2 seconds per well with a gain of 240.

The level of inhibition (% inhibition) of each well containing inhibitor is calculated as follows:

$$\%\cdot inhibition = \left(1 - \left[\frac{RLU\cdot well - RLU\cdot blank}{RLU\cdot control - RLU\cdot blank}\right]\right) * 100$$

The calculated % inhibition values are used to determine EC_{50}, slope factor (n) and maximum inhibition (I_{max}) by the non-linear regression routine NLIN procedure of SAS using the following equation:

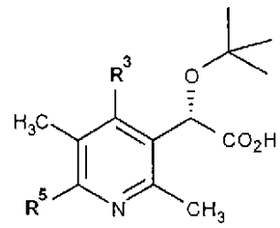
$$\% \cdot inhibition = \frac{I_{\max} \times [inhibitor]^n}{[inhibitor]^n + IC_{50}^n}$$

All compounds of Tables 1 to 6 have EC_{50} values of 500 nM or less against the NL4.3 strain of HIV-1 integrase (SEQ ID NO: 1) as measured by the assay of Example 48. The potency of representative compounds is provided in Table 7.

TABLES OF COMPOUNDS

The following tables list compounds of the invention. Compounds of the invention are particularly effective at inhibiting HIV integrase. Retention times (t_R) for each compound are measured using the standard analytical HPLC or, where indicated, UPLC conditions described in the Examples. As is well known to one skilled in the art, retention time values are sensitive to the specific measurement conditions. Therefore, even if identical conditions of solvent, flow rate, linear gradient, and the like are used, the retention time values may vary when measured, for example, on different HPLC or UPLC instruments. Even when measured on the same instrument, the values may vary when measured, for example, using different individual HPLC or UPLC columns, or, when measured on the same instrument and the same individual column, the values may vary, for example, between individual measurements taken on different occasions.

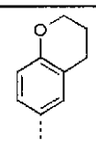
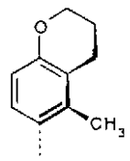
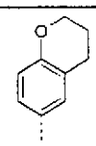
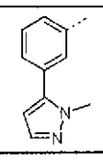
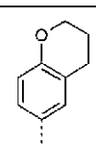
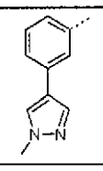
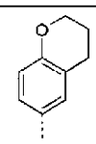
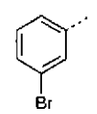
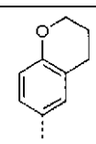
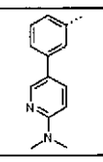
TABLE 1

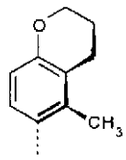
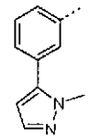
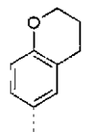
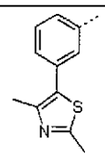
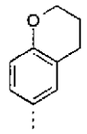
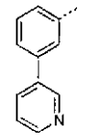
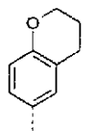
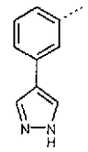
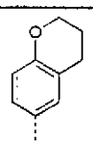
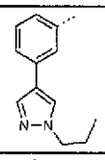
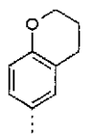
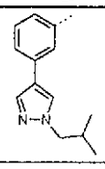
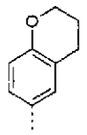
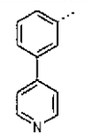
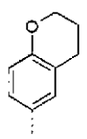
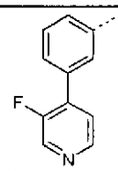
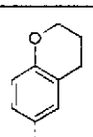
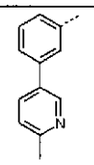


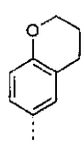
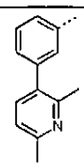
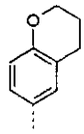
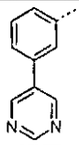
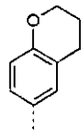
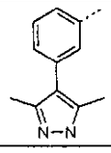
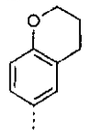
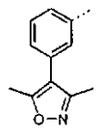
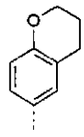
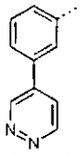
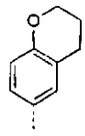
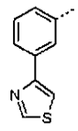
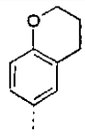
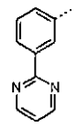
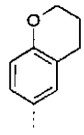
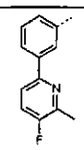
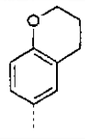
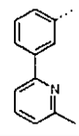
*presence of 2 inter-converting conformers by HPLC

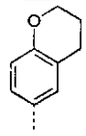
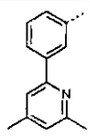
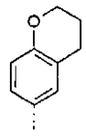
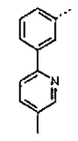
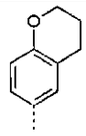
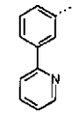
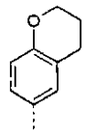
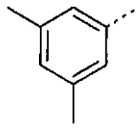
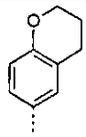
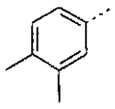
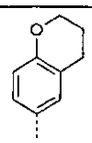
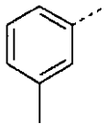
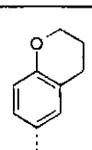
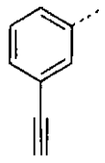
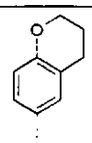
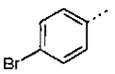
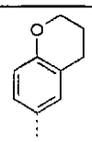
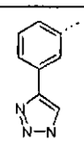
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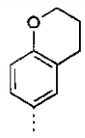
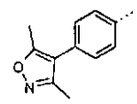
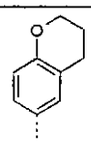
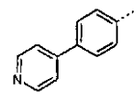
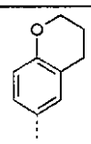
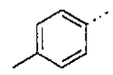
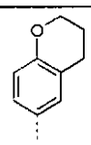
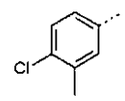
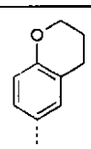
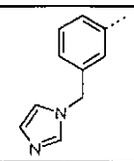
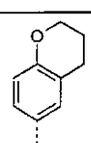
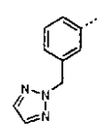
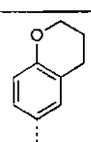
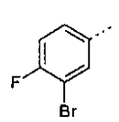
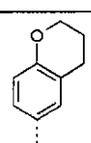
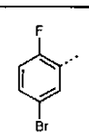
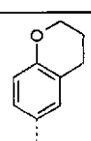
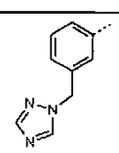
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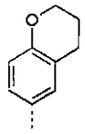
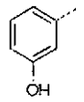
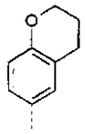
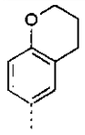
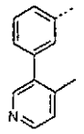
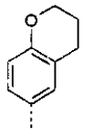
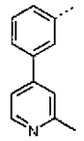
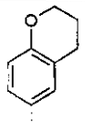
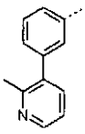
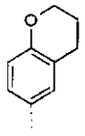
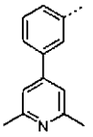
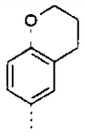
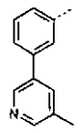
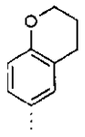
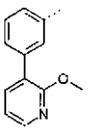
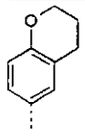
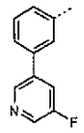
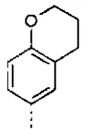
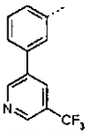
Cpd	R^3	R^5	t_R (min)	MS $(M+H)^+$
1001			5.0/5.1 *	446.2
1002			5.2**	460.3
1003			4.9/5.0 *	526.3
1004			4.9/5.0 *	526.3
1005			5.4/5.5 *	524.1 526.1
1006			4.3/4.4 *	566.3

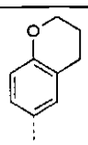
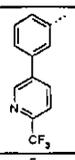
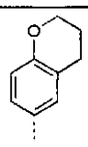
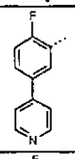
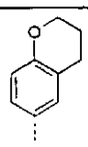
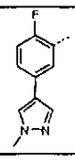
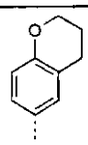
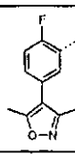
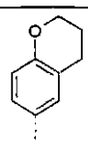
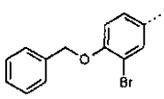
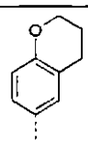
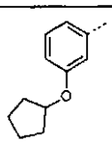
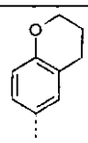
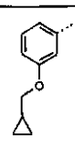
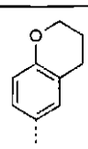
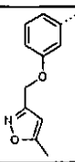
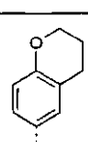
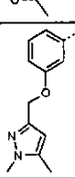
Cpd	R^3	R^5	t_R (min)	MS $(M+H)^+$
1007			3.6	540.2
1008			3.4	557.2
1009			3.0	523.2
1010			4.8	512.2
1011			5.5	554.3
1012			5.8	568.3
1013			4.2	523.2
1014			4.8	541.2
1015			4.1/4.2 *	537.3

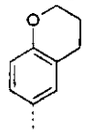
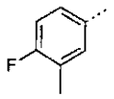
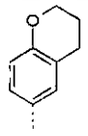
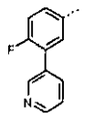
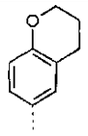
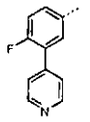
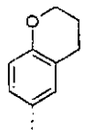
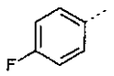
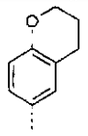
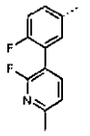
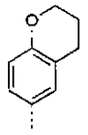
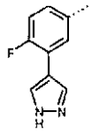
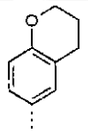
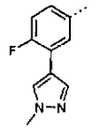
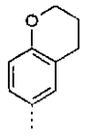
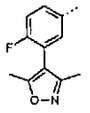
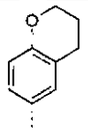
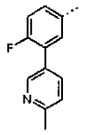
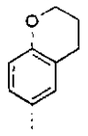
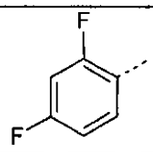
Cpd	R^3	R^5	t_R (min)	MS $(M+H)^+$
1016			4.2	551.2
1017			4.7/4.8 *	524.0
1018			4.5	540.2
1019			5.4	541.2
1020			4.5/4.6 *	524.2
1021			5.2/5.3 *	529.2
1022			5.0/5.1 *	524.2
1023			5.7/5.8 *	555.2
1024			4.2/4.3 *	537.2

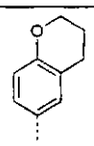
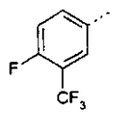
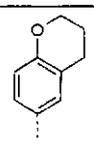
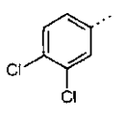
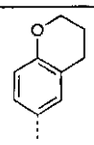
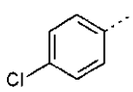
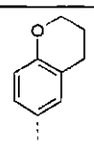
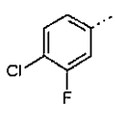
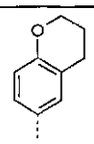
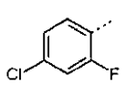
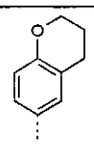
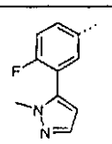
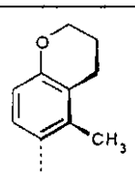
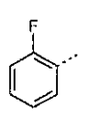
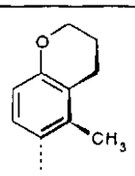
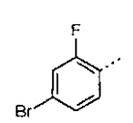
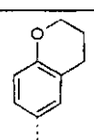
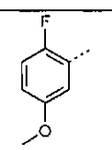
Cpd	R^3	R^5	t_R (min)	MS $(M+H)^+$
1025			4.2/4.3 *	551.3
1026			4.3/4.4 *	537.2
1027			4.3/4.4 *	523.2
1028			5.5/5.6 *	474.2
1029			5.5/5.6 *	474.2
1030			5.3/5.4 *	460.1
1031			5.3/5.4 *	470.3
1032			5.4/5.5 *	524.2/ 526.2
1033			4.7/4.8 *	513.3

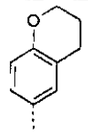
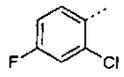
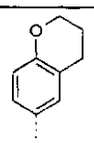
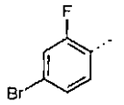
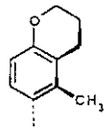
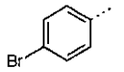
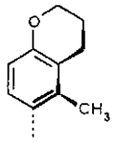
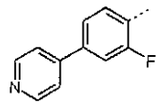
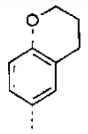
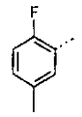
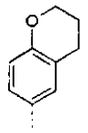
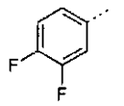
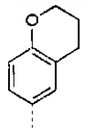
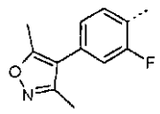
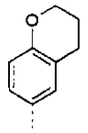
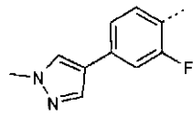
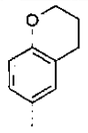
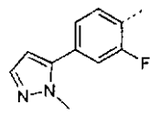
Cpd	R^3	R^5	t_R (min)	MS $(M+H)^+$
1034			5.3/5.4 *	541.4
1035			4.0/4.1 *	523.4
1036			5.4	460.4
1037			5.7	494.3 496.3
1038			4.0	526.3
1039			5.0	527.3
1040			5.5/5.6 *	542.1/ 544.1
1041			5.6/5.7 *	542.1/ 544.1
1042			4.5	527.4

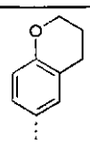
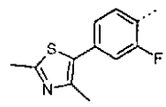
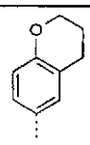
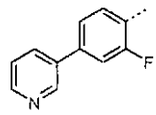
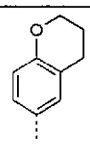
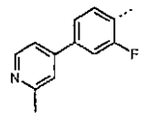
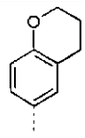
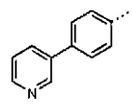
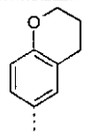
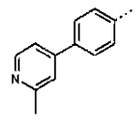
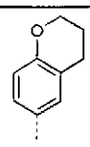
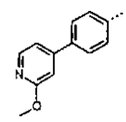
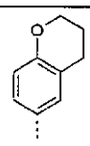
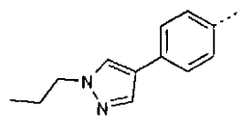
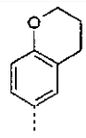
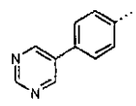
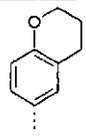
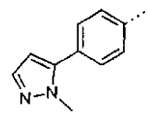
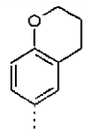
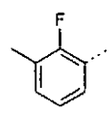
Cpd	R^3	R^5	t_R (min)	MS $(M+H)^+$
1043			3.4	462.3
1044			5.0	464.3
1045			4.1/4.2 *	537.3
1046			4.2	537.3
1047			4.1/4.2 *	537.3
1048			4.2/4.3 *	551.3
1049			4.2/4.3 *	537.3
1050			5.4/5.5 *	553.3
1051			5.1/5.2 *	541.3
1052			5.7	591.3

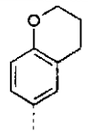
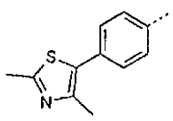
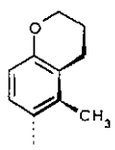
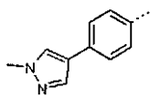
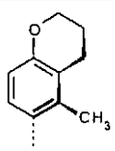
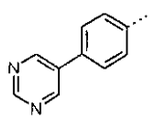
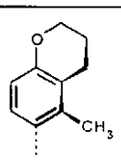
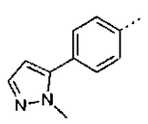
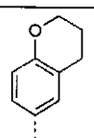
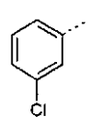
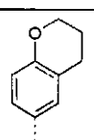
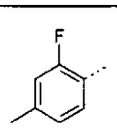
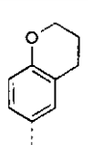
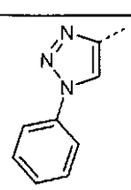
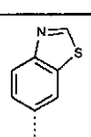
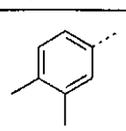
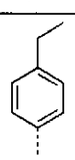
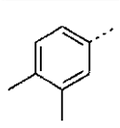
Cpd	R^3	R^5	t_R (min)	MS $(M+H)^+$
1053			5.8	591.3
1054			4.3	541.3
1055			5.1/5.2 *	544.3
1056			5.4/5.5 *	559.3
1057			6.2	630.2/ 632.2
1058			6.0	530.3
1059			5.6	516.3
1060			5.3	557.3
1061			5.0	570.3

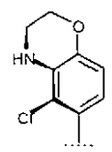
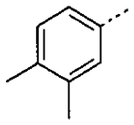
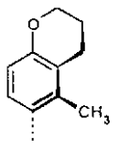
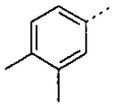
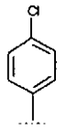
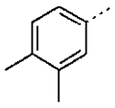
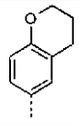
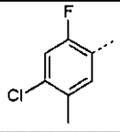
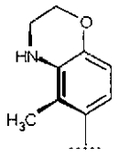
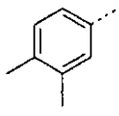
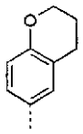
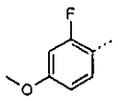
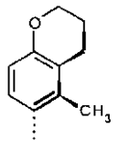
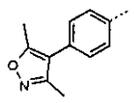
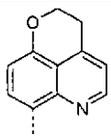
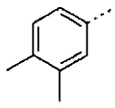
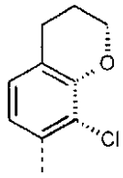
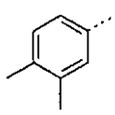
Cpd	R^3	R^5	t_R (min)	MS $(M+H)^+$
1062			5.3/5.4 *	478.3
1063			4.3	541.3
1064			4.1/4.2 *	541.3
1065			5.1/5.2 *	464.3
1066			5.5/5.6 *	573.3
1067			4.9/5.0 *	530.3
1068			5.1/5.2 *	544.3
1069			5.4/5.5 *	559.3
1070			4.3	555.3
1071			5.0	482.2

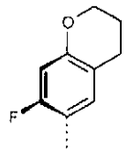
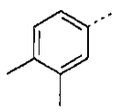
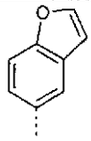
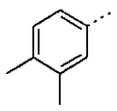
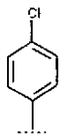
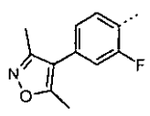
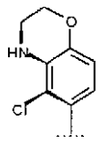
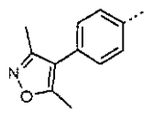
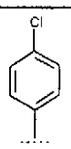
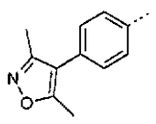
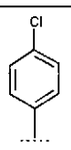
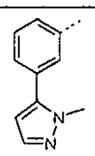
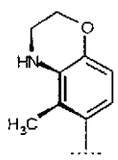
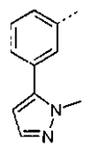
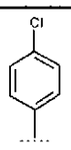
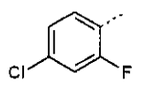
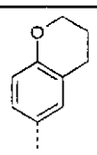
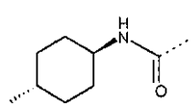
Cpd	R^3	R^5	t_R (min)	MS $(M+H)^+$
1072			5.6	532.2
1073			5.7/5.8 *	514.2/ 516.2 518.2
1074			5.3/5.4 *	480.2/ 482.2
1075			5.5/5.6 *	498.2 500.2
1076			5.4/5.5 *	498.2/ 500.2
1077			5.1	544.3
1078			5.3	478.2
1079			5.8	556.2/ 558.2
1080			6.0/6.1 *	494.2

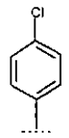
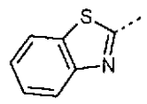
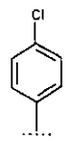
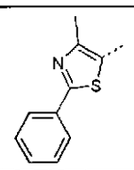
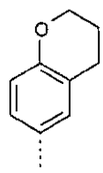
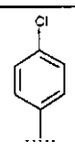
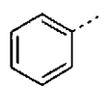
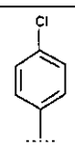
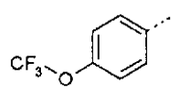
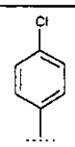
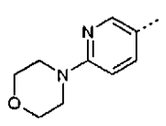
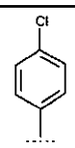
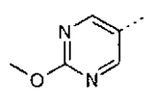
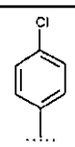
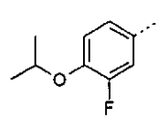
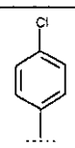
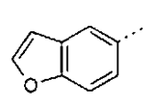
Cpd	R^3	R^5	t_R (min)	MS $(M+H)^+$
1081			6.2	498.2/ 500.2
1082			5.6/5.7 *	542.2/ 544.2
1083			5.6	538.2/ 540.2
1084			4.4	555.2
1085			6.1	478.3
1086			6.0	482.2
1087			5.4/5.5 *	559.3
1088			5.1/5.2 *	544.3
1089			5.1/5.2 *	544.3

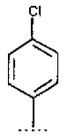
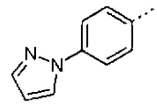
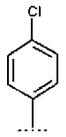
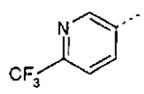
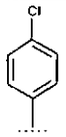
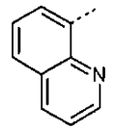
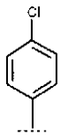
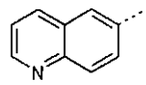
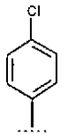
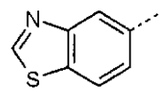
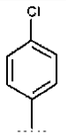
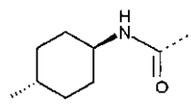
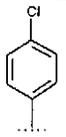
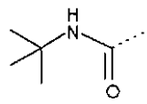
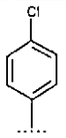
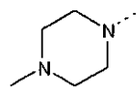
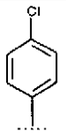
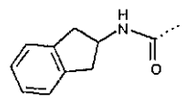
Cpd	R^3	R^5	t_R (min)	MS $(M+H)^+$
1090			5.1/5.2 *	575.3
1091			4.3	541.3
1092			4.3	555.3
1093			4.1	523.3
1094			4.2	537.3
1095			5.0/5.1 *	553.3
1096			5.4/5.5 *	554.3
1097			4.7/4.8 *	524.3
1098			5.6	526.3
1099			6.2	478.3

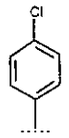
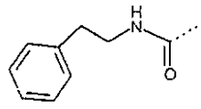
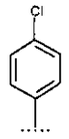
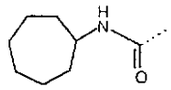
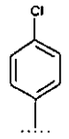
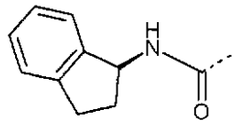
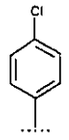
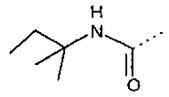
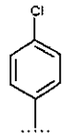
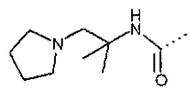
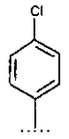
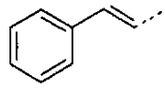
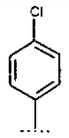
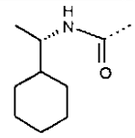
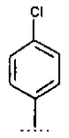
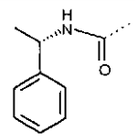
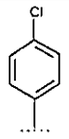
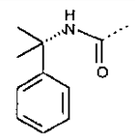
Cpd	R^3	R^5	t_R (min)	MS $(M+H)^+$
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1101			6.0	540.2
1102			5.6	538.3
1103			5.9	540.3
1104			5.1	480.3 482.3
1105			6.0	478.3
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1107			5.2	475.3
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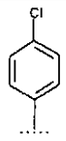
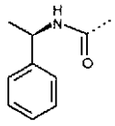
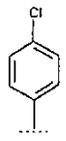
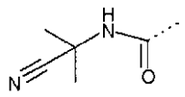
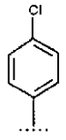
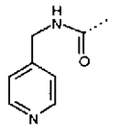
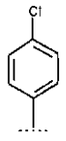
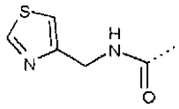
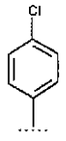
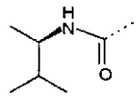
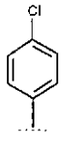
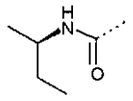
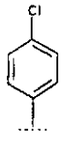
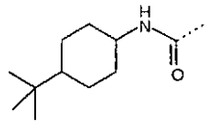
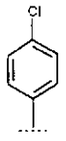
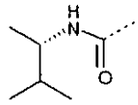
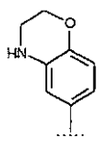
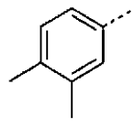
Cpd	R^3	R^5	t_R (min)	MS $(M+H)^+$
1109			5.3**	509.3/ 511.3
1110			6.0**	488.4
1111			5.8	452.3/ 454.3
1112			5.7/5.8 *	512.2/ 514.2
1113			6.0**	489.4
1114			6.0	494.4
1115			6.2	555.4
1116			4.7**	511.3
1117			6.5**	508.1 510.1

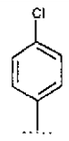
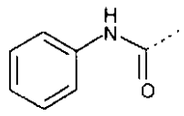
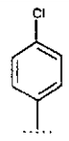
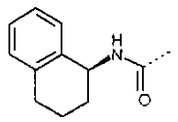
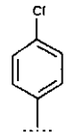
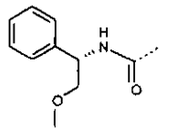
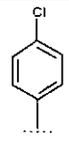
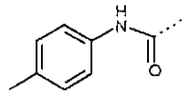
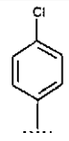
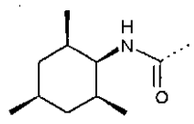
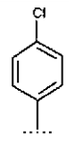
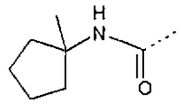
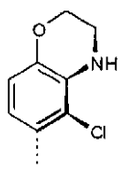
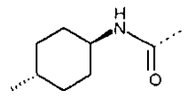
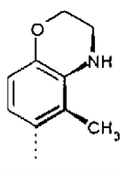
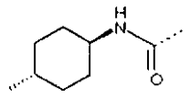
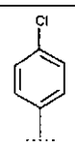
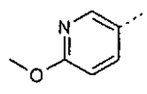
Cpd	R^3	R^5	t_R (min)	MS $(M+H)^+$
1118			6.5**	492.4
1119			3.7*	458.4
1120			6.2	537.2/ 539.2
1121			3.5**	576.1/ 578.1
1122			3.7	519.1/ 521.1
1124			5.1	504.2/ 506.2
1125			4.6**	541.3
1126			5.9	476.1/ 478.1/ 480.1
1127			6.2*	509.3

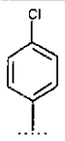
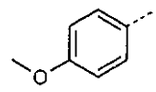
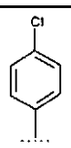
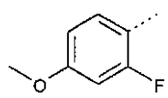
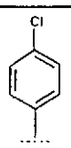
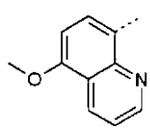
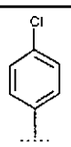
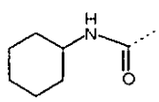
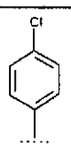
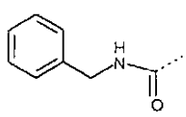
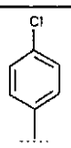
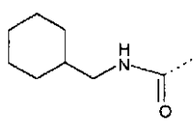
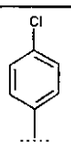
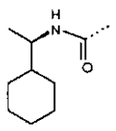
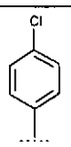
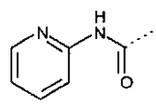
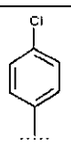
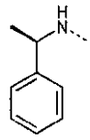
Cpd	R^3	R^5	t_R (min)	MS $(M+H)^+$
1128			7.3	481.1/ 483.1
1129			6.2	521.1/ 523.1
1130		$-CH_3$	4.1/4.2 *	384.2
1131			5.0	424.2/ 426.2
1132			5.8	508.1/ 510.1
1133			4.4	510.2/ 512.2
1134			4.8	456.2/ 458.2
1135			5.7	500.2/ 502.2
1136			5.3	464.1/ 466.1

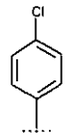
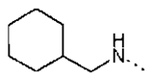
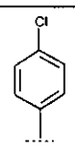
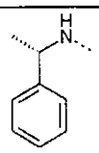
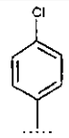
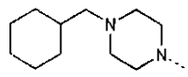
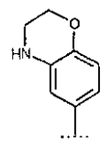
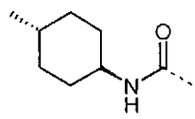
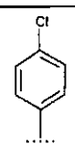
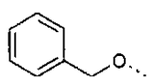
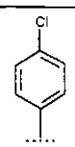
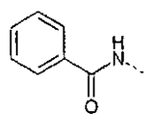
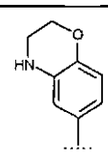
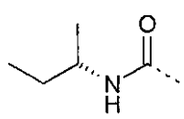
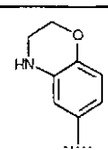
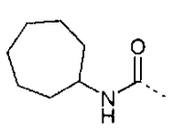
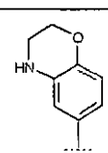
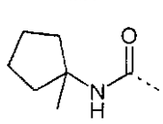
Cpd	R^3	R^5	t_R (min)	MS $(M+H)^+$
1137			5.2	490.2/ 492.2
1138			5.9	493.1/ 495.1
1139			4.9	475.1/ 477.2
1140			4.2	475.2/ 477.2
1141			4.9	481.1/ 483.1
1142			6.6	487.2/ 489.2
1143			6.6	447.2/ 449.2
1144			4.1	446.2/ 448.2
1145			6.5	507.1/ 509.1

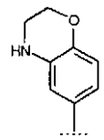
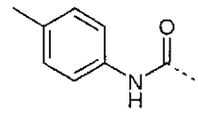
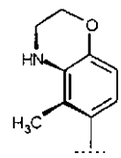
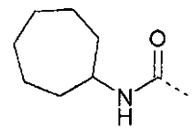
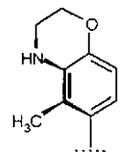
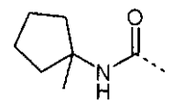
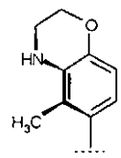
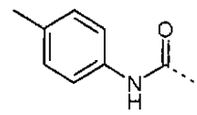
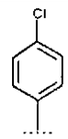
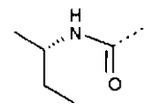
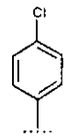
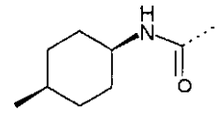
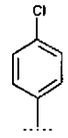
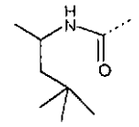
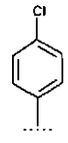
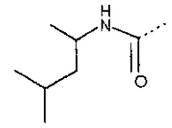
Cpd	R^3	R^5	t_R (min)	MS $(M+H)^+$
1146			6.4	495.1/ 497.1
1147			6.5	487.2/ 489.2
1148			6.6	507.1/ 509.1
1149			6.3	461.1/ 463.1
1150			4.8	516.2/ 518.2
1151			5.5	450.1/ 452.1
1152			6.7	501.2/ 503.2
1153			6.5	495.1/ 497.1
1154			6.6	509.2/ 511.2

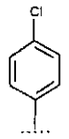
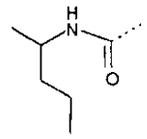
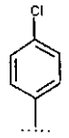
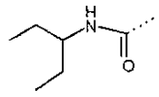
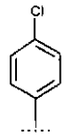
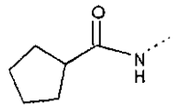
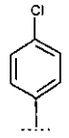
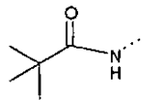
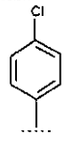
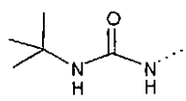
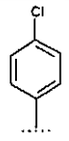
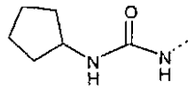
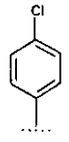
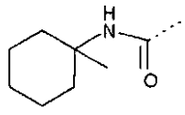
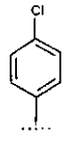
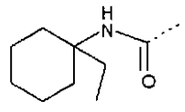
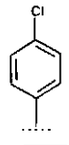
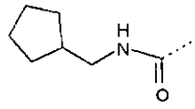
Cpd	R^3	R^5	t_R (min)	MS $(M+H)^+$
1155			5.6	495.1/ 497.1
1156			6.1	458.1/ 460.1
1157			4.4	482.2/ 484.2
1158			5.4	488.2/ 490.2
1159			6.3	461.2/ 463.1
1160			6.0	447.1/ 449.1
1161			7.0	529.2/ 531.2
1162			6.2	461.2/ 463.2
1163			4.9/5.5*	475.5

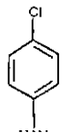
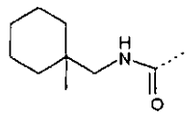
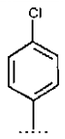
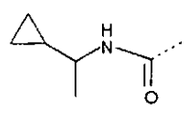
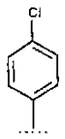
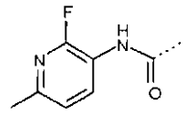
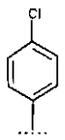
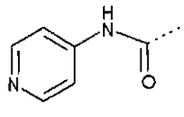
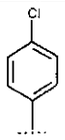
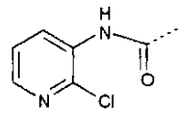
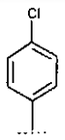
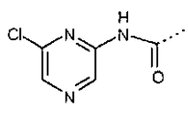
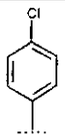
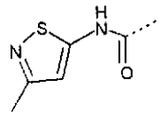
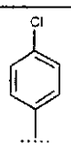
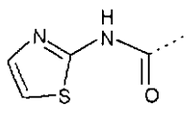
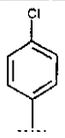
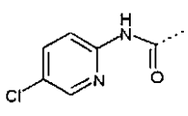
Cpd	R^3	R^5	t_R (min)	MS $(M+H)^+$
1164			6.7	467.1/ 469.1
1165			6.7	521.1/ 523.2
1166			6.4	525.1/ 527.1
1167			6.9	481.0/ 483.0
1168			7.1	515.1/ 517.1
1169			6.3	473.1/ 475.1
1170			6.3*	544.3/ 546.3
1171			5.7*	524.2
1172			4.9	455.1/ 457.1

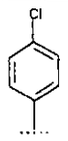
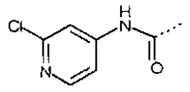
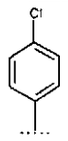
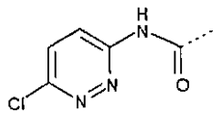
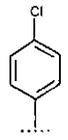
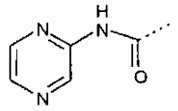
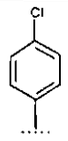
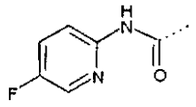
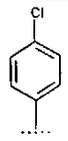
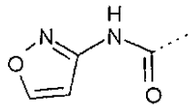
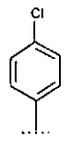
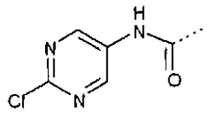
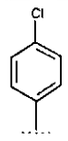
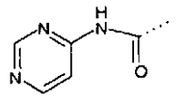
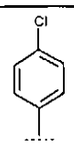
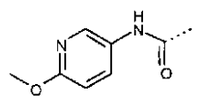
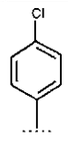
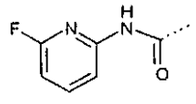
Cpd	R^3	R^5	t_R (min)	MS $(M+H)^+$
1173			5.2	454.1/ 456.1
1174			5.3	472.1/ 474.1
1175			5.2	505.1/ 507.1
1176			6.3	473.1/ 475.1
1177			6.4	481.1/ 483.1
1178			6.6	487.1/ 489.1
1179			6.8	501.1/ 503.1
1180			6.6	468.1/ 470.1
1181			5.6	467.3/ 469.3

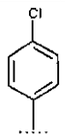
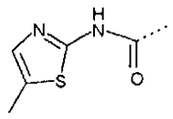
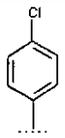
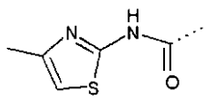
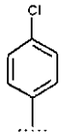
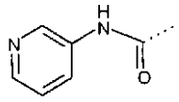
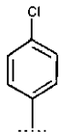
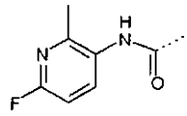
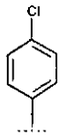
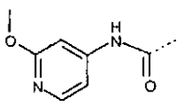
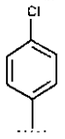
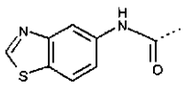
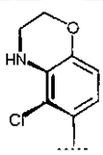
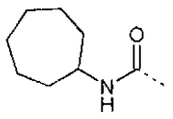
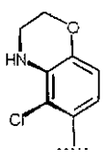
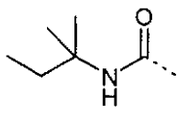
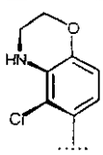
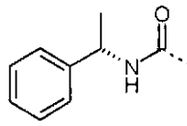
Cpd	R^3	R^5	t_R (min)	MS $(M+H)^+$
1182			5.3	459.2/ 461.1
1183			5.2	467.1/ 469.1
1184			5.1	528.3/ 530.2
1185			5.2/5.6*	510.3
1186			7.2	454.1/ 456.1
1187			5.3	467.1/ 469.1
1188			4.3/4.7*	470.3
1189			5.1/5.5*	510.3
1190			4.7/5.1*	496.3

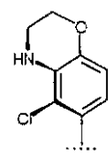
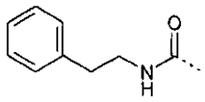
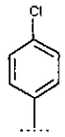
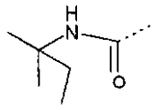
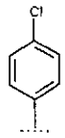
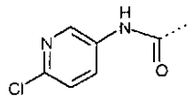
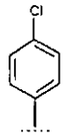
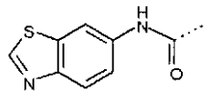
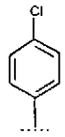
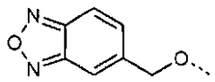
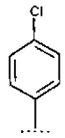
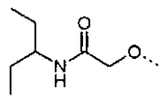
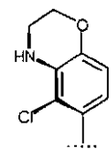
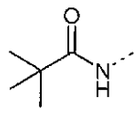
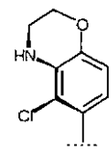
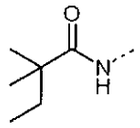
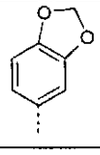
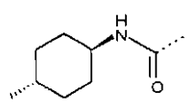
Cpd	R^3	R^5	t_R (min)	MS $(M+H)^+$
1191			5.6/6.2*	504.3
1192			5.6**	524.2
1193			5.2**	510.2
1194			6.2**	518.2
1195			5.3	447.1/ 449.1
1196			6.6	487.1/ 489.1
1197			9.0	489.2/ 491.2
1198			8.3	475.2/ 477.2

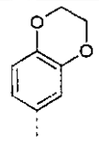
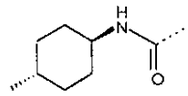
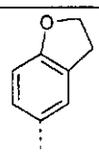
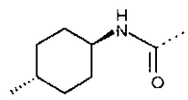
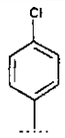
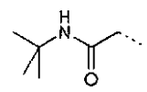
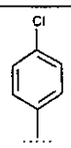
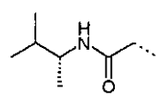
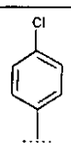
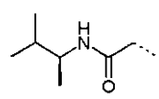
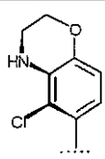
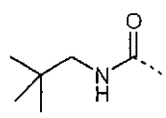
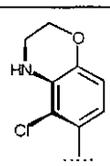
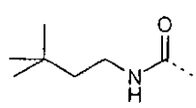
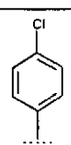
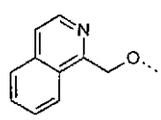
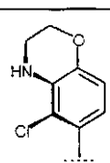
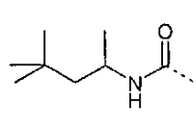
Cpd	R^3	R^5	t_R (min)	MS $(M+H)^+$
1199			7.7	461.1/ 463.1
1200			7.6	461.1/ 463.1
1201			5.1	459.1/ 461.1
1202			5.1	447.1/ 449.1
1203			5.2	462.1/ 464.1
1205			5.3	474.1/ 476.1
1206			8.5	487.1/ 489.1
1207			9.4	501.1/ 503.1
1208			8.1	473.1/ 475.1

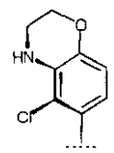
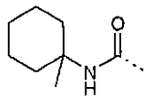
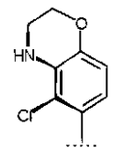
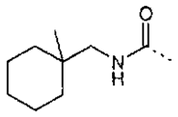
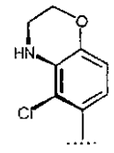
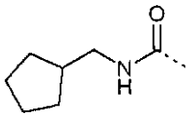
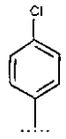
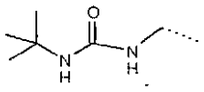
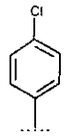
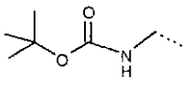
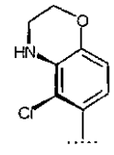
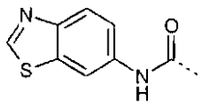
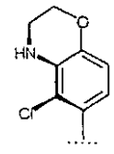
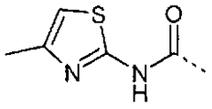
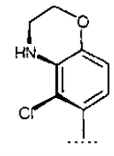
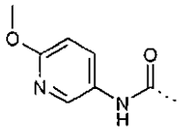
Cpd	R^3	R^5	t_R (min)	MS $(M+H)^+$
1209			9.2	501.2/ 503.1
1210			7.1	459.1/ 461.1
1211			4.6	500.1/ 502.1
1212			3.5	468.1/ 470.1
1213			4.6	502.0/ 504.0/ 506.0
1214			4.7	503.0/ 505.0/ 507.0
1215			4.3	488.0/ 490.0
1216			4.4	474.0/ 476.0
1217			4.7	502.0/ 504.0/ 506.0

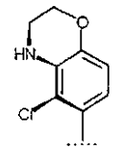
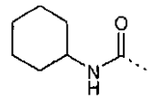
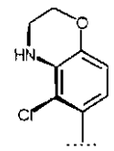
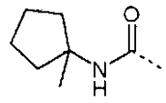
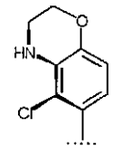
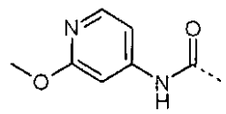
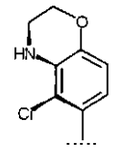
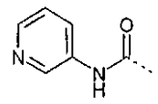
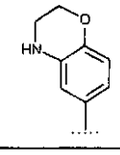
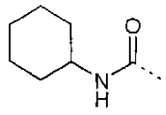
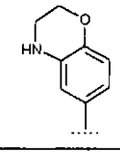
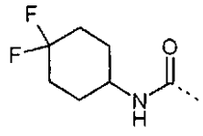
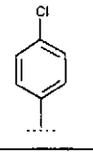
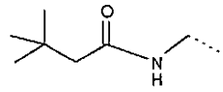
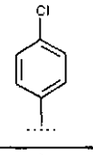
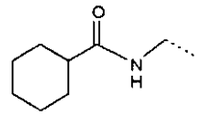
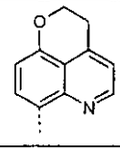
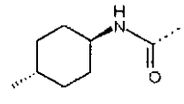
Cpd	R^3	R^5	t_R (min)	MS $(M+H)^+$
1218			4.5	502.0/ 504.0/ 506.0
1219			4.5	503.0/ 505.0/ 507.0
1220			4.4	469.1/ 471.1
1221			4.6	486.1/ 488.1
1222			4.4	458.1/ 460.1
1223			4.5	503.0/ 505.0/ 507.0
1224			4.2	469.1/ 471.1
1225			4.3	498.1/ 500.1
1226			4.6	486.0/ 488.0

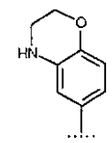
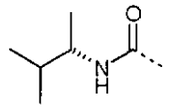
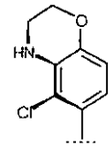
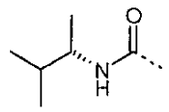
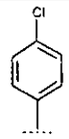
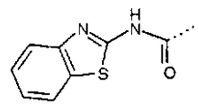
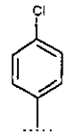
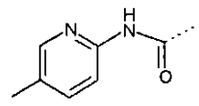
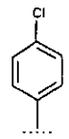
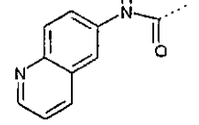
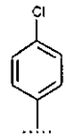
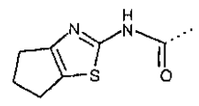
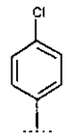
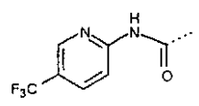
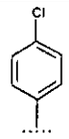
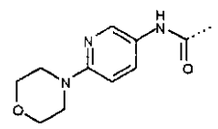
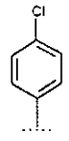
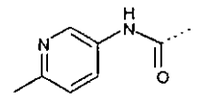
Cpd	R^3	R^5	t_R (min)	MS $(M+H)^+$
1227			4.4	488.0/ 490.0
1228			4.4	488.0/ 490.0
1229			3.4	468.1/ 470.1
1230			4.5	500.1/ 502.1
1231			3.9	498.1/ 500.1
1232			4.4	524.0/ 526.0
1233			6.2**	544.1/ 546.1
1234			5.8**	518.1/ 520.1
1235			6.1**	552.1/ 554.1

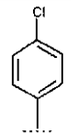
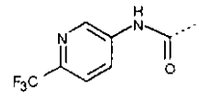
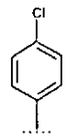
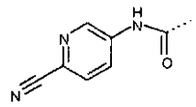
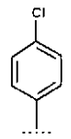
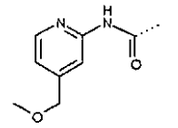
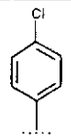
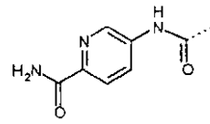
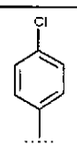
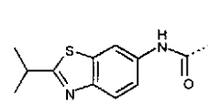
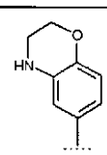
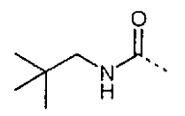
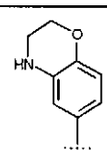
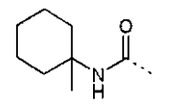
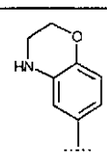
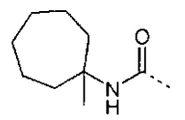
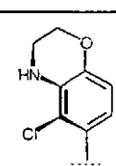
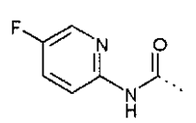
Cpd	R^3	R^5	t_R (min)	MS $(M+H)^+$
1236			6.0**	552.1/ 554.1
1237			5.4	461.1/ 463.1
1238			4.5	502.0/ 504.0/ 506.0
1239			4.4	524.0/ 526.0
1240			7.2	496.0/ 498.0
1241			6.7	491.1/ 493.1
1242			4.7**	504.1/ 506.1
1243			4.9**	518.1/ 520.1
1244			4.2*	497.2

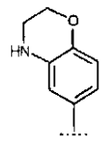
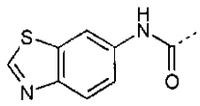
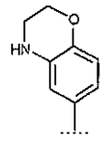
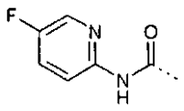
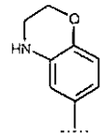
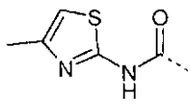
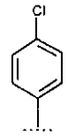
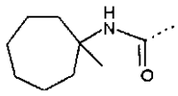
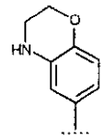
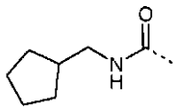
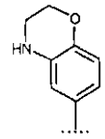
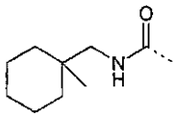
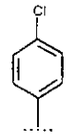
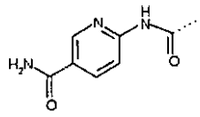
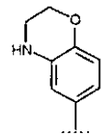
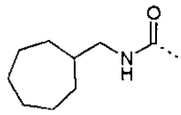
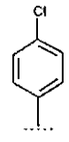
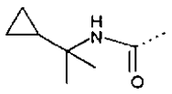
Cpd	R^3	R^5	t_R (min)	MS $(M+H)^+$
1245			4.2*	511.2
1246			4.2*	495.1
1247			4.9	461.1/ 463.1
1248			5.1	475.1/ 477.1
1249			5.1	475.1/ 447.1
1250			7.0**	518.2/ 520.2
1251			7.6**	532.1/ 534.1
1252			5.3	505.1/ 507.1
1253			8.2**	546.1/ 548.1

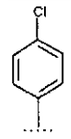
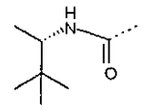
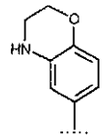
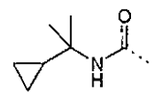
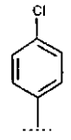
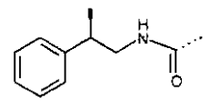
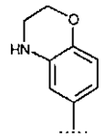
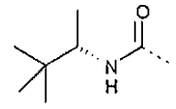
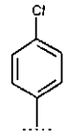
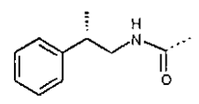
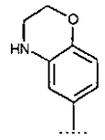
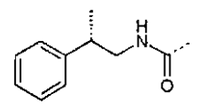
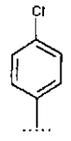
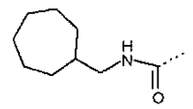
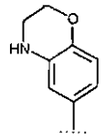
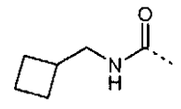
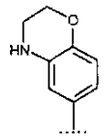
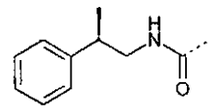
Cpd	R^3	R^5	t_R (min)	MS $(M+H)^+$
1254			7.6**	544.1/ 546.1
1255			8.5**	558.1/ 560.1
1256			7.1**	530.1/ 532.1
1257			4.7	476.1/ 478.1
1258			4.9	477.2/ 479.2
1259			6.3**	581.1/ 583.0
1260			6.3**	545.1/ 547.1
1261			6.0**	555.1/ 557.1

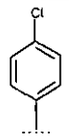
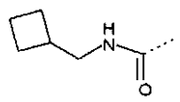
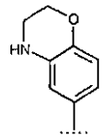
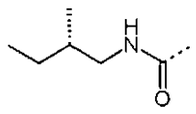
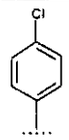
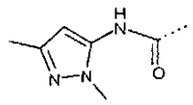
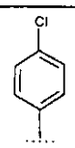
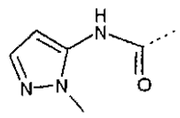
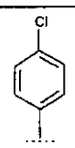
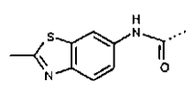
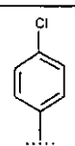
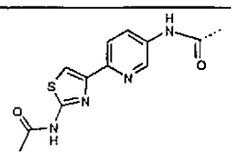
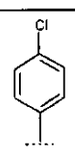
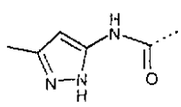
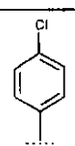
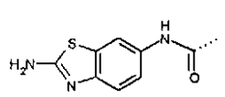
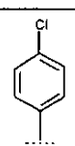
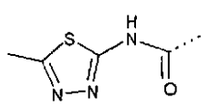
Cpd	R^3	R^5	t_R (min)	MS $(M+H)^+$
1262			5.8**	530.2/ 532.2
1263			5.7**	530.2/ 532.2
1264			5.1**	555.1/ 557.1
1265			4.4**	525.1/ 527.2
1266			4.7/5.2*	496.3
1267			5.3/5.8*	532.3
1268			4.8	475.2/ 477.2
1269			4.9	487.2/ 489.2
1270			5.3**	546.2

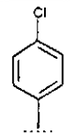
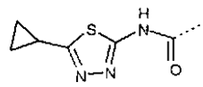
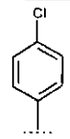
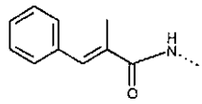
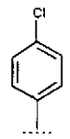
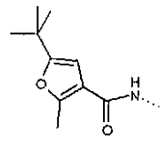
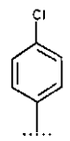
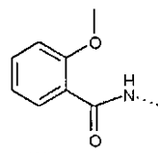
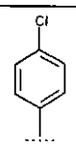
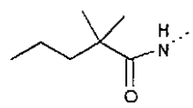
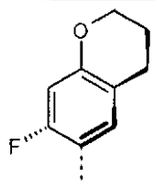
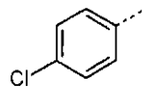
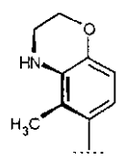
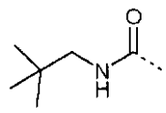
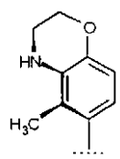
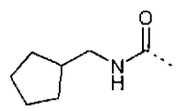
Cpd	R^3	R^5	t_R (min)	MS $(M+H)^+$
1271			4.6/5.1*	484.3
1272			5.7**	518.2/ 520.2
1273			7.1	524.1/ 526.1
1274			5.8	482.2/ 484.2
1275			5.1	518.2/ 520.2
1276			6.9	514.1/ 516.1
1277			7.2	536.1/ 538.1
1278			4.9	553.2/ 555.2
1279			4.8	482.2/ 484.2

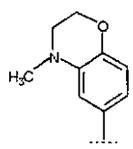
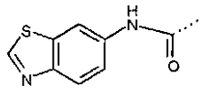
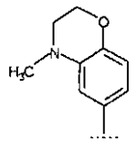
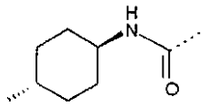
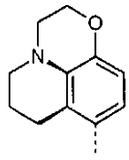
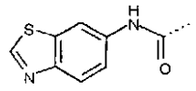
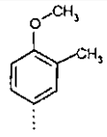
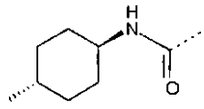
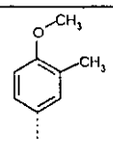
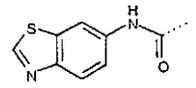
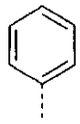
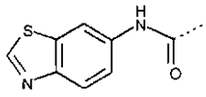
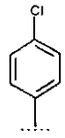
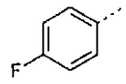
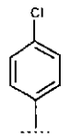
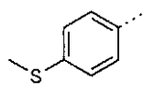
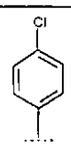
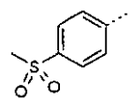
Cpd	R^3	R^5	t_R (min)	MS $(M+H)^+$
1280			6.9	536.1/ 538.1
1281			6.7	493.1/ 495.1
1282			5.8	512.2/ 514.2
1283			5.9	511.2/ 513.2
1284			7.1	566.2/ 568.2
1285			5.8/6.4*	484.3
1286			6.2/6.8*	510.3
1287			6.5/7.3*	524.3
1288			4.4**	543.2/ 545.2

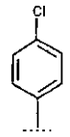
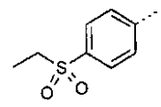
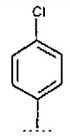
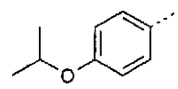
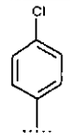
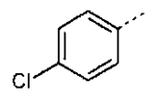
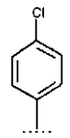
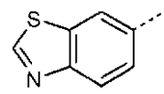
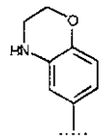
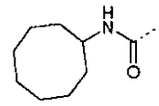
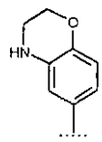
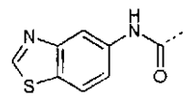
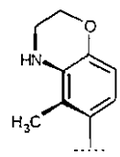
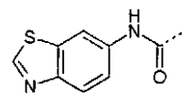
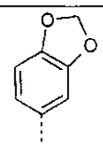
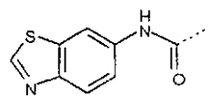
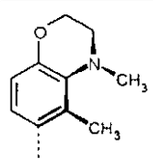
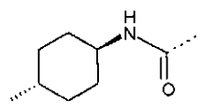
Cpd	R^3	R^5	t_R (min)	MS $(M+H)^+$
1289			3.8/4.1*	547.2
1290			4.0/4.3*	509.2
1291			3.8/4.1*	511.2
1292			9.3	501.1/ 503.1
1293			5.9/6.5*	496.2
1294			6.8/7.7*	524.2
1295			5.9	511.2/ 513.2
1296			5.6/6.0*	524.2
1297			6.2	473.1/ 475.1

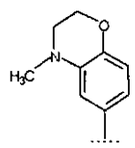
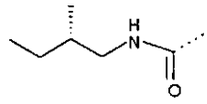
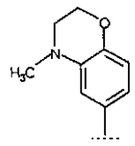
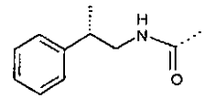
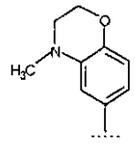
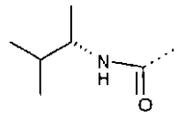
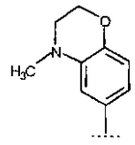
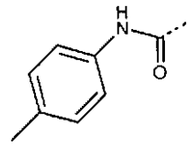
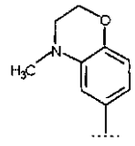
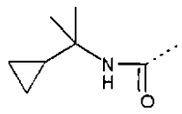
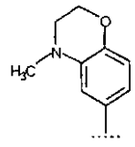
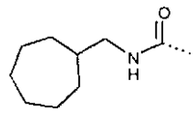
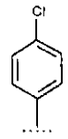
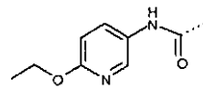
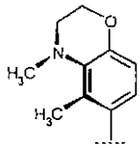
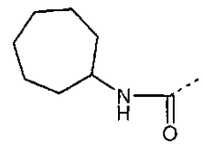
Cpd	R^3	R^5	t_R (min)	MS $(M+H)^+$
1298			6.5	475.3/ 477.2
1299			4.7/5.1*	496.3
1300			6.5	509.0/ 511.0
1301			4.9/5.4*	498.1
1302			6.5	509.0 511.0
1303			5.1/5.6*	532.3
1304			6.8	501.1/ 503.1
1305			4.5/5.0*	482.3
1306			5.1/5.5*	532.3

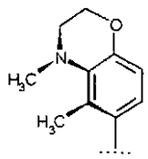
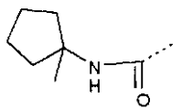
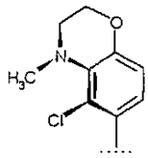
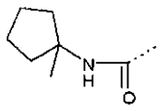
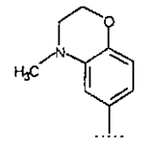
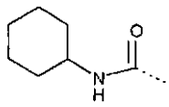
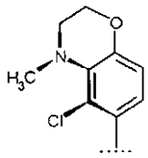
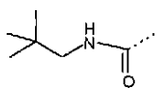
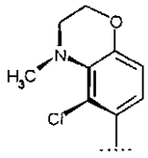
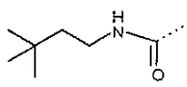
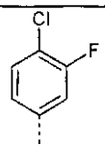
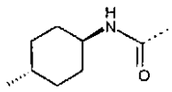
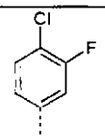
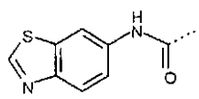
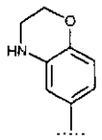
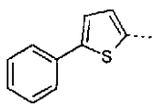
Cpd	R^3	R^5	t_R (min)	MS $(M+H)^+$
1307			6.2	459.1/ 461.0
1308			4.8/5.2*	484.3
1309			6.0	485.2/ 487.2
1310			6.0	471.2/ 473.2
1311			6.7	538.1/ 540.2
1312			5.4	608.2/ 610.2
1313			5.6	471.1/ 473.1
1314			5.0	539.1/ 541.1
1315			6.4	489.0/ 491.0

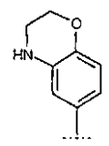
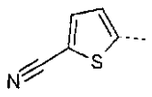
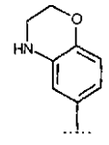
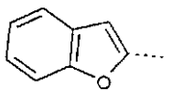
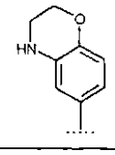
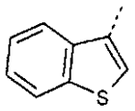
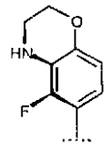
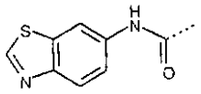
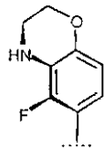
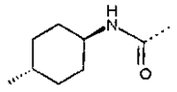
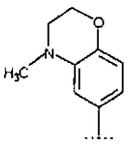
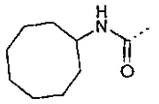
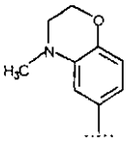
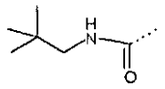
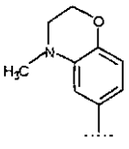
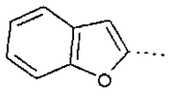
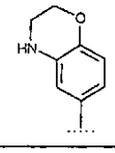
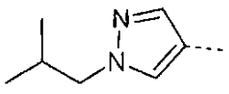
Cpd	R^3	R^5	t_R (min)	MS $(M+H)^+$
1316			6.7	515.0/ 517.0
1317			6.2	507.0/ 509.0
1318			6.2	527.1/ 529.1
1319			5.3	497.0/ 499.0
1320			6.1	475.1/ 477.1
1321			5.6**	498.1 500.1
1322			6.1**	498.3
1323			6.2**	510.3

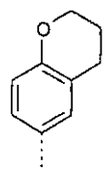
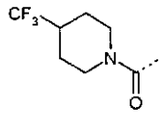
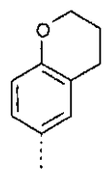
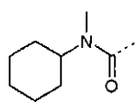
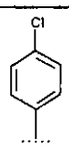
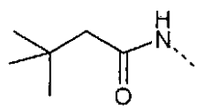
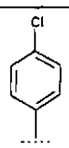
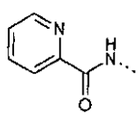
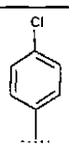
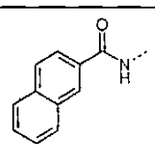
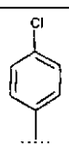
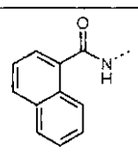
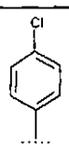
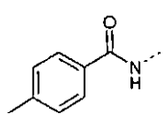
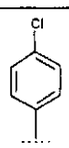
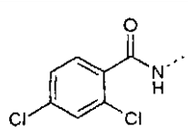
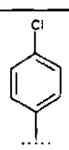
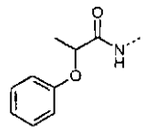
Cpd	R^3	R^5	t_R (min)	MS $(M+H)^+$
1324			4.2/4.3*	561.2
1325			4.1/4.2*	524.3
1326			7.9**	587.3
1327			7.5/7.8*	497.2
1328			7.8/8.2*	534.1
1329			7.5	490.1
1330			5.2	442.1/ 444.1
1331			5.5	470.2/ 472.1
1332			4.9	502.2/ 504.1

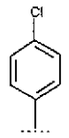
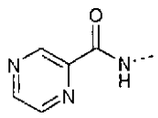
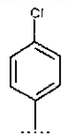
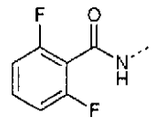
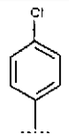
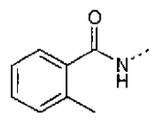
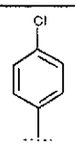
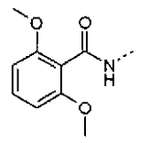
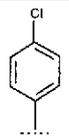
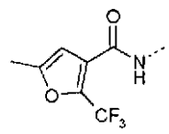
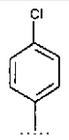
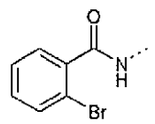
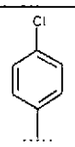
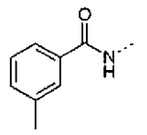
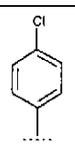
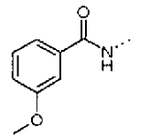
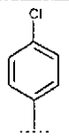
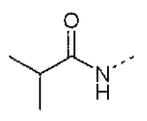
Cpd	R^3	R^5	t_R (min)	MS $(M+H)^+$
1333			5.1	516.2/ 518.1
1335			5.7	482.2/ 484.2
1336			5.5	458.1/ 460.1/ 462.1
1337			4.9	481.1/ 483.1
1338			6.1/6.7*	524.3
1339			3.7/4.0*	547.2
1340			4.1**	561.2
1341			4.2	534.2
1342			5.7**	538.2

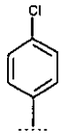
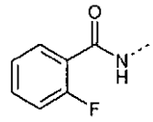
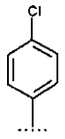
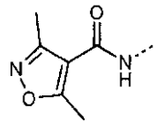
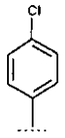
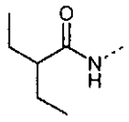
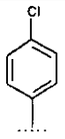
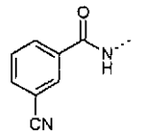
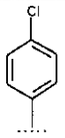
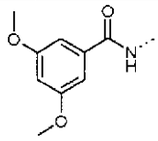
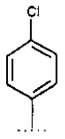
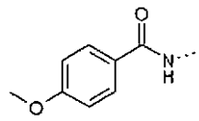
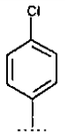
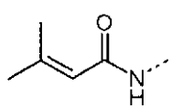
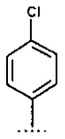
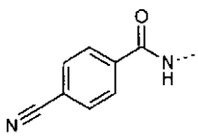
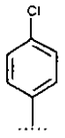
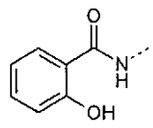
Cpd	R^3	R^5	t_R (min)	MS $(M+H)^+$
1343			5.5/5.7*	498.1
1344			5.8/6.0*	546.1
1345			5.3/5.5*	498.1
1346			6.4/6.5*	518.1
1347			5.4/5.5*	510.1
1348			6.2/6.4*	538.2
1349			6.6	512.2/ 514.2
1350			5.6**	538.3

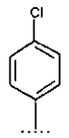
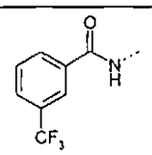
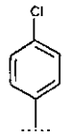
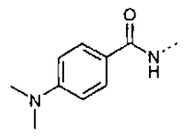
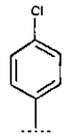
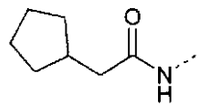
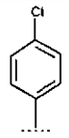
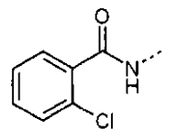
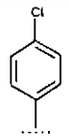
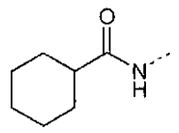
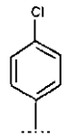
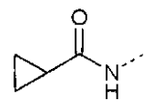
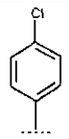
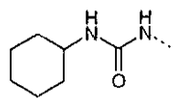
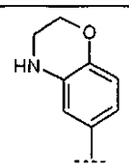
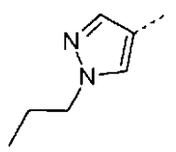
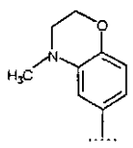
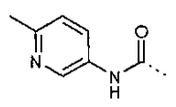
Cpd	R^3	R^5	t_R (min)	MS $(M+H)^+$
1351			5.2**	524.3
1352			5.8**	544.3/ 546.3
1353			5.4/5.6*	510.3
1354			7.1**	532.2/ 534.2
1355			7.8**	546.2/ 548.2
1356			8.9	505.1/ 507.1
1357			8.6	542.0/ 544.0
1358			5.4/5.9*	529.2

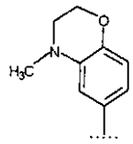
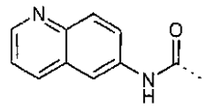
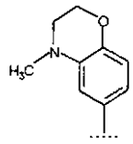
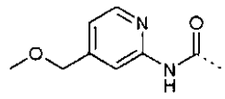
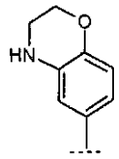
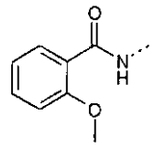
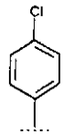
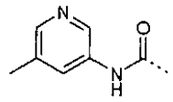
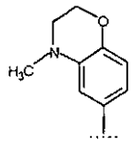
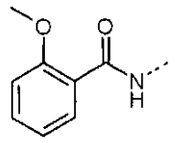
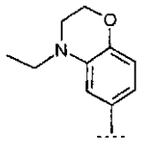
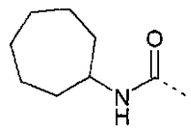
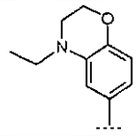
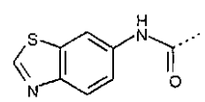
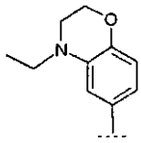
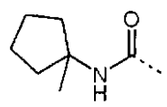
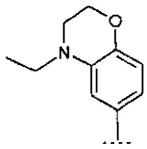
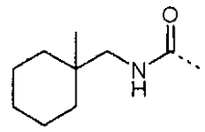
Cpd	R^3	R^5	t_R (min)	MS $(M+H)^+$
1359			5.2/5.8*	478.2
1360			4.7/5.2*	487.2
1361			4.7/5.1*	503.2
1362			7.1**	565.2
1363			7.3**	528.3
1364			7.1/7.4*	538.3
1365			6.3/6.6*	498.3
1366			5.3/5.5*	501.2
1367			4.3/4.7*	493.3

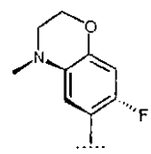
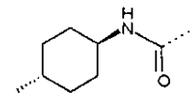
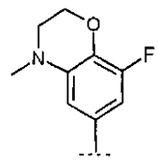
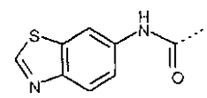
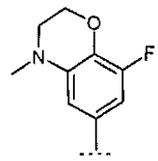
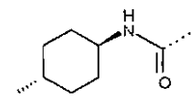
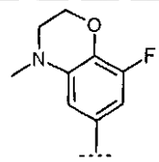
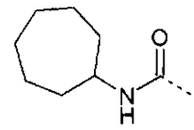
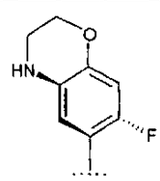
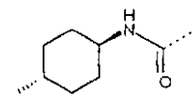
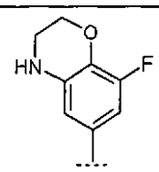
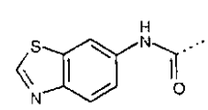
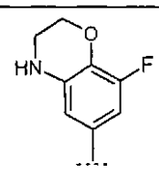
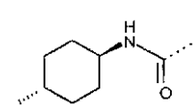
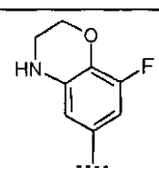
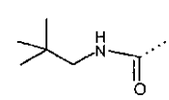
Cpd	R^3	R^5	t_R (min)	MS $(M+H)^+$
1368			5.6	549.3
1369			4.6	509.3
1370			1.9[$]	461.2/ 463.2
1371			1.9[$]	468.1/ 470.1
1372			2.1[$]	517.2/ 519.2
1373			2.1[$]	517.2/ 519.2
1374			2.0[$]	481.2/ 483.1
1375			2.2[$]	537.0/ 539.0
1376			2.1[$]	511.2/ 513.1

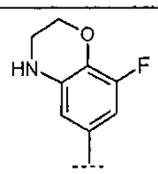
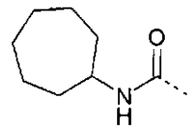
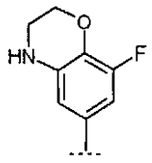
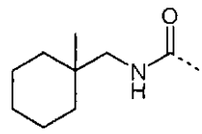
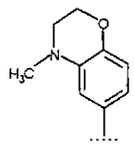
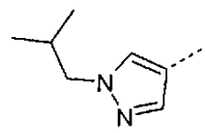
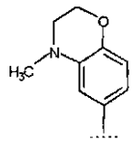
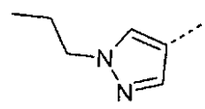
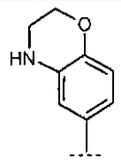
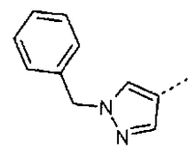
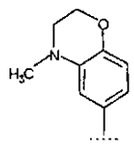
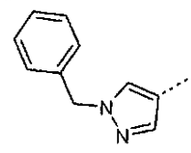
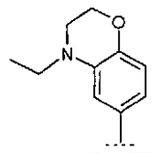
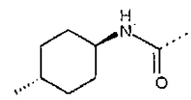
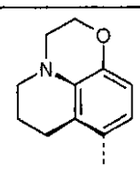
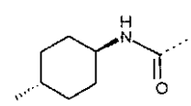
Cpd	R^3	R^5	t_R (min)	MS $(M+H)^+$
1377			1.8$	469.1/ 471.1
1378			2.0$	503.1/ 505.1
1379			2.0$	481.1/ 483.1
1380			1.9$	527.1/ 529.1
1381			2.1$	539.1/ 541.1
1382			2.0$	546.0/ 548.0
1383			2.0$	481.2/ 483.1
1384			2.0$	497.1/ 499.1
1385			1.7$	433.2/ 435.1

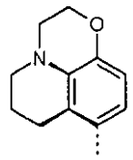
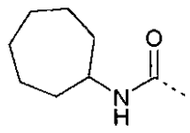
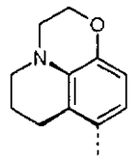
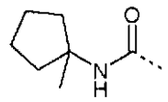
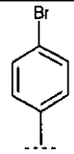
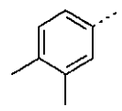
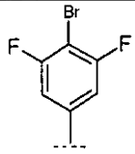
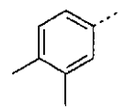
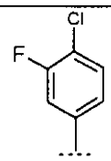
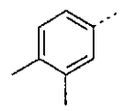
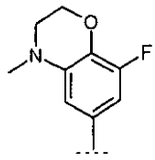
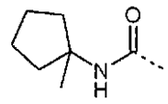
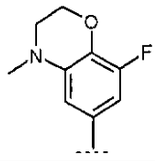
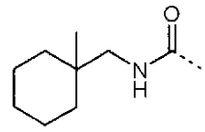
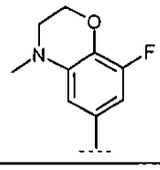
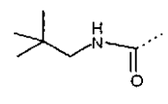
Cpd	R^3	R^5	t_R (min)	MS $(M+H)^+$
1386			2.0$	485.1/ 487.1
1387			1.9$	486.1/ 488.1
1388			1.9$	461.2/ 463.2
1389			2.0$	492.1/ 494.1
1390			2.0$	527.1/ 529.1
1391			1.9$	497.1/ 499.1
1392			1.8$	445.2/ 447.2
1393			2.0$	492.1/ 494.1
1394			1.9$	483.1/ 485.1

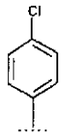
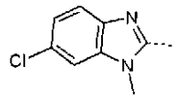
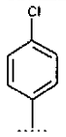
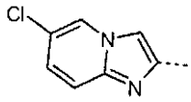
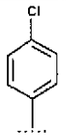
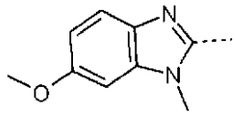
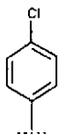
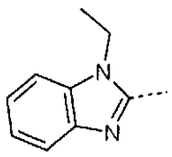
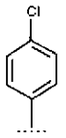
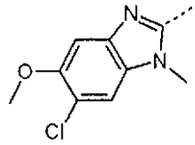
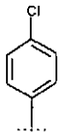
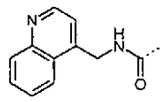
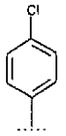
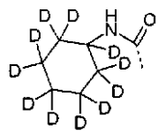
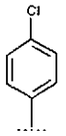
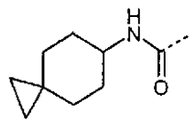
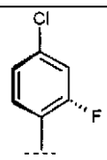
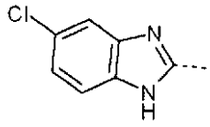
Cpd	R^3	R^5	t_R (min)	MS $(M+H)^+$
1395			2.1[$]	535.1/ 537.1
1396			2.0[$]	510.2/ 512.1
1397			2.0[$]	473.2/ 475.2
1398			2.0[$]	501.1/ 503.1
1399			2.0[$]	473.2/ 475.2
1400			1.7[$]	431.2/ 433.1
1401			2.0[$]	488.2/ 490.2
1402			4.0/4.4*	479.1
1403			4.4/4.5*	519.2

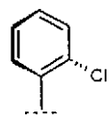
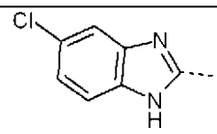
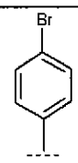
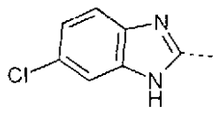
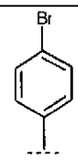
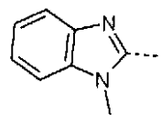
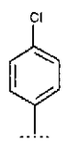
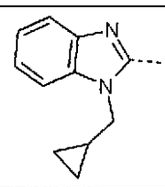
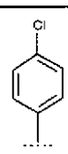
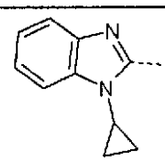
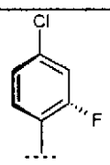
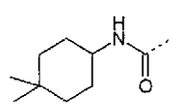
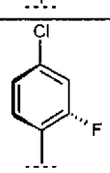
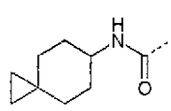
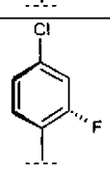
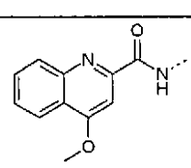
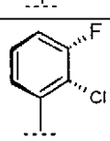
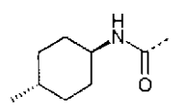
Cpd	R^3	R^5	t_R (min)	MS $(M+H)^+$
1404			4.7/4.8*	555.2
1405			5.2/5.4*	549.3
1406			4.5/4.8*	520.2
1407			4.9	482.2/ 484.2
1408			4.9/5.1*	534.3
1409			6.1/6.2*	538.4
1410			6.3/6.4*	575.3
1411			5.7/5.8*	524.4
1412			6.6	552.4

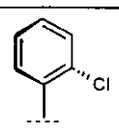
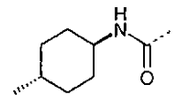
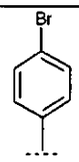
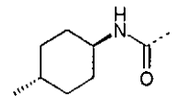
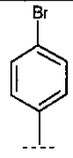
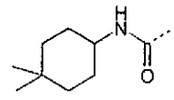
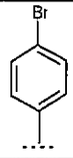
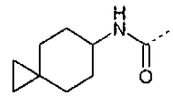
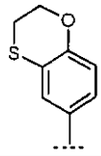
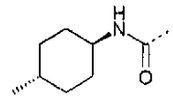
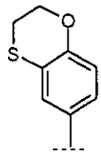
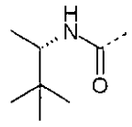
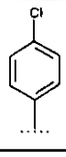
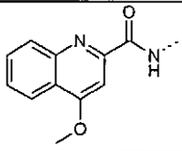
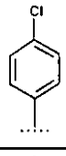
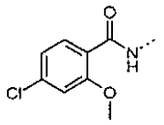
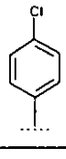
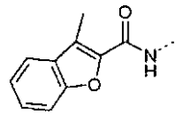
Cpd	R^3	R^5	t_R (min)	MS $(M+H)^+$
1413			6.5**	542.4
1414			6.3/6.4*	579.3
1415			6.3/6.4*	542.2
1416			6.2/6.3*	542.2
1417			6.2**	528.3
1418			4.0/4.2*	565.1
1419			4.0/4.2*	528.2
1420			3.8/4.0*	502.3

Cpd	R^3	R^5	t_R (min)	MS $(M+H)^+$
1421			3.9/4.1*	528.3
1422			4.2/4.3*	542.3
1423			4.8/5.0*	507.3
1424			4.6/4.7*	493.3
1425			4.5/4.8*	527.3
1426			5.0/5.1*	541.3
1427			6.3	538.4
1428			2.2[‡]	550.4

Cpd	R^3	R^5	t_R (min)	MS $(M+H)^+$
1429			2.2[$]	550.2
1430			2.1[$]	536.2
1431			5.5	496.1/ 498.1
1432			6.6	532.0/ 534.0
1433			6.0	470.1/ 472.1
1434			5.8/5.9*	528.2
1435			6.6	556.3
1436			6.0/6.1	516.2

Cpd	R^3	R^5	t_R (min)	MS $(M+H)^+$
1437			2.0$	512.2/ 514.2/ 516.2
1438			4.9	498.1/ 500.1
1439			2.1$	508.0/ 510.0
1440			2.8$	492.1/ 494.1
1441			1.5$	542.2/ 544.2/ 546.2
1442			4.8	532.2/ 534.2
1443			6.4	484.3/ 486.3
1444			4.4	499.2/ 500.2
1445			4.2**	516.0/ 518.0/ 520.0

Cpd	R^3	R^5	t_R (min)	MS $(M+H)^+$
1446			4.1**	498.0/ 500.0/ 502.0
1447			4.2	542.0/ 544.0/ 546.0
1448			3.5	522.1/ 524.1
1449			2.2$	518.2/ 520.2
1450			2.1$	504.0/ 506.0
1451			7.0**	519.2/ 521.2
1452			4.6**	517.3/ 519.3
1453			6.6**	566.2/ 568.2
1454			2.9**$	505.2/ 507.2

Cpd	R^3	R^5	t_R (min)	MS $(M+H)^+$
1455			6.7**	487.4/ 489.4
1456			5.4	531.2/ 533.2
1457			7.6	545.2/ 547.2
1458			7.4	543.2/ 545.2
1459			6.8	527.3
1460			6.6	512.2
1461			6.7	548.3/ 550.2
1462			2.0$	531.2/ 533.1/ 535.1
1463			2.2$	521.3/ 523.3

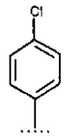
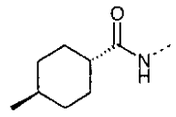
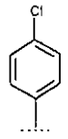
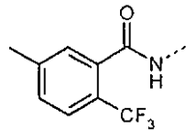
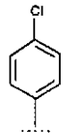
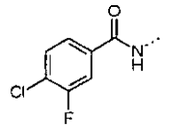
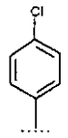
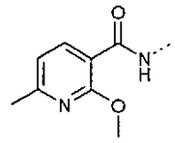
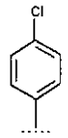
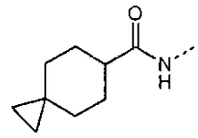
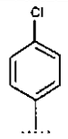
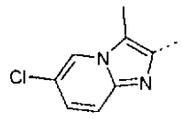
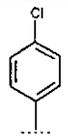
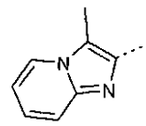
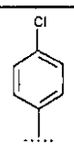
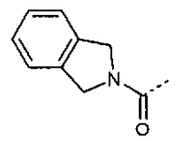
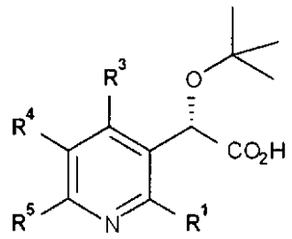
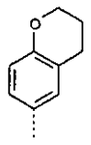
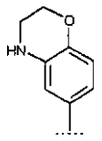
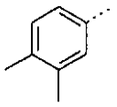
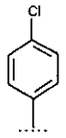
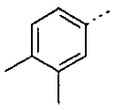
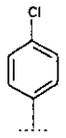
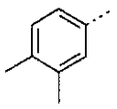
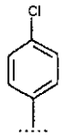
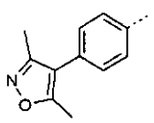
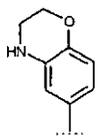
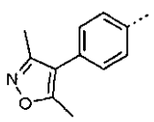
Cpd	R^3	R^5	t_R (min)	MS $(M+H)^+$
1464			2.0[$]	487.3/ 489.3
1465			2.7[$]	549.0/ 551.0
1466			2.2[$]	519.1/ 521.1/ 523.1
1467			5.5	512.2/ 514.2
1468			4.0	499.3/ 501.3
1469			4.8	511.9/ 513.9
1470			4.5	487.0/ 480.0
1471			6.3	493.1/ 495.1

TABLE 2



*presence of 2 inter-converting conformers by HPLC

**Most active atropisomer

Cpd	R^1	R^3	R^4	R^5	t_R (min)	MS $(M+H)^+$
2001	$-CH_3$		-CN	$-CH_3$	5.9	395.1
2002	$-CH_2SMe$		$-CH_3$		5.1/5.6 *	521.2
2003	$-CH_2OMe$		$-CH_3$		5.7	482.0/ 484.0
2004	$-CH_2OEt$		$-CH_3$		5.8	496.2/ 498.2
2005	$-CH_3$		-CN		8.5	530.2/ 532.2
2006	$-CH_3$		-CN		7.2*	553.2

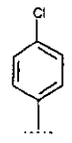
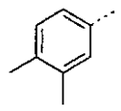
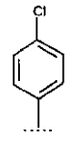
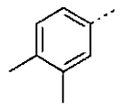
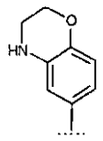
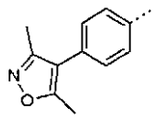
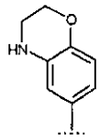
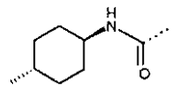
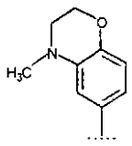
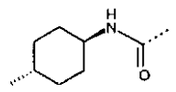
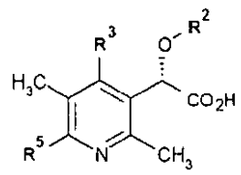
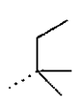
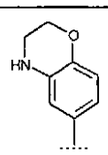
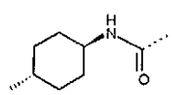
Cpd	R^1	R^3	R^4	R^5	t_R (min)	MS $(M+H)^+$
2007	-CH=CH_2		-CH_3		5.6	464.2/ 466.2
2008			-CH_3		5.8	478.2/ 480.2
2009	-CH_3		-F		6.2	546.1
2010	-CH_2OMe		-CH_3		4.4/5.0 *	540.4
2011	-CH_2OMe		-CH_3		5.3/5.5 *	554.4

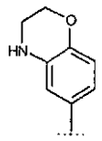
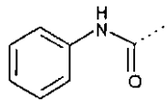
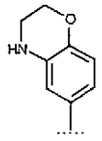
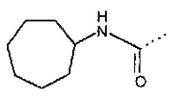
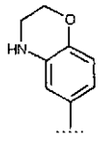
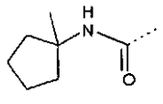
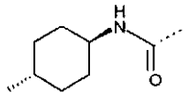
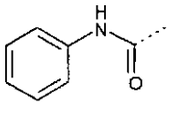
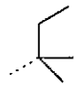
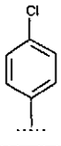
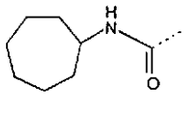
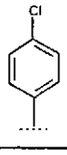
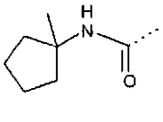
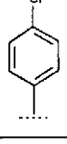
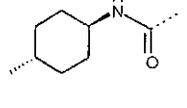
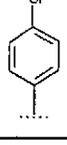
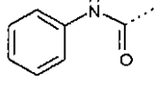
TABLE 3



*presence of 2 inter-converting conformers by HPLC

**Most active atropisomer

Cpd	R^2	R^3	R^5	t_R (min)	MS $(M+H)^+$
3001				5.7/6.2*	524.3

Cpd	R^2	R^3	R^5	t_R (min)	MS $(M+H)^+$
3002				5.9/6.4*	504.3
3003				5.6/6.1*	524.3
3004				5.1/6.6*	510.2
3005				6.8	501.1/ 503.1
3006				6.9	481.1/ 483.1
3007				6.8	501.1/ 503.1
3008				6.6	487.1/ 489.1
3009				6.8	499.1/ 501.1
3010				6.8	479.1/ 481.1

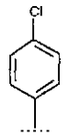
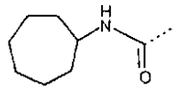
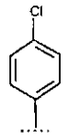
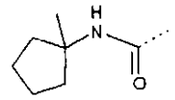
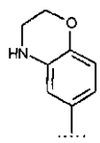
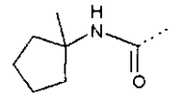
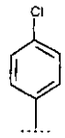
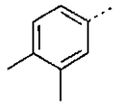
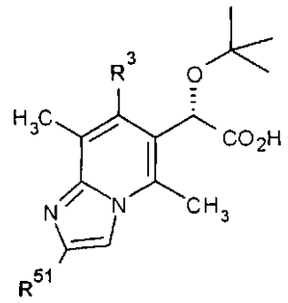
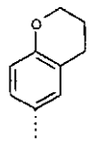
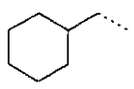
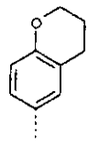
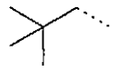
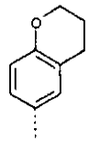
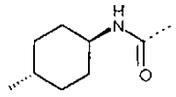
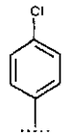
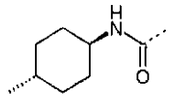
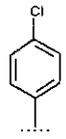
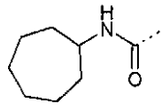
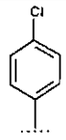
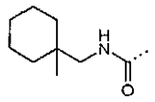
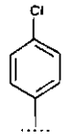
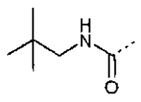
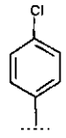
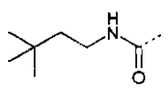
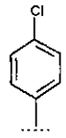
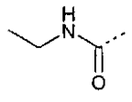
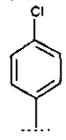
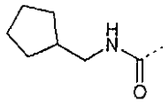
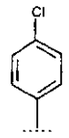
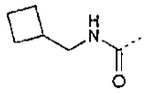
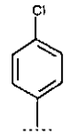
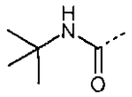
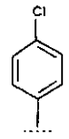
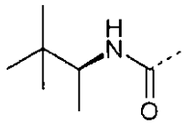
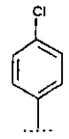
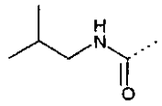
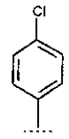
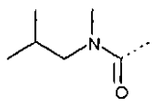
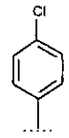
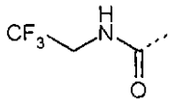
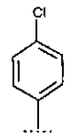
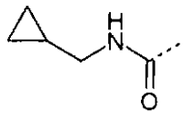
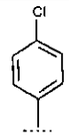
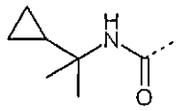
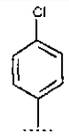
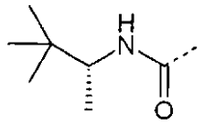
Cpd	R^2	R^3	R^5	t_R (min)	MS $(M+H)^+$
3011				6.7	499.1/ 501.1
3012				6.5	485.1/ 487.1
3013				4.9/5.0*	508.2
3014				5.5	464.2 466.2

TABLE 4



Cpd	R^3	R^{51}	t_R (min)	MS $(M+H)^+$
4001			6.3	505.2

Cpd	R^3	R^{51}	t_R (min)	MS $(M+H)^+$
4002			5.4	479.2
4003			6.3	548.2
4004			7.1	526.1/ 528.1
4005			6.9	526.1/ 528.1
4006			7.9	540.1/ 542.1
4007			6.6	500.1/ 502.1
4008			7.0	514.1/ 516.1
4009			5.3	458.1/ 460.1
4010			6.7	512.1/ 514.1

Cpd	R^3	R^{51}	t_R (min)	MS $(M+H)^+$
4011			6.3	498.1/ 500.1
4012			6.1	486.1/ 488.1
4013			7.0	514.2/ 516.2
4014			6.1	486.1/ 488.1
4015			5.5	500.1/ 502.1
4016			4.7	512.2/ 514.2
4017			4.5	484.3/ 486.3
4018			5.0	512.3/ 514.3
4019			5.1	514.2/ 516.2

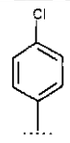
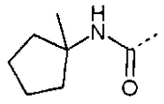
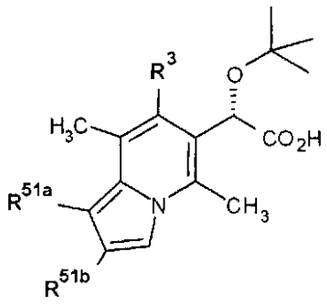
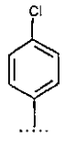
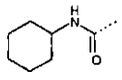
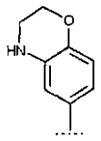
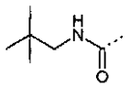
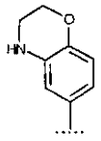
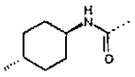
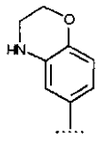
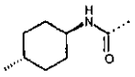
Cpd	R^3	R^{51}	t_R (min)	MS $(M+H)^+$
4020			5.0	512.2/ 514.2

TABLE 5

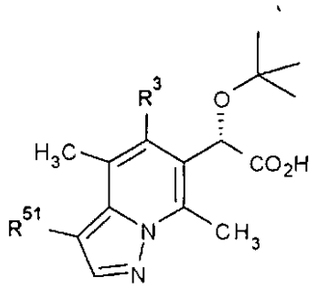


*presence of 2 inter-converting conformers by HPLC

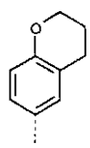
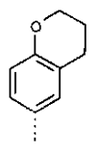
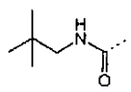
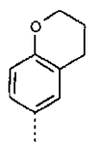
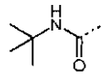
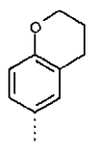
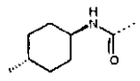
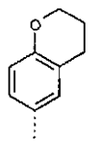
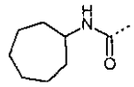
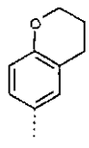
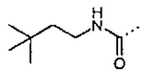
Cpd	R^3	R^{51a}	R^{51b}	t_R (min)	MS $(M+H)^+$
5001			H	8.8	511.2/ 513.2
5002			H	6.0/6.6*	522.3
5003			H	6.5/7.3*	548.4
5004			-CF_3	7.9/8.7*	616.3

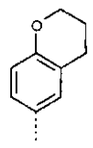
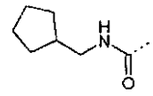
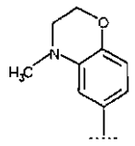
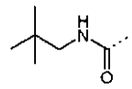
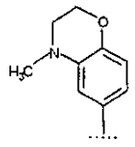
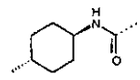
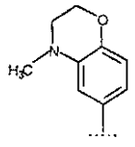
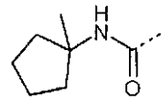
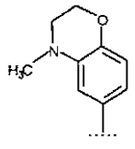
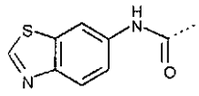
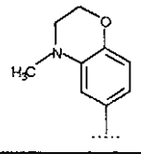
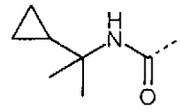
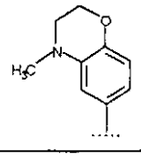
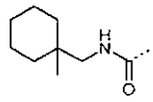
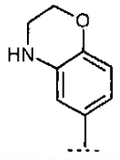
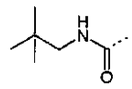
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TABLE 6



*presence of 2 inter-converting conformers by HPLC

Cpd	R^3	R^{51}	t_R (min)	MS $(M+H)^+$
6001		-COOMe	8.2	467.1
6002			7.8	522.2
6003			7.4/7.5 *	506.2
6004			8.5/8.6	548.2
6005			8.5	548.2
6006			8.4	536.2

Cpd	R^3	R^{51}	t_R (min)	MS $(M+H)^+$
6007			8.1	534.2
6008			6.2/6.4 *	537.3
6009			6.5/6.6 *	563.2
6010			6.3/6.5 *	549.2
6011			6.0/6.2 *	600.1
6012			6.3/6.5 *	549.2
6013			6.7/6.8 *	577.2
6014			5.3/5.8 *	523.2

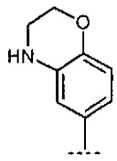
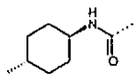
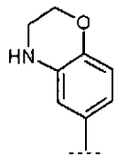
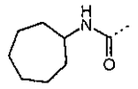
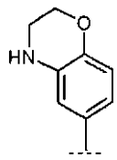
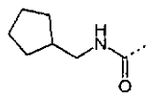
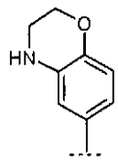
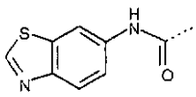
Cpd	R^3	R^{51}	t_R (min)	MS $(M+H)^+$
6015			5.6/5.8 *	549.2
6016			5.7/6.2 *	549.2
6017			5.4/5.9 *	535.2
6018			5.0/5.6 *	586.1

TABLE 7

Antiviral potency

Compound #	EC_{50} nM
1005	19
1009	20
1011	59
1017	21
1018	180
1020	49
1102	17
1111	15
1113	7.7
1116	13
1119	17
1124	81
1127	4.5
1132	9.4
1141	26
1142	7.9
1143	21
1145	35

Compound #	EC_{50} nM
1437	0.75
1438	0.94
1439	4.0
1440	2.4
1441	4.9
1442	16
1443	7.1
1444	9.2
1445	1.9
1446	1.9
1447	0.38
1448	1.4
1449	1.8
1450	7.7
1451	1.7
1452	5.7
1453	2.1
1454	3.7

1146	17
1147	6.9
1152	15
1153	22
1154	27
1160	16
1161	27
1167	9.3
1192	8.3
1202	31
1208	8.9
1242	220
1256	8.1
1275	4.5
1276	68
1280	22
1283	140
1290	11
1293	24
1307	17
1311	26
1316	47

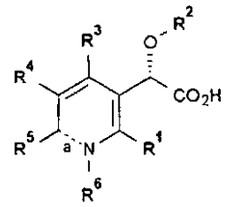
1455	4.0
1456	4.2
1457	4.0
1458	6.9
1459	4.0
1460	1.7
1461	2.5
1462	1.2
1463	2.1
1464	6.2
1465	11
1466	4.9
1467	4.3
1468	15
1469	0.61
1470	5.9
1471	2.4
2003	17
2005	19
3005	9.3
3009	24
4002	73
6001	89

Each of the references including all patents, patent applications and publications cited in the present application is incorporated herein by reference in its entirety, as if each of them is individually incorporated. Further, it would be appreciated that, in the above teaching of invention, the skilled in the art could make certain changes or modifications to the invention, and these equivalents would still be within the scope of the invention defined by the appended claims of the application.

CLAIMS

What is claimed is:

1. A compound of Formula I and a racemate, enantiomer or diastereomer of a compound of formula (I):



(I)

wherein

R^1 is (C_{1-6})alkyl, (C_{2-6})alkenyl or (C_{3-6})cycloalkyl, wherein the (C_{1-6})alkyl is optionally substituted with $-O(C_{1-6})$alkyl or $-S(C_{1-6})$alkyl;

R^2 is (C_{1-8})alkyl or (C_{3-8})cycloalkyl, wherein the (C_{3-8})cycloalkyl is optionally substituted with (C_{1-6})alkyl;

R^3 is aryl, wherein the aryl is optionally fused to one or more cycles, at least one of which is a heterocycle, to form a heteropolycycle, and wherein the aryl or heteropolycycle is optionally substituted with 1 to 4 substituents each independently selected from (C_{1-6})alkyl, halo and $-O(C_{1-6})$alkyl;

R^4 is (C_{1-6})alkyl, -CN, halo, (C_{1-6})haloalkyl, (C_{3-5})cycloalkyl, or $-O(C_{1-6})$alkyl; and

a is a double bond, R^6 is absent and R^5 is R^{51} or $-(C_{1-3})$alkyl-R^{51}; or

a is a single bond and R^5 and R^6 are joined, together with the atoms to which they are bonded, to form a 5-membered ring optionally having 1 to 3 further heteroatoms each independently selected from O, N and S, wherein the 5-membered ring is optionally substituted with 1 to 3 R^{51} substituents;

wherein R^{51} is in each case independently selected from R^{52}, $-OR^{53}$, $-N(R^{54})R^{53}$, $-C(=O)R^{52}$, $-C(=O)OR^{53}$, $-C(=O)N(R^{54})R^{53}$, $-OC(=O)N(R^{54})R^{53}$, $-N(R^{54})C(=O)R^{52}$, $-N(R^{54})C(=O)N(R^{54})R^{53}$ and $-N(R^{54})C(=O)OR^{53}$; wherein

R^{52} is in each case independently selected from R^{53}, (C_{2-8})alkenyl and (C_{2-8})alkynyl,

R^{53} is in each case independently selected from (C_{1-8})alkyl, (C_{3-8})cycloalkyl, (C_{3-8})cycloalkyl-(C_{1-6})alkyl-, aryl, aryl-(C_{1-6})alkyl-, **Het**, and **Het**-(C_{1-6})alkyl-,

and

R^{54} is in each case independently selected from H and (C_{1-3})alkyl;

wherein each of R^{52} and R^{53} is optionally substituted with 1 to 3 substituents each independently selected from R^{55}, halo, -CN, $-OR^{56}$, $-SR^{56}$, $-SOR^{56}$, $-SO_2R^{56}$, $-N(R^{54})R^{56}$, $-N(R^{54})C(=O)R^{55}$, $-N(R^{54})C(=O)N(R^{54})R^{56}$, $-N(R^{54})C(=O)OR^{56}$, $-OC(=O)N(R^{54})R^{56}$, $-C(=O)R^{55}$, $-C(=O)OR^{56}$, and $-CON(R^{54})R^{56}$, wherein

R^{55} is in each case independently selected from R^{56}, (C_{2-8})alkenyl and (C_{2-8})alkynyl, and

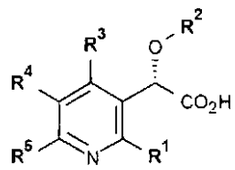
R^{56} is in each case independently selected from H, (C_{1-8})alkyl, (C_{3-8})cycloalkyl, (C_{3-8})cycloalkyl-(C_{1-6})alkyl-, aryl, aryl-(C_{1-6})alkyl-, **Het**, and **Het**-(C_{1-6})alkyl-,

wherein each of R^{55} and R^{56} is, where possible, in each case independently optionally substituted with 1 to 3 substituents each independently selected from (C_{1-6})alkyl, (C_{1-6})haloalkyl, halo, -OH, -O(C_{1-6})alkyl, $-NH_2$, -NH(C_{1-6})alkyl, -N$((C_{1-6})\text{alkyl})_2$ and -NH(C=O)(C_{1-6})alkyl;

wherein **Het** is a 4- to 7-membered saturated, unsaturated or aromatic heterocycle having 1 to 4 heteroatoms each independently selected from O, N and S, or a 7- to 14-membered saturated, unsaturated or aromatic heteropolycycle having wherever possible 1 to 5 heteroatoms, each independently selected from O, N and S;

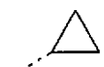
or a salt thereof.

2. The compound according to claim 1, or a pharmaceutically acceptable salt thereof, having the formula:

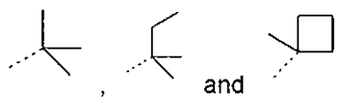


wherein R^1, R^2, R^3, R^4 and R^5 are as defined in claim 1.

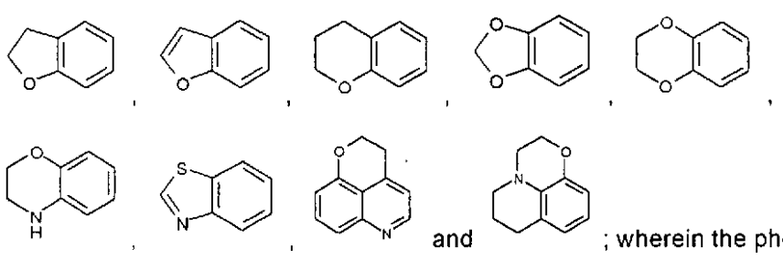
3. The compound according to claim 1 or 2, or a pharmaceutically acceptable salt thereof, wherein R^1 is selected from:

$-CH_3$, $-CH_2OMe$, $-CH_2OEt$, $-CH_2SMe$, $-CH=CH_2$ and  .

4. The compound according to any one of claims 1 to 3, or a pharmaceutically acceptable salt thereof, wherein R^2 is selected from:

 and .

5. The compound according to any one of claims 1 to 4, or a pharmaceutically acceptable salt thereof, wherein R^3 is phenyl or a heteropolycycle selected from:



and ; wherein the phenyl or heteropolycycle is optionally substituted with 1 to 4 substituents each independently selected from (C_{1-6})alkyl, halo and $-O(C_{1-6})$alkyl.

6. The compound according to any one of claims 1 to 5, or a pharmaceutically acceptable salt thereof, wherein R^4 is (C_{1-6})alkyl, -CN, halo or (C_{1-6})haloalkyl.

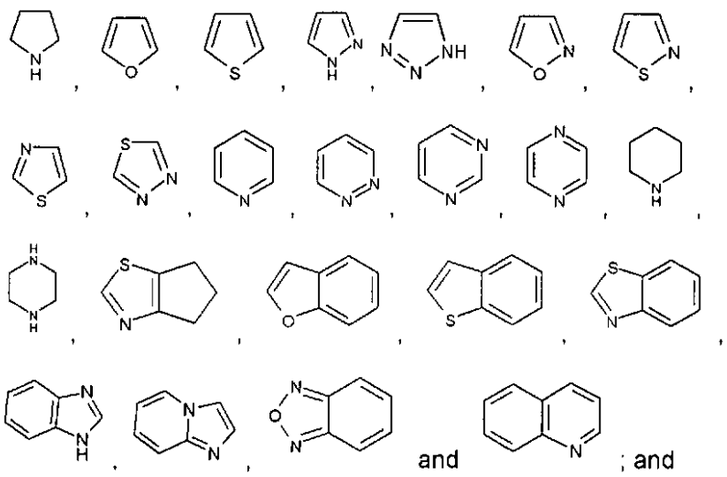
7. The compound according to any one of claims 1 to 6, or a pharmaceutically acceptable salt thereof, wherein R^4 is $-CH_3$.

8. The compound according to any one of claims 1 to 7, or a pharmaceutically acceptable salt thereof, wherein **a** is a double bond, R^6 is absent and R^5 is R^{51} or $-(C_{1-3})$alkyl-R^{51};

wherein R^{51} is selected from R^{52}, $-OR^{53}$, $-C(=O)R^{52}$, $--C(=O)OR^{53}$, $-C(=O)N(R^{54})R^{53}$, $-N(R^{54})C(=O)R^{52}$, $-N(R^{54})C(=O)N(R^{54})R^{53}$ and $-N(R^{54})C(=O)OR^{53}$; wherein

R^{52} is selected from R^{53} and (C_{2-8})alkenyl, and

R^{53} is selected from (C_{1-8})alkyl, (C_{3-8})cycloalkyl, (C_{3-8})cycloalkyl-(C_{1-6})alkyl-, aryl, aryl-(C_{1-6})alkyl-, **Het**, and **Het**-(C_{1-6})alkyl-,
wherein **Het** and the **Het** portion of **Het**-(C_{1-6})alkyl- are in each case independently selected from:

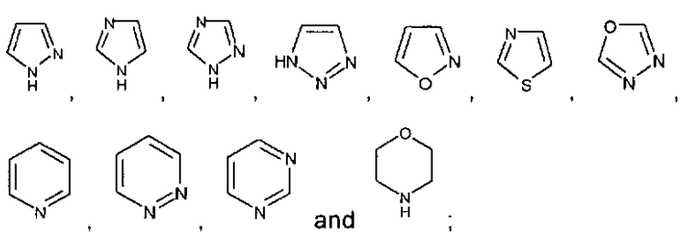


and ; and

R^{54} is in each case independently selected from H and (C_{1-3})alkyl;

wherein each of R^{52} and R^{53} is optionally substituted with 1 to 3 substituents each independently selected from R^{56}, halo, -CN, -OR^{56}, -SR^{56}, -SO_2R^{56}, -$N(R^{54})R^{56}$ and -$CON(R^{54})R^{56}$, wherein

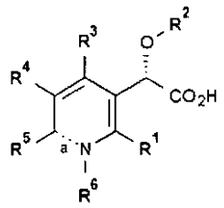
R^{56} is in each case independently selected from H, (C_{1-8})alkyl, (C_{3-8})cycloalkyl, (C_{3-8})cycloalkyl-(C_{1-6})alkyl-, aryl, aryl-(C_{1-6})alkyl-, **Het**, and **Het**-(C_{1-6})alkyl-,
wherein **Het** and the **Het** portion of **Het**-(C_{1-6})alkyl- are in each case independently selected from:



and ;

wherein R^{56} is, where possible, in each case independently optionally substituted with 1 to 3 substituents each independently selected from (C_{1-6})alkyl, (C_{1-6})haloalkyl, halo, -O(C_{1-6})alkyl, -N$((C_{1-6})alkyl)_2$ and -NH(C=O)(C_{1-6})alkyl.

9. A compound and a racemate, enantiomer or diastereomer of a compound having the formula:



wherein

R^1 is (C_{1-6})alkyl, (C_{2-6})alkenyl or (C_{3-6})cycloalkyl, wherein the (C_{1-6})alkyl is optionally substituted with $-O(C_{1-6})$alkyl or $-S(C_{1-6})$alkyl;

R^2 is (C_{1-8})alkyl or (C_{3-8})cycloalkyl, wherein the (C_{3-8})cycloalkyl is optionally substituted with (C_{1-6})alkyl;

R^3 is aryl, wherein the aryl is optionally fused to one or more cycles, at least one of which is a heterocycle, to form a heteropolycycle, and wherein the aryl or heteropolycycle is optionally substituted with 1 to 4 substituents each independently selected from (C_{1-6})alkyl, halo and $-O(C_{1-6})$alkyl;

R^4 is (C_{1-6})alkyl, -CN, halo, (C_{1-6})haloalkyl, (C_{3-5})cycloalkyl, or $-O(C_{1-6})$alkyl; and

a is a double bond, R^6 is absent and R^5 is R^{51} or $-(C_{1-3})$alkyl-R^{51}; or

a is a single bond and R^5 and R^6 are joined, together with the atoms to which they are bonded, to form a 5-membered ring optionally having 1 to 3 further heteroatoms each independently selected from O, N and S, wherein the 5-membered ring is optionally substituted with 1 to 3 R^{51} substituents;

wherein R^{51} is in each case independently selected from R^{52}, $-OR^{53}$, $-N(R^{54})R^{53}$, $-C(=O)R^{52}$, $-C(=O)OR^{53}$, $-C(=O)N(R^{54})R^{53}$, $-OC(=O)N(R^{54})R^{53}$, $-N(R^{54})C(=O)R^{52}$, $-N(R^{54})C(=O)N(R^{54})R^{53}$ and $-N(R^{54})C(=O)OR^{53}$; wherein

R^{52} is in each case independently selected from R^{53}, (C_{2-8})alkenyl and (C_{2-8})alkynyl,

R^{53} is in each case independently selected from (C_{1-8})alkyl, (C_{3-8})cycloalkyl, (C_{5-14})spirocycloalkyl, (C_{3-8})cycloalkyl-(C_{1-6})alkyl-, aryl, aryl-(C_{1-6})alkyl-, **Het**, and **Het**-(C_{1-6})alkyl-, and

R^{54} is in each case independently selected from H and (C_{1-3})alkyl;

wherein each of R^{52} and R^{53} is optionally substituted with 1 to 3 substituents each independently selected from R^{55}, halo, -CN, $-OR^{56}$, $-SR^{56}$,

$-SOR^{56}$, $-SO_2R^{56}$, $-N(R^{54})R^{56}$, $-N(R^{54})C(=O)R^{55}$, $-N(R^{54})C(=O)N(R^{54})R^{56}$, $-N(R^{54})C(=O)OR^{56}$, $-OC(=O)N(R^{54})R^{56}$, $-C(=O)R^{55}$, $-C(=O)OR^{56}$, and $-CON(R^{54})R^{56}$, wherein

R^{55} is in each case independently selected from R^{56}, (C_{2-8})alkenyl and (C_{2-8})alkynyl, and

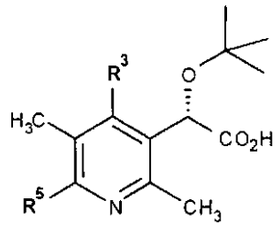
R^{56} is in each case independently selected from H, (C_{1-8})alkyl, (C_{3-8})cycloalkyl, (C_{3-8})cycloalkyl-(C_{1-6})alkyl-, aryl, aryl-(C_{1-6})alkyl-, **Het**, and **Het**-(C_{1-6})alkyl-,

wherein each of R^{55} and R^{56} is, where possible, in each case independently optionally substituted with 1 to 3 substituents each independently selected from (C_{1-6})alkyl, (C_{1-6})haloalkyl, halo, -OH, $-O(C_{1-6})$alkyl, $-NH_2$, $-NH(C_{1-6})$alkyl, $-N((C_{1-6})alkyl)_2$ and $-NH(C=O)(C_{1-6})$alkyl;

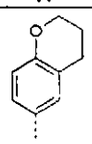
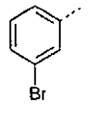
wherein **Het** is a 4- to 7-membered saturated, unsaturated or aromatic heterocycle having 1 to 4 heteroatoms each independently selected from O, N and S, or a 7- to 14-membered saturated, unsaturated or aromatic heteropolycycle having wherever possible 1 to 5 heteroatoms, each independently selected from O, N and S;

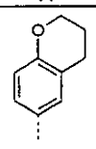
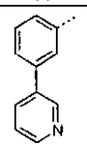
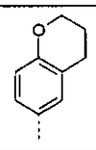
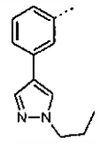
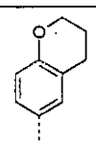
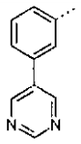
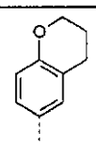
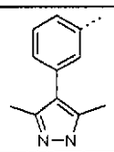
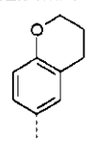
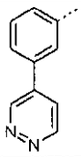
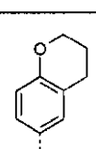
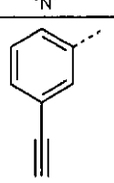
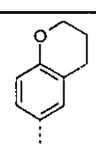
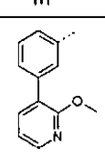
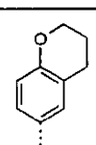
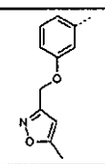
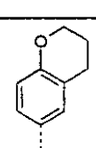
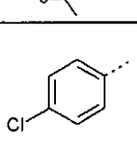
or a salt thereof.

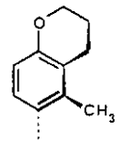
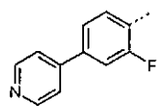
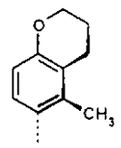
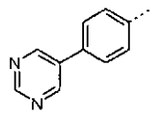
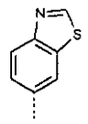
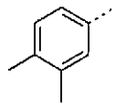
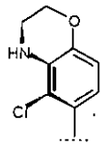
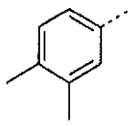
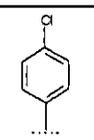
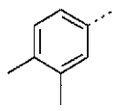
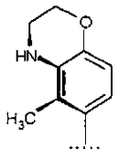
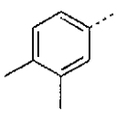
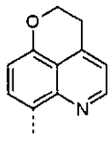
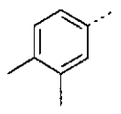
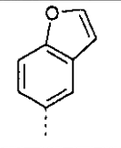
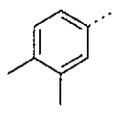
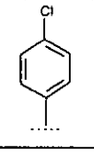
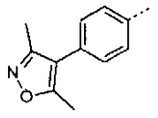
10. A compound according to claim 1, or a pharmaceutically acceptable salt thereof, having the formula:

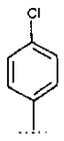
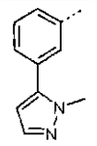
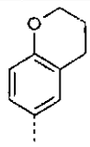
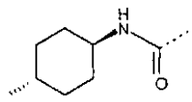
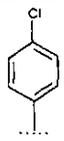
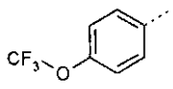
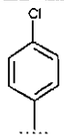
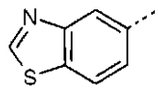
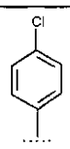
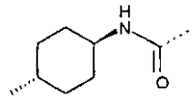
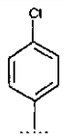
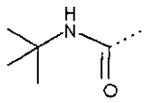
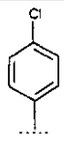
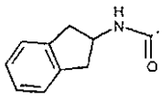
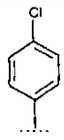
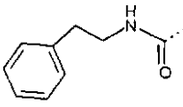
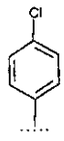
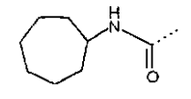


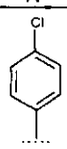
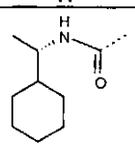
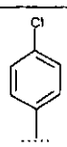
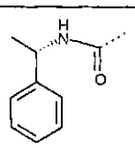
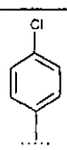
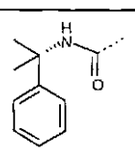
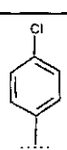
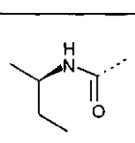
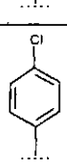
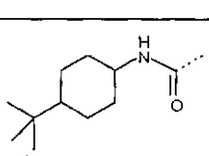
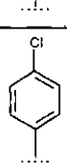
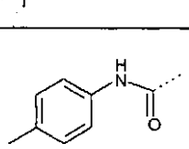
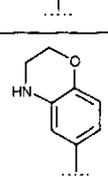
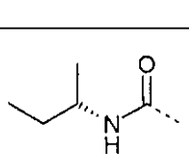
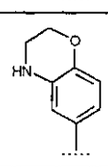
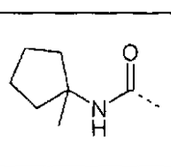
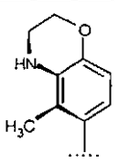
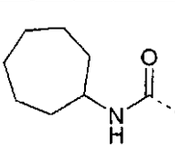
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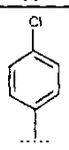
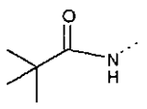
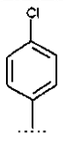
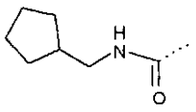
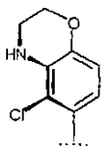
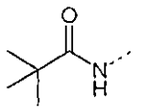
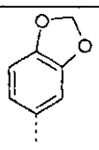
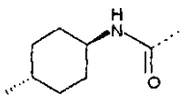
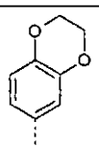
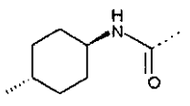
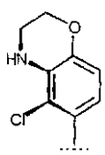
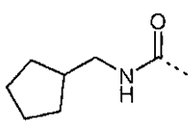
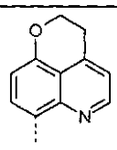
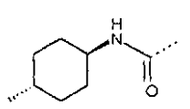
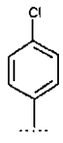
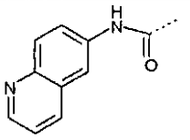
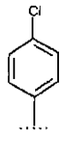
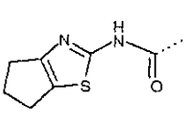
R^3	R^5
	

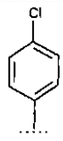
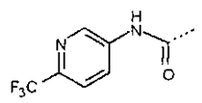
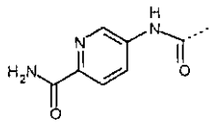
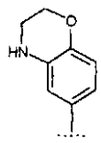
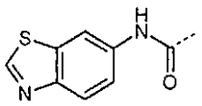
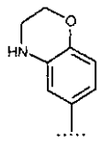
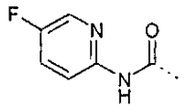
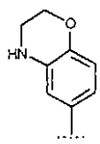
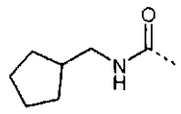
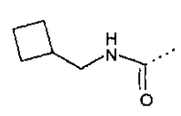
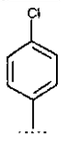
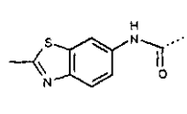
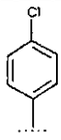
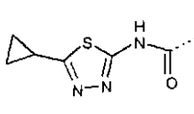
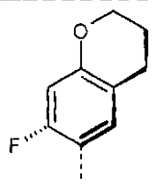
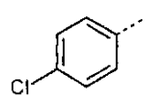
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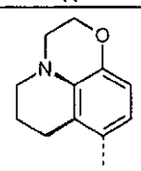
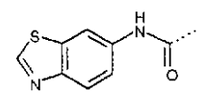
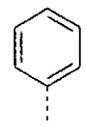
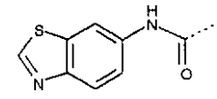
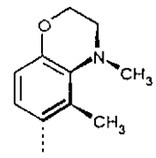
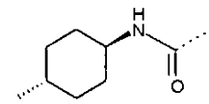
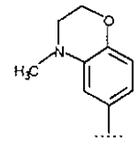
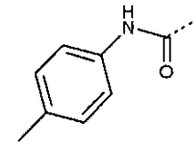
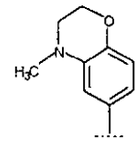
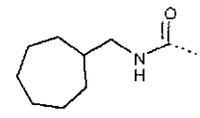
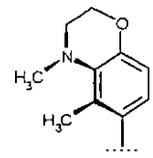
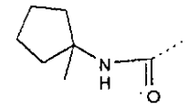
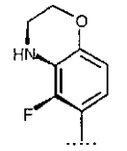
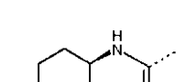
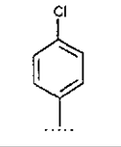
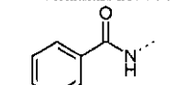
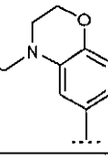
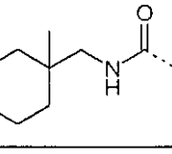
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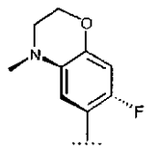
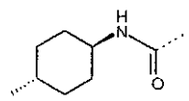
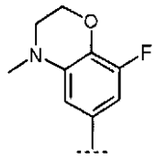
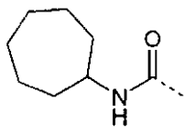
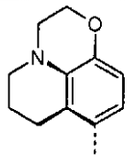
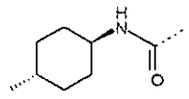
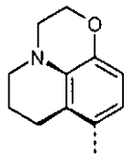
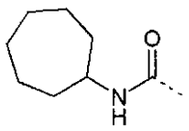
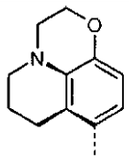
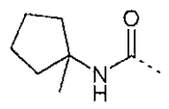
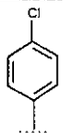
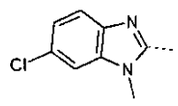
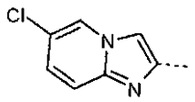
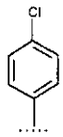
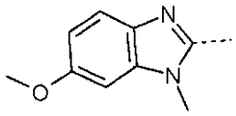
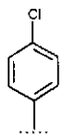
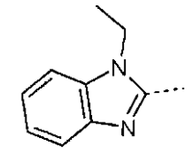
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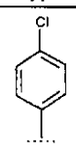
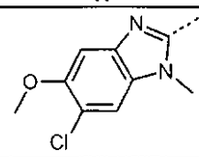
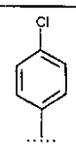
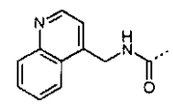
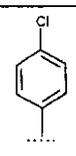
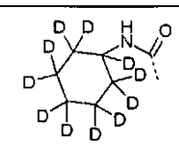
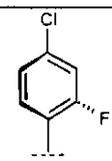
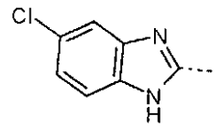
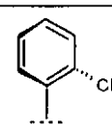
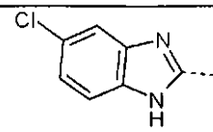
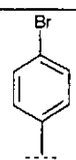
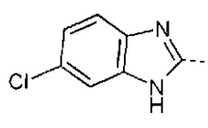
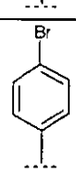
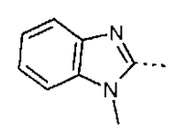
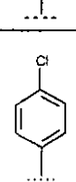
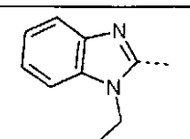
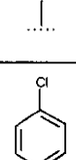
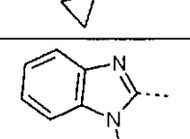
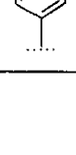
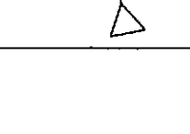
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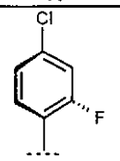
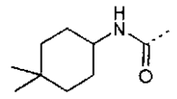
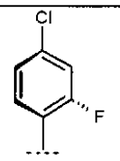
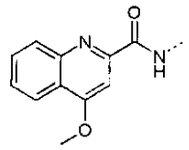
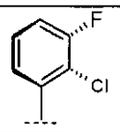
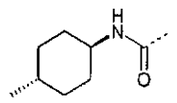
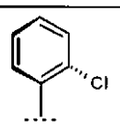
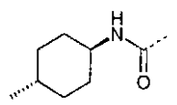
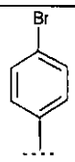
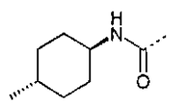
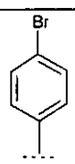
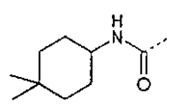
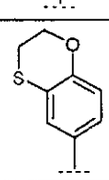
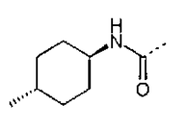
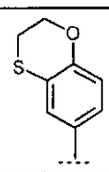
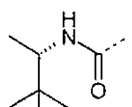
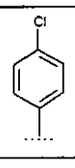
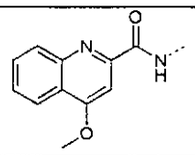
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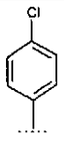
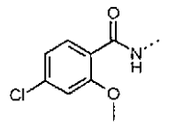
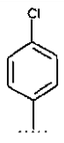
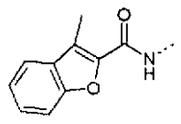
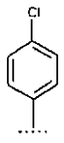
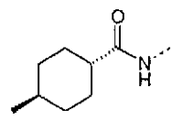
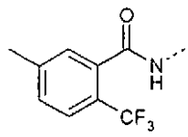
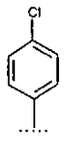
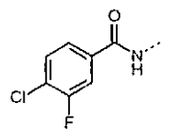
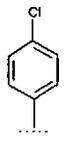
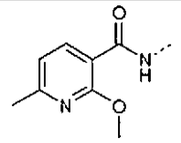
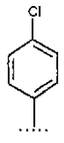
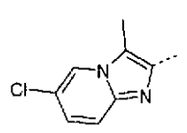
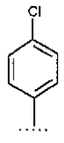
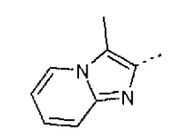
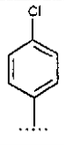
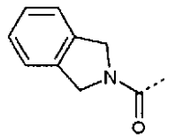
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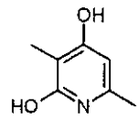
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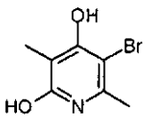
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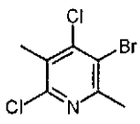
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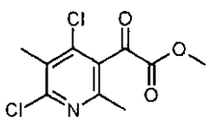
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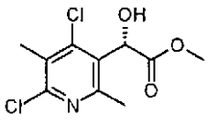
11. A compound represented by a formula selected from the group consisting of:

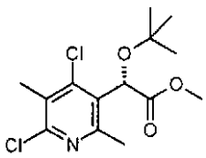

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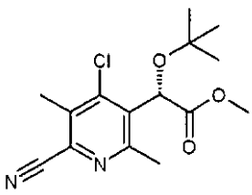

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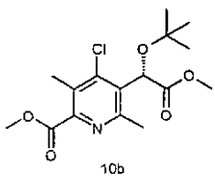

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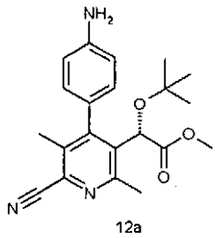

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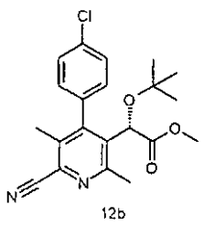

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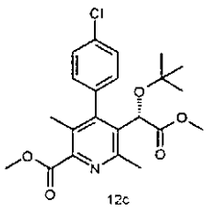

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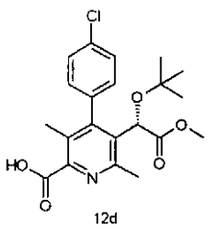

10a ,

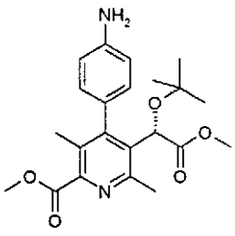

10b ,

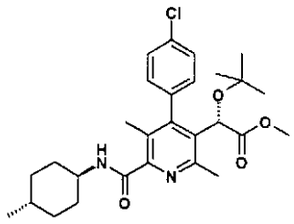

12a ,


12b ,


12c ,


12d ,


36a and


37a .

12. The compound of formula (I) according to any one of claims 1 to 10, or a pharmaceutically acceptable salt thereof, as a medicament.

13. A pharmaceutical composition comprising a therapeutically effective amount of a compound of formula (I) according to any one of claims 1 to 10, or a pharmaceutically acceptable salt thereof; and one or more pharmaceutically acceptable carriers.

14. The pharmaceutical composition according to claim 13 further comprising at least one other antiviral agent.

15. Use of a compound of formula (I) according to any one of claims 1 to 10, or a

pharmaceutically acceptable salt thereof, for the treatment of an HIV infection in a human being having or at risk of having the infection.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CA2010/000707

A. CLASSIFICATION OF SUBJECT MATTER
IPC: ***C07D 213/55*** (2006.01) . ***A61K 31/44*** (2006.01) . ***A61K 31/5375*** (2006.01) . ***A61K 31/54*** (2006.01) . ***A61P 31/18*** (2006.01) . ***C07D 213/60*** (2006.01) (more IPCs on the last page)
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC: ***C07D 213/55*** (2006.01) . ***A61K 31/44*** (2006.01) . ***A61K 31/5375*** (2006.01) . ***A61K 31/54*** (2006.01) . ***A61P 31/18*** (2006.01) . ***C07D 213/60*** (2006.01)

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

Electronic database(s) consulted during the international search (name of database(s) and, where practicable, search terms used)
STN CAPlus chemical structure search, Canadian Patent Database , Espacenet
keywords: HIV, AIDS, integrase, antiviral, pyridine

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	CA2262252 A1 (PFIZER PRODUCTS INC.) 17 August 1999 (17-08-1999) * page 16, line 4*	11
P, A	WO 2009/062285 (BOEHRINGER INGELHEIM INTERNATIONAL GmbH) 22 May 2009 (22-05-2009) *entire document*	1-15

[ ] Further documents are listed in the continuation of Box C. [x] 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
22 July 2010 (22-07-2010)	11 August 2010 (11-08-2010)
Name and mailing address of the ISA/CA Canadian Intellectual Property Office Place du Portage I, C114 - 1st Floor, Box PCT 50 Victoria Street Gatineau, Quebec K1A 0C9 Facsimile No.: 001-819-953-2476	Authorized officer Ursula Wronska (819) 997-6666

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CA2010/000707

Box No. I Nucleotide and/or amino acid sequence(s) (Continuation of item 1.c of the first sheet)

1. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international search was carried out on the basis of a sequence listing filed or furnished:

   a. (means)

      [ ] on paper

      [x] in electronic form

   b. (time)

      [x] in the international application as filed

      [ ] together with the international application in electronic form

      [ ] subsequently to this Authority for the purposes of search

2. [ ] In addition, in the case that more than one version or copy of a sequence listing has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

3. Additional comments :

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/CA2010/000707

Patent Document Cited in Search Report	Publication Date	Patent Family Member(s)	Publication Date
CA2262252A1	17 August 1999 (17-08-1999)	AP9901464D0	31 March 1999 (31-03-1999)
		AU1732999A	02 September 1999 (02-09-1999)
		BG103180A	30 September 1999 (30-09-1999)
		BR9900653A	17 October 2000 (17-10-2000)
		CA2262252C	10 January 2006 (10-01-2006)
		CN1231176A	13 October 1999 (13-10-1999)
		EA199900124A3	29 December 1999 (29-12-1999)
		EP0951906A1	27 October 1999 (27-10-1999)
		HR990054A2	29 February 2000 (29-02-2000)
		HU9900386D0	28 April 1999 (28-04-1999)
		HU9900386A2	29 November 1999 (29-11-1999)
		HU9900386A3	28 December 1999 (28-12-1999)
		ID23218A	30 March 2000 (30-03-2000)
		IL128531D0	31 January 2000 (31-01-2000)
		IS4975A	18 August 1999 (18-08-1999)
		JP11292766A	26 October 1999 (26-10-1999)
		MA26608A1	20 December 2004 (20-12-2004)
		NO990722D0	16 February 1999 (16-02-1999)
		NO990722A	18 August 1999 (18-08-1999)
		OA10976A	05 November 2001 (05-11-2001)
		PA8467401A1	29 September 2000 (29-09-2000)
		PL331507A1	30 August 1999 (30-08-1999)
		SG81261A1	19 June 2001 (19-06-2001)
		TR9900328A2	21 October 1999 (21-10-1999)
		US6043260A	28 March 2000 (28-03-2000)
		ZA9901220A	16 August 2000 (16-08-2000)
WO2009062285A1	22 May 2009 (22-05-2009)	AR069335A1	13 January 2010 (13-01-2010)
		AU2008323558A1	22 May 2009 (22-05-2009)
		PE10002009A1	14 August 2009 (14-08-2009)
		UY31472A1	17 July 2009 (17-07-2009)

C07D 401/00 (2006.01) . *C07D 405/00* (2006.01) . *C07D 413/00* (2006.01) . *C07D 417/00* (2006.01) .
C07D 471/04 (2006.01) . *C07D 491/06* (2006.01) . *C07D 498/06* (2006.01)

INHIBIDORES DE LA REPLICACIÓN DEL VIRUS DE LA INMUNODEFICIENCIA HUMANA

SOLICITUDES RELACIONADAS

Esta solicitud reivindica la prioridad de la solicitud de patente de Estados Unidos con Nº de serie 61/178551, presentada el 15 de mayo de 2009 y de la solicitud de patente de Estados Unidos con Nº de serie 61/285766, presentada el 11 de diciembre 2009, que se incorporan en la presente memoria como referencia.

CAMPO DE LA INVENCIÓN

La presente invención se refiere a compuestos, composiciones y métodos para el tratamiento de una infección por el virus de inmunodeficiencia humana (VIH). En particular, la presente invención proporciona nuevos inhibidores de la enzima integrasa del VIH, composiciones farmacéuticas que contienen a compuestos de este tipo y a métodos para utilizar estos compuestos para reducir la replicación del VIH y en el tratamiento de una infección por VIH.

ANTECEDENTES DE LA INVENCIÓN

El síndrome de inmunodeficiencia adquirida (SIDA) se provoca por el virus de la inmunodeficiencia humana (VIH), en particular la cepa VIH-1. La mayoría de las terapias actuales aprobadas para la infección por VIH se dirigen a las enzimas virales transcriptasa inversa y proteasa. Existen también dos fármacos aprobados dirigidos contra la entrada de VIH y un fármaco aprobado dirigido contra la enzima integrasa. Dentro de las clases de inhibidores de la transcriptasa inversa e inhibidores de proteasa, la resistencia del VIH a los fármacos existentes es un problema. Por lo tanto, es importante descubrir y desarrollar nuevos compuestos anti-retrovirales.

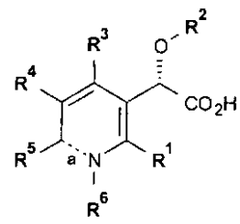
La solicitud de patente internacional WO 2007/131350 y la solicitud de patente de Estados Unidos, publicada, US 2006/0106070 describen compuestos que son activos contra la replicación del VIH.

SUMARIO DE LA INVENCIÓN

La presente invención proporciona una nueva serie de compuestos con actividad inhibidora contra la replicación del VIH. Por lo tanto, los compuestos de la

invención pueden usarse para inhibir la actividad de la integrasa de VIH y pueden usarse para reducir la replicación de VIH.

Un aspecto de la invención proporciona un compuesto de fórmula I y un racemato, enantiómero o diastereoisómero de un compuesto de fórmula (I):



(I)

en la que

R^1 es alquilo (C_{1-6}), alquenilo (C_{2-6}) o cicloalquilo (C_{3-6}), en donde el alquilo (C_{1-6}) está opcionalmente sustituido con –Oalquilo (C_{1-6}) o -Salquilo (C_{1-6});

R^2 es alquilo (C_{1-8}) o cicloalquilo (C_{3-8}), en donde el cicloalquilo (C_{3-8}) está opcionalmente sustituido con alquilo (C_{1-6});

R^3 es arilo, en donde el arilo está opcionalmente condensado a uno o más ciclos, al menos uno de los cuales es un heterociclo, para formar un heteropoliciclo, y en donde el arilo o heteropoliciclo está opcionalmente sustituido con 1 a 4 sustituyentes, cada uno independientemente seleccionado de alquilo (C_{1-6}), halo y -Oalquilo (C_{1-6});

R^4 es alquilo (C_{1-6}), -CN, halo, haloalquilo (C_{1-6}), cicloalquilo (C_{3-5}) o -Oalquilo (C_{1-6}); y

a es un doble enlace, R^6 está ausente y R^5 es R^{51} o -alquil (C_{1-3})-R^{51}; o

a es un enlace sencillo y R^5 y R^6 están unidos, junto con los átomos a los que están unidos, para formar un anillo de 5 miembros que tiene, opcionalmente 1 a 3 heteroátomos adicionales, cada uno independientemente seleccionado de O, N y S, en donde el anillo de 5 miembros está opcionalmente sustituido con 1 a 3 sustituyentes R^{51};

en donde R^{51} se selecciona, en cada caso independientemente, de R^{52}, -OR^{53}, -$N(R^{54})R^{53}$, -$C(=O)R^{52}$, -$C(=O)OR^{53}$, -$C(=O)N(R^{54})R^{53}$, -$OC(=O)N(R^{54})R^{53}$, -$N(R^{54})C(=O)R^{52}$, -$N(R^{54})C(=O)N(R^{54})R^{53}$ y -$N(R^{54})C(=O)OR^{53}$; en la que

R^{52} se selecciona, en cada caso independientemente, de R^{53}, alquenilo (C_{2-8}) y alquinilo (C_{2-8}),

R^{53} se selecciona, en cada caso independientemente, de alquilo (C_{1-6}), cicloalquilo (C_{3-8}), cicloalquil (C_{3-8})-alquilo (C_{1-6}), arilo, aril-alquilo (C_{1-6}), **Het** y

Het-alquilo (C_{1-6}), y

R^{54} se selecciona, en cada caso independientemente, de H y alquilo (C_{1-3});

en donde cada uno de R^{52} y R^{53} está opcionalmente sustituido con 1 a 3 sustituyentes seleccionados, en cada caso independientemente, de R^{55}, halo, -CN, -OR^{56}, -SR^{56}, -SOR^{56}, -SO_2R^{56}, -$N(R^{54})R^{56}$, -$N(R^{54})C(=O)R^{55}$, -$N(R^{54})C(=O)N(R^{54})R^{56}$, -$N(R^{54})C(=O)OR^{56}$, -$OC(=O)N(R^{54})R^{56}$, -$C(=O)R^{55}$, -$C(=O)OR^{56}$ y -$CON(R^{54})R^{56}$, en donde

R^{55} se selecciona, en cada caso independientemente, de R^{56}, alquenilo (C_{2-8}) y alquinilo (C_{2-8}), y

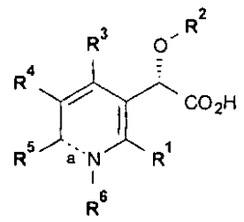
R^{56} se selecciona, en cada caso independientemente, de H, alquilo (C_{1-8}), cicloalquilo (C_{3-8}), cicloalquil (C_{3-8})-alquilo (C_{1-6}), arilo, aril-alquilo (C_{1-6}), **Het** y **Het**-alquilo (C_{1-6}),

en donde cada uno de R^{55} y R^{56} está, siempre que sea posible, en cada caso independientemente, opcionalmente sustituido con 1 a 3 sustituyentes seleccionados, en cada caso independientemente, de alquilo (C_{1-6}), haloalquilo (C_{1-6}), halo, -OH, -Oalquilo (C_{1-6}), -NH_2, -NHalquilo (C_{1-6}), -N(alquilo (C_{1-6}))$_2$ y -NH(C=O)alquilo (C_{1-6});

en donde **Het** es un heterociclo de 4 a 7 miembros saturado, insaturado o aromático que tiene de 1 a 4 heteroátomos, cada uno de ellos seleccionado independientemente entre O, N y S, o un heteropolicíclo de 7 a 14 miembros, saturado, insaturado o aromático que tiene, siempre que sea posible, de 1 a 5 heteroátomos, cada uno de ellos seleccionado independientemente entre O, N y S;

o una de sus sales.

Otro aspecto de la fórmula (I) proporciona un compuesto de fórmula II y un racemato, enantiómero o diastereoisómero de un compuesto de fórmula (II):



(II)

en la que

R^1 es alquilo (C_{1-6}), alquenilo (C_{2-6}) o cicloalquilo (C_{3-6}), en donde el alquilo (C_{1-6})

está opcionalmente sustituido con –Oalquilo (C_{1-6}) o -Salquilo (C_{1-6});

R^2 es alquilo (C_{1-8}) o cicloalquilo (C_{3-8}), en donde el cicloalquilo (C_{3-8}) está opcionalmente sustituido con alquilo (C_{1-6});

R^3 es arilo, en donde el arilo está opcionalmente condensado a uno o más ciclos, al menos uno de los cuales es un heterociclo, para formar un heteropoliciclo, y en donde el arilo o heteropoliciclo está opcionalmente sustituido con 1 a 4 sustituyentes, cada uno independientemente seleccionado de alquilo (C_{1-6}), halo y -Oalquilo (C_{1-6});

R^4 es alquilo (C_{1-6}), -CN, halo, haloalquilo (C_{1-6}), cicloalquilo (C_{3-5}) o -Oalquilo (C_{1-6}); y

a es un doble enlace, R^6 está ausente y R^5 es R^{51} o -alquil (C_{1-3})-R^{51}; o

a es un enlace sencillo y R^5 y R^6 están unidos, junto con los átomos a los que están unidos, para formar un anillo de 5 miembros que tiene, opcionalmente 1 a 3 heteroátomos adicionales, cada uno independientemente seleccionado de O, N y S, en donde el anillo de 5 miembros está opcionalmente sustituido con 1 a 3 sustituyentes R^{51};

en donde R^{51} se selecciona, en cada caso independientemente, de R^{52}, $-OR^{53}$, $-N(R^{54})R^{53}$, $-C(=O)R^{52}$, $-C(=O)OR^{53}$, $-C(=O)N(R^{54})R^{53}$, $-OC(=O)N(R^{54})R^{53}$, $-N(R^{54})C(=O)R^{52}$, $-N(R^{54})C(=O)N(R^{54})R^{53}$ y $-N(R^{54})C(=O)OR^{53}$; en la que

R^{52} se selecciona, en cada caso independientemente, de R^{53}, alquenilo (C_{2-8}) y alquinilo (C_{2-8}),

R^{53} se selecciona, en cada caso independientemente, de alquilo (C_{1-8}), cicloalquilo (C_{3-8}), espirocicloalquilo (C_{5-14}), cicloalquil (C_{3-8})-alquilo (C_{1-6}), arilo, aril-alquilo (C_{1-6}), **Het** y **Het**-alquilo (C_{1-6}), y

R^{54} se selecciona, en cada caso independientemente, de H y alquilo (C_{1-3});

en donde cada uno de R^{52} y R^{53} está opcionalmente sustituido con 1 a 3 sustituyentes seleccionados, en cada caso independientemente, de R^{55}, halo, -CN, $-OR^{56}$, $-SR^{56}$, $-SOR^{56}$, $-SO_2R^{56}$, $-N(R^{54})R^{56}$, $-N(R^{54})C(=O)R^{55}$, $-N(R^{54})C(=O)N(R^{54})R^{56}$, $-N(R^{54})C(=O)OR^{56}$, $-OC(=O)N(R^{54})R^{56}$, $-C(=O)R^{55}$, $-C(=O)OR^{56}$ y $-CON(R^{54})R^{56}$, en donde

R^{55} se selecciona, en cada caso independientemente, de R^{56}, alquenilo (C_{2-8}) y alquinilo (C_{2-8}), y

R^{56} se selecciona, en cada caso independientemente, de H, alquilo

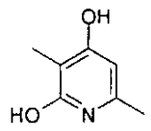
(C_{1-8}), cicloalquilo (C_{3-8}), cicloalquil (C_{3-8})-alquilo (C_{1-6}), arilo, aril-alquilo (C_{1-6}), **Het** y **Het**-alquilo (C_{1-6}),

en donde cada uno de $\mathbf{R^{55}}$ y $\mathbf{R^{56}}$ está, siempre que sea posible, en cada caso independientemente, opcionalmente sustituido con 1 a 3 sustituyentes seleccionados, en cada caso independientemente, alquilo (C_{1-6}), haloalquilo (C_{1-6}), halo, -OH, -Oalquilo (C_{1-6}), $-NH_2$, -NHalquilo (C_{1-6}), -N(alquilo (C_{1-6}))$_2$ y -NH(C=O)alquilo (C_{1-6});

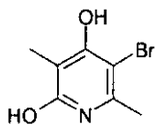
en donde **Het** es un heterociclo de 4 a 7 miembros saturado, insaturado o aromático que tiene de 1 a 4 heteroátomos, cada uno de ellos seleccionado independientemente entre O, N y S, o un heteropoliciclo de 7 a 14 miembros, saturado, insaturado o aromático que tiene, siempre que sea posible, de 1 a 5 heteroátomos, cada uno de ellos seleccionado independientemente entre O, N y S;

o una de sus sales.

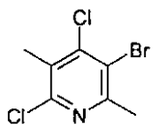
Otro aspecto de la invención proporciona uno o más compuestos intermedios seleccionados de las fórmulas:



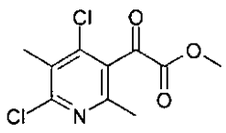
2c



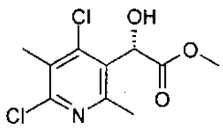
2d



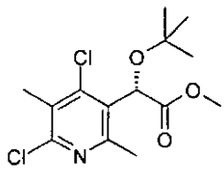
2e



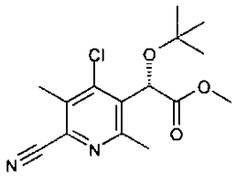
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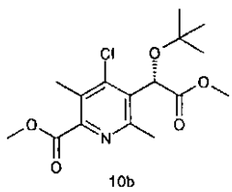
2g



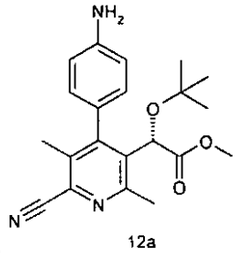
2h



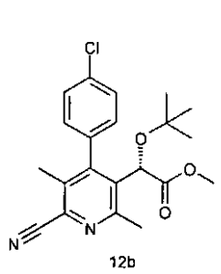
10a



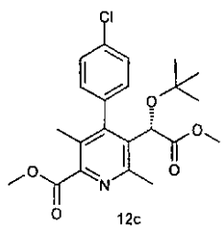
10b



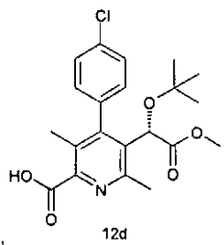
12a



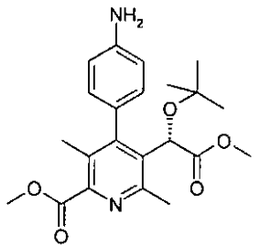
12b



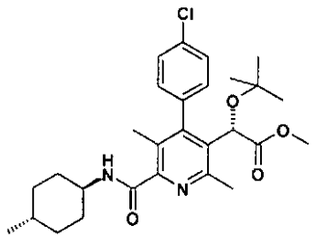
12c



12d



36a



37a

Otro aspecto de esta invención proporciona un compuesto de fórmula (I) o una sal farmacéuticamente aceptable del mismo, en forma de un medicamento.

Otro aspecto más de esta invención proporciona una composición farmacéutica que comprende una cantidad terapéuticamente eficaz de un compuesto de fórmula (I) o una sal farmacéuticamente aceptable del mismo; y uno o más vehículos farmacéuticamente aceptables.

De acuerdo con una realización de este aspecto, la composición farmacéutica de acuerdo con esta invención comprende adicionalmente al menos otro agente antiviral.

La invención también proporciona el uso de una composición farmacéutica según se describe aquí antes para el tratamiento de una infección por VIH en un ser humano que tiene o que está en riesgo de tener la infección.

Un aspecto adicional de la invención implica un método para tratar una infección por VIH en un ser humano que tiene o que está en riesgo de tener la infección, comprendiendo el método administrar al ser humano una cantidad terapéuticamente eficaz de un compuesto de fórmula (I), una sal farmacéuticamente aceptable del mismo, o una composición del mismo como se ha descrito anteriormente en la presente memoria.

Otro aspecto de la invención implica un método para tratar una infección por VIH en un ser humano que tiene o que está en riesgo de tener la infección, comprendiendo el método administrar al ser humano una cantidad

terapéuticamente eficaz de una combinación de un compuesto de fórmula (I), una sal farmacéuticamente aceptable del mismo, y al menos otro agente antiviral; o una composición del mismo.

También dentro del alcance de esta invención se encuentra el uso de un compuesto de fórmula (I) como se describe en la presente memoria, o una sal farmacéuticamente aceptable del mismo, para el tratamiento de una infección por VIH en un ser humano que tiene o que está en riesgo de tener la infección.

Otro aspecto de esta invención proporciona el uso de un compuesto de fórmula (I) como se describe en la presente memoria, o una sal farmacéuticamente aceptable, para fabricar un medicamento para el tratamiento de una infección por VIH en un ser humano que tiene o que está en riesgo de tener la infección.

Un aspecto adicional de esta invención se refiere a un artículo de fabricación que comprende una composición eficaz para tratar una infección por VIH; y un material de envasado que comprende una etiqueta que indica que la composición se puede utilizar para tratar la infección por VIH; en el que la composición comprende un compuesto de fórmula (I) de acuerdo con esta invención o una de sus sales farmacéuticamente aceptables.

Otro aspecto más de esta invención se refiere a un método de inhibir la replicación del VIH, que comprende exponer el virus a una cantidad eficaz del compuesto de fórmula (I), o una sal del mismo, en condiciones en las que se inhibe la replicación del VIH.

Dentro del alcance de la invención también se incluye el uso de un compuesto de fórmula (I) para inhibir la actividad de la enzima integrasa de VIH.

En el alcance de la invención se incluye adicionalmente el uso de un compuesto de fórmula (I), o una sal del mismo, para inhibir la replicación del VIH.

DESCRIPCIÓN DETALLADA DE LA INVENCIÓN

DEFINICIONES

Como se usa en la presente memoria, se aplican las siguientes definiciones salvo que se indique lo contrario:

El término "sustituyente", como se usa en la presente memoria y a menos que se especifique otra cosa, pretende indicar un átomo, radical o grupo que puede estar unido a un átomo de carbono, un heteroátomo o cualquier otro átomo que puede formar parte de una molécula o fragmento de la misma que, de otro modo,

estaría unida a al menos un átomo de hidrógeno. Los sustituyentes contemplados en el contexto de una molécula específica o fragmento de la misma son los que dan origen a compuestos químicamente estables, tal como reconocen los expertos en la técnica.

A menos que se indique de manera específica, a lo largo de la memoria descriptiva y las reivindicaciones adjuntas, una fórmula química o nombre dado debe abarcar sales, incluidas sus sales farmacéuticamente aceptables y sus solvatos, tales como, por ejemplo, hidratos, incluidos solvatos de los compuestos libres o solvatos de una sal del compuesto. Por ejemplo, los compuestos de la presente invención puede existir en formas no solvatadas así como solvatadas con disolventes farmacéuticamente aceptables, tales como agua, etanol y similares. En general, las formas solvatadas se consideran equivalentes a las formas no solvatadas para el fin de la presente invención.

En un aspecto, la presente invención proporciona también compuestos isotópicamente marcados y farmacéuticamente aceptables de la presente invención, en donde uno o más átomos están reemplazados por átomos que tienen el mismo número atómico, pero una masa atómica o un número másico diferente de la masa atómica o del número másico que se encuentra predominantemente en la naturaleza. Ejemplos de isótopos adecuados para la inclusión en los compuestos de la presente invención incluyen isótopos de hidrógeno, por ejemplo 2H o 3H. Compuestos isotópicamente marcados de la presente invención, por ejemplo versiones deuteradas de los compuestos, se pueden preparar por técnicas convencionales, conocidos por los expertos en la técnica o por procedimientos sintéticos análogos a los descritos en la presente solicitud, utilizando reactivos isotópicamente marcados apropiados, en lugar del reactivo no marcado mencionado en esta memoria.

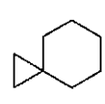
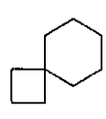
El término "alquilo (C_{1-n})", como se usa en la presente memoria, en el que n es un número entero, ya sea solo o combinado con otro radical, pretende dar a entender radicales alquilo acíclicos, de cadena lineal o ramificada que contienen de 1 a n átomos de carbono. "Alquilo (C_{1-6})" incluye, pero sin limitación, metilo, etilo, propilo (*n*-propilo), butilo (*n*-butilo), 1-metiletilo (*iso*-propilo), 1-metilpropilo (*sec*-butilo), 2-metilpropilo (*iso*-butilo), 1,1-dimetiletilo (*terc*-butilo), pentilo y hexilo. La abreviatura Me significa un grupo metilo; Et significa un grupo etilo, Pr significa un grupo propilo, iPr significa un grupo 1-metiletilo, Bu significa un grupo butilo y tBu

significa un grupo 1,1-dimetiletilo.

El término "alquenilo (C_{2-n})", como se usa en la presente memoria, en el que n es un número entero, solo o combinado con otro radical, pretende indicar un radical insaturado acíclico, de cadena lineal o ramificada que contiene de dos a n átomos de carbono, estando al menos dos de ellos unidos entre sí por un doble enlace. Ejemplos de radicales alquenilo (C_{2-6}) incluyen, pero sin limitación, etenilo (vinilo), 1-propenilo, 2-propenilo y 1-butenilo. Salvo que se especifique lo contrario, se entiende que el término "alquenilo (C_{2-n})" abarca estereoisómeros individuales cuando sea posible, incluyendo, pero sin limitación, isómeros (*E*) y (*Z*) y sus mezclas. Cuando un grupo alquenilo (C_{2-n}) está sustituido, se entiende que está sustituido en cualquier átomo de carbono del mismo que, de otro modo, portaría un átomo de hidrógeno, a menos que se especifique de otro modo, de manera que la sustitución daría lugar a un compuesto químicamente estable, tal como reconocen los especialistas en la técnica.

El término "alquinilo (C_{2-n})", como se usa en la presente memoria, en el que n es un número entero, solo o combinado con otro radical, pretende indicar un radical insaturado acíclico, de cadena lineal o ramificada, que contiene de dos a n átomos de carbono, estando al menos dos de ellos unidos entre sí por un triple enlace. Ejemplos de radicales alquinilo (C_{2-6}) incluyen, pero sin limitación, etinilo, 1-propinilo, 2-propinilo y 1-butinilo. Cuando un grupo alquinilo (C_{2-n}) está sustituido, se entiende que está sustituido en cualquier átomo de carbono del mismo que, de otro modo, portaría un átomo de hidrógeno, a menos que se especifique otra cosa, de manera que la sustitución daría origen a un compuesto químicamente estable, tal como reconocen los expertos en la materia.

El término "cicloalquilo (C_{3-m})", como se usa en la presente memoria, donde m es un número entero, solo o junto con otro radical, pretende indicar un sustituyente cicloalquilo que contiene de 3 a m átomos de carbono. Ejemplos de radicales cicloalquilo (C_{3-7}) incluyen, pero sin limitación, ciclopropilo, ciclobutilo, ciclopentilo, ciclohexilo y cicloheptilo.

El término "espirocicloalquilo (C_{5-n})", en donde n es un número entero, solo o en combinación con otro radical, indica un sistema de múltiples anillos de cicloalquilo que tiene dos anillos enlazados por un átomo común. Ejemplos de espirocicloalquilo incluyen, pero no se limitan a  y  .

La expresión "cicloalquil(C_{3-m})-alquilo (C_{1-n})-", como se usa en la presente memoria, en la que n y m son ambos números enteros, ya sea sola o combinada con otro radical, pretende dar a entender un radical alquilo con 1 a n átomos de carbono como se ha definido anteriormente, que está él mismo sustituido con un radical cicloalquilo que contiene de 3 a m átomos de carbono como se ha definido anteriormente. Ejemplos de cicloalquil(C_{3-7})-alquilo(C_{1-6}) incluyen, pero sin limitación, ciclopropilmetilo, ciclobutilmetilo, ciclopentilmetilo, ciclohexilmetilo, 1-ciclopropiletilo, 2-ciclopropiletilo, 1-ciclobutiletilo, 2-ciclobutiletilo, 1-ciclopentiletilo, 2-ciclopentiletilo, 1-ciclohexiletilo y 2-ciclohexiletilo. Cuando un grupo cicloalquil(C_{3-m})-alquilo(C_{1-n}) está sustituido, se entiende que los sustituyentes pueden estar unidos a la parte de cicloalquilo o de alquilo o a ambas, a menos que se especifique otra cosa, de manera que la sustitución daría lugar a un compuesto químicamente estable, tal como reconocen los expertos en la materia.

El término "arilo", como se usa en la presente memoria, ya sea solo o combinado con otro radical, pretende indicar un grupo monocíclico carbocíclico, aromático, que contiene 6 átomos de carbono que además puede estar condensado con un segundo grupo carbocíclico de 5 ó 6 miembros, que puede ser aromático, saturado o insaturado. Arilo incluye, pero no se limita a fenilo, indanilo, indenilo, 1-naftilo, 2-naftilo, tetrahidronaftilo y dihidronaftilo.

La expresión "aril-alquil (C_{1-n})-", como se usa en la presente memoria, en la que n es un número entero, ya sea sola o combinada con otro radical, pretende indicar un radical alquilo que tiene de 1 a n átomos de carbono, como se ha definido anteriormente, que está él mismo sustituido con un radical arilo como se ha definido anteriormente. Ejemplos de aril-alquil (C_{1-6})- incluyen, pero sin limitación, fenilmetilo (bencilo), 1-feniletilo, 2-feniletilo y fenilpropilo. Cuando un grupo aril-alquil (C_{1-n})- está sustituido, se entiende que los sustituyentes pueden estar unidos a la parte de arilo o de alquilo o a ambas, a menos que se especifique otra cosa, de manera que la sustitución daría lugar a un compuesto químicamente estable, tal como reconocen los expertos en la técnica.

El término "**Het**", como se usa en la presente memoria, ya sea solo o en combinación con otro radical, pretende indicar un heterociclo de 4 a 7 miembros, saturado, insaturado o aromático, que tiene de 1 a 4 heteroátomos, cada uno de ellos seleccionado independientemente entre O, N y S, o un heteropoliciclo de 7 a 14 miembros, saturado, insaturado o aromático que tiene, cuando sea posible, de 1

a 5 heteroátomos, cada uno de ellos seleccionado independientemente entre O, N y S, a menos que se especifique de otro modo. Cuando un grupo **Het** está sustituido, se entiende que los sustituyentes pueden estar unidos a cualquier átomo de carbono o heteroátomo del mismo que, de otro modo, llevaría un átomo de hidrógeno, a menos que se especifique otra cosa, de manera que la sustitución daría lugar a un compuesto químicamente estable, tal como reconocen los expertos en la técnica.

La expresión "**Het**-alquil (C_{1-n})-", como se usa en la presente memoria y a menos que se especifique otra cosa, en la que n es un número entero, ya sea sola o combinada con otro radical, pretende indicar un radical alquilo que tiene de 1 a n átomos de carbono, como se ha definido anteriormente, que está sustituido con un sustituyente **Het** como se ha definido anteriormente. Ejemplos de **Het**-alquil (C_{1-6})- incluyen, pero sin limitación, tienilmetilo, furilmetilo, piperidiniletilo, 2-piridinilmetilo, 3-piridinilmetilo, 4-piridinilmetilo, quinolinilpropilo y similares. Cuando un grupo **Het**-alquil (C_{1-n})- está sustituido, se entiende que los sustituyentes pueden estar fijados a la porción de **Het** o a la porción de alquilo de los mismos o a ambas, a menos que se especifique otra cosa, de manera que la sustitución daría origen a un compuesto químicamente estable, tal como se reconoce por los expertos en la técnica.

El término "heteroátomo", como se usa en la presente memoria, pretende dar a entender O, S o N.

El término "carbociclo", como se usa en la presente memoria, ya sea solo o en combinación con otro radical, pretende dar a entender un radical cíclico de 3 a 8 miembros, saturado, insaturado o aromático, en los que todos los miembros del anillo son átomos de carbono, y que se pueden condensar a uno o más grupos carbocíclicos de 3 a 8 miembros saturados, insaturados o aromáticos. Cuando un carbociclo está sustituido, se entiende que los sustituyentes pueden estar unidos a cualquier átomo de carbono que, de otro modo, llevaría un átomo de hidrógeno, a menos que se especifique de otro modo, de manera que la sustitución daría lugar a un compuesto químicamente estable, tal como reconocen los expertos en la técnica.

El término "heterociclo", como se usa en la presente memoria y a menos que se especifique otra cosa, ya sea solo o combinado con otro radical, pretende indicar un heterociclo de 3 a 7 miembros saturado, insaturado o aromático que

contiene de 1 a 4 heteroátomos, cada uno seleccionado independientemente entre O, N y S; o un radical monovalente derivado de la separación de un átomo de hidrógeno del mismo. Ejemplos de heterociclos de este tipo incluyen, pero no se limitan a azetidina, pirrolidina, tetrahidrofurano, tetrahidrotiofeno, tiazolidina, oxazolidina, pirrol, tiofeno, furano, pirazol, imidazol, isoxazol, oxazol, isotiazol, tiazol, triazol, tetrazol, piperidina, piperazina, azepina, diazepina, pirano, 1,4-dioxano, 4-morfolina, 4-tiomorfolina, piridina, N-óxido de piridina, piridazina, pirazina y pirimidina, y derivados saturados, insaturados y aromáticos de los mismos.

El término "heteropoliciclo", como se usa en la presente memoria y a menos que se especifique otra cosa, ya sea solo o combinado con otro radical, pretende dar a entender un heterociclo como se ha definido anteriormente condensado con uno o más de otros ciclos, que incluyen un carbociclo, un heterociclo o cualquier otro ciclo; o un radical monovalente derivado de la separación de un átomo de hidrógeno del mismo. Ejemplos de heteropoliciclos de este tipo incluyen, pero no se limitan a indol, isoindol, bencimidazol, benzotiofeno, benzofurano, benzopirano, benzodioxol, benzodioxano, benzotiazol, quinolina, isoquinolina y naftiridina, y derivados saturados, insaturados y aromáticos de los mismos.

El término "halo", como se usa en la presente memoria, se pretende que signifique un sustituyente halógeno seleccionado entre flúor, cloro, bromo o yodo.

El término "haloalquilo (C_{1-n})", como se usa en la presente memoria, en el que n es un número entero, ya sea solo o combinado con otro radical, pretende indicar un radical alquilo que tiene de 1 a n átomos de carbono como se ha definido antes, en el que uno o más átomos de hidrógeno se sustituyen cada uno por un sustituyente halo. Cuando dos o más átomos de hidrógeno se reemplazan por sustituyentes halo, los sustituyentes halo pueden ser iguales o diferentes. Ejemplos de haloalquilo (C_{1-6}) incluyen, pero sin limitación, clorometilo, cloroetilo, dicloroetilo, bromometilo, bromoetilo, dibromoetilo, clorobromoetilo, fluorometilo, difluorometilo, trifluorometilo, fluoroetilo y difluoroetilo.

El término "-O-alquilo(C_{1-n}), tal como se usa indistintamente en esta memoria, en donde n es un número entero, ya sea solo o en combinación con otro radical, pretende dar a entender un átomo de oxígeno adicionalmente unido a un radical alquilo con 1 a n átomos de carbono según se define arriba. Ejemplos de -O-alquilo(C_{1-n}) incluyen, pero no se limitan a metoxi (CH_3O-), etoxi (CH_3CH_2O-),

propoxi ($CH_3CH_2CH_2O$-), 1-metiletoxi (*iso*-propoxi; $(CH_3)_2CH$-O-) y 1,1-dimetiletoxi (*terc*-butoxi; $(CH_3)_3C$-O-). Cuando un radical -O-alquilo(C_{1-n}) está sustituido, se entiende que está sustituido en la parte de alquilo (C_{1-n}) del mismo, de modo que la sustitución daría lugar a un compuesto químicamente estable, tal como se reconoce por los expertos en la técnica.

El término "-S-alquilo(C_{1-n}), tal como se usa indistintamente en esta memoria, en donde n es un número entero, ya sea solo o en combinación con otro radical, pretende dar a entender un átomo de azufre adicionalmente unido a un radical alquilo con 1 a n átomos de carbono según se define arriba. Ejemplos de -S-alquilo (C_{1-n}) incluyen, pero sin limitación, metiltio (CH_3S-), etiltio (CH_3CH_2S-), propiltio ($CH_3CH_2CH_2S$-), 1-metiletiltio (*iso*propiltio; $(CH_3)_2CH$-S-) y 1,1-dimetiletiltio (*terc*-butiltio; $(CH_3)_3C$-S-). Cuando un radical -S-alquilo(C_{1-n}), o un derivado oxidado del mismo, tal como un radical -SO-alquilo(C_{1-n}) o un radical -SO_2-alquilo(C_{1-n}), está sustituido, se entiende que cada uno está sustituido en la parte alquilo (C_{1-n}) del mismo, de modo que la sustitución daría lugar a un compuesto químicamente estable, tal como reconocen los expertos en la técnica.

La expresión "grupo protector", tal como se usa en esta memoria, pretende indicar grupos protectores que se pueden utilizar durante la transformación sintética, incluidos pero no limitados a ejemplos que se listan en Greene, "Protective Groups in Organic Chemistry", John Wiley & Sons, Nueva York (1981), y ediciones más recientes del mismo, incorporadas a la presente memoria por referencia.

Las siguientes designaciones ---- y ---- se usan de manera indistinta en sub-fórmulas para indicar el enlace que está conectado con el resto de la molécula como se ha definido.

La expresión "sal del mismo", tal como se utiliza en esta memoria, pretende dar a entender cualquier sal de adición de un ácido y/o una base de un compuesto de acuerdo con la invención, que incluye, pero no se limita a, una sal farmacéuticamente aceptable del mismo.

La expresión "farmacéuticamente aceptable" se emplea en esta memoria para hacer referencia a los compuestos, materiales, composiciones y/o formas farmacéuticas que, basándose en el buen criterio médico, son adecuados para uso en contacto con los tejidos de seres humanos y animales sin una toxicidad, irritación o respuesta alérgica excesivas, ni ningún otro problema o complicación, de acuerdo con una relación beneficio/riesgo razonable.

Tal como se utiliza en esta memoria, "sales farmacéuticamente aceptables" se refieren a derivados de los compuestos descritos, en los que el compuesto original se modifica preparando sales de ácidos o bases del mismo. Ejemplos de sales farmacéuticamente aceptables incluyen, pero sin limitarse a ellas, sales de ácidos minerales u orgánicos de restos de carácter básico, tales como aminas; sales alcalinas u orgánicas de restos de carácter ácido, tales como ácidos carboxílicos; y similares. Por ejemplo, sales de este tipo incluyen acetatos, ascorbatos, aspartatos, bencenesulfonatos, benzoatos, besilatos, bicarbonatos, bitartratos, bromuros/hidrobromuros, edetatos de Ca/edetatos, camsilatos, carbonatos, cloruros/hidrocloruros, citratos, ciclamatos, edisilatos, etano-disulfonatos, estolatos, esilatos, fumaratos, gentisatos (sal de ácido 2,5-dihidroxibenzoico), gluceptatos, gluconatos, glutamatos, glicinatos, glicolatos, glicolilarsenilatos, hexil-resorcinatos, hidrabaminas, hidroximaleatos, hidroxinaftoatos, yoduros, isetionatos, lactatos, lactobionatos, malatos, maleatos, malonatos, mandelatos, metanosulfonatos, mesilatos, bromuros de metilo, nitratos de metilo, sulfatos de metilo, mucatos, napsilatos, nitratos, oxalatos, pamoatos, pantotenatos, fenilacetatos, fosfatos/difosfatos, poligalacturonatos, propionatos, sacarinatos, salicilatos, estearatos, subacetatos, succinatos, sulfamidas, sulfatos, tannatos, tartratos, teoclatos, toluenosulfonatos, trietiyoduros, xinafoatos (sal de ácido 1-hidroxi-2-naftoico), amonio, arginina, benzatinas, cloroprocaínas, colinas, dietanolaminas, etilendiaminas, lisina, megluminas, TRIS (*C,C,C*-tris(hidroximetil)-aminometano o Trometamol) y procaínas. Sales farmacéuticamente aceptables, adicionales, se pueden formar con cationes de metales tales como aluminio, calcio, litio, magnesio, potasio, sodio, zinc y similares. (véase, también, Pharmaceutical salts, Berge, S.M. et al., J. Pharm. Sci., (1977), 66, 1-19 y el Handbook of Pharmaceutical Salts, P.Heinrich Stahl, Camille G. Wermuth (comp.), Wiley-VCH, 2002, ambos de los cuales se incorporan en esta memoria como referencia).

Las sales farmacéuticamente aceptables de la presente invención se pueden sintetizar a partir del compuesto original que contiene un resto básico o ácido por métodos químicos convencionales. En general, sales de este tipo se pueden preparar haciendo reaccionar las formas de ácido o base libre de estos compuestos con una cantidad suficiente de la base o ácido apropiado en agua o en un diluyente orgánico tal como éter, acetato de etilo, etanol, isopropanol o acetonitrilo, o una mezcla de los mismos.

Sales de otros ácidos a los antes mencionados las cuales, por ejemplo, son útiles para purificar o aislar los compuestos de la presente invención comprende también una parte de la invención.

El término "tratamiento", como se usa en la presente memoria, pretende indicar la administración de un compuesto o composición de acuerdo con la presente invención para aliviar o eliminar síntomas de infección por VIH y/o para reducir la carga vírica en un paciente. El término "tratamiento" también abarca la administración de un compuesto o composición de acuerdo con la presente invención después de exposición del individuo al virus, pero antes de la aparición de síntomas de la enfermedad, y/o antes de la detección del virus en la sangre, para prevenir la aparición de síntomas de la enfermedad y/o para prevenir que el virus alcance niveles detectables en la sangre, y la administración de un compuesto o composición de acuerdo con la presente invención para prevenir la transmisión perinatal de VIH de la madre al bebé, mediante administración a la madre antes de dar a luz y al niño en los primeros días de vida.

La expresión "agente antiviral", como se usa en la presente memoria, pretende indicar un agente (compuesto o biológico) que es eficaz para inhibir la formación y/o replicación de un virus en un ser humano, que incluye, pero sin limitación, agentes que interfieren con cualquiera de los mecanismos del hospedador o virus necesarios para la formación y/o replicación de un virus en un ser humano.

La expresión "inhibidor de la replicación de VIH", tal como se usa en esta memoria, se pretende que signifique un agente capaz de reducir o eliminar la capacidad de VIH de replicarse en una célula hospedante, ya sea *in vitro, ex vivo* o *in vivo*.

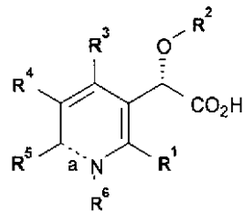
La expresión "integrasa del VIH" o "integrasa", tal como se emplea indistintamente en esta memoria, significa la enzima integrasa codificada por el virus de la inmunodeficiencia humana de tipo 1. La secuencia de polipéptidos de la enzima integrasa de la cepa NL4.3 de VIH-1 se proporciona como SEQ ID NO: 1.

La expresión "cantidad terapéuticamente eficaz" significa una cantidad de un compuesto de acuerdo con la invención que, cuando se administra a un paciente que lo necesita, es suficiente para realizar el tratamiento de estados de enfermedad, afecciones o trastornos para los que tienen utilidad los compuestos. Dicha cantidad debe ser suficiente para activar la respuesta biológica o médica de

un sistema de tejidos o paciente que esté buscando un investigador o médico. La cantidad de un compuesto de acuerdo con la invención que constituye una cantidad terapéuticamente eficaz variará dependiendo de factores tales como el compuesto y su actividad biológica, la composición usada para la administración, el momento de administración, la vía de administración, la velocidad de excreción del compuesto, la duración del tratamiento, el tipo de estado de enfermedad o trastorno que se va a tratar y su gravedad, los fármacos usados en combinación o al mismo tiempo que los compuestos de la invención, y la edad, peso corporal, salud general, sexo y dieta del paciente. Dicha cantidad terapéuticamente eficaz puede determinarse rutinariamente por un especialista en la técnica teniendo en cuenta su propio conocimiento, el estado de la técnica y esta descripción.

REALIZACIONES PREFERIDAS

En las siguientes realizaciones preferidas, se describen con detalle grupos y sustituyentes de los compuestos de fórmula (I):



(I)

de acuerdo con esta invención. Todas y cada una de las definiciones individuales indicadas en la presente memoria pueden combinarse con todas y cada una de las definiciones individuales indicadas en la presente memoria.

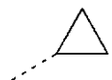
R^1:

R^1-A:

En al menos una realización, **R^1** es alquilo (C_{1-4}), alquenilo (C_{2-4}) o cicloalquilo (C_{3-5}), en donde el alquilo (C_{1-4}) está opcionalmente sustituido con –Oalquilo (C_{1-3}) o -Salquilo (C_{1-3}).

R^1-B:

Al menos en una realización, **R^1** se selecciona entre:

$-CH_3$, $-CH_2OMe$, $-CH_2OEt$, $-CH_2SMe$, $-CH=CH_2$ y  .

R^1-C:

En al menos una realización, R^1 es alquilo (C_{1-4}).

R^1-D:

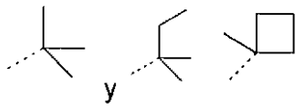
En al menos una realización, R^1 es $-CH_3$.

R^2:

R^2-A:

En al menos una realización, R^2 es alquilo (C_{3-8}) o cicloalquilo (C_{3-8}), en donde el cicloalquilo (C_{3-8}) está opcionalmente sustituido con alquilo (C_{1-6}).

R^2-B:

En al menos una realización, R^2 se selecciona entre:  y .

R^2-C:

En al menos una realización, R^2 es alquilo (C_{3-8}).

R^2-D:

En al menos en una realización, R^2 es  o  .

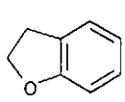
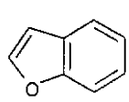
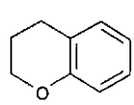
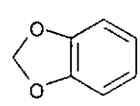
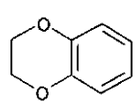
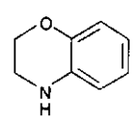
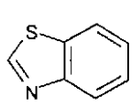
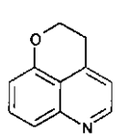
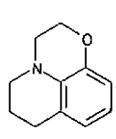
R^3:

R^3-A:

En al menos una realización, R^3 es fenilo o R^3 es fenilo condensado a uno o más ciclos, al menos uno de los cuales es un heterociclo, para formar un heteropoliciclo de 9 a 13 miembros que tiene 1 ó 2 heteroátomos, cada uno independientemente seleccionado de N, O y S; en donde el fenilo o heteropoliciclo está opcionalmente sustituido con 1 a 4 sustituyentes, cada uno independientemente seleccionado de alquilo (C_{1-6}), halo y -Oalquilo (C_{1-6}).

R^3-B:

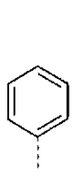
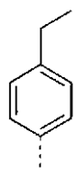
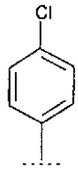
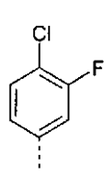
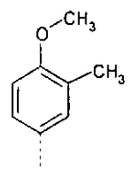
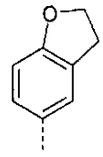
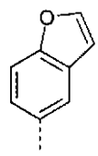
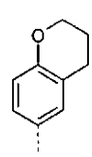
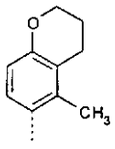
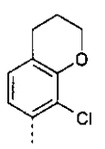
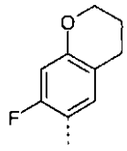
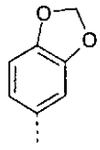
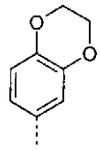
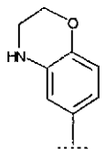
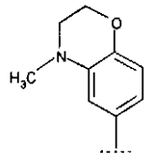
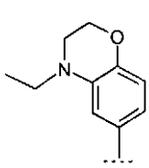
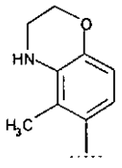
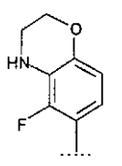
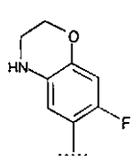
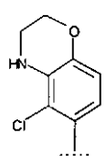
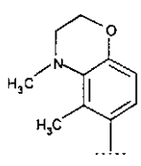
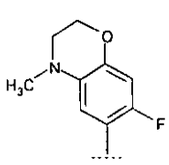
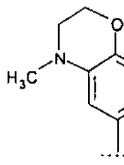
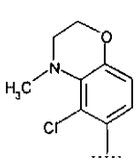
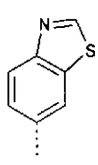
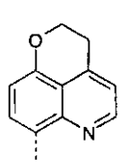
En al menos una realización, R^3 es fenilo o un heteropoliciclo seleccionado de:

, y ; en donde el fenilo o heteropoliciclo está opcionalmente sustituido con 1 a 4 sustituyentes, cada uno independientemente seleccionado de alquilo (C_{1-6}), halo y -Oalquilo (C_{1-6}).

R^3-C:

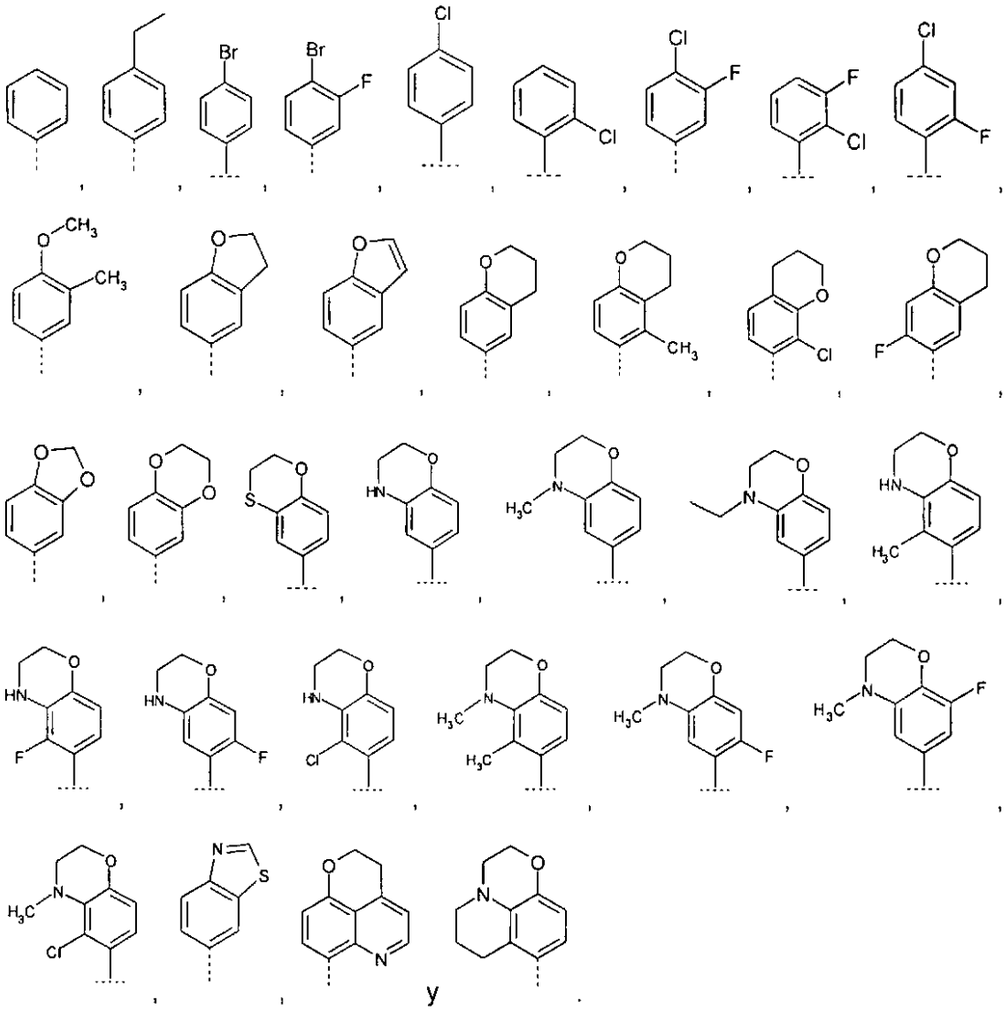
En al menos en una realización, R^3 se selecciona entre:

y .

R^3-D:

En al menos una realización, R^3 se selecciona entre:

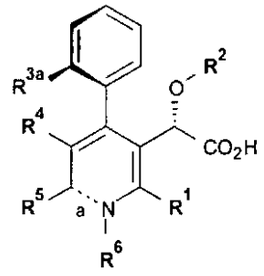


y .

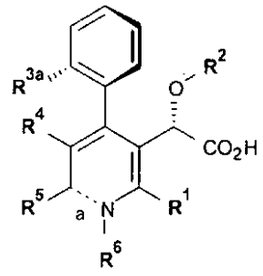
Un experto en la técnica reconocerá que cuando el sustituyente R^3 no está sustituido simétricamente en torno al eje de rotación del enlace que fija R^3 a **Núcleo**, los compuestos de la invención tendrán un eje de rotación de asimetría y, así, son posibles isómeros rotacionales. Cuando la barrera de energía a la rotación es relativamente baja, los isómeros rotacionales se interconvierten rápidamente a la temperatura ambiente y se considera que son conformeros. En contraposición, cuando la barrera de energía a la rotación es relativamente baja, los isómeros rotacionales se interconvierten tan lentamente a la temperatura ambiente que se pueden aislar y se considera que son atropisómeros.

Debido a que los compuestos de la invención poseen también al menos otro centro quiral, a saber, el átomo de carbono quiral unido a $-OR^2$, los isómeros rotacionales existirán como diastereoisómeros. Por ejemplo, cuando el sustituyente

R^3 asimétricamente sustituido porta un sustituyente R^{3a} en una posición *orto* con respecto al enlace que fija R^3 a **Núcleo**, en donde R^{3a} es cualquier átomo o grupo distinto de hidrógeno que es un sustituyente de R^3 en cualquier definición de R^3 recogida en esta memoria, son posibles las siguientes fórmulas **A-1** y **A-2** atropisoméricas, en que, de conformidad con la notación estereoquímica aceptada, los enlaces con cuña oscurecida y/o compacta indica la cara o borde del sustituyente R^3 que se proyecta hacia el observador:



A-1



A-2

A pesar de que para fines de ilustración, R^3 se muestra como fenilo asimétricamente sustituido en la posición orto con un sustituyente R^{3a} en las fórmulas **A-1** y **A-2**, resultará claro para la persona experta en la técnica que existen atropisómeros análogos para otros sustituyentes R^3 asimétricamente sustituidos.

Se ha encontrado que, cuando es posible separar los atropisómeros diastereoisómeros individuales, de modo que se pueden medir sus actividades individuales contra VIH, el atropisómero con la fórmula similar a **A-1** anterior, en que el sustituyente en el grupo R^3 se encuentra en la cara opuesta del plano del anillo de piridina del grupo $-OR^2$, es en algunos casos más activo contra VIH, cuando se mide, por ejemplo, por el proceso del Ejemplo 48 que figura más abajo, que el atropisómero con la fórmula similar a **A-2** anterior, en que el sustituyente en el grupo R^3 se encuentra en la misma cara del plano del anillo de piridina que el grupo $-OR^2$.

R^4

R^4-A:

En al menos una realización, R^4 es alquilo (C_{1-6}), -CN, halo o haloalquilo (C_{1-6}).

R^4-B:

En al menos una realización, R^4 es alquilo (C_{1-6}), -CN o halo.

R^4-C:

En al menos una realización, R^4 se selecciona de $-CH_3$, –CN y -F.

R^4-D:

En al menos una realización, R^4 es alquilo (C_{1-6}).

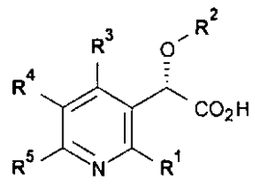
R^4-E:

En al menos una realización, R^4 es $–CH_3$.

<u>Núcleo y R^5/R^6:</u>

Núcleo-A:

En al menos una realización, **a** es un doble enlace y R^6 está ausente, de modo que el compuesto de la invención es un compuesto de fórmula (Ia):



(Ia)

en la que R^1, R^2, R^3, R^4 y R^5 son tal como se define en la presente memoria.

R^5/R^6-A:

En al menos una realización, **a** es un doble enlace, R^6 está ausente y R^5 es R^{51} o -alquil (C_{1-3})-R^{51};

en donde R^{51} se selecciona de R^{52}, $-OR^{53}$, $-N(R^{54})R^{53}$, $-C(=O)R^{52}$, $-C(=O)OR^{53}$, $-C(=O)N(R^{54})R^{53}$, $-N(R^{54})C(=O)R^{52}$, $-N(R^{54})C(=O)N(R^{54})R^{53}$ y $-N(R^{54})C(=O)OR^{53}$; en la que

R^{52} se selecciona de R^{53} y alquenilo (C_{2-8}), y

R^{53} se selecciona alquilo (C_{1-8}), cicloalquilo (C_{3-8}), cicloalquil (C_{3-8})-alquilo (C_{1-6}), arilo, aril-alquilo (C_{1-6}), **Het** y **Het**-alquilo (C_{1-6}), y

R^{54} se selecciona, en cada caso independientemente, de H y alquilo (C_{1-3});

en donde cada uno de R^{52} y R^{53} está opcionalmente sustituido con 1 a 3 sustituyentes, cada uno independientemente seleccionado de R^{56}, halo, -CN, $-OR^{56}$, $-SR^{56}$, $-SO_2R^{56}$, $-N(R^{54})R^{56}$ y $-CON(R^{54})R^{56}$, en donde

R^{56} se selecciona, en cada caso independientemente, de H, alquilo (C_{1-8}), cicloalquilo (C_{3-8}), cicloalquil (C_{3-8})-alquilo (C_{1-6}), arilo,

aril-alquilo (C_{1-6}), **Het** y **Het**-alquilo (C_{1-6}),

en donde R^{56} está, siempre que sea posible, en cada caso independientemente, opcionalmente sustituido con 1 a 3 sustituyentes, cada uno independientemente seleccionado de alquilo (C_{1-6}), haloalquilo (C_{1-6}), halo, -Oalquilo (C_{1-6}), -N(alquilo (C_{1-6}))$_2$ y -NH(C=O)alquilo (C_{1-6});

en donde **Het** es un heterociclo de 4 a 7 miembros saturado, insaturado o aromático que tiene de 1 a 4 heteroátomos, cada uno de ellos seleccionado independientemente entre O, N y S, o un heteropoliciclo de 7 a 14 miembros, saturado, insaturado o aromático que tiene, siempre que sea posible, de 1 a 5 heteroátomos, cada uno de ellos seleccionado independientemente entre O, N y S.

R^5/R^6-B:

En al menos una realización, **a** es un doble enlace, R^6 está ausente y R^5 es R^{51} o -alquil (C_{1-3})-R^{51};

en donde R^{51} se selecciona de R^{52}, -OR^{53}, -$N(R^{54})R^{53}$, -$C(=O)R^{52}$, -$C(=O)OR^{53}$, -$C(=O)N(R^{54})R^{53}$, -$N(R^{54})C(=O)R^{52}$, -$N(R^{54})C(=O)N(R^{54})R^{53}$ y -$N(R^{54})C(=O)OR^{53}$; en la que

R^{52} se selecciona de R^{53} y alquenilo (C_{2-8}), y

R^{53} se selecciona de alquilo (C_{1-8}), cicloalquilo (C_{3-8}), cicloalquil (C_{3-8})-alquil (C_{1-6})-, arilo, aril-alquil (C_{1-6})-, **Het** y **Het**-alquil (C_{1-6})-, en donde **Het** y la porción de **Het** de **Het**-alquil (C_{1-6})- se seleccionan, en cada caso independientemente, de un heterociclo de 5 ó 6 miembros saturado, insaturado o aromático que tiene 1 a 3 heteroátomos, cada uno independientemente seleccionado de O, N y S, y un heteropoliciclo de 8, 9 ó 10 miembros saturado, insaturado o aromático que tiene 1 a 3 heteroátomos, cada uno independientemente seleccionado de O, N y S; y

R^{54} se selecciona, en cada caso independientemente, de H y alquilo (C_{1-3});

en donde cada uno de R^{52} y R^{53} está opcionalmente sustituido con 1 a 3 sustituyentes, cada uno independientemente seleccionado de R^{56}, halo, -CN, -OR^{56}, -SR^{56}, -SO_2R^{56}, -$N(R^{54})R^{56}$ y -$CON(R^{54})R^{56}$, en donde

R^{56} se selecciona, en cada independientemente, de H, alquilo (C_{1-8}),

cicloalquilo (C_{3-8}), cicloalquil (C_{3-8})-alquilo (C_{1-6})-, arilo, aril-alquilo (C_{1-6})-, **Het** y **Het**-alquilo (C_{1-6})-, en donde **Het** y la porción de **Het** de **Het**-alquilo (C_{1-6})- se seleccionan, en cada caso independientemente, de un heterociclo de 5 ó 6 miembros saturado, insaturado o aromático que tienen 1 a 3 heteroátomos, cada uno independientemente seleccionado de O, N y S;

en donde $\mathbf{R^{56}}$ está, siempre que sea posible, en cada caso independientemente, opcionalmente sustituido con 1 a 3 sustituyentes, cada uno independientemente seleccionado de alquilo (C_{1-6}), haloalquilo (C_{1-6}), halo, -Oalquilo (C_{1-6}), -N(alquilo (C_{1-6}))$_2$ y -NH(C=O)alquilo (C_{1-6}).

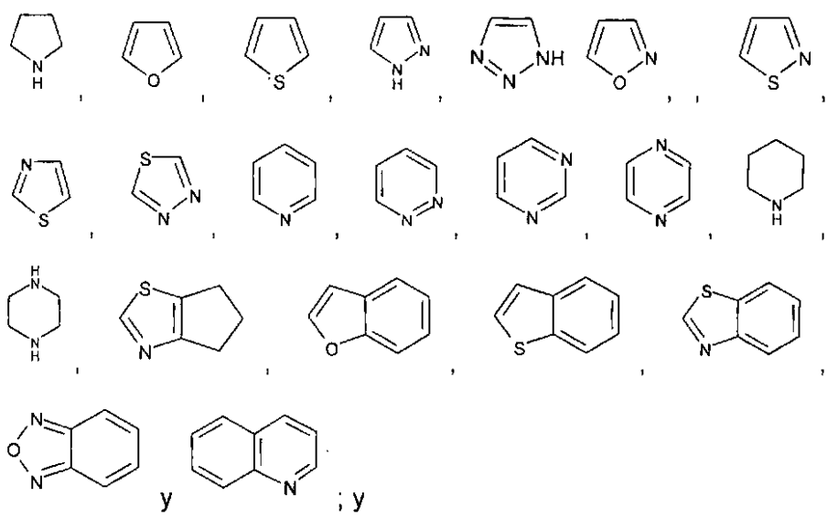
R^5/R^6-C:

En al menos una realización, **a** es un doble enlace, $\mathbf{R^6}$ está ausente y $\mathbf{R^5}$ es $\mathbf{R^{51}}$ o -alquil (C_{1-3})-$\mathbf{R^{51}}$;

en donde $\mathbf{R^{51}}$ se selecciona de $\mathbf{R^{52}}$, -O$\mathbf{R^{53}}$, -N($\mathbf{R^{54}}$)$\mathbf{R^{53}}$, -C(=O)$\mathbf{R^{52}}$, -C(=O)O$\mathbf{R^{53}}$, -C(=O)N($\mathbf{R^{54}}$)$\mathbf{R^{53}}$, -N($\mathbf{R^{54}}$)C(=O)$\mathbf{R^{52}}$, -N($\mathbf{R^{54}}$)C(=O)N($\mathbf{R^{54}}$)$\mathbf{R^{53}}$ y -N($\mathbf{R^{54}}$)C(=O)O$\mathbf{R^{53}}$; en la que

$\mathbf{R^{52}}$ se selecciona de $\mathbf{R^{53}}$ y alquenilo (C_{2-8}), y

$\mathbf{R^{53}}$ se selecciona de alquilo (C_{1-8}), cicloalquilo (C_{3-8}), cicloalquil (C_{3-8})-alquilo (C_{1-6})-, arilo, aril-alquilo (C_{1-6})-, **Het** y **Het**-alquilo (C_{1-6})-, en donde **Het** y la porción de **Het** de **Het**-alquilo (C_{1-6})- se seleccionan, en cada caso independientemente, de:

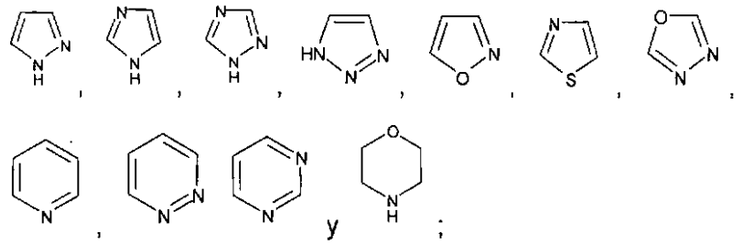


y ; y

R^{54} se selecciona, en cada caso independientemente, de H y alquilo (C_{1-3});

en donde cada uno de R^{52} y R^{53} está opcionalmente sustituido con 1 a 3 sustituyentes, cada uno independientemente seleccionado de R^{56}, halo, -CN, -OR^{56}, -SR^{56}, -SO_2R^{56}, -$N(R^{54})R^{56}$ y -$CON(R^{54})R^{56}$, en donde

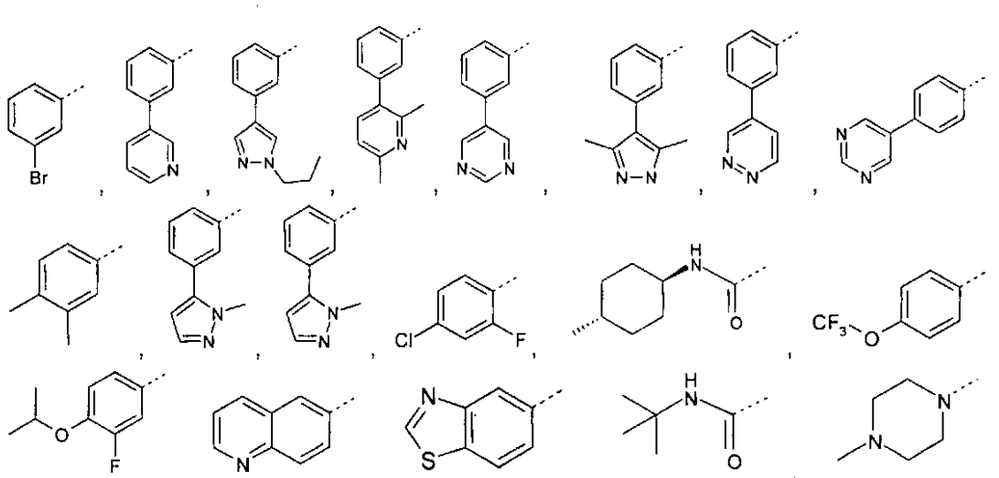
R^{56} se selecciona, en cada caso independientemente, de H, alquilo (C_{1-8}), cicloalquilo (C_{3-8}), cicloalquil (C_{3-8})-alquilo (C_{1-6})-, arilo, aril-alquilo (C_{1-6})-, **Het** y **Het**-alquilo (C_{1-6})-, en donde **Het** y la porción de **Het** de **Het**-alquilo (C_{1-6})- se seleccionan, en cada caso independientemente, de:

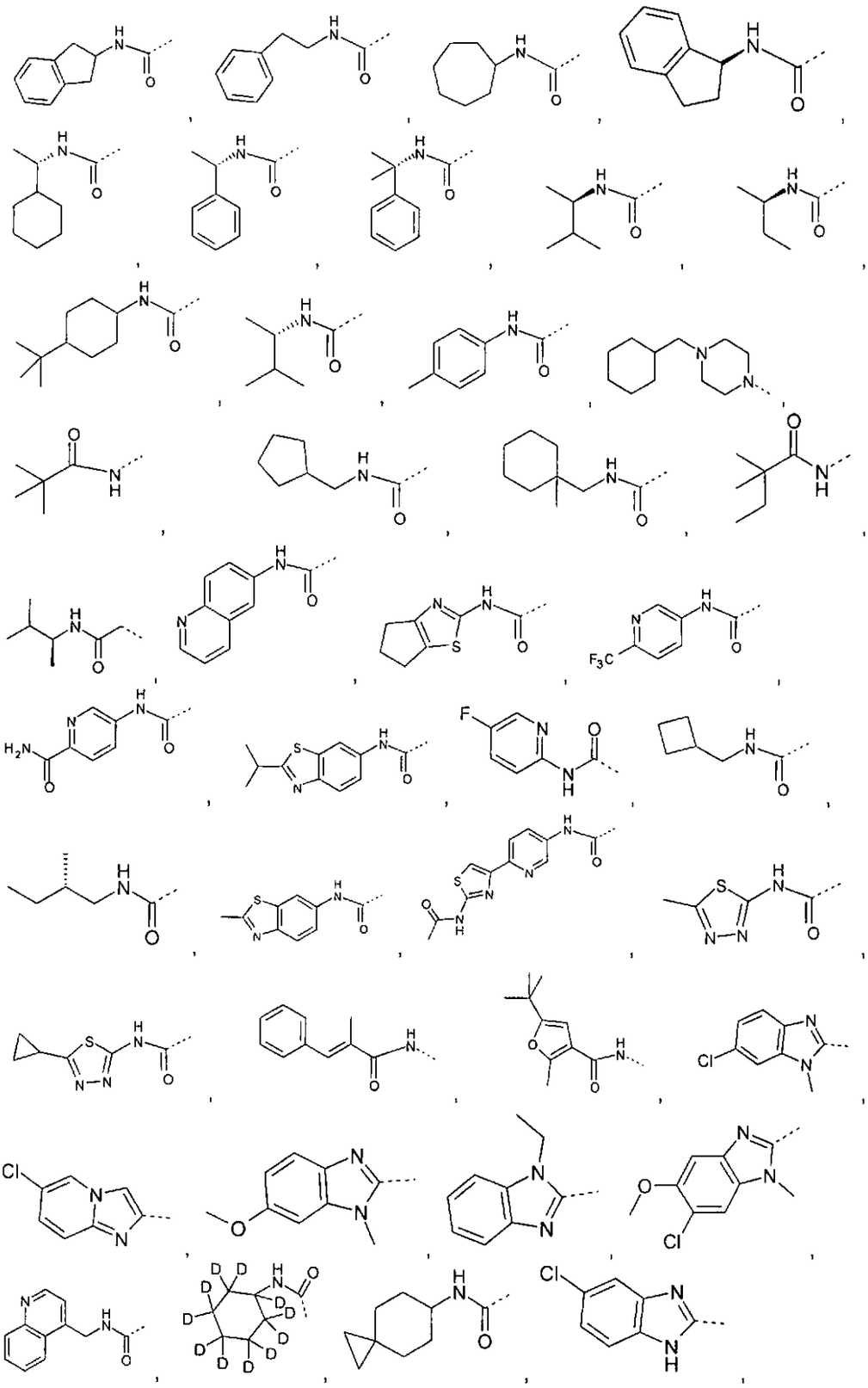


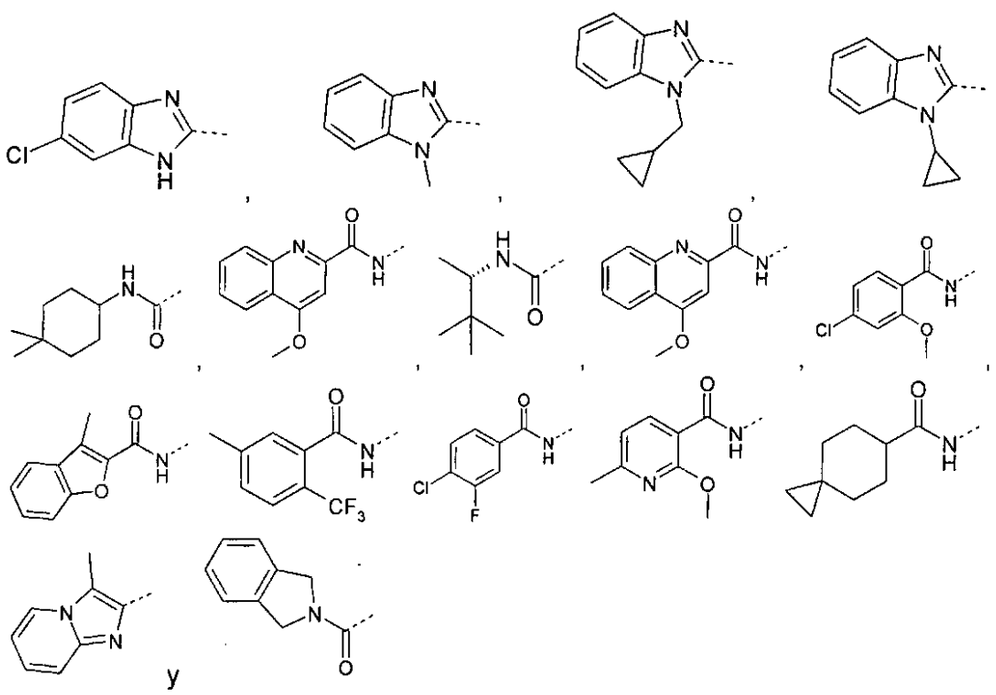
en donde R^{56} está, siempre que sea posible, en cada caso independientemente, opcionalmente sustituido con 1 a 3 sustituyentes, cada uno independientemente seleccionado de alquilo (C_{1-6}), haloalquilo (C_{1-6}), halo, -Oalquilo (C_{1-6}), -N(alquilo (C_{1-6}))$_2$ y -NH(C=O)alquilo (C_{1-6}).

R^5/R^6-D:

En al menos una realización, **a** es un doble enlace, R^6 está ausente y R^5 se selecciona de:







y

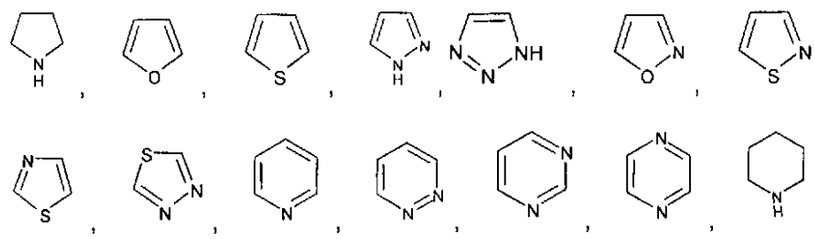
R^5/R^6-E:

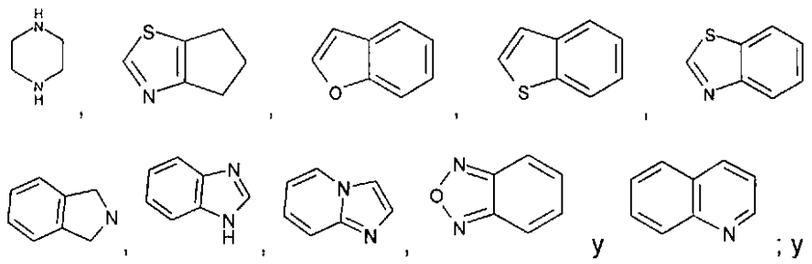
En al menos una realización, **a** es un doble enlace, R^6 está ausente y R^5 es R^{51} o -alquil (C_{1-3})-R^{51};

en donde R^{51} se selecciona de R^{52}, -OR^{53}, -$C(=O)R^{52}$, -$C(=O)OR^{53}$, -$C(=O)N(R^{54})R^{53}$, -$N(R^{54})C(=O)R^{52}$, -$N(R^{54})C(=O)N(R^{54})R^{53}$ y -$N(R^{54})C(=O)OR^{53}$; en la que

R^{52} se selecciona de R^{53} y alquenilo (C_{2-8}), y

R^{53} se selecciona de alquilo (C_{1-8}), cicloalquilo (C_{3-8}), cicloalquil (C_{3-8})-alquilo (C_{1-6})-, arilo, aril-alquilo (C_{1-6})-, **Het** y **Het**-alquilo (C_{1-6})-, en donde **Het** y la porción de **Het** de **Het**-alquilo (C_{1-6})- se seleccionan, en cada caso independientemente, de:



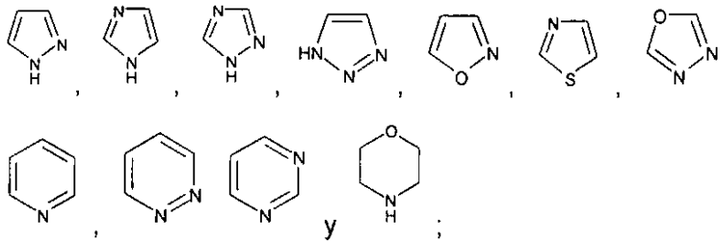


y ; y

R^{54} se selecciona, en cada caso independientemente, de H y alquilo (C_{1-3});

en donde cada uno de R^{52} y R^{53} está opcionalmente sustituido con 1 a 3 sustituyentes, cada uno independientemente seleccionado de R^{56}, halo, -CN, $-OR^{56}$, $-SR^{56}$, $-SO_2R^{56}$, $-N(R^{54})R^{56}$ y $-CON(R^{54})R^{56}$, en donde

R^{56} se selecciona, en cada caso independientemente, de H, alquilo (C_{1-8}), cicloalquilo (C_{3-8}), cicloalquil (C_{3-8})-alquilo (C_{1-6})-, arilo, aril-alquilo (C_{1-6})-, **Het** y **Het**-alquilo (C_{1-6})-, en donde **Het** y la porción de **Het** de **Het**-alquilo (C_{1-6})- se seleccionan, en cada caso independientemente, de:



y ;

en donde R_{56} está, siempre que sea posible, en cada caso independientemente, opcionalmente sustituido con 1 a 3 sustituyentes, cada uno independientemente seleccionado de alquilo (C_{1-6}), haloalquilo (C_{1-6}), halo, -Oalquilo (C_{1-6}), -N(alquilo (C_{1-6}))$_2$ y -NH(C=O)alquilo (C_{1-6}).

R^5/R^6-F:

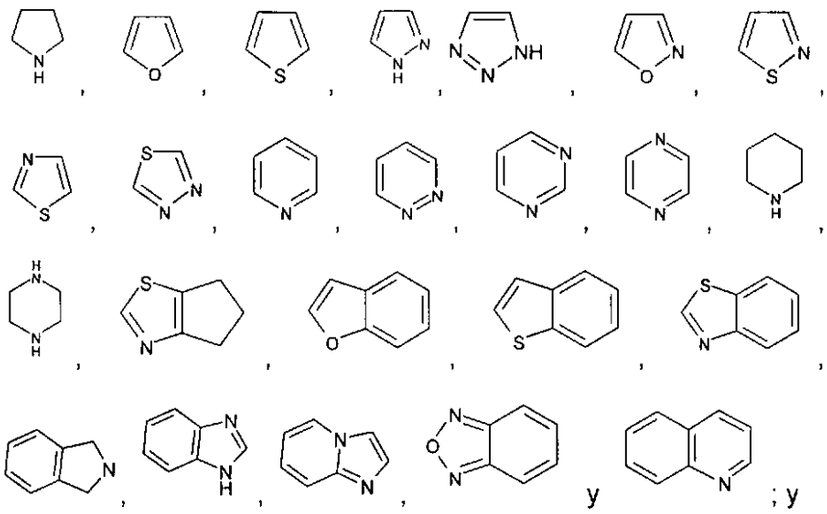
En al menos una realización, **a** es un doble enlace, R^6 está ausente y R^5 es R^{51} o -alquil (C_{1-3})-R^{51};

en donde R^{51} se selecciona de R^{52}, $-OR^{53}$, $-C(=O)R^{52}$, $-C(=O)OR^{53}$, $-C(=O)N(R^{54})R^{53}$, $-N(R^{54})C(=O)R^{52}$, $-N(R^{54})C(=O)N(R^{54})R^{53}$ y $-N(R^{54})C(=O)OR^{53}$; en la que

R^{52} se selecciona de R^{53} y alquenilo (C_{2-8}), y

R^{53} se selecciona de alquilo (C_{1-8}), cicloalquilo (C_{3-8}), espirocicloalquilo

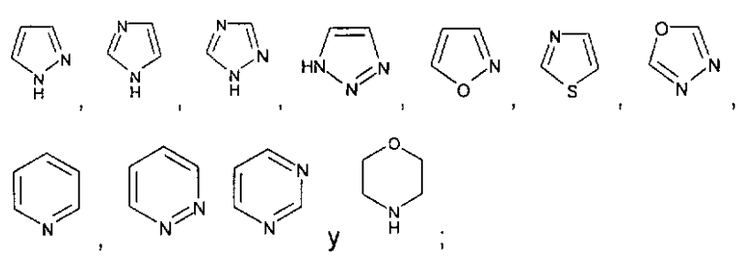
(C_{7-12}), cicloalquil (C_{3-8})-alquilo (C_{1-6})-, arilo, aril-alquilo (C_{1-6})-, **Het** y **Het**-alquilo (C_{1-6})-,
en donde **Het** y la porción de **Het** de **Het**-alquilo (C_{1-6})- se seleccionan, en cada caso independientemente, de:



; y

R^{54} se selecciona, en cada caso independientemente, de H y alquilo (C_{1-3});
en donde cada uno de R^{52} y R^{53} está opcionalmente sustituido con 1 a 3 sustituyentes, cada uno independientemente seleccionado de R^{56}, halo, -CN, -OR^{56}, -SR^{56}, -SO_2R^{56}, -$N(R^{54})R^{56}$ y -$CON(R^{54})R^{56}$, en donde

R^{56} se selecciona, en cada caso independientemente, de H, alquilo (C_{1-8}), cicloalquilo (C_{3-8}), cicloalquil (C_{3-8})-alquilo (C_{1-6})-, arilo, aril-alquilo (C_{1-6})-, **Het** y **Het**-alquilo (C_{1-6})-, en donde **Het** y la porción de **Het** de **Het**-alquilo (C_{1-6})- se seleccionan, en cada caso independientemente, de:



;

en donde R^{56} está, siempre que sea posible, en cada caso independientemente, opcionalmente sustituido con 1 a 3 sustituyentes, cada uno independientemente seleccionado de alquilo

(C_{1-6}), haloalquilo (C_{1-6}), halo, -Oalquilo (C_{1-6}), -N(alquilo (C_{1-6}))$_2$ y -NH(C=O)alquilo (C_{1-6}).

En la siguiente tabla se presentan ejemplos de realizaciones subgenéricas preferidas de la presente invención, en las que cada grupo sustituyente de cada realización se define de acuerdo con las definiciones expuestas anteriormente:

Realización	R^1	R^2	R^3	R^4	Núcleo	R^5/R^6
E-1	R^1-A:	R^2-A	R^3-A	R^4-A	Núcleo-A	R^5/R^6-A
E-2	R^1-A:	R^2-A	R^3-A	R^4-A	Núcleo-A	R^5/R^6-B
E-3	R^1-A:	R^2-A	R^3-A	R^4-B	Núcleo-A	R^5/R^6-A
E-4	R^1-A:	R^2-A	R^3-A	R^4-B	Núcleo-A	R^5/R^6-B
E-5	R^1-A:	R^2-A	R^3-A	R^4-D	Núcleo-A	R^5/R^6-A
E-6	R^1-A:	R^2-A	R^3-A	R^4-D	Núcleo-A	R^5/R^6-B
E-7	R^1-A:	R^2-C:	R^3-A	R^4-A	Núcleo-A	R^5/R^6-A
E-8	R^1-A:	R^2-C:	R^3-A	R^4-A	Núcleo-A	R^5/R^6-B
E-9	R^1-A:	R^2-C:	R^3-A	R^4-B	Núcleo-A	R^5/R^6-A
E-10	R^1-A:	R^2-C:	R^3-A	R^4-B	Núcleo-A	R^5/R^6-B
E-11	R^1-A:	R^2-C:	R^3-A	R^4-D	Núcleo-A	R^5/R^6-A
E-12	R^1-A:	R^2-C:	R^3-A	R^4-D	Núcleo-A	R^5/R^6-B
E-13	R^1-B	R^2-B	R^3-D	R^4-E	Núcleo-A	R^5/R^6-C
E-14	R^1-B	R^2-B	R^3-D	R^4-E	Núcleo-A	R^5/R^6-E
E-15	R^1-B	R^2-D	R^3-B:	R^4-B	Núcleo-A	R^5/R^6-D
E-16	R^1-B	R^2-A	R^3-B:	R^4-D	Núcleo-A	R^5/R^6-D
E-17	R^1-B	R^2-D	R^3-D	R^4-D	Núcleo-A	R^5/R^6-A
E-18	R^1-C	R^2-A	R^3-A	R^4-A	Núcleo-A	R^5/R^6-A
E-19	R^1-C	R^2-A	R^3-A	R^4-A	Núcleo-A	R^5/R^6-B
E-20	R^1-C	R^2-A	R^3-A	R^4-B	Núcleo-A	R^5/R^6-A
E-21	R^1-C	R^2-A	R^3-A	R^4-B	Núcleo-A	R^5/R^6-B
E-22	R^1-C	R^2-A	R^3-A	R^4-D	Núcleo-A	R^5/R^6-A
E-23	R^1-C	R^2-A	R^3-A	R^4-D	Núcleo-A	R^5/R^6-B
E-24	R^1-C	R^2-C:	R^3-A	R^4-A	Núcleo-A	R^5/R^6-A
E-25	R^1-C	R^2-C:	R^3-A	R^4-A	Núcleo-A	R^5/R^6-B
E-26	R^1-C	R^2-C:	R^3-A	R^4-B	Núcleo-A	R^5/R^6-A

Realización	R^1	R^2	R^3	R^4	Núcleo	R^5/R^6
E-27	R^1-C	R^2-C:	R^3-A	R^4-B	Núcleo-A	R^5/R^6-B
E-28	R^1-C	R^2-C:	R^3-A	R^4-D	Núcleo-A	R^5/R^6-A
E-29	R^1-C	R^2-C:	R^3-A	R^4-D	Núcleo-A	R^5/R^6-B
E-30	R^1-C	R^2-B	R^3-B:	R^4-A	Núcleo-A	R^5/R^6-C
E-31	R^1-C	R^2-A	R^3-A	R^4-B	Núcleo-A	R^5/R^6-F
E-32	R^1-D:	R^2-B	R^3-B:	R^4-E	Núcleo-A	R^5/R^6-C
E-33	R^1-D:	R^2-D	R^3-C:	R^4-E	Núcleo-A	R^5/R^6-E
E-34	R^1-D:	R^2-D	R^3-C:	R^4-B	Núcleo-A	R^5/R^6-E
E-35	R^1-D:	R^2-B	R^3-C:	R^4-B	Núcleo-A	R^5/R^6-B
E-36	R^1-D:	R^2-D	R^3-C:	R^4-E	Núcleo-A	R^5/R^6-F
E-37	R^1-D:	R^2-D	R^3-C:	R^4-B	Núcleo-A	R^5/R^6-F

Son ejemplos de compuestos más preferidos de acuerdo con esta invención cada compuesto individual indicado en las siguientes Tablas 1 a 6.

A menos que se indique específicamente, a lo largo de la memoria descriptiva y las reivindicaciones anejas, una fórmula química o nombre dado deberá abarcar tautómeros, y todos los estereoisómeros, isómeros ópticos y geométricos (por ejemplo, enantiómeros, diastereoisómeros, isómeros E/Z, atropisómeros) que resultan de toda posible estereoquímica en un centro quiral para el cual no se describe estereoquímica específica, y sus racematos, así como mezclas en diferentes proporciones de los enantiómeros separados, mezclas de diastereoisómeros, o mezclas de cualesquiera de las formas que anteceden en donde existen isómeros y enantiómeros de este tipo.

Es bien conocido en la técnica que la actividad biológica y farmacológica de un compuesto es sensible a la estereoquímica del compuesto. Por lo tanto, por ejemplo, los enantiómeros muestran, a menudo, actividades biológicas extraordinariamente diferentes incluyendo, pero sin limitación, diferencias en propiedades farmacocinéticas, incluyendo, pero sin limitación, el metabolismo, unión a proteínas y similares, y en propiedades farmacológicas incluyendo, pero sin limitación, el tipo de actividad desplegada, el grado de actividad, la toxicidad y similares. De esta manera, un experto en la técnica apreciará que un enantiómero puede ser más activo o puede presentar efectos beneficiosos cuando está en mayor cantidad que el otro enantiómero o cuando se separa del otro enantiómero.

Además, un experto en la técnica conocería el modo de separar, enriquecer o preparar selectivamente los enantiómeros de los compuestos de la presente invención a partir de esta descripción y del conocimiento en la técnica.

La preparación de estereoisómeros puros, por ejemplo enantiómeros y diastereoisómeros, o de mezclas con un exceso enantiomérico (ee) deseado o con pureza enantiomérica, se consigue por uno o más de los muchos métodos de (a) separación o resolución de enantiómeros, o (b) síntesis enantioselectiva conocida por los expertos en la técnica, o una combinación de los dos métodos. Estos métodos de resolución generalmente se basan en el reconocimiento quiral e incluyen, pero no están limitados a cromatografía usando fases estacionarias quirales, formación de complejos hospedante-huésped enantioselectivos, resolución o síntesis usando auxiliares quirales, síntesis enantioselectiva, resolución cinética enzimática y no enzimática, o cristalización enantioselectiva espontánea. Dichos métodos se describen, en general, en Chiral Separation Techniques: A Practical Approach (2ª Ed.), G. Subramanian (ed.), Wiley-VCH, 2000; T. E. Beesley y R. P. W. Scott, Chiral Chromatography, John Wiley & Sons, 1999; y Satinder Ahuja, Chiral Separations by Chromatography, Am. Chem. Soc., 2000. Además, existen métodos igualmente bien conocidos para la cuantificación del exceso enantiomérico o pureza, incluyendo, pero sin limitación, GC, HPLC, CE o RMN, y para la asignación de la configuración absoluta y la conformación, incluyendo, pero sin limitación, CD, ORD, cristalografía de rayos X o RMN.

COMPOSICIÓN FARMACÉUTICA

Preparaciones adecuadas para administrar los compuestos de la invención resultarán evidentes para aquellos con una experiencia ordinaria en la técnica e incluyen, por ejemplo, comprimidos, píldoras, cápsulas, supositorios, pastillas, trociscos, soluciones, jarabes, elixires, bolsitas, inyectables, productos inhalativos y polvos. El contenido del o de los compuestos farmacéuticamente activos debe estar en el intervalo de 0,05 a 90% en peso, preferiblemente de 0,1 a 50% en peso de la composición en su totalidad.

Comprimidos adecuados se pueden obtener, por ejemplo, mezclando uno o más compuestos de acuerdo con la invención con excipientes conocidos, por ejemplo diluyentes inertes, vehículos, disgregantes, adyuvantes, tensioactivos, aglutinantes y/o lubricantes. Los comprimidos también pueden comprender varias

capas.

Cuando un enantiómero de un ingrediente activo quiral tiene una actividad biológica diferente del otro, se contempla que la composición farmacéutica de acuerdo con la invención pueda comprender una mezcla racémica del ingrediente activo, una mezcla enriquecida en un enantiómero del ingrediente activo o un enantiómero puro del ingrediente activo. Se contempla que la mezcla enriquecida en un enantiómero del principio activo contenga desde más de 50% hasta aproximadamente 100% de un enantiómero del principio activo y desde aproximadamente 0% hasta menos de 50% del otro enantiómero del principio activo. Preferiblemente, cuando la composición comprende una mezcla enriquecida en un enantiómero del principio activo o un enantiómero puro del principio activo, la composición comprende de más de 50% hasta aproximadamente 100% de, o sólo, el enantiómero fisiológicamente activo y/o el enantiómero menos tóxico. Es bien conocido que un enantiómero de un principio activo puede ser el más activo fisiológicamente para una indicación terapéutica, mientras que el otro enantiómero del principio activo puede ser el más fisiológicamente activo para una indicación terapéutica diferente; por lo tanto, la constitución enantiomérica preferida de la composición farmacéutica puede diferir para el uso de la composición en el tratamiento de diferentes indicaciones terapéuticas.

Por lo tanto, de acuerdo con una realización, la composición farmacéutica de acuerdo con la invención comprende una mezcla racémica del compuesto de fórmula (I), o una sal farmacéuticamente aceptable del mismo.

Una realización alternativa proporciona una composición farmacéutica que comprende una mezcla enriquecida en un enantiómero del compuesto de fórmula (I), o una sal farmacéuticamente aceptable del mismo.

Una realización adicional proporciona una composición farmacéutica que comprende un enantiómero puro del compuesto de fórmula (I), o una sal farmacéuticamente aceptable del mismo.

El intervalo de dosis de los compuestos de la invención aplicable por día es habitualmente de 0,001 a 100 mg/kg de peso corporal, preferiblemente de 0,01 a 50 mg/kg de peso corporal. Cada unidad de dosificación puede contener, convenientemente, de 5% a 95% de compuesto activo (p/p). Preferentemente, dichas preparaciones contienen de 20% a 80% del compuesto activo.

La cantidad farmacéuticamente eficaz real o dosis terapéutica dependerá

naturalmente de factores conocidos por los especialistas en la técnica tales como la edad y peso del paciente, vía de administración y gravedad de la enfermedad. En cualquier caso, la combinación se administrará a dosificaciones y de una manera que permita suministrar una cantidad farmacéuticamente eficaz, basado en el estado singular del paciente.

Cuando la composición de esta invención comprende una combinación de un compuesto de la invención y uno o más agentes terapéuticos o profilácticos adicionales, tanto el compuesto como el agente adicional deben estar presentes a niveles de dosificación comprendidos entre aproximadamente 10 y 100% y, de manera más preferible, entre aproximadamente 10 y 80% de la dosificación normalmente administrada en un régimen de monoterapia.

TERAPIA DE COMBINACIÓN

Se contempla una terapia de combinación en la que un compuesto de acuerdo con la invención, o una de sus sales farmacéuticamente aceptable, se co-administra con al menos un agente antiviral adicional. Los agentes adicionales se pueden combinar con compuestos de esta invención para crear una forma de dosificación individual. Como alternativa, estos agentes adicionales se pueden administrar por separado, al mismo tiempo o secuencialmente, como parte de una forma de dosificación múltiple.

Cuando la composición farmacéutica de esta invención comprende una combinación de un compuesto de acuerdo con la invención, o una sal farmacéuticamente aceptable del mismo, y uno o más agentes antivirales adicionales, tanto el compuesto como el agente adicional deberían estar presentes a niveles de dosificación de entre aproximadamente 10 y 100%, y más preferiblemente entre aproximadamente 10 y 80% de la dosificación normalmente administrada en un régimen de monoterapia. En el caso de una interacción sinérgica entre el compuesto de la invención y el agente o los agentes antivirales adicionales, la dosificación de cualquiera o de todos los agentes activos en la combinación se puede reducir en comparación con la dosificación administrada normalmente en un régimen de monoterapia.

Los agentes antivirales contemplados para usar en dicha terapia de combinación incluyen agentes (compuestos o agentes biológicos) que son eficaces para inhibir la formación y/o replicación de un virus en un ser humano, que incluye,

pero sin limitación, agentes que interfieren con cualquiera de los mecanismos del hospedante o del virus necesarios para la formación y/o replicación de un virus en un ser humano. Estos agentes se pueden seleccionar de:

- NRTI (inhibidores de transcriptasa inversa nucleosídicos o nucleotídicos) incluyendo, pero sin limitación, zidovudina/RETROVIR® (GSK), didanosina/VIDEX® (BMS), estavudina/ZERIT® (BMS), lamivudina/EPIVIR® (GSK/Shire), emtricitabina/EMTRIVA® (Gilead Sciences), abacavir/ZIAGEN® (GSK) y tenofovir/VIREAD® (Gilead Sciences), apricitabina (Avexa), elvucitabina (Achillion) y OBP-601 (Oncolys), amdoxovir (RFS Pharma);
- NNRTI (inhibidores de transcriptasa inversa no nucleosídicos) incluyendo, pero sin limitación, nevirapina/VIRAMUNE® (Boehringer Ingelheim), delavirdina/Rescriptor® (Pfizer), efavirenz/SUSTIVA® (BMS), etravirina/INTELENCE® (Johnson & Johnson), rilpivirina (Johnson & Johnson), UK-453,061 (Pfizer) y RDEA806 (Ardea Biosciences), IDX-899 (GSK);
- inhibidores de proteasa incluyendo, pero sin limitación, ritonavir/NORVIR® (Abbott), tipranavir/APTIVUS® (Boehringer Ingelheim), saquinavir/INVIRASE® (Hoffmann LaRoche), nelfinavir/VIRACEPT® (Pfizer), indinavir/CRIXIVAN® (Merck), fosamprenavir/LEXIVA® (GSK/Vertex), atazanavir/REYATAZ® (BMS), lopinavir/KALETRA® (Abbott) y darunavir/PREZISTA® (Johnson & Johnson);
- inhibidores de entrada que incluyen, pero sin limitación,
- antagonistas de CCR5 incluyendo, pero sin limitación, maraviroc/SELZENTRY® (Pfizer), vicriviroc (Schering-Plough), INCB9471 (Incyte), PF-232798 (Pfizer), PRO-140 (Progenics Pharm), GSK706769 (GSK), PF-232798 (Pfizer), TBR-220 y TBR-652 (Tovira Therapeutics);
- antagonistas de CXCR4 que incluyen, pero sin limitación, AMD-11070 (Genzyme),
- inhibidores de la fusión incluyendo, pero sin limitación, enfuvirtida/FUZEON® (Trimeris), sifuvirtida (Fasogen), albuvirtida (Frontier Bio), FRI-1144 (Trimeris); y
- otros que incluyen, pero sin limitación, BMS-488043 (BMS);
- inhibidores de integrasa incluyendo, pero sin limitación,

raltegravir/ISENTRESS® (Merck), elvitegravir (Gilead Sciences), GSK1349572 y GSK1265744 (GSK), JTK-656 (Japan Tobacco);

- inhibidores de TAT;
- inhibidores de la maduración incluyendo, pero sin limitación, bevirimat (Myriad Genetics), vivecon (Myriad Genetics); y
- agentes inmunomoduladores incluyendo, pero sin limitación levamisol/ERGAMISOL® (Janssen-Ortho). y
- otros agentes antivirales que incluyen hidroxiurea, ribavirina, IL-2, IL-12 y pentafusida.

Además, un compuesto de acuerdo con la invención se puede utilizar con al menos otro compuesto de acuerdo con la invención o con uno o más agentes antifúngicos o antibacterianos (que incluyen, pero sin limitación, fluconazol).

Por lo tanto, de acuerdo con una forma de realización, la composición farmacéutica de esta invención comprende adicionalmente uno o más agentes antivirales.

Una realización adicional proporciona la composición farmacéutica de esta invención, en la que el uno o más agentes antivirales comprende al menos un NNRTI.

De acuerdo con otra realización de la composición farmacéutica de esta invención, el uno o más agentes antivirales comprenden al menos un NRTI.

De acuerdo con otra realización más de la composición farmacéutica de esta invención, el uno o más agentes antivirales comprenden al menos un inhibidor de proteasas.

De acuerdo con otra realización más de la composición farmacéutica de esta invención, el uno o más agentes antivirales comprende al menos un inhibidor de entrada.

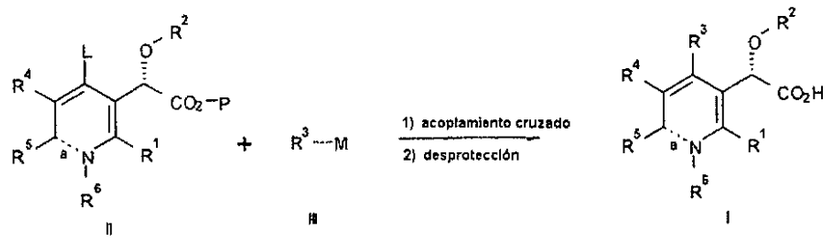
De acuerdo con una realización adicional de la composición farmacéutica de esta invención, el uno o más agentes antivirales comprende al menos un inhibidor de integrasa.

METODOLOGÍA Y SÍNTESIS

La síntesis de compuestos de fórmula (I) de acuerdo con esta invención se logra convenientemente siguiendo los procesos generales esbozados en los esquemas que figuran más abajo, en donde **a**, $\mathbf{R^1}$, $\mathbf{R^2}$, $\mathbf{R^3}$, $\mathbf{R^4}$, $\mathbf{R^5}$ y $\mathbf{R^6}$ son como se

definen en esta memoria. En la técnica se conocen bien otros procedimientos mediante los cuales se pueden preparar los compuestos de la invención, o se exponen en los siguientes ejemplos.

Esquema 1



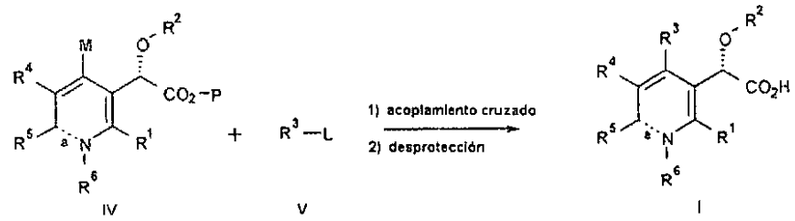
II III I

Compuestos intermedios **II**, en donde **a**, R^1, R^2, R^4, R^5 y R^6 son como se definen en esta memoria, **L** es un grupo lábil que incluye, pero no se limita a yodo, bromo, cloro u -OTf, y **P** es un grupo protector, seleccionado de grupos protectores comúnmente utilizados para ácidos carboxílicos, que incluyen, pero no se limitan a éster metílico o etílico, y compuestos intermedios **III**, en donde R^3 es como se define en esta memoria y **M** es un grupo adecuado para reaccionar con un grupo **L** en una reacción de acoplamiento, tales como son bien conocidos en la técnica, que incluyen, pero no se limitan a $-B(OH)_2$ o un éster de boronato, que incluyen, pero no se limitan a $-B(OCH_3)_2$ y $-B(OC(CH_3)_2C(CH_3)_2O)$; -I; $-SnR_3$, en donde **R** es alquilo (C_{1-6}); o -Zn**X**, en donde **X** es halo, están comercialmente disponibles o se preparan mediante reacciones bien conocidas en la técnica o según se recogen en los ejemplos que figuran más abajo. Derivados protegidos de compuestos de fórmula (I) se pueden preparar por reacciones de acoplamiento, bien conocidas, de compuestos intermedios **II** y **III**, que incluyen, pero no se limitan a acoplamiento cruzado de Suzuki entre un derivado **III** de ácido borónico o éster boronato y un derivado **II** de halo o triflato; acoplamiento cruzado de Ullmann, catalizado por cobre, entre derivados **II** y **III** de yodo; acoplamiento cruzado de Negishi entre un reactivo **III** de arilzinc y un derivado **II** de yodo o triflato; y acoplamiento de Stille entre un reactivo **III** de aril-estaño y un derivado **II** de bromo o yodo. Los productos protegidos de la reacción de acoplamiento se desprotegen después, por ejemplo por saponificación, para proporcionar compuestos de fórmula (I).

Alternativamente, tal como se muestra en el Esquema 2 que figura más abajo, los compuestos intermedios **IV** y **V**, en donde **a**, R^1, R^2, R^3, R^4, R^5, R^6, **L**, **M** y **P** son como se definen en esta memoria, se pueden acoplar utilizando los métodos

de acoplamiento cruzado arriba descritos, seguidos de desprotección, para proporcionar compuestos de fórmula (I).

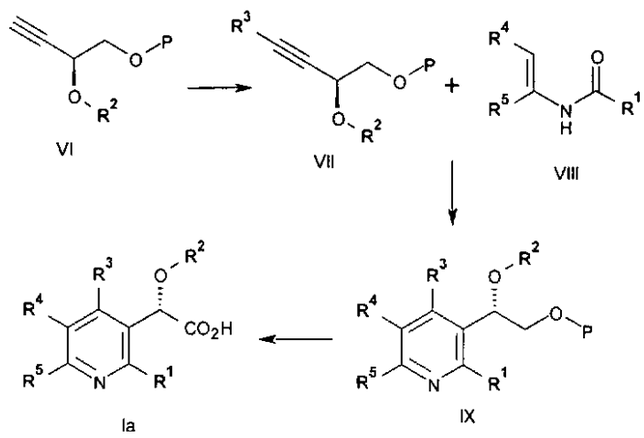
Esquema 2



IV V I

Además, compuestos de fórmula (Ia), en donde **a** es un enlace sencillo, R^6 está ausente y R^1, R^2, R^3, R^4 y R^5 son como se definen en esta memoria, se preparan convenientemente utilizando el proceso general ilustrado en el Esquema 3 que figura más abajo.

Esquema 3



VI VII VIII IX Ia

Compuestos intermedios **VI** y **VIII**, en donde R^1, R^2, R^3, R^4 y R^5 son como se definen en esta memoria y **P** es un grupo protector adecuado, bien conocido en la técnica, están comercialmente disponibles o se preparan por reacciones bien conocidas en la técnica o según se recogen en los ejemplos que figuran más abajo. Compuestos intermedios **VI** se transforman, convenientemente, en compuestos intermedios **VII** utilizando condiciones bien conocidas por los expertos en la técnica, que incluyen pero no se limitan a un acoplamiento de Sonogashira entre compuestos intermedios **VI** y R^3-I. Compuestos intermedios **VII** y **VIII** sufren una reacciòn de ciclocondensación en condiciones bien conocidas, que incluyen pero no

se limitan a reacción con $(CF_3SO_2)_2O$ (anhídrido tríflico) en presencia de 2-cloropiridina para dar compuestos intermedios **IX**. La desprotección del compuesto intermedio **IX**, seguido de oxidación del alcohol primario utilizando condiciones bien conocidas en la técnica, que incluyen, pero no se limitan a oxidación con peryodinano de Dess-Martin, seguido de oxidación con clorito de sodio, proporciona compuestos de fórmula (Ia).

Resultará evidente para un experto en la técnica que un compuesto de fórmula (I), o cualesquiera de los compuestos intermedios **II** a **XI** implicados en su preparación, en donde cualesquiera de los sustituyentes **a**, R^1, R^2, R^3, R^4, R^5 y R^6 tiene un significado según se define en esta memoria, se puede transformar en otro compuesto de fórmula (I), o cualesquiera de los compuestos intermedios **II** a **XI** implicados en su preparación según sea apropiado, en donde cualquiera de los sustituyentes **a**, R^1, R^2, R^3, R^4, R^5 y R^6 tiene un significado diferente según se define en esta memoria, en cualquier etapa químicamente conveniente en la preparación. Ejemplos de transformaciones de este tipo incluyen, pero no se limitan a alquilación, conversión de un grupo amino primario aromático en un sustituyente de cloro o bromo, utilizando una reacción de Sandmeyer, y deshalogenación reductiva. Además, los sustituyentes R^1, R^2, R^3, R^4, R^5 y R^6 pueden protegerse y/o desprotegerse en etapas intermedias en la preparación de un compuesto de fórmula (I), como se reconocerá por la persona experta.

Ejemplos

Otras características de la presente invención resultarán evidentes a partir de los siguientes ejemplos no limitantes que ilustran, a modo de ejemplo, los principios de la invención. Resultará evidente para un especialista que se pueden utilizar los procesos ejemplificados que figuran más abajo, con modificaciones apropiadas, para preparar otros compuestos de la invención como se describe en la presente memoria.

Como es bien conocido para el experto en la técnica, las reacciones se realizan en una atmósfera inerte (que incluye, pero sin limitación, nitrógeno o argón) en caso necesario, para proteger los componentes de la reacción del aire o la humedad. Las temperaturas se dan en grados centígrados (°C). Los porcentajes y relaciones en solución expresan una relación volumen a volumen, a menos que se indique otra cosa. La cromatografía de resolución ultrarrápida se lleva a cabo en gel de sílice (SiO2) de acuerdo con el procedimiento de W.C. Still et al., J. Org. Chem.,

(1978), 43, 2923. Los análisis de espectros de masas se registran usando espectrometría de masas de electropulverización. Un cierto número de compuestos intermedios y productos finales se purifican usando un aparato CombiFlash® Companion o RF, adquirido de Teledyne Isco Inc, empleando cartuchos de gel de sílice precargados y EtOAc y hexanos como disolventes. Estos cartuchos están disponibles en Silicycle Inc (SiliaFlash, sílice de 40-63 µm) o en Teledyne Isco (RediSep, sílice de 40-63 µm). La HPLC preparativa se realiza en condiciones convencionales usando una columna de fase inversa SunFire™ Prep C18 OBD 5 µm, 19 x 50 mm y un gradiente lineal usando TFA al 0,1%/acetonitrilo y TFA al 0,1%/agua como disolventes. Cuando corresponde, los compuestos se aíslan en forma de sales de TFA.

Alternativamente, la HPLC preparativa se realiza en condiciones convencionales usando una columna de fase inversa SunFire™ Prep C18 OBD 5 µm, 19 x 50 mm y un gradiente lineal empleando formiato de amonio 10 mM en H_2O (pH = 3,8); y MeOH.

Alternativamente, la HPLC preparativa se realiza en condiciones convencionales usando una columna de fase inversa XBridge™ Prep C18 OBD 5 µm, 19 x 50 mm y un gradiente lineal empleando bicarbonato de amonio 10 mM en H_2O (pH = 10,0); y MeOH.

La HPLC analítica se lleva a cabo bajo condiciones estándares utilizando una columna de fase inversa SunFire™ C18 (3,5 µm, 4,6 x 30 mm) a 220 nm, elución con un gradiente lineal, según se describe en la tabla siguiente (el disolvente A es TFA al 0,06% en H_2O; el disolvente B es TFA al 0,06% en CH_3CN):

Tiempo (min)	Flujo (ml/min)	Disolvente A (%)	Disolvente B (%)
0	2,5	98	2
0,5	2,5	98	2
6,0	2,5	50	50
10,5	3,0	0	100
11.5	3,0	0	100

Alternativamente, la HPLC analítica se lleva a cabo bajo condiciones estándares utilizando una columna de fase inversa SunFire™ C18 (3,5 µm, 4,6 x 30

mm) a 220 nm, elución con un gradiente lineal, según se describe en la tabla siguiente (el disolvente A es TFA al 0,06% en H_2O; el disolvente B es TFA al 0,06% en CH_3CN):

Tiempo (min)	Flujo (ml/min)	Disolvente A (%)	Disolvente B (%)
0	2,5	98	2
0,6	2,5	98	2
5,5	2,5	50	50
7,3	3,0	0	100
7,9	3,0	0	100

Alternativamente, la HPLC analítica se lleva a cabo bajo condiciones estándares utilizando una columna de fase inversa SunFire™ C18 (3,5 µm, 4,6 x 30 mm) a 220 nm, elución con un gradiente lineal, según se describe en la tabla siguiente (el disolvente A es TFA al 0,06% en H_2O; el disolvente B es TFA al 0,06% en CH_3CN):

Tiempo (min)	Flujo (ml/min)	Disolvente A (%)	Disolvente B (%)
0	2,5	98	2
0,6	2,5	98	2
3,4	2,5	50	50
4,5	3,0	0	100
4,9	3,0	0	100

Alternativamente, la HPLC analítica se lleva a cabo bajo condiciones estándares utilizando una columna de fase inversa SunFire™ C18 (3,5 µm, 4,6 x 30 mm) a 220 nm, elución con un gradiente lineal, según se describe en la tabla siguiente (el disolvente A es formiato de amonio 10 mM en H_2O (pH = 3,8); el disolvente B es MeOH):

Tiempo (min)	Flujo (ml/min)	Disolvente A (%)	Disolvente B (%)
0	4,0	98	2
2,85	4,0	0	100
2,86	5,0	0	100
3,60	5,0	0	100

Alternativamente, la HPLC analítica se lleva a cabo utilizando un tiempo de funcionamiento más corto utilizando una columna de fase inversa Aquity™ HSST3 (1,8 µm, 2,1 x 50 mm) a 220 nm, elución con un gradiente lineal, según se describe en la tabla siguiente (el disolvente A es TFA al 0,06% en H_2O; el disolvente B es TFA al 0,06% en CH_3CN):

Tiempo (min)	Flujo (ml/min)	Disolvente A (%)	Disolvente B (%)
0	0,9	98	2
1,5	0,9	50	50
2,6	0,9	0	100

Alternativamente, la HPLC analítica se lleva a cabo utilizando un tiempo de funcionamiento más corto utilizando una columna de fase inversa Aquity™ HSST3 (1,8 µm, 2,1 x 50 mm) a 220 nm, elución con un gradiente lineal, según se describe en la tabla siguiente (el disolvente A es formiato de amonio 10 mM en (pH = 3,8); el disolvente B es MeOH):

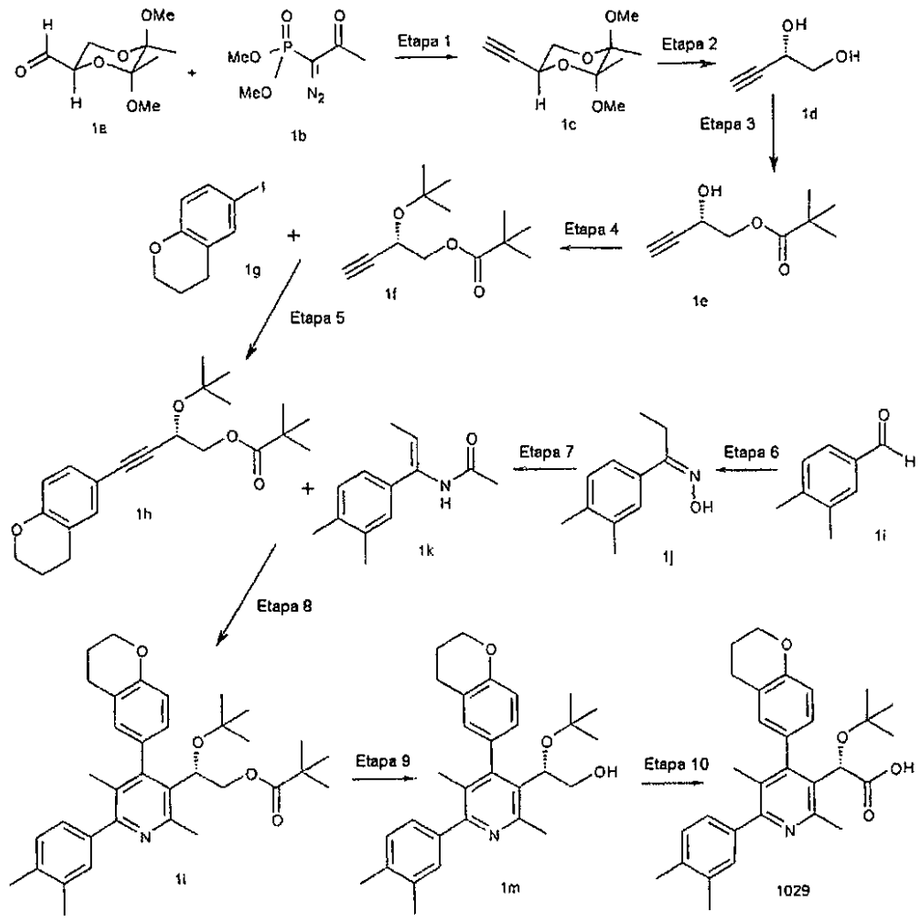
Tiempo (min)	Flujo (ml/min)	Disolvente A (%)	Disolvente B (%)
0	0,8	95	5
2,30	0,9	0	100
2,32	1,0	0	100
3,00	1,0	0	100

Las abreviaturas o los símbolos usados en la presente memoria incluyen:

Ac: acetilo; **AcOH:** ácido acético; **Ac_2O:** anhídrido acético; **BOC** o **Boc**: *terc*-butiloxicarbonilo; **BSA**: albúmina de suero bovino; **Bu:** butilo; **DABCO**: 1,4-diazabiciclo[2.2.2]octano; **DBU:** 1,8-diazabiciclo[5,4,0]undec-7-eno; **DCE**: dicloroetano; **DEAD**: azodicarboxilato de dietilo; **DCM:** diclorometano; **DIAD:** azodicarboxilato de diisopropilo; **DIBAL**: hidruro de diisobutilaluminio; **DMA**: dimetil-acetamida; **DMAP:** N,N-dimetil-4-aminopiridina; **DME:** 1,2-dimetoxietano **DMF:** N,N-dimetilformamida; **DMSO:** dimetilsulfóxido; **DPPA**: difenilfosforil azida; **Dppf**: 1,1'-bis(difenilfosfino)ferroceno; **CE_{50}:** concentración eficaz al 50%; **eq**: equivalente; **Et:** etilo; **Et_3N:** trietilamina; **Et_2O:** éter dietílico; **EtOAc:** acetato de etilo; **EtOH:** etanol; **HPLC:** cromatografía líquida de alto rendimiento; **CI_{50}:** concentración inhibidora al 50%; **^{i}Pr** o **i-Pr:** 1-metiletilo (*iso*-propilo); **LiHMDS**: hexametildisilazida de litio; **Me:** metilo; **MeCN:** acetonitrilo; **MeOH:** metanol; **MOI**: multiplicidad de infección; **MS:** espectrometría de masas (ES: electropulverización); **n-BuONa**: n-butóxido de sodio; **n-BuOH**: n-butanol; **n-BuLi**: n-butillitio; **NMP:** N-metilpirrolidona; **RMN:** espectroscopía de resonancia magnética nuclear; **Ph:** fenilo; PhMe: tolueno; **PG:** grupo protector; **Pr:** propilo; **RPMI:** Roswell Park Memorial Institute (medio de cultivo celular); **TA:** temperatura ambiente (aproximadamente 18ºC a 25ºC); **MP**: Material de partida; **TBTU:** tetrafluoroborato de 2-(1H-benzotriazol--1-il)--1,1,3,3-tetrametiluronio;***terc*-butilo** o **t-butilo**: 1,1-dimetiletilo; **Tf**: trifluorometanosulfonilo; **Tf_2O**: anhídrido trifluorometanosulfónico; **TFA:** ácido trifluoroacético; **THF:** tetrahidrofurano; **TLC:** cromatografía en capa fina; y **UPLC**: cromatografía líquida de ultra-alto rendimiento.

EJEMPLO 1

SÍNTESIS DEL COMPUESTO 1029 (TABLA 1)



Etapa 1:

Una mezcla de aldehído **1a** (5,85 g, 28,6 mmol; preparada de acuerdo con Michel, P. y Ley, S. V. *Synthesis* **2003**, *10*, 1598-1602), fosfonato **1b** (6,6 g, 34 mmol) y K_2CO_3 (8,8 g, 64 mmol) en MeOH (125 mL) se agita durante una noche a TA. La mezcla se concentra casi hasta sequedad y el residuo se reparte entre H_2O (250 mL) y EtOAc (500 mL). La capa acuosa se lava con EtOAc (2 x 250 mL) y las capas orgánicas combinadas se secan sobre Na_2SO_4 anhidro y se concentran para dar el alquino **1c**.

Etapa 2:

Una mezcla de alquino **1c** (5,0 g, 25 mmol) en TFA (35 mL) y agua (3,6 mL) se agita a TA durante aproximdamente 30 min. La mezcla se concentra a presión reducida y el residuo se purifica mediante CombiFlash® Companion para dar el diol

1d.

Etapa 3:

Una solución del diol **1d** (1,2 g, 14 mmol) y Et_3N (1,7 mL, 12 mmol) en DCM (80 mL) se enfría a 0°C en una atmósfera de N_2. Se añade gota a gota cloruro de trimetilacetilo y se deja que la mezcla resultante se agite durante una noche a TA. La reacción se enfría bruscamente con MeOH (100 mL) y se continúa agitando durante aproximadamente 20 min. La mezcla se concentra a presión reducida y el residuo se purifica mediante CombiFlash® Companion para dar el monoéster **1e** deseado.

Etapa 4:

En un matraz de reacción, que puede cerrarse herméticamente, se enfría una solución del alcohol propargílico **1e** (375 mg, 2,20 mmol) y resina Amberlyst® H-15 (150 mg) en hexano (3 mL) a -78°C. Después, se burbujea isobuteno a través de la solución hasta que el volumen aproximadamente se duplica. Después el tubo se cierra, se lleva a TA y se agita durante una noche. Después, el tubo se enfría a -78°C, se abre y se lleva de nuevo a la TA. La mezcla se filtra luego a través de un tarugo de SiO_2 (lavado con EtOAc) y se concentra a presión reducida para proporcionar *terc.*-butil-éter **1f** puro.

Etapa 5:

Se añaden sucesivamente $Pd(PPh_3)_4$ sólido (444 mg, 0,385 mmol) y CuI (146 mg, 0,769 mmol) a una mezcla de **1g** (10 g, 34 mmol) y el alquino **1f** (11 g, 55 mmol) en DMF (23 mL) y Et_2NH (115 mL). La mezcla de reacción se agita durante una noche a TA y después se concentra, se diluye con EtOAc (300 mL) y se lava sucesivamente con salmuera, solución acuosa de HCl 1 N y agua. La capa orgánica se seca sobre Na_2SO_4 y el residuo se purifica mediante CombiFlash® Companion para dar el alquino **1h**.

Etapa 6:

A una mezcla de 3,4-dimetilbenzaldehído (**1i**; 500 mg, 3,73 mmol) y Et_2O (12 mL) se añade, gota a gota, bromuro de etilmagnesio (3 M, 1,4 mL, 1,2 mmol). Después de 15 min, la reacción se enfría bruscamente con NH_4Cl acuoso saturado (50 mL) y las capas se separan. La capa orgánica se lava con NH_4Cl acuoso saturado (50 mL), se seca sobre Na_2SO_4 y se concentra para dar el alcohol bencílico intermedio. A una mezcla de este material y DCM (28 mL) se añade gel de sílice (2,2 g) seguido de clorocromato de piridinio (1,5 g, 7,2 mmol). La mezcla se

agita durante 45 min y la mezcla se filtra a través de un taco de sílice (3 x 1,5 cm) que después se lava con DCM (total de 50 mL). El filtrado se evapora hasta sequedad para dar la cetona intermedia. Este material se combina con acetato de sodio (102 mg, 1,25 mmol) e hidrocloruro de hidroxilamina (87 mg, 1,25 mmol) en MeOH (0,8 mL) y se calienta hasta 85°C en un tubo sellado. Después de 1 h, la reacción se deja enfriar hasta la temperatura ambiente y se concentra sobre gel de sílice (2 g). El producto se purifica mediante CombiFlash® Companion para dar la oxima **1j** en forma de una mezcla de isómeros *cis* y *trans*.

Etapa 7:

Una mezcla de oxima **1j** (130 mg, 0,73 mmol) y PhMe (1,7 mL) se desgasifica burbujeando gas N_2 a través de la solución durante 30 min. Se añade Ph_3P (0,23 g, 0,88 mmol) y la mezcla se agita durante 10 min a TA. Se añade Ac_2O (84 µL, 0,89 mmol) y la mezcla se agita a reflujo durante 16 h, se enfría hasta la temperatura ambiente y se concentra *en vacío*. Una mezcla del residuo, MeOH (3 mL) y K_2CO_3 en exceso (200 mg) se agita durante **1 h** y el metanol se separa *en vacío*. El residuo se disuelve en EtOAc (10 mL) y agua (5 mL). La capa orgánica se lava con agua, se concentra y se purifica mediante CombiFlash® Companion para dar la amida **1k** en forma de una mezcla de isómeros *cis* y *trans*.

Etapa 8:

Se añade Tf_2O (48 µL, 0,29 mmol) con jeringuilla a lo largo de 1 min a una mezcla agitada de la amida **1k** (55 mg, 0,27 mmol) y 2-cloropiridina (34 µL, 0,36 mmol) en DCM (0,7 mL) a -78 °C. Después de 5 min, el matraz de reacción se pone en un baño de hielo-agua y se calienta a 0°C. Se añade alquino **1h** (69 mg, 0,19 mmol) en DCM (0,7 mL) a través de una jeringa y la mezcla se deja calentar hasta TA. Después de agitar durante 30 min, se añade Et_3N (1 mL) y la mezcla se evapora hasta sequedad. El residuo se disuelve en EtOAc (10 mL) y se lava con agua. La capa orgánica se seca sobre Na_2SO_4 y se concentra y el residuo se purifica mediante CombiFlash® Companion, dando la piridina **1l**.

Etapa 9:

Se añade $LiBH_4$ en THF (2 M, 470 µL, 0,940 mmol) a una solución de éster **1l** (51 mg, 0,094 mmol) disuelta en THF (0,85 mL) y la mezcla de reacción se calienta hasta 85°C y se agita durante 30 min. Reactivo en exceso se enfría bruscamente con HCl (2 mL) y la mezcla se neutraliza con $NaHCO_3$ (10 mL) y se extrae con EtOAc (3 x 10 mL). Las capas orgánicas reunidas se secan sobre

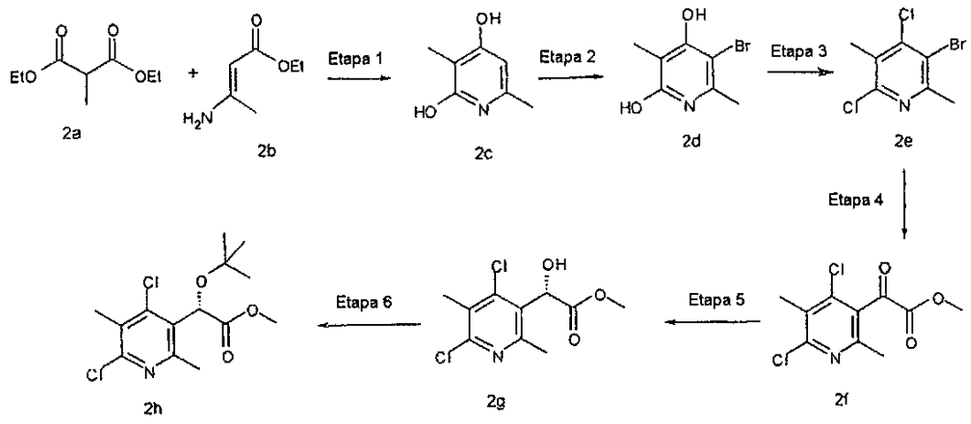
Na_2SO_4 y se concentran para dar el alcohol **1m**.

Etapa 10:

Se añade peryodinano de Dess-Martin (71 mg, 0,17 mmol) a una mezcla de alcohol **1m** (43 mg, 0,094 mmol) y DCM (1,7 mL). Después de 2h, la mezcla de reacción se concentra, el residuo se disuelve en 1:1 THF/tBuOH (2 mL) y se añade 2,3-dimetil-2-buteno (1 M en THF, 0,75 mL, 0,75 mmol). Una mezcla separada de $NaClO_2$ (71 mg, 0,79 mmol) y NaH_2PO_4 (71 mg, 0,59 mmol) en agua (1 mL) se añade a la primera mezcla y la mezcla se agita a TA. Después de 30 min, la mezcla se diluye con agua (5 mL) y se extrae con EtOAc (3 x 10 mL). La capa orgánica se seca sobre Na_2SO_4 y se concentra. El residuo se purifica por HPLC preparativa para dar el compuesto **1029** (Tabla 1).

EJEMPLO 2

SÍNTESIS DEL COMPUESTO INTERMEDIO 2H



Etapa 1:

A una solución de etóxido de sodio (1,48 L, 3,74 mol, al 21% p/p en EtOH) a TA se añade una solución de metilmalonato de dietilo **2a** (645 mL, 3,72 mol) en PhMe anhidro (330 mL). La solución resultante se agita durante 30 min y se añade una solución de 3-aminocrotonato de etilo **2b** (485 mL, 3,71 mol) en PhMe anhidro (490 mL). La mezcla se agita a reflujo durante 39 h, se separa EtOH (1-1,5 L) mediante destilación en vacío, la mezcla se enfría y se añade agua (1,6 L). La mezcla se agita durante ~2 h a 40°C, después se enfría y las fases se separan. La fase acuosa se lava con PhMe (2 x 50 mL) y luego se ajusta a pH 5-6 con HCl conc. El sólido se filtra y se seca para proporcionar dihidroxipiridina **2c**.

Etapa 2:

A una mezcla de dihidroxipiridina **2c** (100 g, 0,718 mol) y DCM (800 mL) a la temperatura ambiente se añade, gota a gota, Br_2 (37 mL, 150 g, 0,72 mol) en DCM (550 mL) a lo largo de 16 min. La mezcla resultante se agita a TA durante 1 h y el compuesto intermedio **2d** se recoge mediante filtración (sal HBr).

Etapa 3:

La bromopiridina **2d** (191 g, sal HBr) se calienta a reflujo en $POCl_3$ (850 mL) durante 18 h y se enfría hasta TA. El $POCl_3$ en exceso se separa mediante evaporación y el residuo se vierte sobre hielo. La mezcla se ajusta a pH de carácter básico utilizando NaOH 10 N y $NaHCO_3$ sólido. La mezcla se filtra y el filtrado se extrae con DCM (3 x 800 mL) y se seca sobre Na_2SO_4. La solución se hace pasar a través de una columna de SiO_2 (600 g) y se concentra para proporcionar **2e**.

Proceso alternativo para la etapa 3:

Bromopiridina **2d** (370 g, sal HBr) se calienta a reflujo en $POCl_3$ (1,25 L) durante 18 h. La mezcla se enfría y se evapora $POCl_3$ en exceso. Al residuo se añade $PhPOCl_2$ (1,2 L) y la mezcla se calienta a 150°C durante 28 h. La mezcla se deja enfriar hasta TA y se vierte sobre hielo, luego se ajusta a pH de carácter básico con Na_2CO_3 sólido. La mezcla se filtra y el filtrado se extrae con EtOAc (3 x 1500 mL) se seca sobre Na_2SO_4 y se filtra. El filtrado se hace pasar a través de una columna de SiO_2 (600 g) y se concentra, y el residuo se tritura con EtOAc para dar **2e** (196 g). El filtrado se concentra y se purifica mediante CombiFlash® Companion para dar una segunda cosecha de **2e**.

Etapa 4:

A una solución de bromuro **2e** (105 g, 0,411 mol) en THF anhidro (1,14 L) se añade Cu(I)Br (15 g, 0,1 mol). A la mezcla resultante a TA se añade iPrMgCl-LiCl (400 mL, 0,52 mol, 1,3 M en THF) a lo largo de 30 min. La mezcla se deja agitar durante 1 h, se añade cloro-oxoacetato de metilo (80 mL, 0,87 mol) y la agitacion se continúa durante 1 h. La reacción se enfría bruscamente con $NaHCO_3$ saturado y $NaHCO_3$ solido y la mezcla se extrae con EtOAc (3 x 1,2 L). El extracto orgánico se seca sobre Na_2SO_4 y se filtra. El extracto se hace pasar a través de una columna de SiO_2 (300 g), se concentra y el residuo se purifica mediante CombiFlash® Companion (EtOAc/ hexanos) para proporcionar **2f**.

Etapa 5:

A una mezcla de éster **2f** (65 g, 0,248 mol) en PhMe anhidro (400 mL) en un

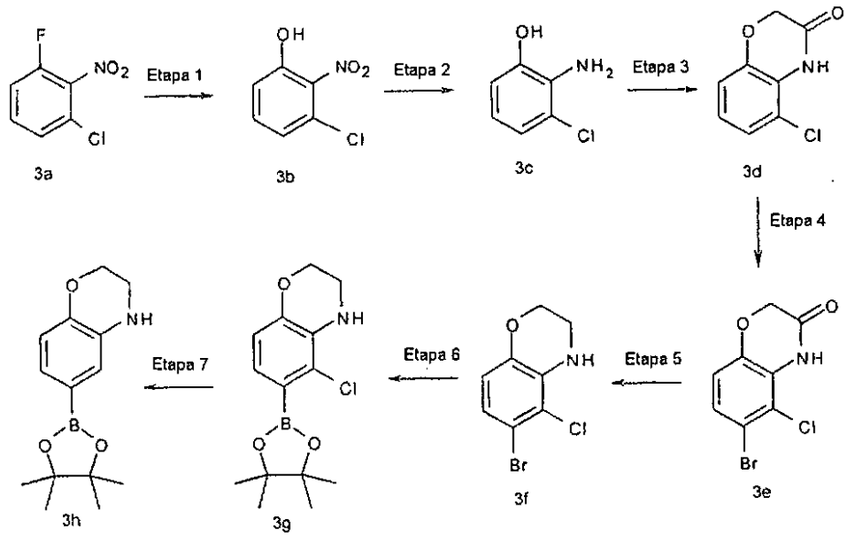
matrz de fondo redondo de 5 L de 3 bocas, equipado con una varilla de agitación magnética, embudo de adición, termómetro y entrada de gas, se añade, con agitación, (R)-2-metil-CBS-oxazoborolidina (solución 1 M en tolueno, 50 mL, 50 mmol). La mezcla se enfría hasta -35°C y se añade una solución de catecoloborano (36 mL, 40,5 g, 338 mmol) en tolueno (240 mL) a lo largo de un periodo de 2 h. La agitación se continúa a -35°C durante 30 min. La mezcla se deja calentar hasta -15°C y se diluye con EtOAc (400 mL) y Na_2CO_3 acuoso (al 15 % en peso, 800 mL). La mezcla se agita vigorosamente durante 30 min, y la fase orgánica se separa y se lava con Na_2CO_3 acuoso (al 15 % en peso, 2 x 200 mL; agitación vigorosa durante 30 min cada vez) y NH_4Cl acuoso (al 15 % en peso, 2 x 300 mL; agitación vigorosa durante 30 min cada vez). La capa orgánica se separa, se hace pasar a través de SiO_2 (300 g) eluyendo con EtOAc, y se concentra *en vacío*. El residuo se purifica mediante CombiFlash® Companion para proporcionar **2g**.

Etapa 6:

Una mezcla de **2g** (33,8 g, 0,128 mol) y acetato de t-butilo (2,4 L) se enfría en un baño de hielo, y se añade rápidamente ácido perclórico (al 70% ac.) (300 mL). El matraz se sella y se deja agitar durante 6 h a ~0-5°C. La reacción se enfría bruscamente con una solución saturada de Na_2CO_3 (850 mL) y la mezcla se ajusta a pH 8 -9 con Na_2CO_3 sólido. La mezcla se filtra, la capa orgánica se separa y la capa acuosa se extrae con EtOAc (3 x 750 mL), se seca sobre Na_2SO_4, se filtra y se concentra. Se añade DCM al residuo y la mezcla se filtra. La fase orgánica se concentra y se purifica utilizando el CombiFlash® Companion (hexano/EtOAc: 1% a 30%) para proporcionar **2h** (>98% ee mediante HPLC quiral) y se recupera material de partida **2g**.

EJEMPLO 3

SÍNTESIS DE LOS COMPUESTOS INTERMEDIOS 3G Y 3H



Etapa 1:

A una mezcla de 2-cloro-6-fluoronitrobenceno **3a** (6,62 g, 37,7 mmol) y $LiOH \cdot H_2O$ (6,33 g, 151 mmol) en THF (45 mL) y agua (65 mL) se añade H_2O_2 acuosa (al 30%, 8,6 mL, 80,0 mmol). La mezcla se sella y se calienta hasta 60°C con rápida agitación. Después de 3 días, la mezcla se enfría, se añade a una solución acuosa semisaturada de tiosulfato sódico (200 mL) y se agita vigorosamente en un embudo de separación. La mezcla se acidifica hasta pH < 3 con HCl 1 N, se extrae con EtOAc (500 mL) y se lava con salmuera (400 mL). Los extractos reunidos se secan sobre sulfato de magnesio, se filtran y se evaporan para dar el fenol **3b**.

Etapa 2:

A una mezcla de fenol **3b** (6,37 g, 36,7 mmol) y THF (100 mL) se añade polvo de estaño (17,4 g, 147 mmol), seguido de HCl 1 N (220 mL, 220 mmol) y la mezcla se agita vigorosamente a TA durante 16 h. La mezcla se enfría hasta 0°C y se neutraliza con NaOH 10 N (22 mL), y se agita vigorosamente durante aproximadamente 15 min. La mezcla se filtra a través de una almohadilla de Celite® y los sólidos se lavan a fondo con EtOAc (4 x 200 mL). El filtrado se acidifica con HCl 1 N (4 mL) y se diluye con salmuera (400 mL) y la fase orgánica se lava con salmuera (400 mL). El extracto se seca sobre sulfato de sodio, se filtra y se concentra para proporcionar aminofenol **3c**.

Etapa 3:

Se añade cloruro de cloroacetilo (1,94 mL, 24,3 mmol) a una mezcla enfriada con hielo del aminofenol **3c** (2,91 g, 20,3 mmol) y K_2CO_3 (8,40 g, 60,8 mmol) en DMF anhidra (200 mL) en una atmósfera de N_2. Después de 5 min, la reacción se deja calentar a TA y después de otros 45 min, se calienta a 50°C. Después de 15 h, la reacción se enfría y se extrae con EtOAc (600 mL) y se lava con agua/salmuera (1 L), solución semisaturada de bicarbonato de sodio (1 L) y salmuera (600 mL). La fase orgánica se seca luego sobre $MgSO_4$, se filtra y se concentra para proporcionar lactama **3d**.

Etapa 4:

Bromo (1,8 mL, 35 mmol) se añade lentamente, gota a gota, a una mezcla agitada de lactama **3d** (3,15 g; 17,1 mmol) en DCM anhidra (40 ml) a T.a. Después de 3 h, la mezcla se añade lentamente a tiosulfato sódico acuoso saturado (200 mL) y se extrae con DCM (4 x 100 mL). Los extractos combinados se lavan con salmuera (200 mL), se secan sobre $MgSO_4$, se filtran y se evaporan para proporcionar el bromuro **3e**.

Etapa 5:

Se añade una solución de borano en THF (1,0 M, 18,5 mL, 18,5 mmol) gota a gota a una mezcla enfriada con hielo de la lactama **3e** (4,00 g, 15,2 mmol) en THF anhidro (75 mL), y la reacción se deja calentar a TA. Después de aproximadamente 30 min, la solución se calienta a reflujo suave en atmósfera de N_2. Después de 2 h, la mezcla se enfría hasta 0°C, se enfría bruscamente, con cuidado, con NaOH 1 N (19 mL) y se agita durante aproximadamente 15 min. La mezcla se diluye con agua (30 mL) y el THF es evapora. El residuo acuoso se extrae con EtOAc (400 mL + 50 mL) y se lava con agua/salmuera (200 mL), NaOH 0,5 N (200 mL) y salmuera (100 mL). Los extractos reunidos se secan sobre sulfato de magnesio, se filtran y evaporan para proporcionar el derivado de morfolina **3f**.

Etapa 6:

DMF anhidra (30 mL) se añade a un matraz cargado con bromuro de arilo **3f** (1,84 g, 7,42 mmol), *bis*-(pinacolato)diborano (2,83 g, 11,1 mmol) y acetato de potasio (2,47 g, 26,0 mmol), y la mezcla se desoxigena burbujeando una corriente de gas N_2 a traves de la mezcla durante aproximadamente 15 min. Se añade 1,1'-bis(difenilfosfino)ferroceno (909 mg, 1,11 mmol) y la mezcla se desoxigena durante aproximadamente 5 min adicionales y luego se calienta hasta 95°C. Después de

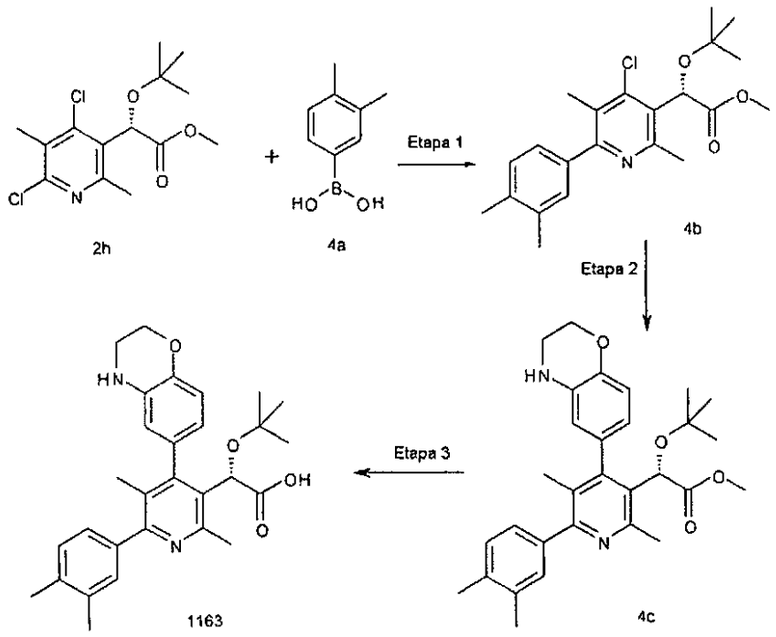
aproximadamente 16 h, la mezcla de reacción se enfría, se extrae con EtOAc (300 mL) y el extracto se lava con 1:1 de agua/salmuera (500 mL) y salmuera (200 mL), se seca sobre $MgSO_4$, se filtra y se concentra. El residuo se purifica mediante cromatografía sobre gel de sílice (EtOAc/hexanos) para proporcionar el boronato **3g** contaminado con 0,8 eq del reactivo de diboro.

Etapa 7:

Paladio sobre carbón vegetal activado (Pd al 10% en peso, 1,08 g) se añade a una mezcla de cloruro de arilo **3g** (3,0 g, 10 mmol) y formiato de amonio (6,4 g, 0,10 mol) en MeOH (75 mL). La mezcla se calienta a reflujo durante 30 min, se enfría hasta TA y se filtra a través de Celite®. La torta de filtración se aclara con MeOH, el filtrado se concentra hasta sequedad, y el residuo se reparte entre agua (50 mL) y EtOAc (100 mL). La capa orgánica se lava con salmuera (20 mL), se seca sobre $MgSO_4$ anhidro y se concentra para obtener éster borónico **3h**.

EJEMPLO 4

SÍNTESIS DEL COMPUESTO 1163 (TABLA 1)



Etapa 1:

A una solución de la dicloropiridina **2h** (Ejemplo 2) (2,0 g, 6,25 mmol) y ácido 3,4-dimetilfenilborónico **4a** (1,12 g, 7,5 mmol) en DMF (20 mL) se añade Na_2CO_3 2

M (7,8 mL, 16 mmol) seguido de $PdCl_2(PPh_3)_2$ (440 mg, 0,62 mmol). La mezcla de reacciòn se desgasifica mediante burbujeo con argón (10 min), el recipiente de reacción se sella y la mezcla se calienta a 110°C durante 16 h. La mezcla enfriada se diluye con EtOAc, se lava con agua y salmuera, se seca sobre $MgSO_4$ y se filtra. El residuo se purifica por CombiFlash® Companion (hexanos/EtOAc) para dar **4b**.

Etapa 2:

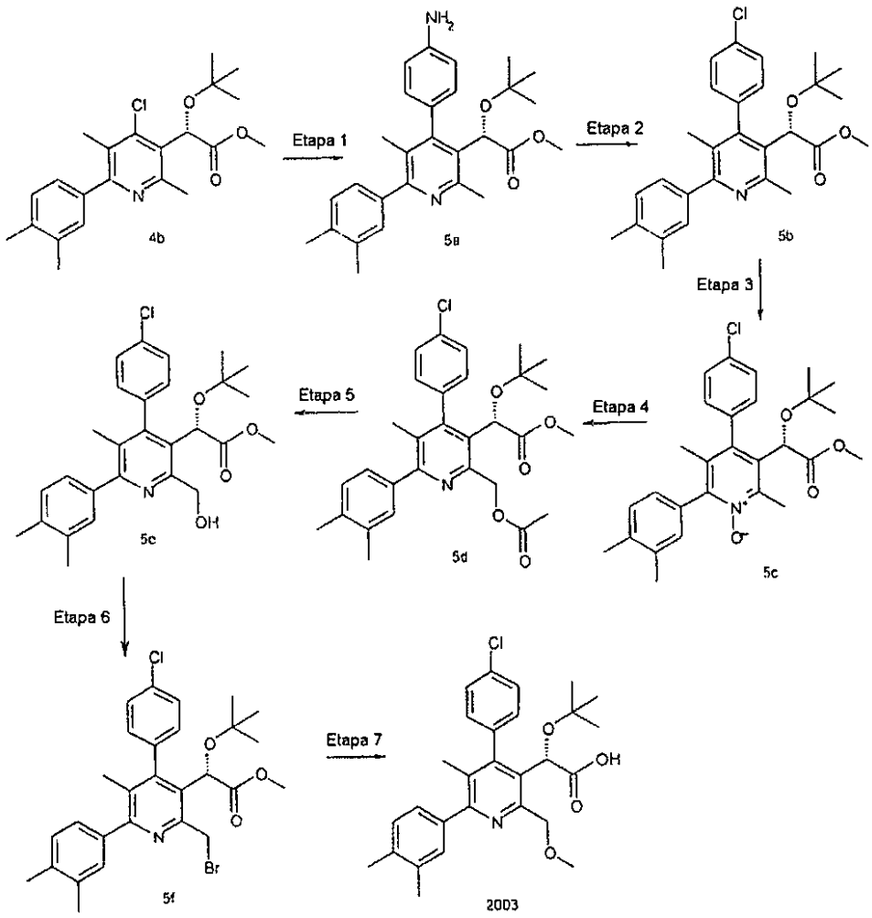
A una mezcla de cloropiridina **4b** (250 mg, 0,64 mmol) en DMA (5,6 mL) se añade éster de boronato **3h** (Ejemplo 3) (218 mg, 0,83 mmol), $Pd([P(t\text{-}Bu)_3]_2$ (33 mg, 0,064 mmol) y $NaHCO_3$ (269 mg, 3,2 mmol), seguido de agua (565 µL). La mezcla se desgasifica mediante burbujeo con argón bajo tratamiento con ultrasonidos durante 10 min, el recipiente de reacción se sella y la mezcla se calienta a 130°C durante 16 h. La mezcla de reacciòn se diluye con EtOAc (30 mL) y se lava con salmuera (2 veces), agua y salmuera, se seca sobre $MgSO_4$, se filtra y se concentra, y el residuo se purifica por CombiFlash® Companion (EtOAc al 30%/hexanos) para proporcionar **4c**.

Etapa 3:

A una mezcla del éster **4c** (191 mg, 0,39 mmol) y THF (8 mL)/MeOH (4 mL) se le añade NaOH 1,0 N (4 mL, 4,0 mmol) a TA. La mezcla se agita a 50°C durante 18 h, se enfría hasta TA, se enfría bruscamente con AcOH y se diluye con EtOAc. La mezcla se lava con agua y salmuera, se seca ($MgSO_4$), se filtra y se concentra en vacío. El residuo se purifica por CombiFlash® Companion (DCM/MeOH, 0-5%) y el producto se diluye con $MeCN/H_2O$, se congela y liofiliza para dar el compuesto **1163** (Tabla 1).

EJEMPLO 5

SÍNTESIS DEL COMPUESTO 2003 (TABLA 2)



Etapa 1:

A una solución de cloropiridina **4b** (Ejemplo 4) (2,0 g, 5,1 mmol) en DMA (40 mL) se añade 4-(4,4,5,5-tetrametil-1,2,3-dioxaborolan-2-il)anilina (1,6 g; 7,2 mmol) seguido de $NaHCO_3$ (2,2 g, 26 mmol) y agua destilada (3 mL). La mezcla se divide en dos matraces de microondas y se burbujean corrientes de gas argón a través de las mezclas vigorosamente agitadas durante 30 min. A cada matraz se añade catalizador de *bis*-(tri-*terc.*-butilfosfina) paladio (0) (131 mg; 0,256 mmol) y el burbujeo de argón continúa durante 10 min. Los matraces se sellan y se calientan a 130°C durante 16 h. Las dos mezclas de reacción se agrupan juntas, se diluyen con EtOAc (300 mL) y se lavan con agua/salmuera (1:1 v/v; 5 x 100 mL) y salmuera (2 x 100 mL). La fase orgánica se seca sobre $MgSO_4$, se filtra y se concentra. El residuo se purifica con CombiFlash® Companion para proporcionar el compuesto intermedio

5a.

Etapa 2:

A una mezcla de cloruro de cobre (II) (558 mg, 4,15 mmol) y MeCN seco (20 mL) a 0°C bajo una atmósfera de nitrógeno se añade, gota a gota, nitrito de *t*-butilo (0,55 mL; 4,17 mmol). Una solución de anilina **5a** (1,3 g, 2,9 mmol) en MeCN seco (20 mL) se añade gota a gota a lo largo de 5 min y el baño de hielo se retira después de 15 min. Después de 16 h, el disolvente se evapora y el residuo se adsorbe sobre gel de sílice, se purifica por CombiFlash® Companion y se seca bajo alto vacío para proporcionar el compuesto intermedio **5b**.

Etapa 3:

Se añade ácido *meta*-cloroperbenzoico (al 80%, 455 mg, 2,11 mmol) a una mezcla agitada de piridina **5b** (546 mg, 1,17 mmol) en DCM anhidro (10 mL) y la reacción se deja agitar a la temperatura ambiente. Después de 2 días, se añaden ácido *meta*-cloroperbenzoico (200 mg) y DCM (2 mL) adicionales y se continúa la agitación. Después de un día adicional, la mezcla se extrae con EtOAc (2 x 50 mL) y se lava con $NaHCO_3$ saturado y salmuera. Las fases orgánicas reunidas se secan sobre $MgSO_4$ y se concentran para proporcionar el N-óxido **5c**.

Etapa 4:

N-óxido de piridina **5c** (1,17 mmol) se disuelve en Ac_2O (7,5 mL, 79 mmol) y la solución resultante se calienta hasta 60°C bajo una atmósfera de nitrógeno. Después de 2 h, la solución se concentra bajo alto vacío y el residuo se seca bajo alto vacío durante 1 h. El residuo se extrae con EtOAc (100 mL) y se lava con $NaHCO_3$ saturado y salmuera. El extracto se seca sobre $MgSO_4$ y se concentra para proporcionar el compuesto intermedio **5d**.

Etapa 5:

Se añade HCl en dioxano (4N; 1,0 mL, 4,0 mmol) a una mezcla agitada de **5d** (1,17 mmol) y MeOH seco (4,2 mL) enfriado hasta 0°C, y la mezcla se deja calentar hasta temperatura ambiente. Después de 21 h, la mezcla se extrae con EtOAc (80 + 20 mL) y se lava con $NaHCO_3$ saturado y salmuera. Los extractos reunidos se secan sobre $MgSO_4$ y se evaporan para proporcionar el alcohol **5e**.

Etapa 6:

A una mezcla agitada de alcohol **5e** (1,17 mmol) y DCM anhidro (8 mL) a temperatura ambiente se añade CBr_4 (427 mg, 1,3 mmol) seguido de trifenilfosfina (339 mg; 1,3 mmol). La mezcla se agita a temperatura ambiente durante 16 h, luego

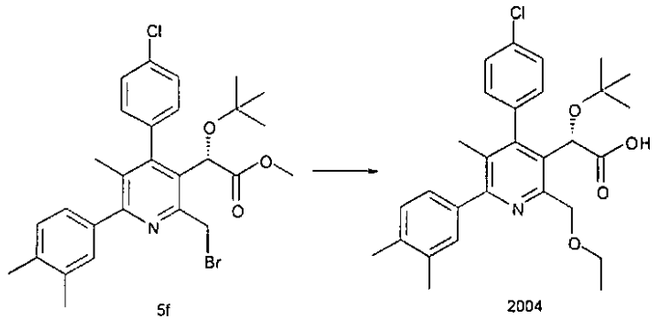
se diluye con DCM, se absorbe sobre gel de sílice y se purifica por CombiFlash® Companion para proporcionar el bromuro **5f**.

Etapa 7:

Se añade NaH (dispersión al 60 % en aceite; *aprox.* 2 mg) a una mezcla de bromuro **5f** (30 mg, 0,055 mmol), THF anhidro (0,5 mL) y MeOH anhidro (50 µL, 1,2 mmol) y la mezcla se agita en un vial sellado a temperatura ambiente. Después de 2 h, se añade NaH adicional (*aprox.* 2 mg) y se continúa la agitación. Después de 17 h, la mezcla de reacción se acidifica con ácido acético, se diluye con agua, se filtra a través de un filtro Millex, se divide en dos porciones y se purifica por HPLC preparatoria. Las fracciones relevantes se agrupan y se liofilizan para proporcionar el compuesto **2003** (Tabla 2, sal de TFA).

EJEMPLO 6

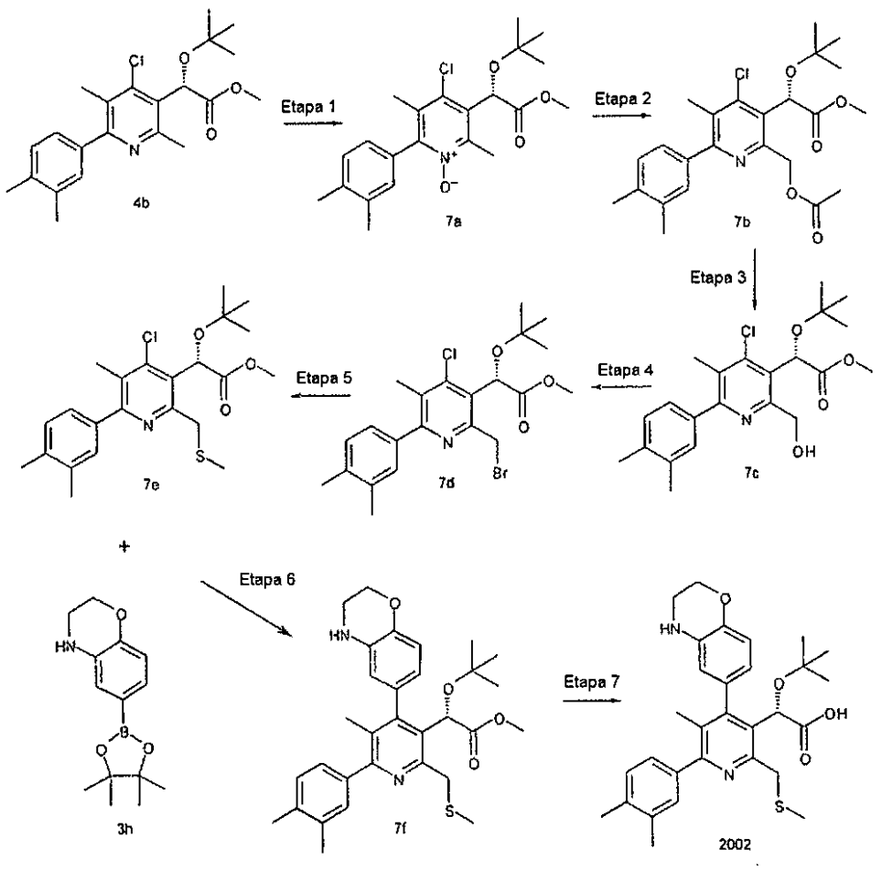
SÍNTESIS DEL COMPUESTO 2004 (TABLA 2)



El compuesto intermedio **5f** (Ejemplo 5) se transforma en el compuesto **2004** (Tabla 2), utilizando el proceso descrito en la etapa 7 del Ejemplo 5, excepto que MeOH es reemplazado por EtOH absoluto.

EJEMPLO 7

SÍNTESIS DEL COMPUESTO 2002 (TABLA 2)



Etapa 1 a Etapa 4:

El compuesto intermedio **4b** (Ejemplo 4) se transforma en el compuesto intermedio **7d**, utilizando los procesos descritos en las etapas 3 a 6 del Ejemplo 5.

Etapa 5:

A una solución agitada de bromuro **7d** (314 mg, 0,67 mmol) en DMF anhidra (2,0 mL) a temperatura ambiente se añade tiometóxido de sodio (57 mg, 0,81 mmol). La agitación se continúa durante 1 h y la solución se extrae con EtOAc (75 mL) y se lava con $NaHCO_3$ saturado y salmuera. El extracto se seca sobre $MgSO_4$ y se concentra y el residuo se purifica mediante CombiFlash® Companion, para proporcionar el tioéter **7e**.

Etapa 6:

A una mezcla de cloropiridina **7e** (63 mg, 0,14 mmol), éster de boronato **3h** (Ejemplo 3) (53 mg, 0,20 mmol), catalizador de *bis*-(tri-*terc.*-butilfosfina) paladio(0)

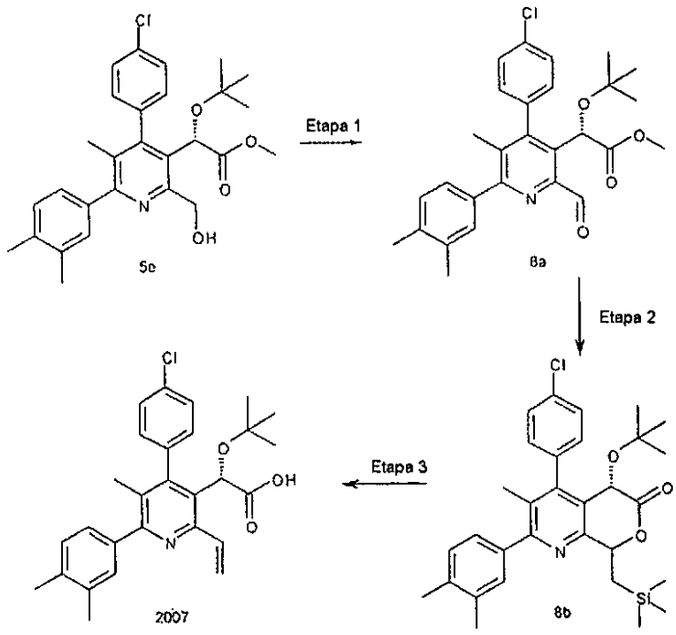
(16 mg; 0,031 mmol), ligando Dave-Phos (24 mg, 0,061 mmol) y $NaHCO_3$ (60 mg, 0,71 mmol) en DMA (1,3 mL) en un vial de microondas se añade agua destilada (0,13 mL), y la mezcla se desoxigena burbujeando argón durante 15 min. El vial se sella y se calienta hasta 130°C. Después de 16 h, la mezcla se extrae con EtOAc (40 mL) y se lava con agua y salmuera. El extracto se seca sobre $MgSO_4$ y se concentra y el residuo se purifica mediante CombiFlash® Companion, para proporcionar el compuesto intermedio **7f**.

Etapa 7:

A una mezcla de éster **7f** (15 mg, 0,028 mmol) y $LiOH \cdot H_2O$ (10 mg, 0,24 mmol) se añade THF (0,70 mL) seguido de agua destilada (0,15 mL) y MeOH (0,1 mL), y la mezcla se calienta hasta 45°C. Después de 16 h, la mezcla se acidifica con AcOH, se diluye con MeCN / agua, se divide en dos porciones y se purifica por HPLC preparatoria. Las fracciones relevantes se agrupan y se liofilizan para proporcionar el compuesto **2002** (Tabla 2) (sal de TFA).

EJEMPLO 8

SÍNTESIS DEL COMPUESTO 2007 (TABLA 2)



Etapa 1:

Una mezcla de alcohol **5e** (Ejemplo 5) (200 mg, 0,49 mmol), peryodinano de Dess-Martin (251 mg; 0,59 mmol) y DCM anhidro (6 mL) se agita a TA bajo una

atmósfera de nitrógeno durante 18 h. La mezcla de reacción se agita vigorosamente con $NaHCO_3$ saturado / $Na_2S_2O_3$ (1:1, v/v, 12 mL) durante 20 min y se extrae con DCM. Los extractos reunidos se lavan con $NaHCO_3$ saturado, se secan sobre $MgSO_4$ y se concentran para proporcionar el aldehído **8a**.

Etapa 2:

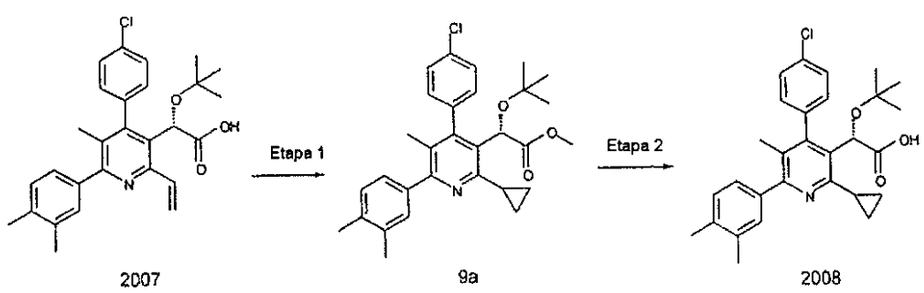
Se añade bromuro de trimetilsililmetilmagnesio (90%, solución 1M en Et_2O, 0,34 mL, 0,31 mmol) gota a gota a una solución agitada de aldehído **8a** (125 mg, 0,26 mmol) en THF anhidro (2,0 mL) enfriada hasta -35°C bajo una atmósfera de nitrógeno. Después de 1 h, se añade solución de bromuro de trimetilsililmetil-magnesio (0,26 mL; 0,23 mmol) adicional. Después de 2 h adicionales, la reacción se enfría bruscamente con NH_4Cl saturado (1 mL) y la mezcla se extrae con EtOAc (20 mL) y se lava con $NaHCO_3$ al 5% y salmuera. El extracto se seca sobre $MgSO_4$, se filtra y evapora y el residuo se purifica mediante CombiFlash® Companion, para proporcionar la lactona **8b**.

Etapa 3:

A una mezcla agitada de la lactona **8b** (98 mg; 0,183 mmol) y THF anhidro (3,0 mL) bajo una atmósfera de nitrógeno se añade, gota a gota, solución de fluoruro de tetrabutilamonio (solución 1 M en THF; 0,27 ml; 0,27 mmol). La mezcla se deja agitar a 0°C durante 30 min, y después se deja calentar a temperatura ambiente. Después de 1 h, la reacción se concentra hasta sequedad y el residuo se disuelve en MeCN (10 mL). Se separa una parte alícuota (1 mL) y la solución restante se adsorbe sobre gel de sílice y se purifica por CombiFlash® para proporcionar el compuesto **2007** (Tabla 2). La parte alícuota de 1 ml se purifica por HPLC preparatoria para proporcionar el compuesto **2007** (Tabla 2) (sal de TFA).

EJEMPLO 9

SÍNTESIS DEL COMPUESTO 2008 (TABLA 2)



2007 9a 2008

Etapa 1:

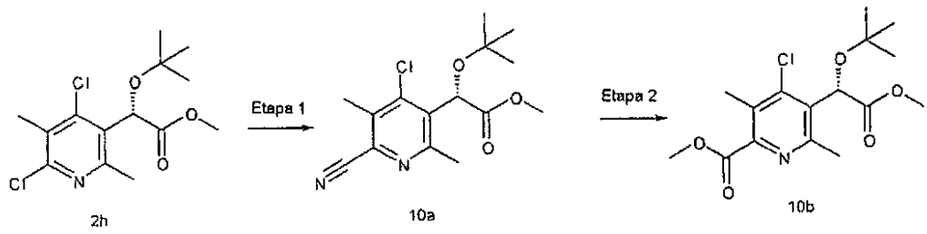
A una solución agitada y enfriada con hielo de compuesto **2007** (Ejemplo 8) (12 mg, 0,026 mmol) se añade gota a gota una solución de diazometano en Et_2O (aprox. 0,7 M, 2 mL) *vía* una pipeta de plástico. Después de 5 min, se añade acetato de paladio(II) (5 mg, 0,02 mmol) y la mezcla se agita durante 15 min. Gas nitrógeno se burbujea a través de la solución para separar diazometano en exceso, y el residuo se seca bajo un alto vacío durante 10 min para proporcionar el compuesto intermedio **9a**.

Etapa 2:

El compuesto intermedio **9a** se convierte en un compuesto **2008** utilizando el proceso descrito en la etapa 7 del Ejemplo 7.

EJEMPLO 10

SÍNTESIS DEL PRODUCTO INTERMEDIO 10B



Etapa 1:

Dicloropiridina **2h** (Ejemplo 2) (11 g, 33 mmol), $Zn(CN)_2$ (7,8 g, 66 mmol) y $Pd[PPh_3]_4$ (1,9 g, 1,6 mmol) se reunen en DMA (100 mL) y se calienta en un tubo sellado hasta 115°C. Después de 6 h, la reacción se enfría hasta TA, se añade $Pd[PPh_3]_4$ (1,9 g, 1,6 mmol) y la reacción se deja continuar durante 1 h. La mezcla se enfría hasta TA, se diluye con EtOAc (250 mL) y se lava con agua (250 mL). La capa acuosa se lava con EtOAc (100 mL) y las capas orgánicas reunidas se lavan con agua (250 mL). La capa orgánica se seca sobre Na_2SO_4 y se concentra. El residuo se purifica mediante CombiFlash® Companion para dar **10a**.

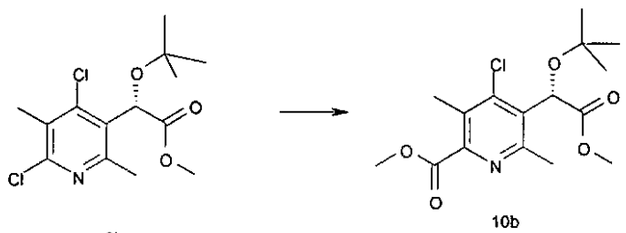
Etapa 2:

Una mezcla de nitrilo **10a** (1,0 g, 3,2 mmol), NaOH acuoso (10 N, 3,4 mL, 32 mmol) y EtOH (3,2 mL) se calienta a 90°C en un tubo sellado durante 16 h. La mezcla se enfría hasta TA y se diluye con HCl acuoso concentrado (12 N, 4 mL, 48 mmol) y agua (50 mL). La mezcla se extrae con EtOAc (3 x 50 mL) y las capas orgánicas reunidas se secan sobre Na_2SO_4y se concentran hasta sequedad. El

residuo se recoge en MeOH (1 mL) y Et_2O (10 mL) y se trata lentamente con una solución en hexano de $TMSCH_2N_2$ (2 M, 3,5 mL, 7,0 mmol), y la mezcla se agita durante 10 min. La mezcla se evapora hasta sequedad y el producto se purifica por CombiFlash® Companion para dar el diéster **10b**.

EJEMPLO 11

SÍNTESIS ALTERNATIVA DEL PRODUCTO INTERMEDIO 10B

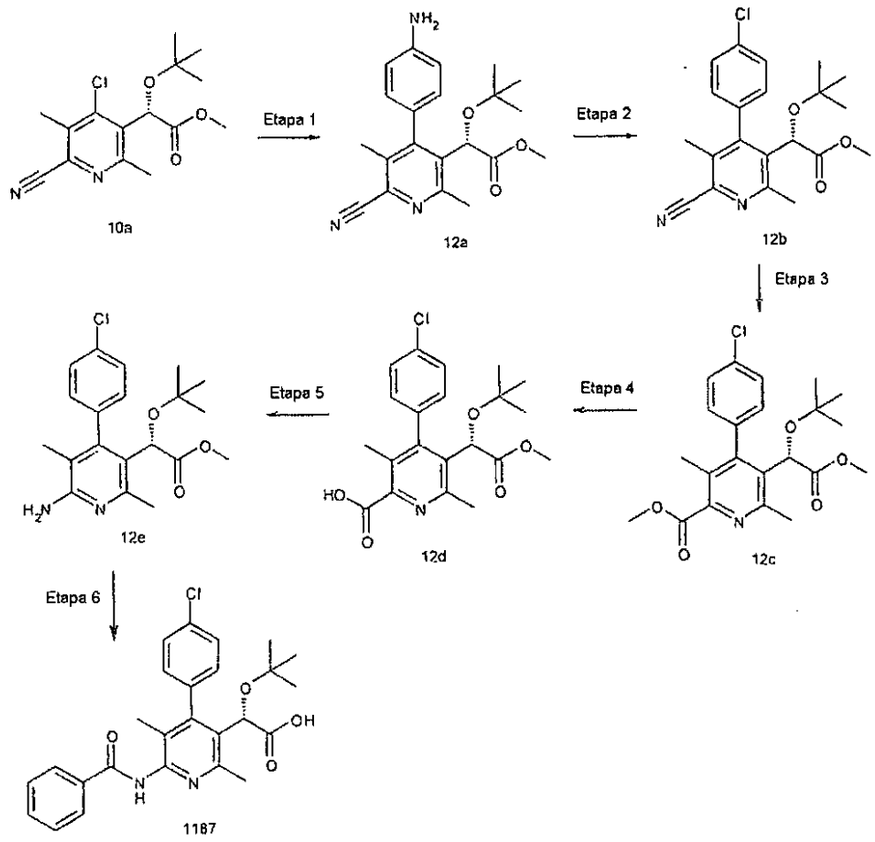


2h 10b

Una mezcla de $Pd(OAc)_2$ (70 mg, 0,31 mmol), tetrafluoroborato de 1,3-propileno bis(diciclohexilfosfonio) (0,38 g, 0,63 mmol), dicloropiridina **2h** (Ejemplo 2) (2,0 g, 6,2 mmol) y carbonato de potasio (1,3 g, 9,4 mmol) se añade a tamices moleculares de 4Å secados (3,0 g) en un matraz de fondo redondo secado en estufa (100 mL), equipado con una varilla de agitación magnética revestida con Teflon®, sellado con un tabique de caucho y se enfría en vacío. El tabique de caucho se fija envolviéndolo con una cinta eléctrica y DMF (20 mL) y MeOH (2,5 mL, 62 mmol) se añaden a través de una jeringa. Un globo de CO se conecta al recipiente de reacción utilizando un tramo corto del entubado de caucho (~ 2,64 cm.), un adaptador de aguja y una aguja de 20 G. La atmósfera inerte se intercambia entonces por monóxido de carbono, exponiendo brevemente el recipiente de reacción a vacío (1-2 s) y volviéndolo a llenar con monóxido de carbono (3 veces). La mezcla de reacción se calienta a 120°C y se agita vigorosamente durante 16 h, luego se deja enfriar hasta temperatura ambiente, y se diluye con EtOAc (20 mL), se reune y se filtra a través de un taco de Celite (eluyendo con EtOAc). El filtrado se lava con agua y salmuera, se seca sobre $MgSO_4$, se filtra y se concentra. El residuo se purifica por CombiFlash® Companion (EtOAc/hexanos) para dar el diéster **10b**.

EJEMPLO 12

SÍNTESIS DEL COMPUESTO 1187 (TABLA 1)



Etapa 1:

Una mezcla de nitrilo **10a** (Ejemplo 10) (1,7 g, 5,4 mmol), ácido 2-aminofenilborónico (1,0 g, 7,3 mmol), *bis*[tri-*t*-butilfosfina]paladio(0) (276 mg, 0,54 mmol), $NaHCO_3$ (2,25 g, 26,7 mmol), DMA (50 mL) y agua (5 mL) se desgasifica burbujeando Ar(g) bajo tratamiento con ultrasonidos durante 5 min. La mezcla se calienta hasta 130°C y se agita durante 15 h, luego se enfría hasta TA y se reparte entre EtOAc (225 mL) y agua (200 mL). La capa acuosa se extrae con EtOAc (2 x 100 mL) y las capas orgánicas reunidas se lavan con agua, se secan sobre Na_2SO_4 y se concentran. El residuo se purifica mediante CombiFlash® Companion para dar la anilina **12a**.

Etapa 2:

La anilina **12a** se convierte en el compuesto intermedio **12b** utilizando el proceso descrito en la etapa 2 del Ejemplo 5.

Etapa 3:

Una mezcla de **12b** (3,8 g, 9,8 mmol), NaOH acuoso (10 N, 9,8 mL, 98 mmol) y EtOH (10 mL) se calienta a 90ºC en un tubo sellado durante 16 h. La mezcla se enfría hasta TA y se diluye con HCl acuoso concentrado (12 N, 10 mL, 120 mmol) y agua (500 mL). La mezcla se extrae con EtOAc (3 x 500 mL) y las capas orgánicas reunidas se secan sobre Na_2SO_4 y se concentran hasta sequedad. El residuo se recoge en MeOH (5 mL) y Et_2O (50 mL) y se trata lentamente con una solución en hexano de $TMSCH_2N_2$ (2 M, 3,5 mL, 15,0 mmol), y la mezcla se agita durante 10 min, y luego se evapora hasta sequedad. El residuo se purifica mediante CombiFlash® Companion para dar el diéster **12c**.

Etapa 4:

Una mezcla de diéster **12c** (2,9 g, 6,9 mmol), THF (9 mL) y MeOH (3 mL) se trata con LiOH (1 N, 9,7 mL, 9,7 mmol). La mezcla se agita durante 10 min, luego se acidifica con HCl acuoso (1N, 15 mL, 15 mmol), se diluye con salmuera y se extrae con EtOAc (3 x 50 mL). Las capas orgánicas reunidas se secan sobre Na_2SO_4 y se concentran para dar el ácido carboxílico **12d**.

Etapa 5:

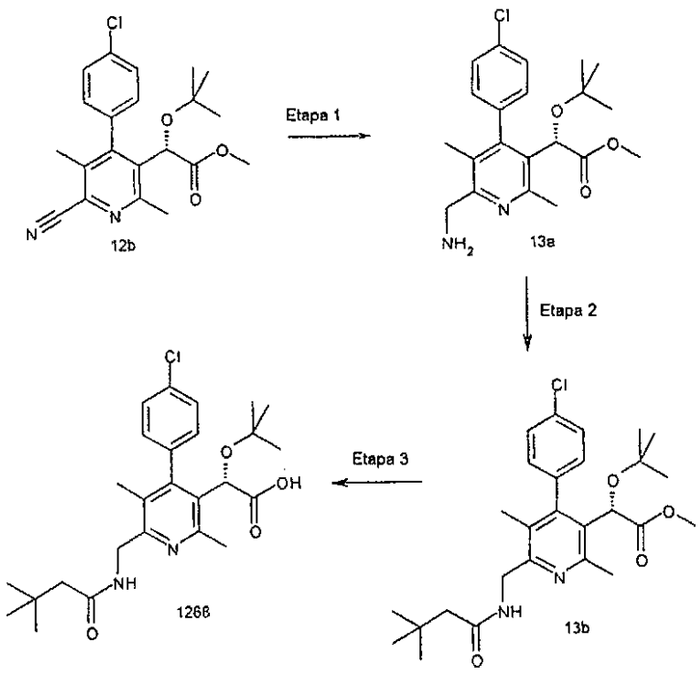
A una mezcla de **12d** (1,9 g, 4,6 mmol) y Et_3N (1,3 mL, 9,3 mmol) en PhMe (63 mL) se añade agua (0,4 mL, 23 mmol) seguido de DPPA (2,0 mL, 9,3 mmol). La mezcla se calienta a 90°C durante 30 min, y luego se añade una porción adicional de DPPA (500 µL, 2,3 mmol). La agitación se continúa durante 40 min y la mezcla se enfría hasta TA, se diluye con EtOAc (100 mL) y se lava con $NaHCO_3$ acuoso saturado, agua y salmuera. La capa orgánica se seca sobre Na_2SO_4 y se concentra y el residuo se purifica mediante CombiFlash® Companion, para dar el compuesto intermedio **12e**.

Etapa 6:

Una mezcla de aminopiridina **12e** (30 mg, 0,08 mmol) en THF (2 mL) se trata con Et_3N (22 µL, 0,16 mmol) seguido de cloruro de bencilo (12 µL, 0,10 mmol) y la mezcla se calienta a 50ºC durante 2 h. La mezcla se diluye con MeOH (0,5 mL), se añade NaOH acuoso (5 N, 80 µL, 0,40 mmol) y la mezcla se agita a 55ºC durante 2 h. La mezcla se concentra casi hasta sequedad y se diluye con AcOH (1,5 mL) y DMF (0,5 mL), y se purifica mediante HPLC preparativa para dar el compuesto **1187** (Tabla 1).

EJEMPLO 13

SÍNTESIS DEL COMPUESTO 1268 (TABLA 1)



Etapa 1:

Una mezcla de nitrilo **12b** (Ejemplo 12) (6 g, 15,4 mmol) y AcOH (100 mL) se trata con Pd al 10%/C (1,64 g, 1,54 mmol). La mezcla se purga con gas hidrógeno y se almacena a TA durante 1,5 h. En el matraz se hace el vacío varias veces y el catalizador se separa por filtración a través de Celite® con líquidos de lavado de EtOAc. La mezcla se concentra *en vacío* y el residuo se recoge en EtOAc, se lava con $NaHCO_3$ saturado y salmuera saturada, se seca sobre $MgSO_4$ y se concentra. El residuo se purifica por CombiFlash® Companion (gradiente de MeOH/DCM al 1-10% con Et_3N al 1%) para proporcionar, tras la concentración, la amina **13a**.

Etapa 2:

A una solución de la amina **13a** (85 mg, 0,22 mmol) en DCM (2 mL) se añade Et_3N (61 µL, 0,44 mmol) seguido de cloruro de t-butilacetilo (34 µL, 0,24 mmol). La mezcla se agita a TA durante 2 h y se concentra hasta sequedad. La amida **13b** que contiene el material bruto se utiliza en la etapa siguiente.

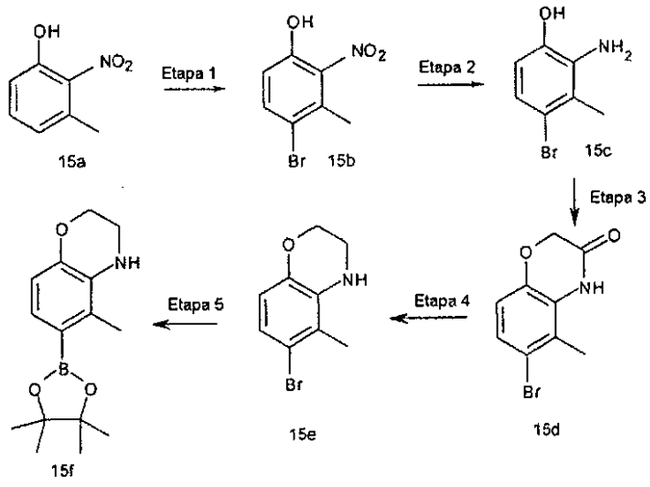
Etapa 3:

Una mezcla de **13b** (106 mg, 0,22 mmol), MeOH (0,5 mL) y THF (1,5 mL) se

trata con NaOH 5 N (217 µL, 1,08 mmol). La mezcla se agita a 50°C durante 16 h y se concentra hasta sequedad. El residuo se disuelve en AcOH/DMSO (1 mL en cada caso) y se purifica mediante HPLC preparativa para proporcionar, después de la congelación y la liofilización, el compuesto **1268** (Tabla 1).

EJEMPLO 14

SÍNTESIS DEL COMPUESTO 3010 (TABLA 3)



Etapa 1:

A P_2O_5 sólido (652 mg, 4,6 mmol) en un matraz RB seco se añade lentamente H_3PO_4 al 85% (503 µL, 7,34 mmol) a través de una jeringa. Esta mezcla se deja agitar durante unos pocos minutos; luego se añade DCM (20 mL) seguido de alcohol **2g** (Ejemplo 2) (970 mg, 3,67 mmol). A esta mezcla se añade $BF_3{\cdot}Et_2O$ (931 µL, 7,34 mmol) y metilenciclobutano (3,4 mL, 37 mmol). La mezcla se agita a TA durante 2 h y luego se enfría bruscamente de forma rápida con $NaHCO_3$ acuoso. La mezcla de reacción se diluye con EtOAc, se lava con salmuera saturada, se seca ($MgSO_4$), se filtra y se concentra. El residuo se purifica utilizando el Combi-Flash® Companion (hexanos/EtOAc) para dar el éter **14a** y se recupera el alcohol **1g** de partida.

Etapa 2:

Una mezcla de **14a** (825 mg, 2,48 mmol), $Zn(CN)_2$ (583 mg, 5 mmol), $Pd(PPh_3)_4$ (430 mg, 0,37 mmol) y DMA (12 mL) se sella en un recipiente de microondas y se calienta en el microondas a 125°C (10 min) utilizando un Biotage Initiator Sixty. La mezcla de reacción se enfría, se vierte en EtOAc y se lava con

salmuera saturada. La fase orgánica se seca sobre $MgSO_4$, se filtra y se concentra, y el residuo se purifica mediante Combi-Flash® Companion (hexanos/EtOAc) para dar el nitrilo **14b**.

Etapa 3:

El compuesto intermedio **14b** se transforma en el compuesto intermedio **14c**, utilizando el proceso descritos en las etapas 1 y 2 del Ejemplo 12.

Etapa 4:

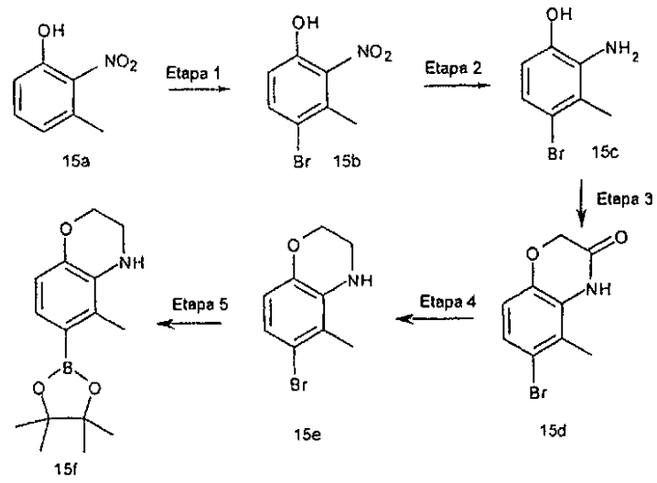
A nitrilo **14c** (176 mg, 0,44 mmol) en MeOH (4 mL) se añade NaOH 5 N (441 µL, 4,4 mmol). La mezcla se calienta a 65°C (24 h), se enfría hasta TA, se acidifica con HCl 1N (pH ~1-2) y se extrae con EtOAc (3 veces). Las fases orgánicas reunidas se secan ($MgSO_4$), se filtran y concentran para dar el diácido **14d**.

Etapa 5:

A una solución de diácido **14d** (181 mg, 0,45 mmol) en THF anhidro (8 mL) se añade Et_3N (263 µL, 1,9 mmol) y cloruro de pivaloílo (116 µL, 0,94 mmol) a TA y la mezcla se agita durante 1 h. A una porción de esta solución patrón (2 mL, 0,11 mmol) se añade anilina (11,3 µL, 0,12 mmol) y la mezcla se deja agitar a TA durante 16 h. La mezcla de reacción se trata con NaOH 10 N (112 µL, 1,12 mmol) durante 4 h y se concentra hasta sequedad, se purifica por HPLC preparativa y se liofiliza para dar el compuesto **3010** (Tabla 3).

EJEMPLO 15

SÍNTESIS DEL COMPUESTO INTERMEDIO 15F



Etapa 1:

Una mezcla de nitrofenol **15a** (5,23 g, 34,1 mmol) y AcOH (20 mL) se enfría en un abño de hielo y se añade, gota a gota y con agitación, bromo (1,75 mL, 34,15 mmol, disuelto en 5 mL de AcOH). La mezcla se agita durante aproximadamente 1 h a 0°C y se vierte en agua helada (250 mL). La mezcla se extrae con EtOAc (2 X 100 mL), se lava con $NaHCO_3$ al 5%, se seca sobre $MgSO_4$ anhidro, se filtra y se concentra para dar **15b**. Este material se usa en la siguiente etapa sin purificación adicional.

Etapa 2:

A una solución en etanol (75 mL) de **15b** (8,1 g, 34,9 mmol) bien agitada, se añade $SnCl_2$ (20 g, 105 mmol) y la mezcla de reacción se agita a reflujo durante 2,5 h. Se añade una porción adicional de $SnCl_2$ (2 g, 10 mmol) y se continúa el calentamiento a reflujo durante 1 h. La mezcla se enfría hasta TA y se vierte en hielo (250 g), y el pH se ajusta a aproximadamente 7,5 con $NaHCO_3$ acuoso al 5%. La mezcla se extrae con EtOAc (3 X 100 mL) y el extracto orgánico se lava con salmuera, se seca sobre $MgSO_4$ anhidro, se filtra y se concentra hasta sequedad para dar el compuesto intermedio anilina **15c**.

Etapa 3:

A una mezcla agitada, enfriada con hielo, de K_2CO_3 (2,05 g, 14,8 mmol), anilina **15c** (750 mg, 3,71 mmol) y DMF (5 mL) bajo nitrógeno, se añade, gota a gota, cloruro de cloroacetilo (355 µL, 4,45 mmol). La mezcla se deja calentar a TA a lo largo de un periodo de aproximadamente 15 min y después se calienta hasta 60°C durante 1 h. La mezcla se deja enfriar a TA, se vierte en una mezcla de hielo/agua (250 mL) y se agita durante aproximadamente 15 min. La suspensión se centrifuga, y el líquido sobrenadante se descarta. El material sólido se deja secar bajo succión durante una noche para dar el compuesto intermedio **15d**.

Etapa 4:

A una mezcla, enfriada con hielo, de la amida cíclica **15d** (280 mg, 1,16 mmol) y THF (6 mL) bajo nitrógeno se añade lentamente uan solución de borano-THF (1 M en THF, 1,74 mL, 1,74 mmol). La mezcla de reacción se deja calentar lentamente hasta TA, luego se agita a TA durante 1,5 h y luego se calienta suavemente a reflujo durante 1 h. La mezcla se enfría en un baño de hielo y se enfría bruscamente con cuidado con NaoH acuoso 1 M (4 mL) a lo largo de aproximadamente 10 min. La mezcla de reacción se reparte entre EtOAc (150 mL)

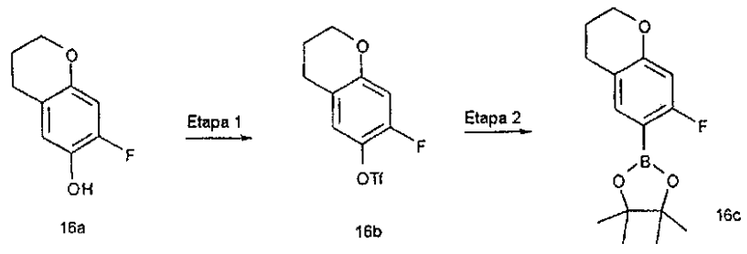
y agua (25 mL). La capa orgánica se lava con NaOH 1 N acuoso (20 mL) y NaCl acuoso saturado y se seca sobre $MgSO_4$ anhidro, se filtra y se concentra para dar **15e**.

Etapa 5:

Una mezcla, bien agitada, del bromuro de arilo **15e** (0,50 g, 2,2 mmol), acetato de potasio (728 g, 7,7 mmol) y bis(pinacolato)diborano (0,83 g, 3,3 mmol) se desgasifica burbujeando Ar a través de la solución durante aproximadamente 20 min. Se añade $PdCl_2$(dppf)-DCM (320 mg, 0,44 mmol) y la desgasificación se continúa durante aproximadamente 15 min. El sistema se cierra herméticamente (recipiente con tapón roscado de teflon) bajo Ar y se calienta hasta 90°C durante 5 h. La mezcla de reacción se deja enfriar hasta TA, se diluye con EtOAc (150 mL), se lava con salmuera y agua, se seca sobre $MgSO_4$ anhidro, se filtra y se concentra hasta sequedad. El residuo se purifica por CombiFlash® Companion (EtOAc/hexanos) para dar el boronato **15f** deseado.

EJEMPLO 16

SÍNTESIS DEL COMPUESTO INTERMEDIO 16c



Etapa 1:

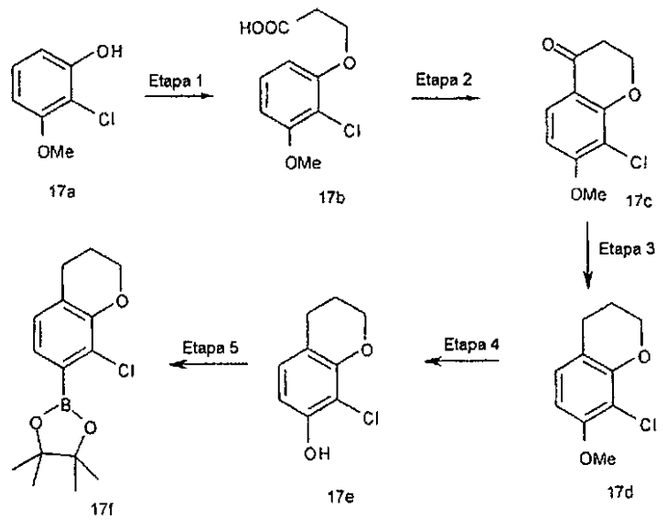
Se añade gota a gota Tf_2O puro (0,56 mL, 3,3 mmol) a una mezcla enfriada (0°C) del fenol **16a** (350 mg, 2,1 mmol; preparado según Doi *et al., Bull. Chem. Soc. Jpn.* **2004** *77*, 2257-2263) y piridina (0,91 mL, 11 mmol) en DCM (10 mL) bajo una atmósfera de Ar. La mezcla se deja calentar a TA y se agita durante 2 h. La reacción se enfría bruscamente mediante la adición de una solución al 10% de ácido cítrico (20 mL) y se extrae con DCM (3 x 20 mL). Las capas orgánicas reunidas se lavan con agua, se secan sobre $MgSO_4$, se filtran y se concentran a sequedad. El residuo se purifica por CombiFlash® Companion para proporcionar el triflato **16b**.

Etapa 2:

Una mezcla del triflato **16b** (510 mg, 1,7 mmol), bis[pinocolato]diborano (560 mg, 2,2 mmol) y acetato potásico (500 mg, 5,1 mmol) en DMF (18 mL) se desgasifica con Ar durante 5 min, y se añade complejo de $PdCl_2$dppf-DCM (140 mg, 0,17 mmol). La mezcla de reacción se desgasifica durante 5 min adicionales y se calienta hasta 100°C mediante irradiación por microondas durante 10 min, y luego se enfria hasta TA. La mezcla se diluye con EtOAc (60 mL) y se lava con salmuera, se seca sobre $MgSO_4$, se filtra y se concentra. El residuo se purifica adicionalmente mediante CombiFlash® Companion para proporcionar el éster borónico **16c**.

EJEMPLO 17

SÍNTESIS DEL COMPUESTO INTERMEDIO 17F



Etapa 1:

Una solución de fenol **17a** (0,91 g, 5,74 mmol) en DMF seca (1 mL) se añade, gota a gota, a una mezcla de NaH (al 60% en aceite, 0,60 g, 15 mmol) en DMF seca (1 mL) enfriada hasta 15°C, y la mezcla se agita durante 20 min. Se añade gota a gota una solución de ácido 3-bromopropiónico (1,1 g, 6,9 mmol) en DMF seca (0,5 mL) y la mezcla se agita a TA durante una noche. Después de 16 h, se añade MeOH (1,2 mL) y la mezcla de reacción se añade a HCl diluido (12 mL de HCl 1 N en 100 mL de agua) y se extrae con EtOAc (80 mL; el pH de la fase acuosa se ajusta a pH <3). La capa orgánica se seca sobre Na_2SO_4 anhidro, se filtra y concentra para dar **17b** contaminado con algo de material de partida que no ha

reaccionado.

Etapa 2:

Una mezcla de **17b** (1.53 g, 6.63 mmol) y ácido polifosfórico (7 g) se calienta hasta 75°C. Después de 4 h, la reacción se enfría y se añaden lentamente hielo y agua con agitación rápida. La mezcla se extrae con EtOAc (100 mL) y el extracto orgánico se lava con agua, $NaHCO_3$ saturado y salmuera, se seca sobre $MgSO_4$ anhidro y se concentra para dar **17c** (bruto).

Etapa 3:

AcOH (80 mL) se añade a una mezcla de cromanona **17c** (6,2 g, 29 mmol) y polvo de zinc recientemente activado (38 g, 580 mmol). La mezcla se agita a 100°C durante 15 h y se filtra a través de Celite, y la almohadilla de Celite se aclara repetidamente con EtOAc (4 x 25 mL). El filtrado se concentra y se extrae con EtOAc (400 mL) y el extracto orgánico se lava con $NaHCO_3$ saturado (2 x 400 mL) y salmuera (200 mL). La fase orgánica se seca sobre $MgSO_4$ y se evapora para proporcionar cromano **17d** bruto.

Etapa 4:

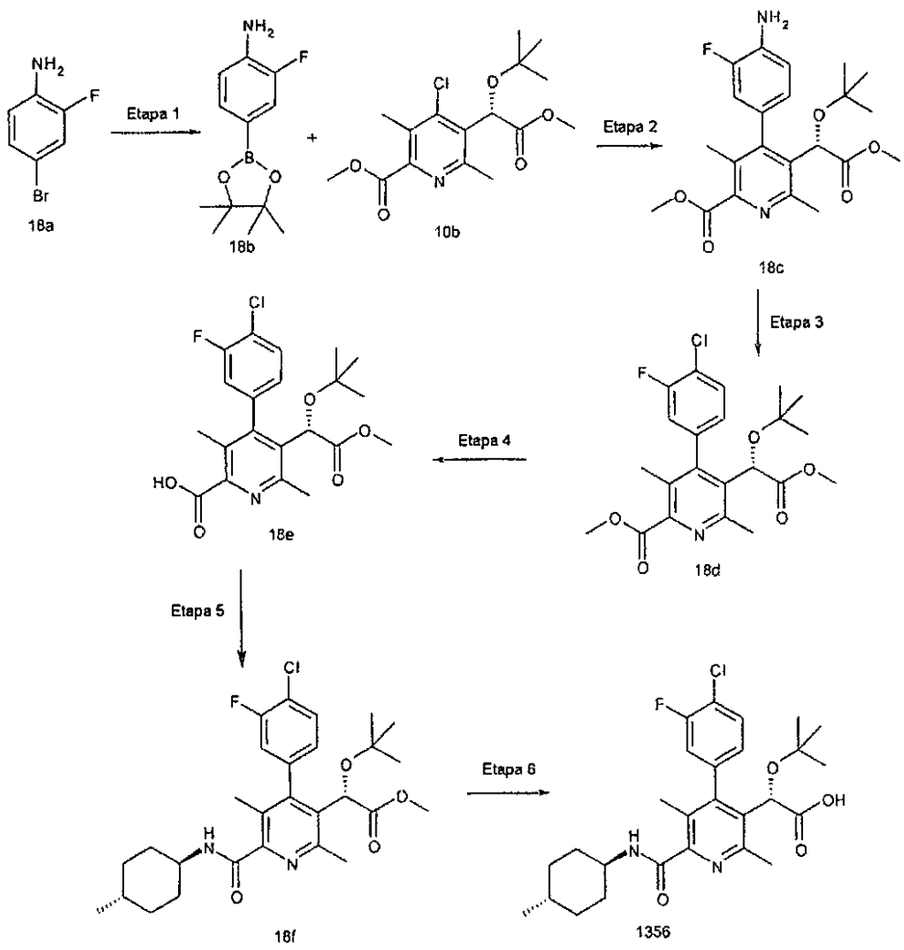
Una mezcla de anisol **17d** (4.0 g, 20 mmol) y diclorometano seco (40 mL) se enfría hasta -78°C. Una solución de BBr_3 (1M en DCM, 44 mL, 44 mmol) se añade gota a gota y luego la mezcla de reacción se retira del baño de hielo seco. Después de 45 min, la mezcla se enfría (aprox. 0°C) y la reacción se enfría bruscamente con agua (25 mL) añadida gota a gota. La mezcla se dluye con agua (400 mL) y se neutraliza cuidadosamente con $NaHCO_3$ acuoso saturado (pH final aprox. 8). Esta mezcla se extrae luego con DCM (300 mL y luego 100 mL) y las capas orgánicas reunidas se secan sobre Na_2SO_4 y se evaporan hasta sequedad. El producto se purifica por CombiFlash® Companion para proporcionar el fenol **17e**.

Etapa 5:

Utilizando el proceso descrito en las Etapas 1 y 2 del Ejemplo 16, el compuesto **17e** se transforma en el compuesto **17f**.

EJEMPLO 18

SÍNTESIS DEL COMPUESTO 1356 (TABLA 1)



Etapa 1:

DMF anhidra (20 mL) se añade a una mezcla de bromuro **18a** (1,0 g, 5,3 mmol), *bis*-(pinacolato)diboro (1,9 g, 7,4 mmol) y acetato de potasio (1,6 g, 16 mmol), y la mezcla se desoxigena burbujeando una corriente de gas N_2 a traves de la mezcla durante aproximadamente 25 min. Se añade 1,1'-bis(difenilfosfino)ferroceno (0.58 mg, 0,79 mmol) y la mezcla se desoxigena durante aproximadamente 5 min adicionales y luego se calienta hasta 95°C. Después de 5 h, la mezcla de reacción se enfría, se diluye con EtOAc (200 mL) y se lava con salmuera (2 x 100 mL). Las capas se filtran a través de una almohadilla de Celite y se vuelve a separar. La fase orgánica se seca sobre $MgSO_4$ anhidro, se filtra y se concentra, y el residuo se purifica mediante Combi-Flash® Companion

(EtOAc/hexanos) para proporcionar el boronato **18b**.

Etapa 2:

El compuesto intermedio **18b** se acopla al compuesto intermedio **10b** (Ejemplo 10) utilizando el proceso descrito en la etapa 1 del Ejemplo 12 para dar el compuesto intermedio **18c**.

Etapa 3:

El compuesto intermedio **18c** se transforma en el compuesto intermedio **18d**, utilizando el proceso descritos en la etapa 2 del Ejemplo 5.

Etapa 4:

El compuesto intermedio **18d** se transforma en el compuesto intermedio **18e**, utilizando el proceso descritos en la etapa 4 del Ejemplo 12.

Etapa 5:

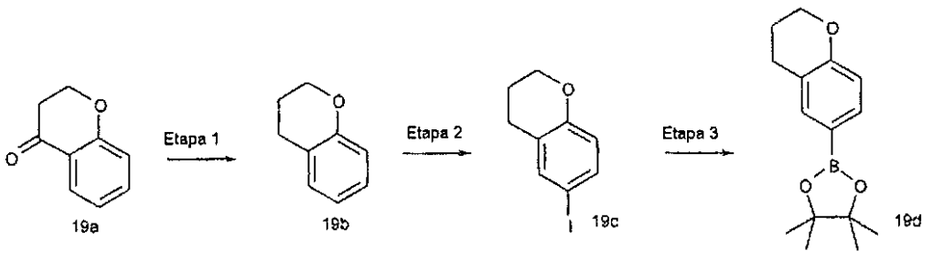
Una mezcla de ácido carboxílico **18e** (44 mg, 0,10 mmol) en NMP se trata con Et_3N (58 µL, 0,42 mmol) y TBTU (67 mg, 0,21 mmol). La mezcla se agita durante 5 min y se añade *trans*-4-metilciclohexilamina (35 µL, 0,31 mmol). La mezcla se agita durante 1 h, se diluye con EtOAc (40 mL), se lava con agua y salmuera, se seca sobre $MgSO_4$, se filtra y se concentra. La mezcla bruta se purifica por CombiFlash® Companion utilizando un gradiente de EtOAc/hexanos para proporcionar la amida **18f** deseada.

Etapa 6:

Una mezcla de amida **18f** (42 mg, 0,080 mmol), THF (1.5 mL) y MeOH (0.75 mL) se trata con LiOH 1,0 N (0,75 mL, 0,75 mmol). La mezcla se agita a 55°C durante 1 h, se neutraliza con AcOH y se purifica por HPLC preparativa. Una mezcla del producto y DCM (3 mL) se ajusta a pH > 10 con NaOH 1N y se neutraliza con AcOH. La mezcla se hace pasar a través de un filtro de separador de fases y la capa orgánica se concentra *en vacío*, se diluye con una mezcla de MeCN / agua y se liofiliza para dar el compuesto **1356**.

EJEMPLO 19

SÍNTESIS DEL COMPUESTO INTERMEDIO 19D



Etapa 1:

Una mezcla de cromanona **19a** (9,78 g, 66,0 mmol) y AcOH (20 mL) se añade a una mezcla de polvo de cinc (108 g, 1,65 mol) en AcOH (150 mL). La mezcla se calienta hasta 100°C y se agita durante una noche, después se filtra a través de Celite® (lavado con EtOAc, 100 mL), se diluye con PhMe (300 mL) y se concentra para dar el compuesto intermedio **19b**.

Etapa 2:

Se añaden secuencialmente $AgNO_3$ (12,0 g, 70,6 mmol) e I_2 (15,8 g, 62,3 mmol) a una mezcla de **19b** (8,45 g, 63,0 mmol) y MeOH (225 mL). La mezcla se deja en agitación durante aproximadamente 1 h y se filtra a través de Celite® y el filtrado se concentra a presión reducida. El residuo se diluye con EtOAc (250 mL) y se lava con tiosulfato sódico saturado (250 mL). La capa orgánica se lava con agua (200 ml), se seca sobre Na_2SO_4, se filtra y se concentra. El residuo se purifica adicionalmente mediante CombiFlash® Companion para dar 6-yodocromano **19c**.

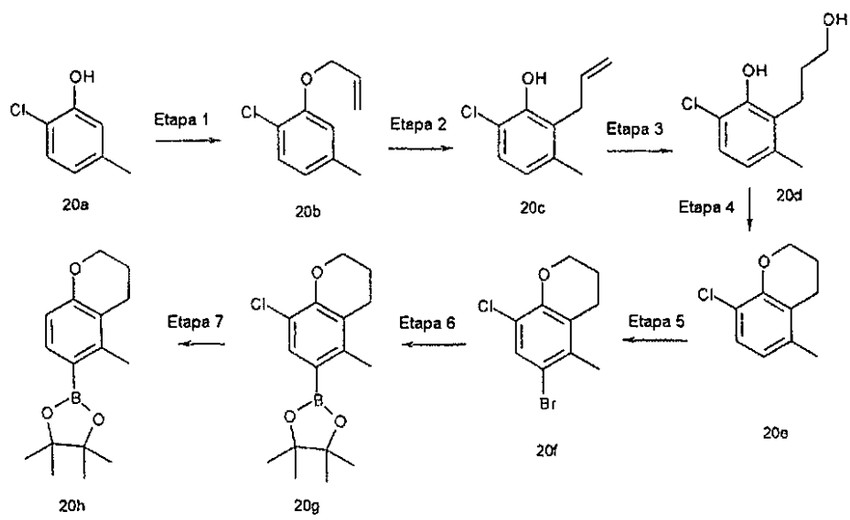
Etapa 3:

Una mezcla del 6-yodocromano **19c** (1,0 g, 3,85 mmol), bis[pinocolato]diborano (1,22 g, 4,81 mmol) y acetato de potasio (1,10 g, 11,5 mmol) en DMF (36 mL) se desgasifica con Ar durante aproximadamente 5 min, seguido de la adición del complejo de $PdCl_2$dppf-DCM (314 mg, 0,38 mmol). La mezcla de reacción se desgasifica luego durante aproximadamente 5 min adicionales y se calienta hasta 95°C durante 5 h. La mezcla se enfría luego hasta TA, se diluye con agua y se extrae con EtOAc (3 x 100 mL). Los extractos orgánicos reunidos se lavan con agua (100 mL) y salmuera (100 mL), se secan sobre $MgSO_4$, se filtran y se concentran. El residuo se purifica adicionalmente por CombiFlash® Companion utilizando un gradiente de EtOAc/hexanos para

proporcionar el compuesto intermedio **19d**.

EJEMPLO 20

SÍNTESIS DEL COMPUESTO INTERMEDIO 20H



Etapa 1:

Una mezcla de fenol **20a** (6,75 g, 47,3 mmol) y DMF (270 mL) se trata con bromuro de alilo (6,55 mL, 75,7 mmol). A esta mezcla se añade en porciones NaH (al 60%, 4 g, 99,4 mmol) y se continúa agitando durante una noche. La mezcla de reacción se diluye con EtOAc (500 mL) y se lava con H_2O. La capa orgánica se seca sobre $MgSO_4$, se filtra y se concentra hasta sequedad para obtener el producto **20b** deseado.

Etapa 2:

El éter **20b** (8,6 g) se agita y caliente a 240°C durante 20 min en un vial de microondas para proporcionar **20c**.

Etapa 3:

A una mezcla del compuesto intermedio de alilo **20c** (9,3 g, 45,8 mmol) en THF anhidro (300 mL) a 0°C, se añade borano (1 M en THF, 96 mL, 96 mmol, 2,1 eq). La mezcla se deja calentar a TA y después se agita durante 2,5 h. La mezcla se enfría después a 0°C y se trata gota a gota con NaOH 10 N, seguido de la adición lenta de H_2O_2 al 30% (104 ml, 916 mmol). La mezcla resultante se deja calentar a TA y se agita a TA durante 1 h. La mezcla de reacción se diluye con HCl (al 10%, 100 mL) y se extrae con EtOAc (3 x 200 mL). Las fases orgánicas

combinadas se secan sobre $MgSO_4$ y se concentran. El residuo se purifica mediante CombiFlash® Companion para dar **20d**.

Etapa 4:

A una mezcla del diol **20d** (7,1 g, 35,3 mmol) en THF (500 mL), se añade PPh_3 (12 g, 45,9 mmol) seguido de DEAD (7,2 mL, 45,9 mmol). La mezcla se agita a TA durante 4 h. La mezcla de reacción se concentra a presión reducida y se purifica por CombiFlash® Companion para obtener el producto deseado **20e**.

Etapa 5:

Una mezcla del derivado de cromano **20e** (5,26 g, 28,8 mmol) y AcOH (70 mL) se trata con Br_2 (19,2 mL, 37,4 mmol) en AcOH (40 mL). La mezcla se agita a TA durante 15 min, y después se diluye con tolueno y se concentra a sequedad. El residuo se recoge en EtOAc (25 mL) y se lava con solución saturada de $Na_2S_2O_3$ (25 mL) y solución saturada de $NaHCO_3$ (25 mL). La capa orgánica se seca sobre $MgSO_4$, se concentra y se purifica mediante CombiFlash® Companion para obtener el producto **20f** deseado.

Etapa 6:

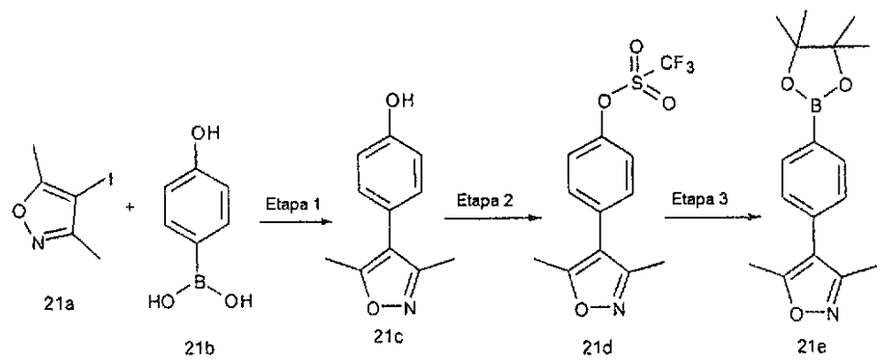
Una mezcla del bromuro **20f** (2,71 g, 10,4 mmol) y DMF (120 mL) se trata con bispinocolatoborano (4 g, 15,5 mmol) y acetato de potasio (3,45 g, 36,3 mmol). La mezcla se desgasifica (utilizando un globo de Ar) y se añade $PdCl_2$dppf (845 mg, 1,04 mmol). La mezcla se desgasifica de nuevo (utilizando un globo de Ar) y se calienta a 95°C durante 16 h. La mezcla se enfría hasta TA, se diluye con H_2O (300 mL) y se extrae con EtOAc (2 x 300 mL). Las capas orgánicas reunidas se lavan con agua, se secan sobre $MgSO_4$, se filtran y se concentran. El residuo se purifica por CombiFlash® Companion y se tritura con hexanos para proporcionar el compuesto intermedio **20g**.

Etapa 7:

Paladio sobre carbón vegetal activado (Pd al 10% en peso, 0,63 mg, 0,59 mmol) se añade a una solución de cloruro de arilo **20g** (0,91 g, 2,95 mmol) y formiato de amonio (1,92 g, 30,4 mmol) disueltos en MeOH, y la mezcla se calienta a reflujo. Después de 15 min, la reacción se enfría hasta TA y se filtra a través de Celite®, y la almohadilla de Celite® se aclara con MeOH. El filtrado se concentra a sequedad y el residuo se reparte entre agua y EtOAc (10 mL en cada caso). La capa orgánica se seca sobre $MgSO_4$ anhidro y se concentra para obtener éster borónico **20h**.

EJEMPLO 21

SÍNTESIS DEL COMPUESTO INTERMEDIO 21E



Etapa 1:

Una mezcla de **21a** (1,0 g, 4,5 mmol), **21b** (0,72 g, 5,2 mmol), carbonato de potasio (1,6 g, 12 mmol) y *trans*-diclorobis(trifenilfosfina)paladio (II) (0,36 g, 0,62 mmol) en DMF (8,3 mL) y agua (0,88 mL) se calienta en microondas durante 15 min a 130°C. La mezcla se reparte entre EtOAc (25 mL) y agua (25 mL) y la capa orgánica se lava con agua, se seca sobre Na_2SO_4, se filtra y se concentra. El residuo se purifica por CombiFlash® Companion utilizando un gradiente de EtOAc/hexanos para proporcionar el alcohol **21c**.

Etapa 2:

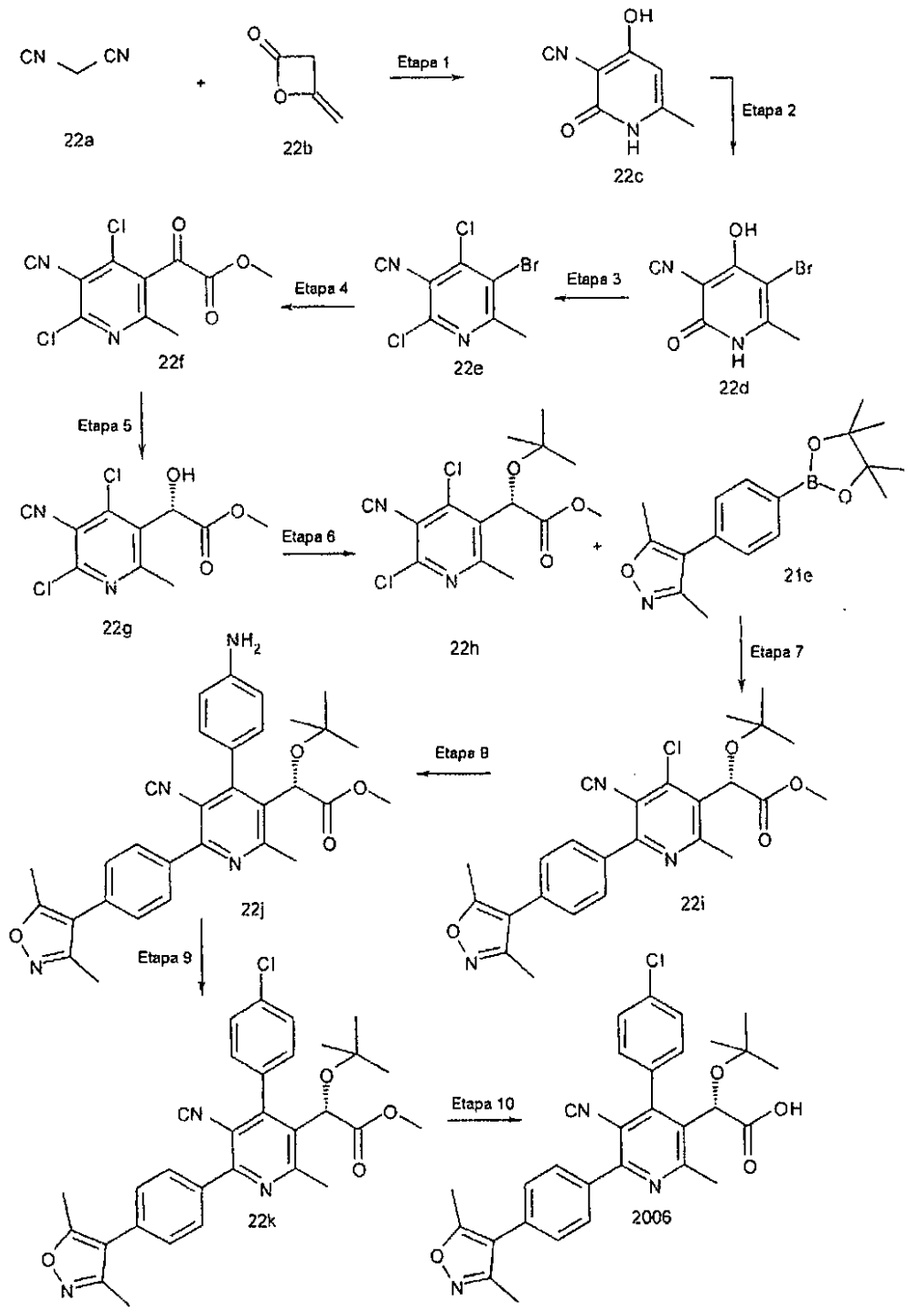
Una mezcla de alcohol **21c** (0,70 g, 3,7 mmol) en piridina (15 mL) se trata con Tf_2O (0,95 mL, 5,6 mmol) y se agita a 23°C durante 30 min. La mezcla se concentra y el residuo se reparte entre DCM (50 mL) y HCl al 10% (50 mL). La capa orgánica se lava con HCl al 10% y solución saturada de $NaHCO_3$ y se hace pasar a través de un separador de fases. La evaporación de la capa orgánica da el triflato **21d**.

Etapa 3:

Una solución del triflatro **21d** (1,2 g, 3,7 mmol), bis(pinocolato)diborano (1,4 g, 5,5 mmol) y acetato de potasio (1,2 g, 13 mmol) en DMF (50 mL) se desgasifica con Ar durante aproximadamente 5 min, seguido de la adición del complejo de $PdCl_2$dppf-DCM (0.39 mg, 0,48 mmol). La mezcla de reacción se desgasifica luego durante aproximadamente 5 min adicionales antes de ser calentada hasta 95°C durante una noche. La mezcla de reacción se enfría luego hasta TA, se diluye con agua (150 mL) y se extrae con EtOAc (3 x 100 mL). Los extractos orgánicos reunidos se lavan con agua, se secan sobre Na_2SO_4, se filtran y se concentran. El

EJEMPLO 22

SÍNTESIS DEL COMPUESTO 2006 (TABLA 2)



Etapa 1:

4-hidroxipiridona **22c** se sintetiza utilizando el proceso descrito por T. Kato;

Y. Kubota; M. Tanaka; H. Takahashi y T. Chiba; *Heterocicles* **1978**, *9*, 811.

Etapa 2:

El compuesto intermedio **22c** se transforma en el compuesto intermedio **22d**, utilizando procesos descritos en la etapa 2 del Ejemplo 2.

Etapa 3:

El compuesto intermedio **22d** se transforma en el compuesto intermedio **22e**, utilizando procesos descritos en la etapa 3 del Ejemplo 2.

Etapa 4:

El compuesto intermedio **22e** se transforma en el compuesto intermedio **22f**, utilizando procesos descritos en la etapa 4 del Ejemplo 2.

Etapa 5:

El compuesto intermedio **22f** se transforma en el compuesto intermedio **22g**, utilizando procesos descritos en la etapa 5 del Ejemplo 2.

Etapa 6:

El compuesto intermedio **22g** se transforma en el compuesto intermedio **22h**, utilizando procesos descritos en la etapa 6 del Ejemplo 2.

Etapa 7:

El compuesto intermedio **22h** se transforma en el compuesto intermedio **22i**, utilizando procesos descritos en la etapa 1 del Ejemplo 4.

Etapa 8:

El compuesto intermedio **22i** se transforma en el compuesto intermedio **22j**, utilizando procesos descritos en la etapa 1 del Ejemplo 5.

Etapa 9:

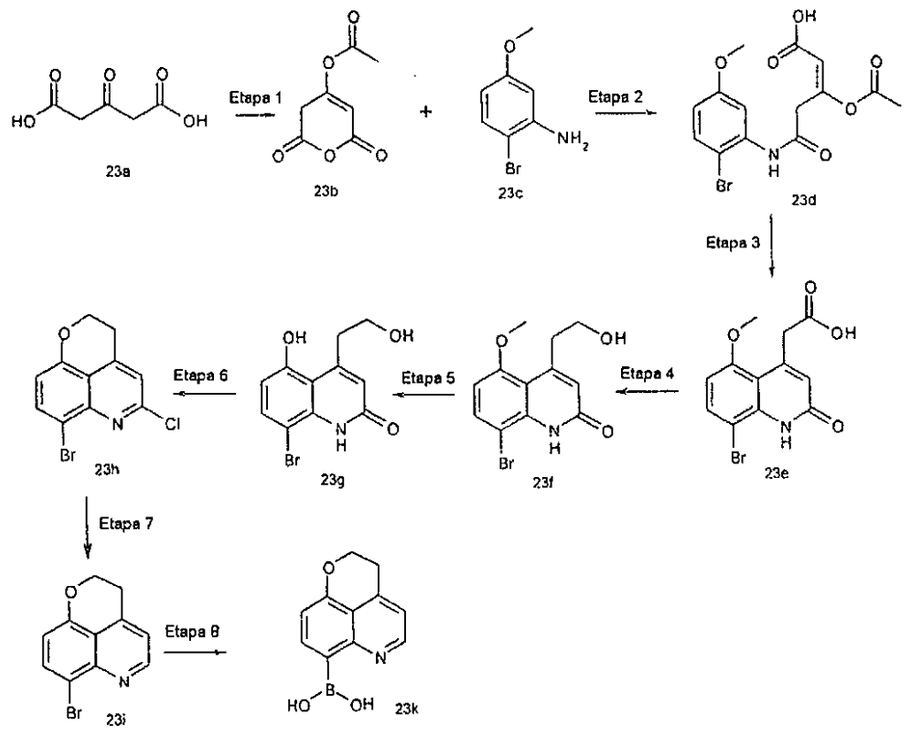
El compuesto intermedio **22j** se transforma en el compuesto intermedio **22k**, utilizando procesos descritos en la etapa 2 del Ejemplo 5.

Etapa 10:

El compuesto intermedio **22j** se transforma en el compuesto **2006**, utilizando procesos descritos en la etapa 3 del Ejemplo 4.

EJEMPLO 23

SÍNTESIS DEL COMPUESTO INTERMEDIO 23K



Etapa 1:

Ácido 1,3-acetonadicarboxílico **23a** (30 g; 205,3 mmol) se añade en porciones a Ac_2O (55 g; 587,7 mmol) y la mezcla se agita a 35°C durante 23 h, y luego se filtra. El filtrado se diluye con benceno (200 mL) y la solución se almacena a 5°C durante 3 h. El precipitado se filtra y se seca en vacío para dar el compuesto intermedio **23b**.

Etapa 2:

A una solución agitada de anilina **23c** (7,5 g, 44 mmol) en AcOH (50 mL) se añade **23b** (8,0 g, 40 mmol) en porciones. La mezcla de reacción se calienta a 35°C durante 2 h, después se enfría a temperatura ambiente y se vierte en hielo/agua (600 mL). El precipitado resultante se aísla por filtración, se aclara con agua (100 mL) y se seca al vacío para dar el compuesto **23d**.

Etapa 3:

El compuesto intermedio **23d** (5,7 g, 15,4 mmol) se añade en porciones a ácido sulfúrico concentrado (20 mL) a TA, de modo que la temperatura de la mezcla de reacción se mantiene por debajo de 30°C durante la adición. La mezcla se agita

a TA durante 30 min y se vierte en hielo/agua (400 mL). El precipitado resultante se aísla por filtración, se aclara con agua y se seca al vacío para dar **23e**.

Etapa 4:

Una solución de borano (1,0 M en THF, 10,5 ml, 10,5 mmol) se añade gota a gota a una solución, enfriada con hielo, de quinolona **23e** (1,5 g, 4,8 mmol) en THF seco (40 mL) bajo una atmósfera de N_2. La mezcla se deja calentar hasta TA y se agita durante 22 h. Se añade un equivalente adicional de BH_3 a 0°C y la mezcla de reacción se calienta hasta 45°C durante 2 h. La reacción se enfría bruscamente con cuidado con NaOH 1,0 N (10 mL) y THF se separa en vacío. La mezcla se vierte en EtOAc (100 mL) y el precipitado se recoge mediante filtración y se seca en vacío para proporcionar **23f**.

Etapa 5:

A una mezcla de **23f** (1,1 g, 3,8 mmol) y DCM (60 mL) a -78°C se añade gota a gota una solución de BBr_3 1,0 M (23 mL, 23 mmol). El baño de enfriamiento se separa después de 1 h y la mezcla se agita a TA durante 16 h. La mezcla se vierte en hielo/agua (100 mL) y el precipitado se recoge mediante filtración y se seca en vacío para dar **23g**.

Etapa 6:

A una solución de compuesto intermedio **23g** (773 mg, 2,27 mmol) en THF (30 mL) se añade PPh_3 (928 mg, 3,5 mmol), seguido de DIAD (0,69 ml, 3,5 mmol) (gota a gota) y la solución se agita a TA durante 2 h. La mezcla de reacción se concentra en vacío y el producto bruto se añade directamente en porciones a $POCl_3$ (2 mL) a TA. La mezcla de reacción se agita a 100°C durante 45 min y luego se enfría hasta temperatura ambiente. La mezcla se concentra en vacío y el producto bruto se diluye con DCM. La fase orgánica se lava con NaOH 1,0 N, agua y salmuera, se seca ($MgSO_4$), se filtra y se concentra en vacío. El producto bruto se purifica por combiFlash® (Hex/EtOAc 9/1 a 1/1) para dar **23h**.

Etapa 7:

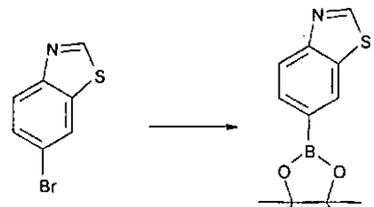
A una solución de cloroquinolina **23h** (300 mg, 1 mmol) en TFA (10 mL) se añade zinc (340 mg, 5 mmol) y la mezcla se agita a TA durante 16 h. La mezcla se filtra y se concentra en vacío, y el residuo se diluye con NaOH 1,0 N (50 mL) y se extrae con DCM (3 veces). Los extractos orgánicos reunidos se lavan con agua y salmuera, se secan ($MgSO_4$), se filtran y se concentran en vacío. El residuo se purifica por combiFlash® (Hex/EtOAc 6/4 a 4/6) para dar **23i**.

Etapa 8:

Una mezcla de haluro de arilo **23i** (5 g, 20 mmol), Et_2O (400 mL) bajo una atmósfera de nitrógeno se calienta hasta 43°C y luego se enfría hasta -75°C en un baño de hielo seco/acetona. Se añade, gota a gota, una solución de n-butil-litio (1,38 M en hexanos, 21,7 mL, 30 mmol) (4 min de tiempo adicional, temp. interna por debajo de 70°C). La mezcla se agita durante 5 min adicionales y se añade una solución de n-butil-litio (880 µL, 1,2 mmol). Después de 5 min, se añade borato de triisopropilo (16,9 mL, 72 mmol), al tiempo que la temperatura se mantiene a -74°C. La mezcla de reacción se deja calentar hasta -42°C y se añaden 5 mL (21 mmol) de borato de triisopropilo. La mezcla se agita durante 10 min a -18°C, y se añaden 2,5 mL (11 mmol) de borato de triisopropilo, seguido de HCl acuoso 2 N (200 mL, 400 mmol). La mezcla se deja agitar a temperatura ambiente durante 2,5 h, luego se diluye con Et_2O (50 mL) y HCl 2 N (50 mL). (Las capas se separan y la capa acuosa se ajusta a pH = 7 con NaOH 10 N (45 mL) y NaOH 1 N (20 mL). El precipitado se filtra y se seca durante 16 h a alto vacío, proporcionando el compuesto **23k** deseado.

EJEMPLO 24

SÍNTESIS DEL PRODUCTO INTERMEDIO 24B

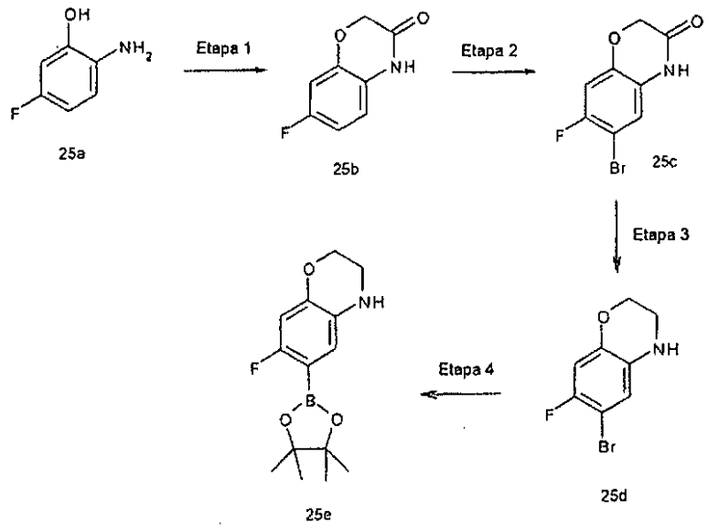


24a 24b

A una mezcla del bromuro **24a** (152 mg, 0,71 mmol) y DMF (5 mL) se añade bis(pinacolato)diboro (234 mg, 0,92 mmol) y KOAc (210 mg, 2,13 mmol). La solución se desgasifica con gas argón bajo tratamiento con ultrasonidos (10 min) y se añade aducto de dicloro[1,1'-bis(difenilfosfino)ferroceno]paladio (II) DCM (87 mg, 0,10 mmol). La mezcla se calienta a 90°C durante 16 h y se enfría hasta TA. La mezcla se diluye con EtOAc, se lava con salmuera saturada, se seca ($MgSO_4$), se filtra y se concentra. El residuo se purifica utilizando el CombiFlash® Companion (hexanos/EtOAc) para dar el boronato **24b**.

EJEMPLO 25

SÍNTESIS DEL COMPUESTO INTERMEDIO 25E



Etapa 1:

A una mezcla fría (0°C) de **25a** (15,0 g, 118 mmol) y DMF (180 mL) se añade K_2CO_3 (48,9 g, 354 mmol) seguido de la adición, gota a gota, de cloruro de cloroacetilo (9,40 mL, 118 mmol). La mezcla de reacción se deja calentar hasta TA y luego se calienta hasta 60°C durante 2 h. La mezcla de reacción se enfría hasta TA, se vierte en hielo-agua (2,0 L) y se agita durante 30 min. La mezcla se filtra y el sólido se aclara con agua y se seca a presión reducida para proporcionar **25b**.

Etapa 2:

A una mezcla enfriada (10°C) de **25b** (12,4 g, 74,4 mmol), DCM (150 mL) y Ac_2O glacial (150 mL) se añade, gota a gota y a lo largo de 1,5 horas, una solución de Br_2 (4,6 mL, 89 mmol) en DCM (75 mL). Después de 2 horas a 10°C, se añade una cantidad adicional de Br_2 (2,30 mL, 44,6 mmol) en DCM (40 mL) a lo largo de 1 h con agitación a 10°C. La agitación se continúa durante 1 h y la mezcla de reacción se concentra a presión reducida. El residuo se tritura con Et_2O (500 mL) para proporcionar el bromuro **25c**.

Etapa 3:

A una solución de **25c** (13,4 g, 54,5 mmol) en THF (300 mL) a 0°C, se añade lentamente un complejo de borano-sulfuro de metilo (55,0 mL, solución 2,0 M en THF, 110 mmol). La mezcla se deja calentar a temperatura ambiente y luego se agita a reflujo durante 1 h. La mezcla de reacción se enfría hasta 0°C, se enfría

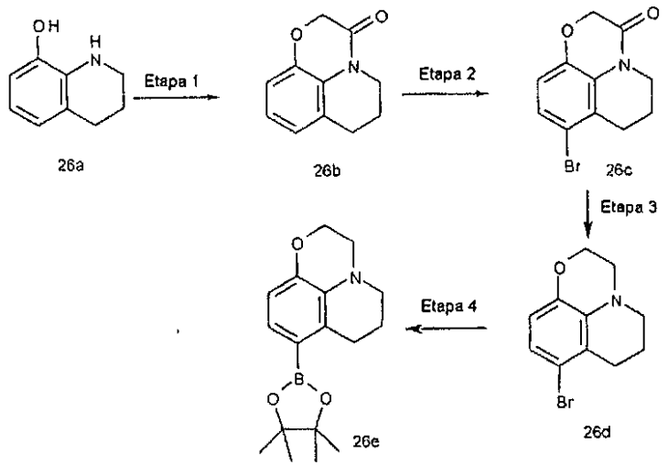
bruscamente, de forma lenta, con HCl acuoso 1 M (27 mL), y luego se somete a reflujo durante 1 h. La mezcla se diluye con Et_2O, se neutraliza con NaOH acuoso 1 M y, después de una extracción adicional, se concentra. El residuo se purifica mediante cromatografía en columna de resolución rápida (EtOAc al 15 a 30%/hexanos) para proporcionar el compuesto intermedio **25d**.

Etapa 4:

Una mezcla de **25d** (10,0 g, 43,1 mmol), de bis(pinacolato)diboro (16,4 g, 64,7 mmol) y KOAc (12,7 g, 129 mmol) en 1,4-dioxano (430 mL) se desgasifica con nitrógeno durante 30 min a TA y se calienta a 100°C bajo una atmósfera de nitrógeno. Después de 30 min, se añade aducto dicloro[1,1'-bis(difenilfosfino)ferroceno]paladio (II) y DCM (3,5 g, 4,3 mmol) y se continúa la agitación a 100°C (15 h). La mezcla de reacción se enfría hasta TA y se filtra a través de una almohadilla de Celite®. La almohadilla de Celite® se aclara con EtOAc y el filtrado reunido se concentra a presión reducida. El residuo se purifica por cromatografía en columna de resolución rápida (dos veces con EtOAc al 25%/hexanos, seguido de EtOAc al 5%/DCM) para proporcionar **25e**.

EJEMPLO 26

SÍNTESIS DEL COMPUESTO INTERMEDIO 26E



Etapa 1:

A una solución fría (0°C) de 1,2,3,4-tetrahidroquinolin-8-ol **26a** (6,00 g, 40 mmol) en DMF (60 mL) se añade K_2CO_3 (16,7 g, 121 mmol) seguido de la adición, gota a gota, de cloruro de cloroacetilo (4,25 mL, 53,6 mmol). La mezcla de reacción

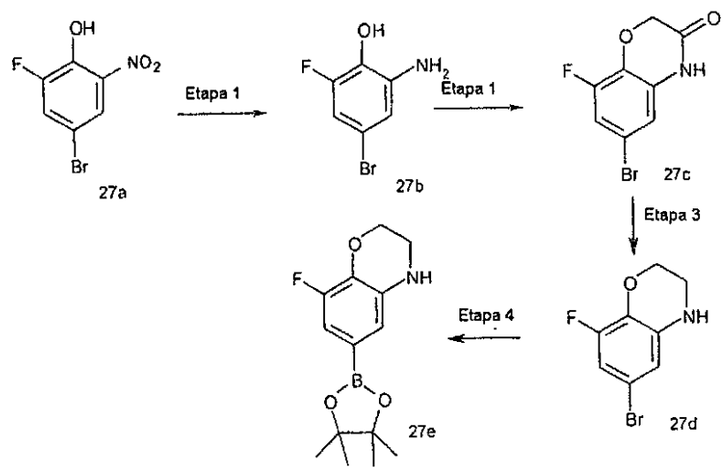
se calienta hasta TA y se calienta a 60°C durante 2 h. La mezcla de reacción se enfría hasta TA, se vierte en hielo-agua (1,5 L) y se agita durante 30 min. La mezcla resultante se filtra y el sólido se aclara con agua y se seca a presión reducida (16 h) para proporcionar la amida **26b**.

Etapas 2, 3 y 4:

El compuesto intermedio **26b** se transforma en el compuesto intermedio **26e**, utilizando procesos descritos en las etapas 2 a 4 del Ejemplo 25.

EJEMPLO 27

SÍNTESIS DEL COMPUESTO INTERMEDIO 27E



Etapa 1:

A una mezcla de 4-bromo-2-fluoro-6-nitrofenol **27a** (12,0 g, 51 mmol) y EtOH (375 mL) se añade una solución de ditionito de sodio (35,4 g, 203 mmol) en agua (125 mL). La mezcla se calienta a reflujo durante 1 h, y luego se enfría hasta 0°C y se neutraliza lentamente con $NaHCO_3$ acuoso saturado (150 mL). La mezcla se concentra y el residuo se tritura con MeOH al 10%/EtOAc (1,0 L) y se filtra a través de una almohadilla de Celite®. La concentración del filtrado a presión reducida proporciona la anilina **27b**.

Etapa 2:

El compuesto intermedio **27b** se transforma en el compuesto intermedio **27c**, utilizando el proceso descritos en la etapa 1 del Ejemplo 25.

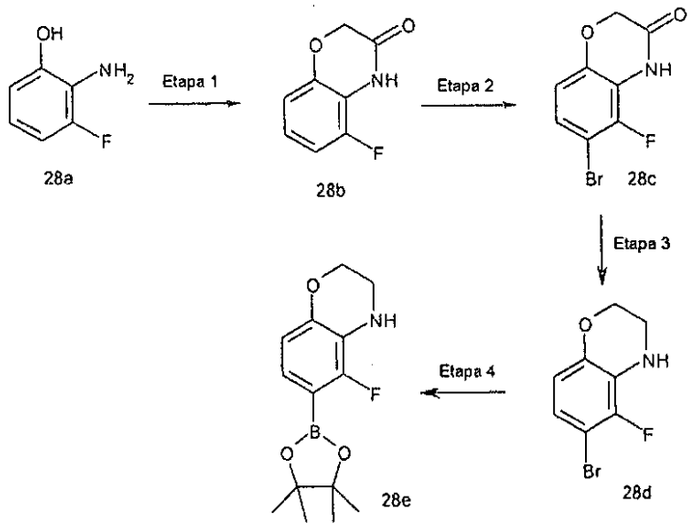
Etapas 3 y 4:

El compuesto intermedio **27c** se transforma en el compuesto intermedio **27e**,

utilizando los procesos descritos en las etapas 3 y 4 del Ejemplo 25.

EJEMPLO 28

SÍNTESIS DEL COMPUESTO INTERMEDIO 28E

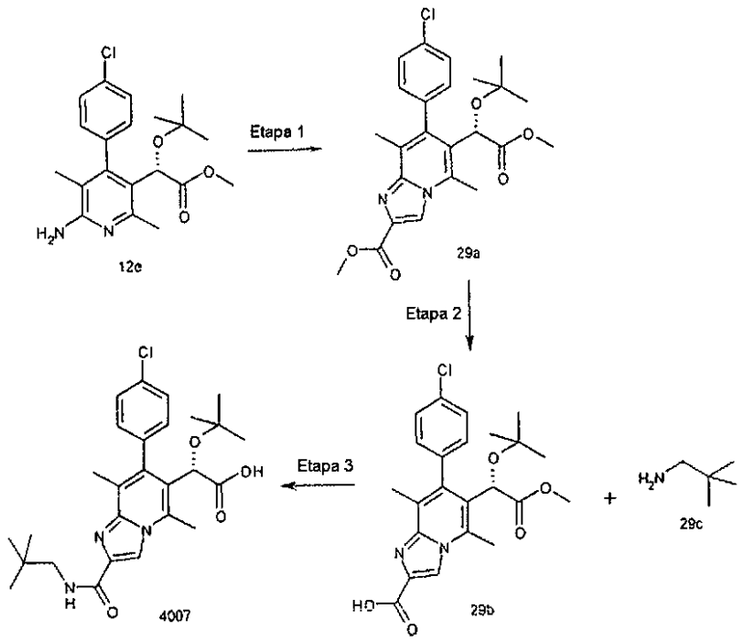


Etapas 1 a 4:

El compuesto intermedio **28a** se transforma en el compuesto intermedio **28e**, utilizando procesos descritos en las etapas 1 a 4 del Ejemplo 25.

EJEMPLO 29

SÍNTESIS DEL COMPUESTO 4007 (TABLA 4)



Etapa 1:

A una mezcla de **12e** (Ejemplo 12) (570 mg, 1,5 mmol), EtOH (11 mL) y acetona (2,2 mL) se añade $NaHCO_3$ (197 mg, 1,6 mmol) y bromopiruvato de metilo (177 µL, 1,7 mmol). Se calienta a 85 °C la mezcla durante 16 h, y los disolventes se evaporan a vacío. El residuo se disuelve en DCM (20 mL), se lava dos veces con agua, se seca sobre $MgSO_4$ y se concentra *en vacío* dando **29a**.

Etapa 2:

Una mezcla de **29a** (620 mg, 1,4 mmol), THF (18,7 mL) y MeOH (6,2 mL) se trata con LiOH (1 N, 1,4 mL, 1,4 mmol) a 23°C durante 15 h. Se añade una porción adicional de LiOH 1 N (1,4 mL, 1,4 mmol) y la mezcla se agita durante 4 h a 23°C. Luego se añade NaOH 1 N (0,1 mL, 0,1 mmol) y la reacción se continúa hasta que se detecta la conversión completa en el producto por UPLC-MS. La mezcla se ajusta hasta pH 1 con HCl 1 N y se extrae con DCM (3 veces), y el extracto orgánico se seca sobre $MgSO_4$. El residuo se purifica por CombiFlash® (5% de MeOH / 94 % de DCM / 1% de AcOH) proporcionando **29b** puro.

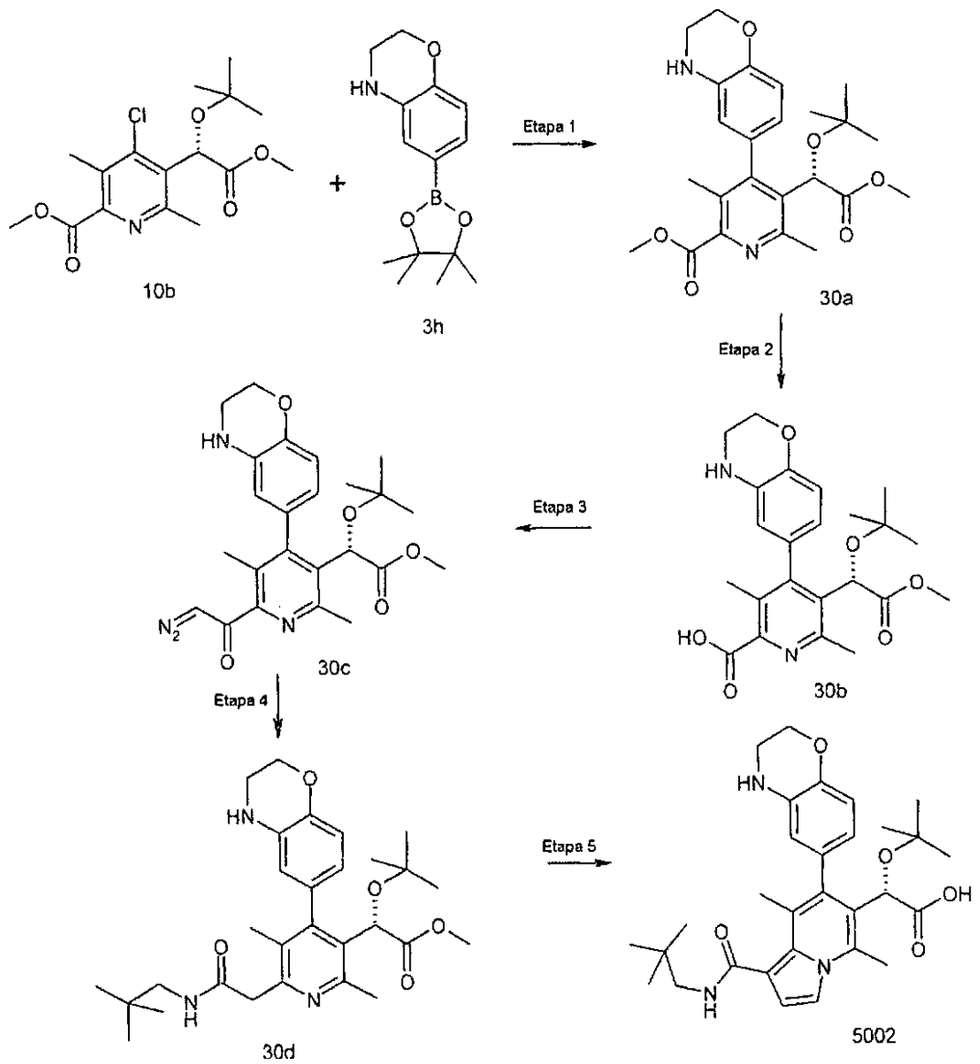
Etapa 3:

A una mezcla de **29b** (50 mg, 0,11 mmol) y NMP (1 mL) se añade Et_3N (63

μL, 0,45 mmol), seguido de tetrafluoroborato de N,N,N',N'-tetrametil-O-(benzotriazol-1-il)uronio (72 mg, 0,22 mmol). La mezcla se agita durante 10 min, se trata con neopentilamina **29c** (30 mg, 0,34 mmol) y se agita durante 16 h a 23ºC. Se añade NaOH 1 N (0,5 mL, 0,5 mmol) a la mezcla de reacción y se continúa la agitación durante 2 h a 60°C. La solución se neutraliza con AcOH y se añade EtOAc (75 mL). La capa orgánica se lava con agua y salmuera, se seca sobre $MgSO_4$, se filtra y se concentra *en vacío* y el residuo se purifica por HPLC prep. Una mezcla del producto y DCM (3 mL) se trata con NaOH 1N (pH > 10) y se neutraliza con AcOH. La mezcla se hace pasar a través de un filtro de separador de fases y la capa orgánica se concentra *en vacío*. El residuo se diluye con una mezcla de MeCN / agua y se liofiliza para dar el compuesto **4007**.

EJEMPLO 30

SÍNTESIS DEL COMPUESTO 5002 (TABLA 5)



Etapa 1:

Los compuestos intermedios **10b** (Ejemplo 10) y **3h** (Ejemplo 3) se transforman en el compuesto intermedio **30a** utilizando el proceso descrito en la etapa 2 del Ejemplo 4.

Etapa 2:

El compuesto intermedio **30a** se transforma en el compuesto intermedio **30b**, utilizando el proceso descritos en la etapa 4 del Ejemplo 12.

Etapa 3:

Se añade gota a gota cloroformiato de isobutilo (205 μL, 1,6 mmol) a una mezcla de **30b** (700 mg, 1,5 mmol), Et_3N (420 μL, 3,0 mmol) y THF (15 mL) a 0°C.

La mezcla se agita a 0°C durante 30 min, y se añade diazometano (0,67 M en Et_2O, 11,2 mL, 7,5 mmol). Se deja que la mezcla alcance 23°C y se agita durante 2 h, y luego se concentra *en vacío*. Se añade una mezcla de EtOAc y agua al residuo, las capas se separan y la capa orgánica se lava con $NaHCO_3$ saturado, agua y salmuera, se seca sobre Na_2SO_4, se filtra y se concentra *en vacío*, proporcionando **30c**.

Etapa 4:

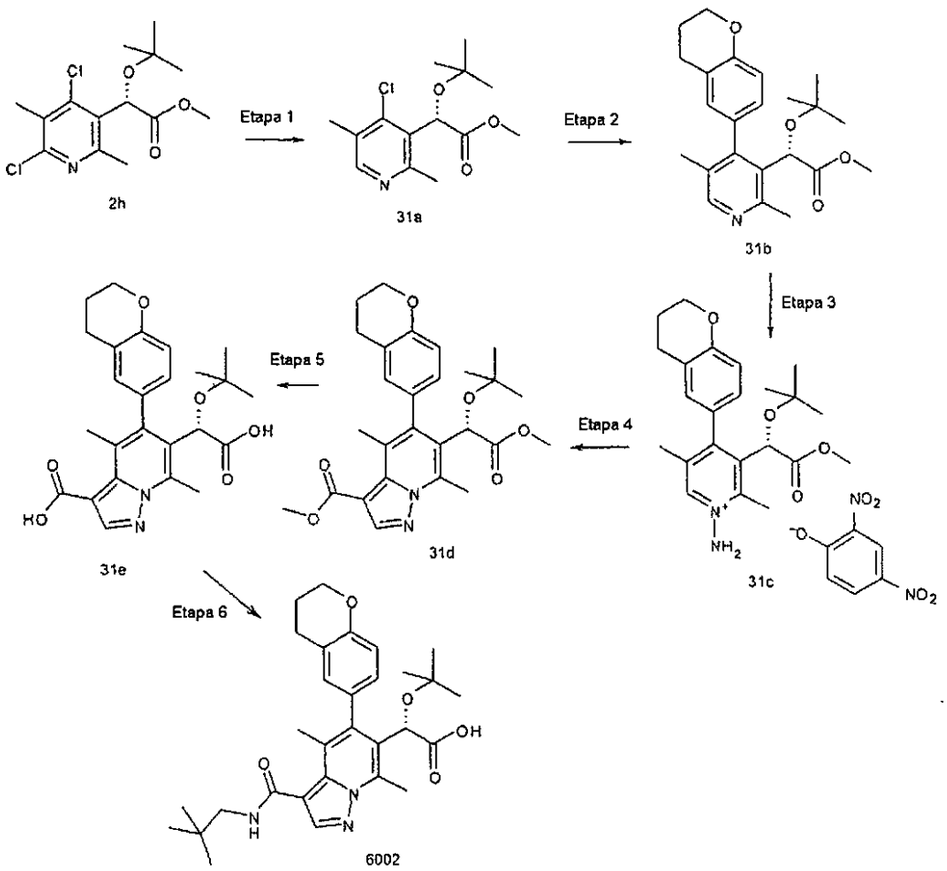
Una mezcla de **30c** (125 mg, 0,28 mmol) y DCM (1 mL) se trata con neopentilamina **29c** (Ejemplo 29) (65 µL, 0,55 mmol) y Et_3N (47 µL, 0,34 mmol), seguido de la adición de benzoato de plata (16 mg, 0,07 mmol). La mezcla se agita a 23°C durante 16 h. La mezcla se diluye con DCM, se lava con NH_4Cl saturado, $NaHCO_3$ saturado y agua, se seca sobre Na_2SO_4, se filtra y se concentra *en vacío*, proporcionando **30d**.

Etapa 5:

Una mezla de **30d** (40 mg, 0,08 mmol), cloroacetaldehído (al 50% en agua, 15 µL, 0,12 mmol) y $NaHCO_3$ (19,7 mg, 0,23 mmol) en EtOH (0,5 mL) se calienta a reflujo durante 16 h. La mezcla se enfría hasta 23°C y se filtra, y el disolvente se evapora *en vacío*. El residuo se mezcla con THF (1 mL) y MeOH (0.3 mL) y se añade NaOH (1 N, 0,3 mmol). La mezcla se agita a 45°C hasta completarse la reacción, luego se enfría hasta 23°C, ae ajusta a pH 5 con AcOH y se purifica por HPLC prep. para dar el compuesto **5002**.

EJEMPLO 31

SÍNTESIS DEL COMPUESTO 6002 (TABLA 6)



Etapa 1:

A una mezcla del compuestro intermedio **2h** (Ejemplo 2) (5 g, 15,6 mmol) en AcOH (100 mL) se añade zinc (15,3 g, 234 mmol). La mezcla se agita a 60°C durante 120 min, después se enfría hasta 23°C y se filtra a través de una almohadilla de Celite®, y el filtrado se concentra *en vacío*. El residuo se neutraliza lentamente con $NaHCO_3$ saturado y se extrae dos veces con EtOAc. Las capas orgánicas se reunen, se lavan con agua y salmuera, se secan sobre $MgSO_4$, se filtran y se concentran *en vacío* para dar el compuesto intermedio **31a** deseado.

Etapa 2:

Una mezcla de DMA (15,8 mL) y agua destilada (1,58 mL) se desgasifica durante 10 min con nitrógeno y se añade, mediante jeringa, a una mezcla del compuesto intermedio **31a** (1 g, 3,5 mmol), 6-(4,4,5,5-tetrametil-[1,3,2]dioxaborolan-2-il)-cromano **19d** (Ejemplo 19) (1 g, 3,85 mmol) y $NaHCO_3$ (1,47 gr, 17,5 mmol)

bajo una atmósfera de nitrógeno en un recipiente resellable de 48 mL, equipado con una varilla de agitación magnética y se fija con un tabique de caucho. Se añade bis(tri-*t*-butilfosfina)paladio (179 mg, 0,35 mmol) a la mezcla de reacción y el recipiente se coloca en un dispositivo de ultrasonidos durante 10 min, al tiempo que se purga con nitrógeno. El recipiente se sella con un tapón de Teflon y se calienta a 130°C durante 4 h. La mezcla se diluye con EtOAc y se filtra a través de Celite®, y el extracto orgánico se lava con agua y salmuera, se seca sobre $MgSO_4$ y se concentra *en vacío*. El residuo se purifica por cromatografía de resolución rápida (10-25-100% acetato de etilo: hexanos) proporcionando **31b**.

Etapa 3:

A un recipiente resellable de 15 mL, equipado con una varilla de agitación magnética, se añade el compuesto intermedio **31b** (500 mg, 1,3 mmol), *O*-(2,4-dinitrofenil)hidroxilamina (300 mg, 1,5 mmol; preparado según se describe en *Tet.Lett.* **1972**, *28*, 3833-3843) y MeCN (1,7 mL). El recipiente de reacción se sella con un tapón de Teflon y la mezcla se agita a 40°C durante 24 h, después se enfría hasta 23°C y se concentra en vacío, proporcionando **31c**.

Etapa 4:

A una mezcla de **31c** (521 mg, 1,3 mmol) y DMF (17,4 mL) se añade K_2CO_3 (198 mg, 1,43 mmol). La mezcla de reacción se agita durante 5 min a 23°C (expuesta al aire), luego se añade proprionato de metilo (132 mg, 1,56 mmol) y la agitación continúa durante 18 h. La mezcla se diluye con EtOAC y se lava con $NaHCO_3$ saturado, agua y salmuera. La capa orgánica se seca sobre $MgSO_4$, se filtra y se concentra *en vacío* y el residuo se purifica por cromatografía de resolución rápida (10-100% acetato de etilo: hexanos) proporcionando **31d**.

Etapa 5:

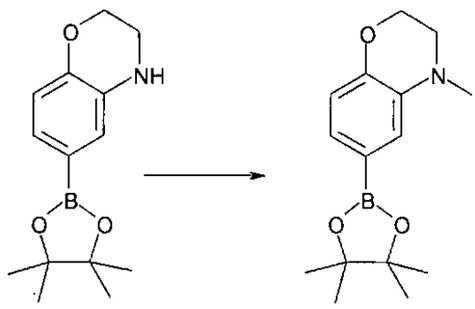
Una mezcla de **31d** (250 mg, 0,52 mmol), THF (2,5 mL) y MeOH (0,83 mL) se trata con una solución de NaOH 10 N (0,42 mL, 4,2 mmol) a 60°C durante 18 h. La mezcla se ajusta a pH 1 con HCl 1 N y se extrae con DCM (3 veces). Las capas orgánicas reunidas se secan sobre $MgSO_4$, se filtran y se concentran *en vacío*, proporcionando el compuesto intermedio **31e**.

Etapa 6:

El compuesto intermedio **31e** se transforma en el compuesto **6002** utilizando el proceso descrito en la etapa 3 del Ejemplo 29.

EJEMPLO 32

SÍNTESIS DEL COMPUESTO INTERMEDIO 32A

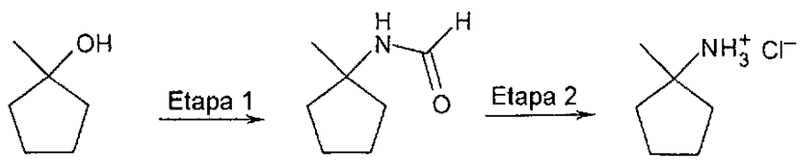


3h 32a

A una mezcla de boronato **3h** (Ejemplo 3) (0,80 g, 3,1 mmol) y acetona (20 mL) se añade K_2CO_3 (5,23 g, 38 mmol) seguido de yoduro de metilo (2,9 mL, 39 mmol). El recipiente de reacción se sella y la mezcla de reacción se agita a TA (24 h). La mezcla se diluye con EtOAc y salmuera saturada. La fase acuosa se extrae con EtOAc (2 veces) y las fases orgánicas reunidas se secan ($MgSO_4$), se filtran y se concentran a sequedad para proporcionar el boronato **32a** deseado.

EJEMPLO 33

SÍNTESIS DEL COMPUESTO INTERMEDIO 33C



33a 33b 33c

Etapa 1:

A una mezcla de metilciclopentanol **33a** (2,0 g, 20 mmol) y AcOH (2,0 mL) se añade KCN (1,43 g, 22 mmol) en porciones, seguido de la adición, gota a gota, de H_2SO_4 conc. (3,0 mL) a una tasa para mantener la temperatura en 30-35°C. La mezcla se calienta hasta 60°C durante 30 min y luego se agita a TA (16 h). Se añade agua helada (35 mL) y la mezcla se ajusta a pH de carácter básico con K_2CO_3 sólido y se extrae con Et_2O (5 veces). Las fases orgánicas reunidas se secan sobre $MgSO_4$, se filtran y concentran para dar **33b**.

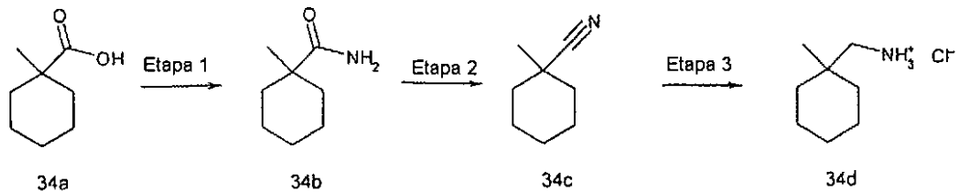
Etapa 2:

Una mezcla del derivado **33b** (1,5 g, 11,8 mmol) y dioxano (8 mL) se trata

con HCl 5 N (8,0 mL) y EtOH (4 mL). La mezcla se calienta a suave reflujo durante 4 h y después etanol y dioxano se separan en vacío. La fase acuosa se lava con hexanos y luego se concentra. Trazas de agua se separan por separación azeotrópica con EtOH. El sólido resultante se seca bajo alto vacío para dar la sal hidrocloruro de amina **33c**.

EJEMPLO 34

SÍNTESIS DEL COMPUESTO INTERMEDIO 34D



34a 34b 34c 34d

Etapa 1:

Una mezcla de ácido 1-metilciclohexano-carboxílico **34a** (25 g, 176 mmol) en DCM (125 mL) se enfría hasta 0°C y se añade una cantidad catalítica de DMF (250 µL). Luego se añade gota a gota cloruro de oxalilo (20 mL, 228 mmol) a lo largo de 30 min y la mezcla se deja agitar durante 45 min. La mezcla de reacción se calienta luego hasta TA y se agita durante 2,5 h adicionales. La mezcla se concentra hasta sequedad y se seca, y el residuo se mezcla con 1,4-dioxano (125 mL). A esta mezcla se añade en porciones una solución de hidróxido de amonio al 20% (125 mL) a TA (1 h). La mezcla se diluye con agua (200 mL) y se extrae con EtOAc (3 veces). Los extractos orgánicos reunidos se lavan con salmuera saturada, se secan ($MgSO_4$), se filtran y se concentran para dar un sólido bruto. Este material se disuelve en hexanos calientes (125 mL) y se deja a 4°C (18 h). El sólido formado se filtra y se lava con hexanos fríos para proprocionar la amida **34b**.

Etapa 2:

En un matraz de fondo redondo, de 2 bocas, equipado con un condensador, se añade **34b** (18,0 g, 128 mmol) en cloruro de tionilo (12 mL, 106 mmol). La mezcla se calienta a reflujo durante 2 h hasta que cesa el desprendimiento de gas, luego se enfría hasta TA y se diluye con Et_2O (125 mL) con la adición cuidadosa de agua (75 mL). La mezcla se agita vigorosamente durante 5 min y después se ajusta a pH de carácter básico con Na_2CO_3 sólido. La fase orgánica se separa y se lava con Na_2CO_3 saturado y salmuera saturada, se seca sobre $MgSO_4$, se trata con

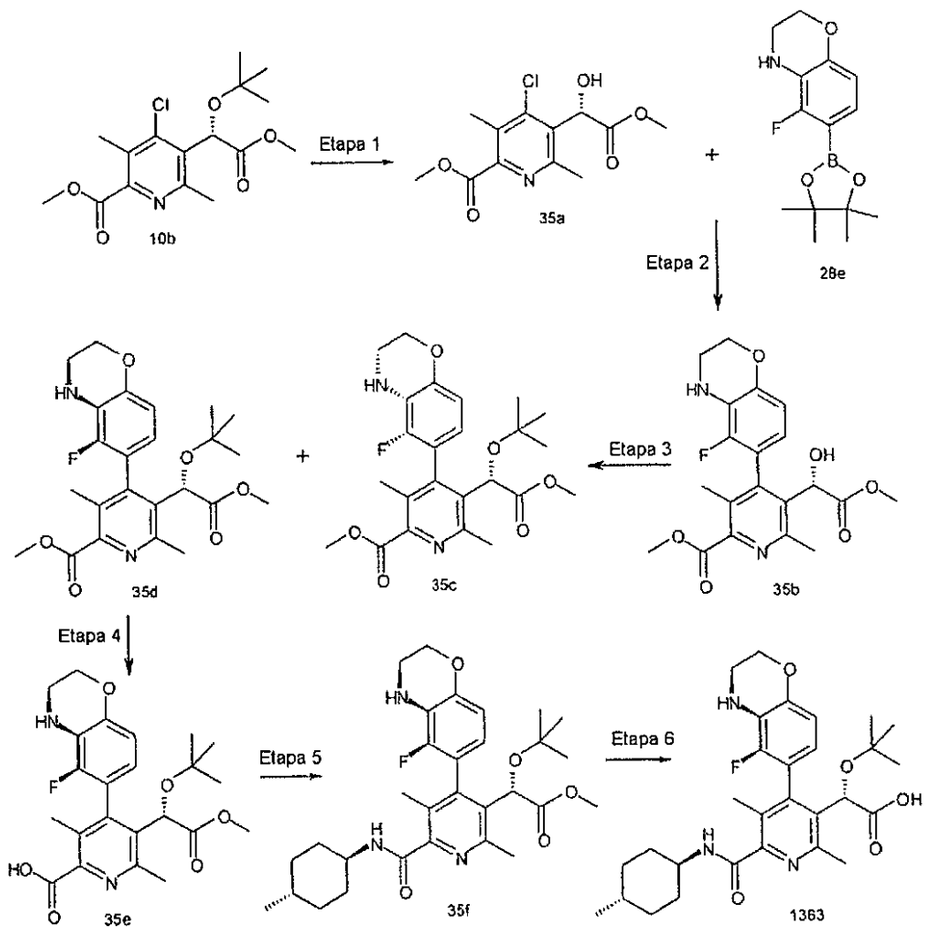
carbón vegetal y se filtra a través de Celite®. El filtrado se concentra en vacío a TA para dar **34c**.

Etapa 3:

A una mezcla de EtOH (50 mL) y HCl (g) (8,3 g, 0,23 mmol) a 0°C se añade **34c** (14,7 g, 119 mmol) seguido de óxido de platino (400 mg). La mezcla se coloca en un agitador Parr y se trata con H_2(g) a 2,8 kg/cm^2 durante 48 h. La atmósfera se agita y la mezcla se filtra a través de Celite® y se lava con EtOH. El filtrado se concentra a sequedad y el residuo se lava con éter, se filtra y se seca para dar el compuesto intermedio **34d** en forma de la sal hidrocloruro.

EJEMPLO 35

SÍNTESIS DEL COMPUESTO 1363 (TABLA 1), INCLUIDA LA SEPARACIÓN DE ATROPISÓMEROS



Etapa 1:

A una mezcla del diéster **10b** (1,0 g, 2,91 mmol), DCM (7 mL) y MeOH (0,25 mL) se añade TFA (8 mL). La mezcla se deja agitar a TA durante 2 h y se concentra hasta sequedad. El residuo se recoge en EtOAc y se lava con $NaHCO_3$ saturado, se seca (Na_2SO_4), se filtra y se concentra para dar el alcohol **35a**.

Etapa 2:

Una mezcla de boronato **28e** (400 mg, 1,43 mmol), alcohol **35a** (420 mg, 1,46 mmol), 2-diciclohexilfosfino-2',6'-dimetoxibifenilo (S-Phos, 59 mg, 0,1 mmol), tris(dibencilidenacetona)dipaladio(0) (39 mg, 0,04 mmol) y Na_2CO_3 (607 mg, 5,7 mmol) en 2-metil-tetrahidrofurano (5,6 mL) y agua (1,4 mL) se coloca en un recipiente sellable. La mezcla se desgasifica burbujeando argón a través de la solución (10 min) y el recipiente se sella y se calienta a 75°C (20 h). Se añaden porciones adicionales del catalizador y ligando y la mezcla se calienta de nuevo a 75°C (20 h). La mezcla enfriada se filtra, se diluye con EtOAc, se lava con salmuera, se seca sobre Na_2SO_4, se filtra y se concentra. El residuo se purifica por CombiFlash® Companion para dar una mezcla de isómeros **35b**.

Etapa 3:

La mezcla de alcoholes **35b** (362 mg, 0,90 mmol) en acetato de terc.-butilo (7,1 mL, 53 mmol) se enfría hasta 0°C en un baño de hielo y se trata en porciones con ácido perclórico (al 70% p/p en agua, 1,2 mL, 13,4 mmol). El recipiente se cierra y la mezcla de reacción se agita a 0°C hasta completarse aproximadamente el 50%. La reacción se enfría bruscamente con NaOH 1 N (pH~9) y la mezcla se extrae con EtOAc. La fase orgánica se lava con agua y salmuera, se seca sobre Na_2SO_4 y se concentra. El residuo se purifica por CombiFlash® Companion (20 to 100% de EtOAc/hexanos) para dar los isómeros separados **35c** y **35d**, más alcoholes de partida **35b** que no han reaccionado.

Etapa 4:

A una mezcla de diéster **35d** (87 mg, 0,19 mmol), MeOH (0,4 mL) y THF (1,2 mL) se añade LiOH 1 N (0,21 mL, 0,21 mmol). La mezcla se deja agitar a TA (16 h), luego se acidifica con HCl 1N y se extrae con EtOAc (2 veces). El extracto orgánico se seca sobre Na_2SO_4, se filtra y se concentra para dar el ácido **35e.**

Etapa 5:

Una mezcla de ácido **35e** (30 mg, 0,06 mmol) y NMP (1 mL) se trata con TBTU (40 mg, 0,12 mmol) y Et_3N (35 µL, 0,25 mmol). La mezcla se deja agitar a TA

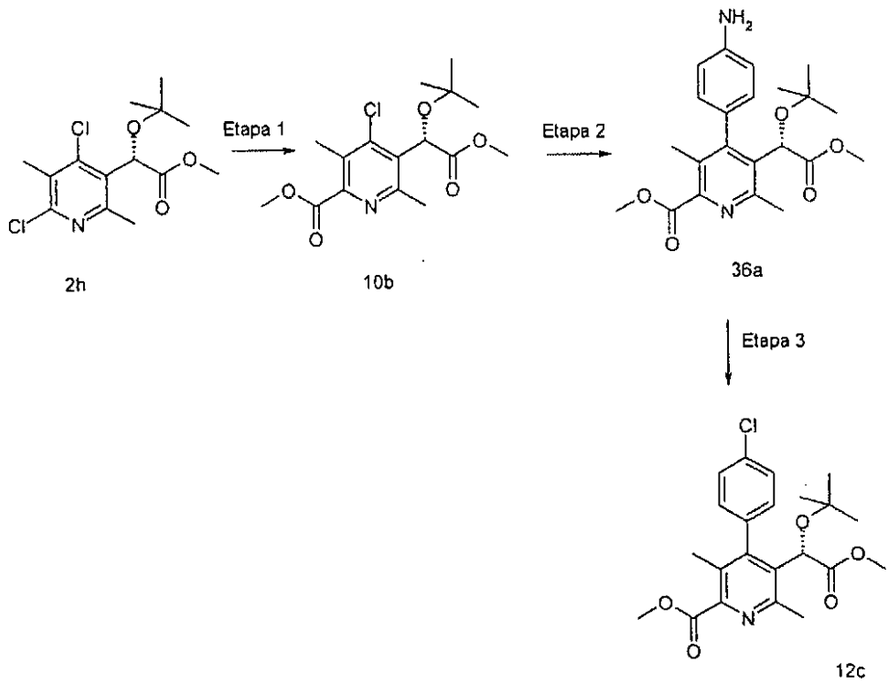
durante 5 min y luego se añade trans-4-metilciclohexilamina (25 µL, 0,19 mmol). La reacción se deja agita a TA (2 h) y después se diluye con EtOAc. La fase orgánica se lava con NH_4Cl saturado, H_2O y salmuera, se seca sobre $MgSO_4$, se filtra y se concentra a sequedad para proporcionar la amida **35f**.

Etapa 6:

Una mezcla de amida **35f**, THF (0.9 mL) y MeOH (0.3 mL) se trata con NaOH 1 N (0,29 ml, 0,29 mmol) a 50°C (1 h). La solución se acidifica con AcOH y se purifica mediante HPLC preparativa. Las fracciones puras se reúnen, se concentran para separar MeCN y luego se extrae en DCM. La fase orgánica se seca sobre Na_2SO_4, se filtra y se concentra. Este sólido se re-disuelve en DCM y se trata con 10 gotas de NaOH 1N y luego se neutraliza con AcOH. Las fases se separan y la capa acuosa se extrae con DCM. Las fases orgánicas reunidas se concentran y se liofilizan para dar el compuesto **1363**.

EJEMPLO 36

SÍNTESIS ALTERNATIVA DEL COMPUESTO INTERMEDIO 12C



Etapa 1:

Una bomba de acero se carga con el compuesto **2h** (11 g, 34,3 mmol), $Pd(OAc)_2$ (0,17 mg, 0,68 mmol), bis(difenilfosfino)ferroceno (0,42 g, 0,76 mmol) y

2,6-lutidina (8,0 mL, 68,7 mmol). Se añade MeOH desgasificado (50 mL) y el sistema se sella. El sistema se purga con N_2 (2 veces) y CO (3 veces). La mezcla se agita a 110°C bajo 14 kg/cm^2 de CO durante 48 h. La mezcla de reacción se filtra, se concentra y se purifica por Combiflash® Companion para dar **10b**.

Etapa 2:

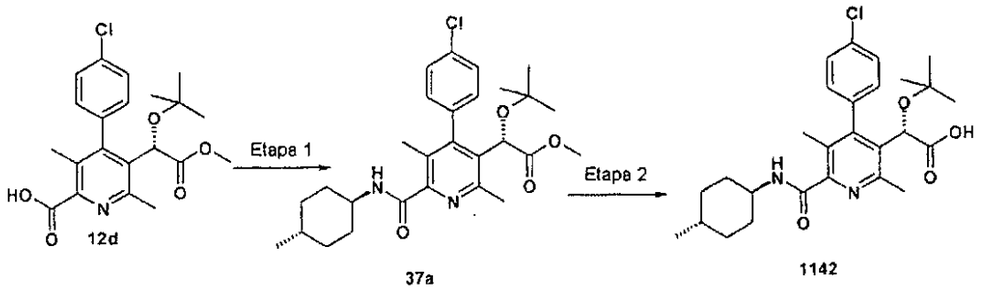
El compuesto intermedio **10b** se transforma en el compuesto intermedio **36a**, utilizando el proceso descritos en la etapa 1 del Ejemplo 12.

Etapa 3:

El compuesto intermedio **36a** se transforma en el compuesto intermedio **12c**, utilizando el proceso descritos en la etapa 2 del Ejemplo 5.

EJEMPLO 37

SÍNTESIS DEL COMPUESTO 1142 (TABLA 1)



Etapa 1:

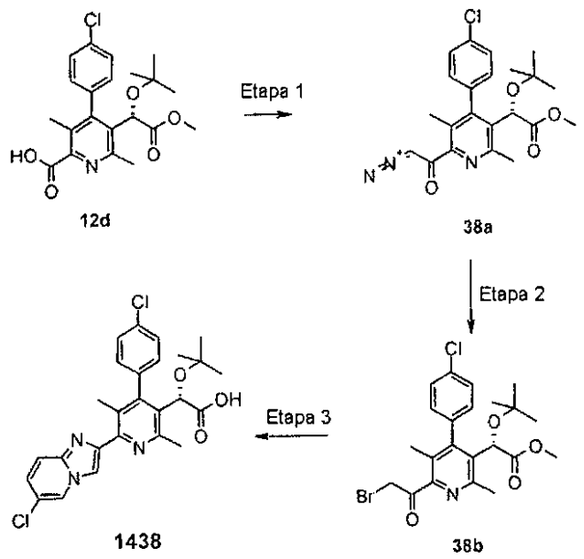
El compuesto intermedio **12d** se transforma en el compuesto intermedio **37a**, utilizando el proceso descrito en la etapa 5 del Ejemplo 35.

Etapa 2:

Una mezcla de la amida **37a**, (30 mg, 0,06 mmol), THF (2,5 mL) y MeOH (0,75 mL) se trata con NaOH 5 N (65 µL, 0,33 mmol) a 60°C (1 h). La solución se neutraliza con AcOH (19 µL, 0,33 mmol) y se evapora a sequedad. El residuo se purifica luego mediante CombiFlash® Companion para dar el compuesto **1142**.

EJEMPLO 38

SÍNTESIS DEL COMPUESTO 1438 (TABLA 1)



Etapa 1:

A **12d** (1 g, 2,5 mmol) y Et_3N (481 µL, 3,5 mmol) en THF (13 mL) a 0°C se añade, gota a gota, cloroformiato de isobutilo (448 µL, 3,5 mmol). La mezcla se agita a 0°C durante 1 h. Se añade lentamente una solución de diazometano (0,67 M en dietil-éter, 37 mL, 25 mmol) y se deja que la mezcla alcance 23°C. Después de 1 h, la mezcla se concentra *en vacío* y luego se añaden EtOAc y agua. La capa orgánica se lava con una solución acuosa saturada de $NaHCO_3$, agua, salmuera, se seca sobre Na_2SO_4, se filtra y se concentra *en vacío*. El producto bruto se purifica mediante CombiFlash® Companion para dar **38a**.

Etapa 2:

A una solución de **38a** (828 mg, 2,5 mmol) en THF (16 mL) a 0°C se añade gota a gota una solución de HBr (48% ac., 1,09 mL, 9,6 mmol). La mezcla se agita durante 1h a 0°C. La solución se diluye con EtOAc, se lava con $NaHCO_3$ (sat.), agua, salmuera, se seca sobre Na_2SO_4, se filtra y se concentra *en vacío*, para proporcionar **38b**.

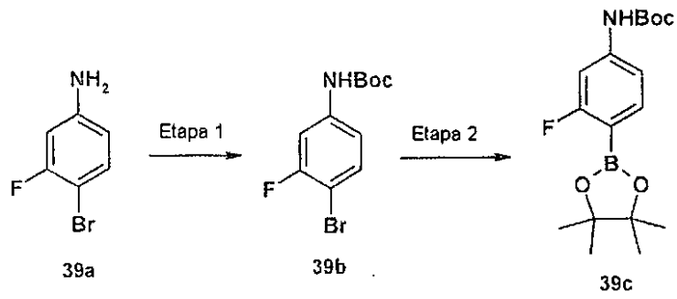
Etapa 3:

A **38b** (50 mg, 0,1 mmol) en una mezcla de EtOH (750 µL) y acetona (150 µL) se añade $NaHCO_3$ (8,1 mg, 0,11 mmol) y 2-amino-5-cloropiridina (14,7 mg, 0,11 mmol) en un tubo sellado. La mezcla se calienta a 85°C durante 30 min y luego se concentra *en vacío*. El residuo se diluye con THF (1 mL), MeOH (300 µL) y una

solución de NaOH (5 N, 103 µL, 0,52 mmol) y la mezcla resultante se agita luego durante 15 min a 60°C. La mezcla se enfría hasta 23°C y el pH se ajusta a ~5-6 con AcOH. La mezcla bruta se purifica mediante HPLC prep. (MeOH/agua que contiene bicarbonato de amonio 10 mM (pH10)). Las fracciones deseadas se recogen y concentran a presión reducida. El residuo se disuelve en MeCN (1,5 mL) y se liofiliza para dar **1438**.

EJEMPLO 39

SÍNTESIS DEL COMPUESTO INTERMEDIO 39C



39a 39b 39c

Etapa 1:

A una solución de THF (90 mL) de **39a** (7,2 g, 38 mmol) se añade $NaHCO_3$ sólido (16 g, 190 mmol) y agua (9 mL) a TA. Esta mezcla se agita durante 10 min antes de la adición, en porciones, de dicarbonato de di-t-butilo sólido (16,5 g, 76 mmol). La mezcla se agita a 55°C durante 16 h o hasta compleción. La mezcla se filtra y luego se reparte entre EtOAc y agua. La fase acuosa se extrae con EtOAc y las fases orgánicas reunidas se lavan con salmuera, se secan ($MgSO_4$), se filtran y se concentran. El producto bruto se purifica mediante CombiFlash® Companion para dar **39b**.

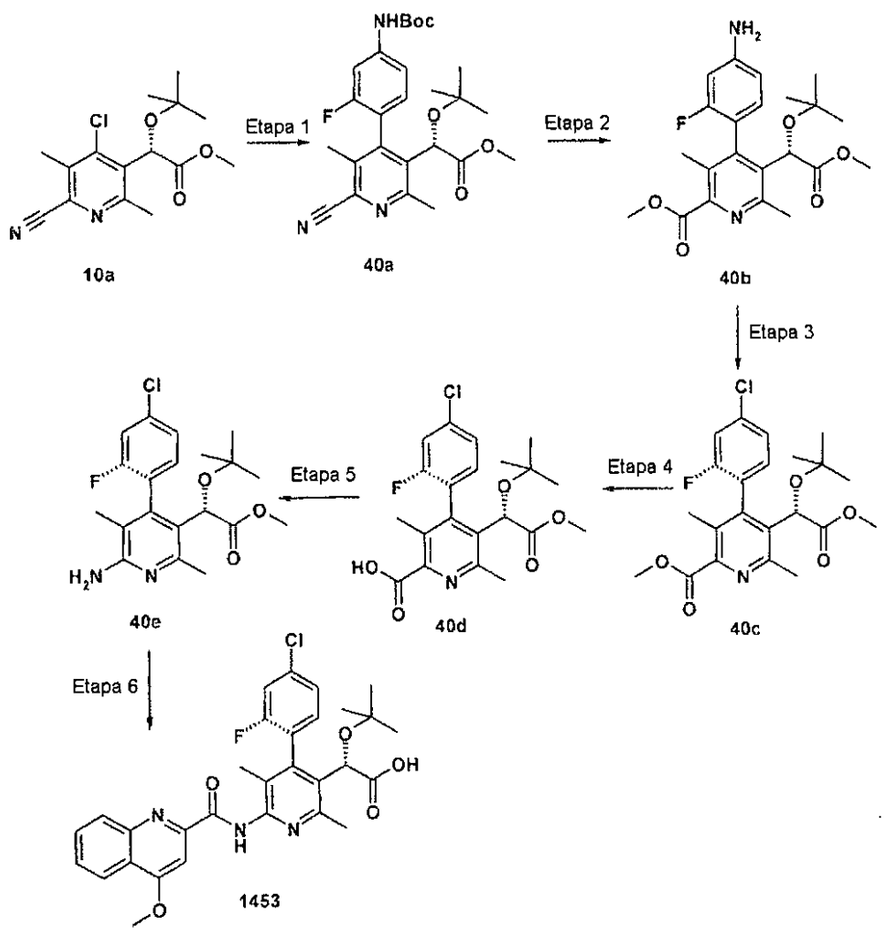
Etapa 2:

A **39b** (11 g, 37,8 mmol), disuelto en 1,4-dioxano seco (120 mL) se añade bis(pinacolato)diboro (13,7 g, 54 mmol) y acetato de potasio (9,9 g, 101 mmol) antes de ser desoxigenado burbujeando una corriente de argón durante 15 min. A esta mezcla se añade 1,1'-bis(difenilfosfino)ferroceno (2,75 g, 3,4 mmol). Esta mezcla se desgasifica durante 5 min adicionales antes de ser soemtida a reflujo a 100°C durante 16 h. La mezcla enfriada se diluye con EtOAc y agua y luego se filtra a través de Celite. Las fases se separan y la capa orgánica se lava con agua y salmuera, se seca ($MgSO_4$), se filtra y se concentra. El residuo resultante se purifica

mediante CombiFlash® Companion para dar el compuesto intermedio **39c**.

EJEMPLO 40

SÍNTESIS DEL COMPUESTO 1453 (TABLA 1)



Etapa 1:

El compuesto intermedio **10a** (4,0 g, 12,9 mmol) se trata con boronato **39c** (5,2 g, 15,5 mmol) utilizando el proceso descrito en la etapa 1 del Ejemplo 12 para proporcionar **40a**.

Etapa 2:

El compuesto intermedio **40a** se transforma en el diéster **40b**, utilizando el proceso descrito en la etapa 3 del Ejemplo 12.

Etapa 3:

Anilina **40b** (2,86 g, 6,84 mmol) se convierte en el compuesto intermedio **40c**, utilizando el proceso descrito en la etapa 2 del Ejemplo 5. Los atropisómeros

se separan en esta fase por CombiFlash® Companion para dar **40c**.

Etapa 4:

El diéster **40c** se convierte en el mono-ácido **40d**, utilizando el proceso descrito en la etapa 4 del Ejemplo 12.

Etapa 5:

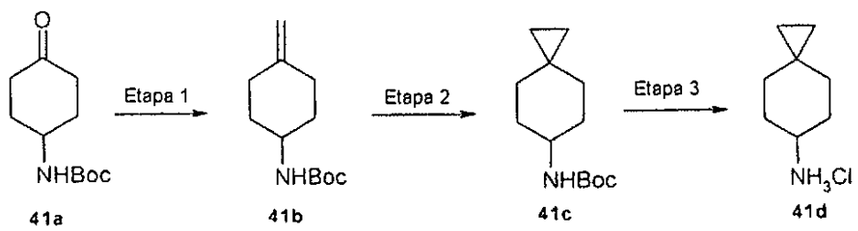
El compuesto intermedio **40d** se transforma en el compuesto intermedio **40e**, utilizando el proceso descrito en la etapa 5 del Ejemplo 12.

Etapa 6:

A una solución de ácido 4-metoxi-2-quinolina-carboxílico (302 mg, 1,5 mmol) y DMF (15 µL) en DCM (7 mL) se añade cloruro de oxalilo en forma de una solución 2M en DCM (968 µL, 1,94 mmol) gota a gota a TA (con desprendimiento de gas). Después de 20 min, la solución se concentra a sequedad y luego se disuelve en THF (2 mL). A esta solución se añade el compuesto intermedio **40e** (294 mg, 0,74 mmol) y DIPEA (650 µL, 3,72 mmol) y luego se calienta a 50°C durante 2 h. La mezcla de reacción enfriada se diluye con EtOAC y se lava consecutivamente con una solución de NH_4Cl (sat), una solución de $NaHCO_3$ (sat) y salmuera. La fase orgánica se seca ($MgSO_4$), se filtra y se concentra a sequedad. La solución del éster bruto (431 mg, 0,74 mmol) en THF (4 mL) y MeOH (2 mL) se calienta a 50°C antes de ser tratada con NaOH 5 N (743 µL, 3,72 mmol). La reacciòn se detiene después de 1 h mediante enfriamiento brusco con AcOH (500 µL) y la mezcla se concentra a sequedad. El residuo se recoge en MeOH y se purifica mediante HPLC preparativa para dar, después de la liofilización, el compuesto **1453**.

EJEMPLO 41

SÍNTESIS DEL COMPUESTO INTERMEDIO 41D



41a 41b 41c 41d

Etapa 1:

El compuesto **41a** se convierte en **41b** utilizando dimsilo sódico y bromuro de metil-trifenilfosfonio según se describe en J. Am. Chem. Soc., **1980**, *102*, 1404-1408.

Etapa 2:

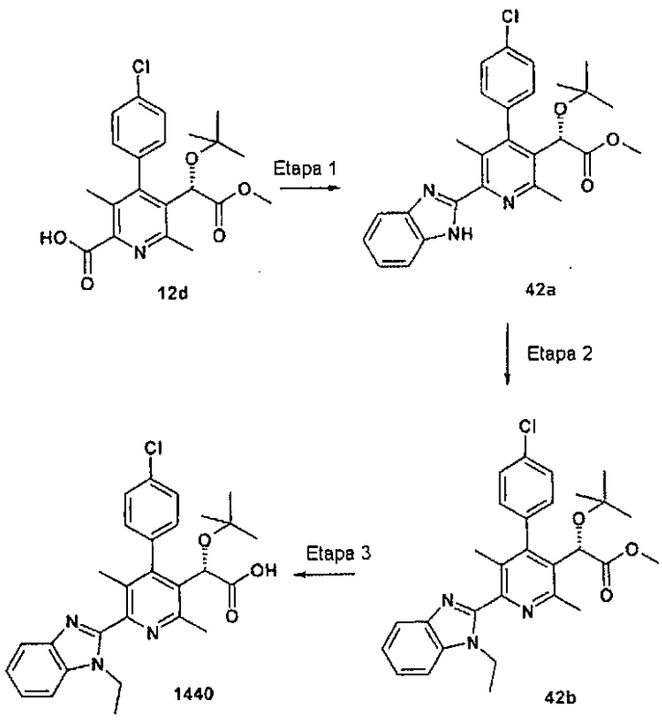
El compuesto intermedio **41b** (250 mg, 1,18 mmol) se disuelve en dietil-éter (5 mL) y se enfría hasta 0°C antes de ser tratado con diazometano en éter (40 mL, 2,8 mmol). A esta solución enfriada se añade, en porciones, acetato de paladio (II) (5 x 5 mg). Esta secuencia se repite hasta que se completa la reacción mediante análisis por RMN. La solución se filtra y se concentra para dar **41c**.

Etapa 3:

A **41c** (261 mg, 1,16 mmol) se añade HCl 4M /dioxano (5 mL, 20 mmol) y la mezcla se deja agitar a TA durante 2 h. La solución se concentra y después se trata con dietil-éter. Esta mezcla se trata con ultrasonidos para proporcionar un sólido que se filtra para dar **41d** en forma de la sal HCl.

EJEMPLO 42

SÍNTESIS DEL COMPUESTO 1440 (TABLA 1)



Etapa 1:

Una solución de 2-aminoanilina (27 mg, 0,25 mmol), HATU (110 mg, 0,30 mmol) y **12d** (0,10 g, 0,25 mmol) en DMF (3 mL) a TA se trata con Et_3N (0,10 mL, 0,74 mmol). Esta mezcla se agita a TA durante 1 h. Se añade EtOAc (10 mL) y la

solución se lava con salmuera, se seca ($MgSO_4$), se filtra y el disolvente se evapora. La amida bruta se disuelve en AcOH (4 mL) y se calienta a 80°C (1 h). La solución se concentra, se añade EtOAc (10 mL) y la solución se lava con $NaHCO_3$ saturado y salmuera. Las capas se separan y la capa orgánica se evapora para dar el bencimidazol bruto. El producto se purifica mediante CombiFlash® Companion para proporcionar **42a**.

Etapa 2:

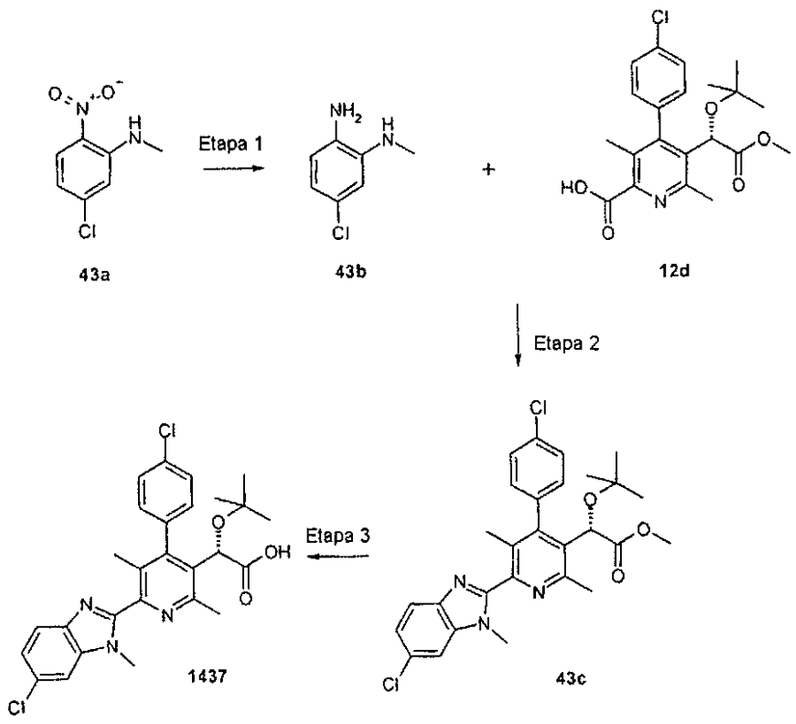
Una solución del bencimidazol **42a** (120 mg, 0,25 mmol) en DMF (1,5 mL) se trata con NaH (dispersión al 60% en aceite mineral, 11 mg, 0,27 mmol) y la mezcla se agita durante 15 min. Se añade yodoetano (30 µL, 0,37 mmol) y la reacción se agita durante 1 h. La reacción se diluye con agua (15 mL) y se extrae con EtOAc (15 mL). La capa orgánica se seca ($MgSO_4$) y se evapora a sequedad para dar el compuesto **42b.**

Etapa 3:

Una mezcla de la amida **42b**, (125 mg, 0,25 mmol) en THF (3,5 mL) y MeOH (0,5 mL) se trata con NaOH 5 N (250 µL, 1,5 mmol) a 50°C (3 h). La solución se acidifica con AcOH y se evapora a sequedad. El residuo se disuelve luego en MeOH (1 mL) y se purifica mediante HPLC preparativa. Las fracciones que contienen compuesto puro se agrupan, se evaporan a sequedad, se re-disuelvenen 1:1 MeCN / agua (50 mL), se congelan y se liofilizan para dar el compuesto **1440**.

EJEMPLO 43

SÍNTESIS DEL COMPUESTO 1437 (TABLA 1)



Etapa 1:

A una solución del compuesto **43a** (1,9 g, 10 mmol) en THF se añade polvo de estaño y HCl 1 N (50 mL, 50 mmol). Después de agitación vigorosa durante 1 h, se añade lentamente NaOH 1 N (50 mL) a la reacción. La mezcla se filtra sobre Celite y la torta de filtración se lava con EtOAc (200 mL). El filtrado se extrae con EtOAc y las capas orgánicas reunidas se secan (Na_2SO_4) y se concentran hasta sequedad para dar el compuesto **43b**.

Etapa 2:

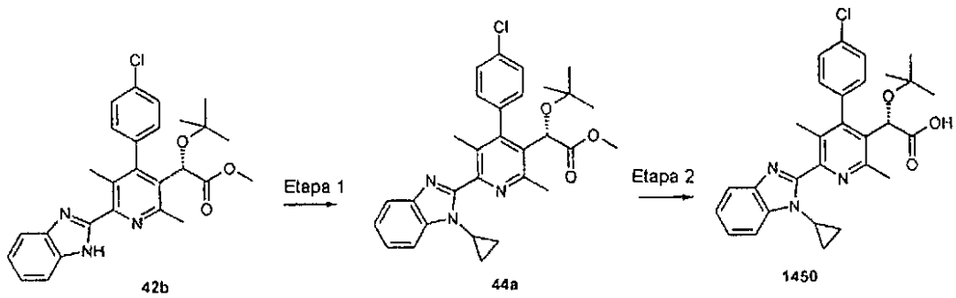
Los compuestos intermedios **43b** y **12d** se acoplan para dar el compuesto intermedio **43c**, utilizando el proceso descrito en la etapa 1 del Ejemplo 42.

Etapa 3:

El compuesto intermedio **43c** se transforma en el compuesto **1437** utilizando el proceso descrito en la etapa 3 del Ejemplo 42.

EJEMPLO **44**

SÍNTESIS DEL COMPUESTO **1450** (TABLA 1)



Etapa 1:

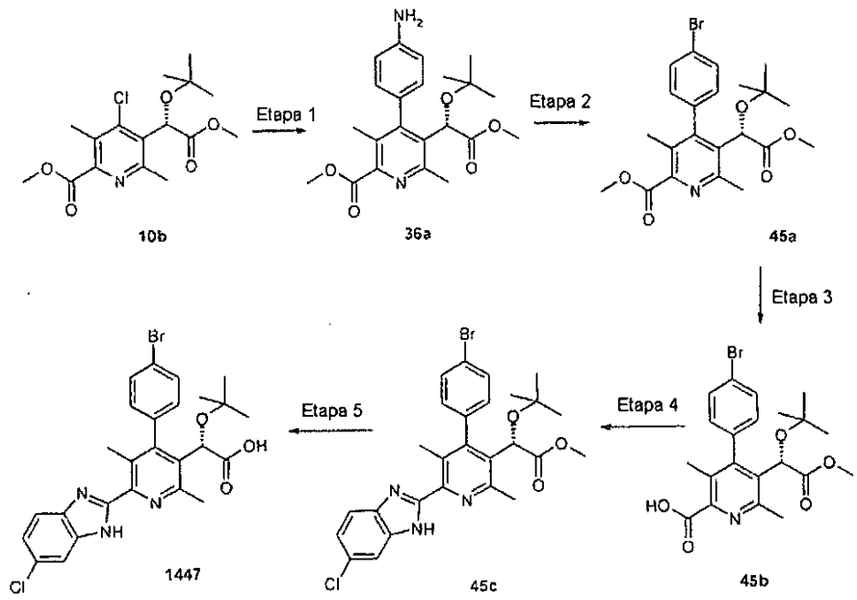
Una mezcla de bencimidazol **42b** (88 mg, 0,19 mmol), ácido ciclopropilborónico (32 mg, 0,37 mmol), acetato de cobre (34 mg, 0,19 mmol), 2,2-bipiridilo (29 mg, 0,19 mmol) y Na_2CO_3 (39 mg, 0,37 mmol) en DCE (3 ml) se calienta hasta 70 °C durante 18 h. La mezcla se enfría hasta TA y se lava con una mezcla de agua / NH_4Cl saturado (15 mL cada uno). La capa acuosa se extrae con DCM y la capa orgánica se lava con salmuera, se seca ($MgSO_4$), se filtra y se concentra para dar el compuesto **44a**.

Etapa 2:

El compuesto intermedio **44a** se transforma en el compuesto **1450** utilizando el proceso descrito en la etapa 3 del Ejemplo 42.

EJEMPLO 45

SÍNTESIS DEL COMPUESTO 1447 (TABLA 1)



Etapa 1:

El compuesto intermedio **10b** se transforma en el compuesto intermedio **36a**, utilizando el proceso descritos en la etapa 1 del Ejemplo 12.

Etapa 2:

Se añade nitrito de t-butilo (al 90% p/p, 1,0 mL, 7,9 mmol) a una suspensión agitada de $CuBr_2$ (1,6 g, 7,3 mmol) en MeCN anhidro, desoxigenado (12 mL), enfriada hasta 0°C bajo una atmósfera de nitrógeno. Se añade, gota a gota, uan solución de compuesto **36a** en MeCN seco, desoxigenado (aclarado con 15 mL + 5 mL) y se deja que la reacción se caliente hasta TA. Después de 4 h, se añade nitrito de t-butilo adicional (0,3 mL, 2,4 mmol) y se continúa con la agitación. Después de 16 h, se añade gel de sílice (30 g) y el disolvente se evapora. El producto se purifica mediante CombiFlash® Companion para proporcionar el compuesto intermedio **45a**.

Etapa 3:

El compuesto intermedio **45a** se transforma en el compuesto intermedio **45b**, utilizando el proceso descrito en la etapa 4 del Ejemplo 12.

Etapa 4:

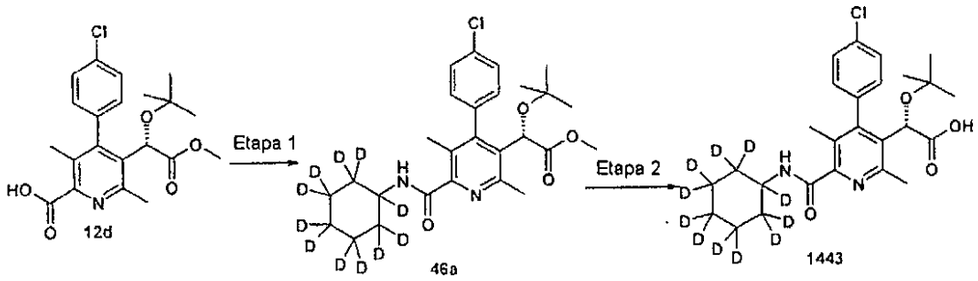
El compuesto intermedio **45c** se transforma en el compuesto intermedio **45c**, utilizando el proceso descritos en la etapa 1 del Ejemplo 42.

Etapa 5:

El compuesto intermedio **45c** se transforma en el compuesto intermedio **1447**, utilizando el proceso descritos en la etapa 3 del Ejemplo 42.

EJEMPLO 46

SÍNTESIS DEL COMPUESTO 1443 (TABLA 1)



Etapa 1:

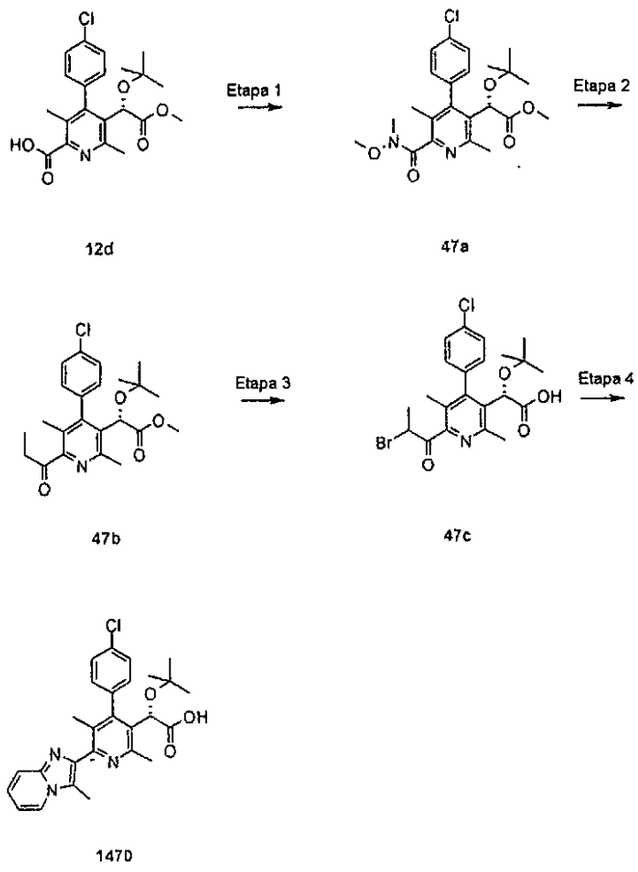
El compuesto intermedio **12d** y D-11 ciclohexilamina (isótopos de CDN) comercialmente disponible se acoplan para dar el compuesto intermedio **46a** utilizando el proceso descrito en la etapa 5 del Ejemplo 35.

Etapa 2:

El compuesto intermedio **46a** se transforma en el compuesto **1443** utilizando el proceso descrito en la etapa 2 del Ejemplo 37.

EJEMPLO 47

SÍNTESIS DEL COMPUESTO 1470 (TABLA 1)



12d 47a 47b 47c 1470

Etapa 1:

A **12d** (200 mg, 0,49 mmol) en *N*-metilpirrolidinona (2,5 mL) se añade Et_3N (137 µL, 0,99 mmol), seguido de tetrafluoroborato de N,N,N',N'-tetrametil-O-(benzotriazol-1-il)uronio (320 mg, 0,99 mmol). La mezcla se agita durante 10 min, se trata con hidrocloruro de *N,O*-dimetilhidroxilamina (96 mg, 0,99 mmol) y luego se agita durante 60 h a 23ºC. A la mezcla se añade una solución acuosa saturada de cloruro de amonio. La solución se diluye con agua y se extrae con EtOAc (2 veces). Las capas orgánicas reunidas se lavan con agua (2 veces), salmuera, se secan sobre $MgSO_4$, se filtraron y se evaporan a vacío. El producto bruto se purifica por CombiFlash® Companion con un gradiente eluyente de 20 a 100% de EtOAc / hexanos para proporcionar **47a**.

Etapa 2:

A una solución de **47a** (163 mg, 0,36 mmol) en THF (3,6 mL) a -78°C se añade gota a gota una solución de bromuro de etilmagnesio (2,2 M en THF, 198 µL, 0,44 mmol). La mezcla se agita durante 30 min a -40°C. A la mezcla de reacción se añade una solución de HCl 1N (~10-15 mL) y luego la mezcla se extrae con dietil-éter (2 veces). Las capas orgánicas combinadas se lavan con salmuera, se secan sobre Na_2SO_4, se filtran y se concentran al vacío. El producto bruto se purifica por CombiFlash® Companion con un gradiente eluyente de 5 a 20% de EtOAc / hexanos proporcionando **47b** puro.

Etapa 3:

A **47b** (100 mg, 0,24 mmol) en THF (1 mL) se añade tribromuro de fenil-trimetilamonio (94,5 mg, 0,25 mmol). La mezcla de reacción se agita a reflujo durante 20 h. La solución se recoge en EtOAc, se lava con $NaHCO_3$ (sat.), salmuera, se seca sobre Na_2SO_4, se filtra y se concentra *en vacío*, para dar **47c**.

Etapa 4:

A **47c** (50 mg, 0,1 mmol) en una mezcla de EtOH (729 µL) y acetona (145 µL) se añade $NaHCO_3$ (8,8 mg, 0,11 mmol) y 2-aminopiridina (14,2 mg, 0,11 mmol) en un tubo resellable. La mezcla se calienta a 85°C durante 2 h y luego se concentra *en vacío*. El residuo se diluye con THF (1 mL), MeOH (300 µL), solución acuosa de NaOH (5 N, 140 µL, 0,70 mmol) ÿ se agita durante 60 h a 23°C. El pH de la mezcla se ajusta a aproximadamente 5-6 con AcOH. La mezcla bruta se purifica mediante HPLC prep. (MeOH: agua que contiene formiato de amonio 10 mM (pH 3,8)). Las fracciones deseadas se recogen y concentran a presión reducida. Los residuos se disuelven en AcCN (1,5 mL) y se liofilizan para proporcionar **1470**.

EJEMPLO 48

ENSAYO DE LA LUCIFERASA EN EL VIH-1 EN C8166 (CE_{50})

Células C8166 se derivan de una línea de linfocitos de la sangre del cordón de virus de tipo-1 T-linfotrópico humano, inmortalizada pero no expresante (obtenida de J. Sullivan y originalmente producida en el laboratorio de R. Gallo, Virology 1983; 129: 51-64) y son muy permisivas a la infección por VIH-1. El plásmido pGL3 Basic LTR/TAR se prepara introduciendo la secuencia LTR HxB2 del VIH-1 desde el nucleótido -138 al +80 (Sca1-HindIII) situado más arriba del gen de la luciferasa en el vector pGL3 Basic (un vector de expresión de luciferasa sin promotor procedente de Promega nº de catálogo E1751), y con el gen de

resistencia a blasticidina clonado en él. Las células informadoras se construyen al electroporar células C8166 con el plásmido pGL3 Basic LTR/TAR y al seleccionar los clones positivos con blasticidina. El clon C8166-LTRluc nº A8-F5-G7 se selecciona por 3 vueltas consecutivas de dilución limitante con selección con blasticidina. Los cultivos se mantienen en medios completos (consistentes en: medio del Roswell Park Memorial Institute (RPMI) 1640 + FBS al 10% + β-mercaptoetanol 10^{-5} M + gentamicina 10 µg/ml) con blasticidina 5 µg/ml, sin embargo la selección con blasticidina se quita de las células antes de llevar a cabo el ensayo de replicación vírica.

PROTOCOLO PARA EL ANÁLISIS DE LA LUCIFERASA

Preparación de los compuestos

Se preparan diluciones seriadas de los compuestos inhibidores del VIH-1 en medio completo a partir de soluciones de reserva en DMSO a 10 mM. Se hicieron once diluciones seriadas a una concentración final de 2,5X a 8X en una placa (96 pocillos) de titulación con pocillos profundos de 1 mL. El 12º pocillo contiene medio completo sin inhibidor y sirve de control positivo. Todas las muestras contienen la misma concentración de DMSO (≤ 0,1% de DMSO). Se añade una parte alícuota de 25 µL de inhibidor, a pocillos triplicados, de una placa de microtitulación negra de visión clara de 96 pocillos (Corning Costar, nº de catálogo 3904) tratada de cultivo de tejidos. El volumen total por pocillo es de 200 µL de medio que contienen las células y el inhibidor. La última fila se reserva para las células C8166 LTRluc sin infectar para servir de control blanco del fondo, y la primera fila es solamente medio.

Infección de las células

Células C8166 LTRluc se recuentan y se colocan en un volumen mínimo de RPMI 1640 completo en un matraz de cultivo de tejidos (por ejemplo: 30 X 10^6 células en 10 mL de medio/matraz de 25 cm^2). Las células se infectan con VIH-1 o virus con variante de integrasa generada como se describe a continuación a una multiplicidad de infección (moi) de 0,005. Las células se incuban durante 1,5 horas a 37 °C en un bastidor de rotación en una incubadora con 5% de CO_2 y se vuelven a suspender en RPMI completo para dar una concentración final de 25.000 células/175 µL. Se añaden 175 µL de la mezcla de células a los pocillos de una placa de microtitulación de 96 pocillos que contienen 25 µL de los inhibidores 8X.

Se añaden 25.000 células C8166- LTRluc sin infectar/pocillo en 200 µL de RPMI completo a la última fila para hacer de control del fondo. Se incuban células a 37°C en una incubadora con 5% de CO_2 durante 3 días.

Ensayo de la luciferasa

Se añaden 50 µL de Steady Glo (sustrato de la luciferasa, $T_{1/2}$ = 5 horas, Promega nº de catálogo E2520) a cada pocillo de la placa de 96 pocillos. La unidad de luz relativa (RLU - siglas en inglés) de luciferasa se determina utilizando el luminómetro LUMIstar Galaxy (BMG LabTechnologies). Las placas se leen desde abajo durante 2 segundos por pocillo con una ganancia de 240.

El nivel de inhibición (% de inhibición) de cada pocillo que contiene inhibidor se calcula como sigue:

$$\%\cdot de\ inhibición = \left(1 - \left[\frac{RLU\cdot pocillo - RLU\cdot blanco}{RLU\cdot control - RLU\cdot blanco}\right]\right) * 100$$

Los valores de % de inhibición calculados se usan para determinar la CE_{50}, la pendiente (n) y la inhibición máxima (I_{max}) mediante el procedimiento NLIN rutinario de regresión no lineal del SAS usando la siguiente ecuación:

$$\%\cdot de\ inhibición = \frac{I_{max} \times [inhibidor]^n}{[inhibidor]^n + CI_{50}{}^n}$$

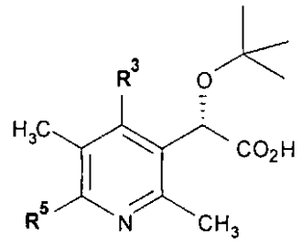
Todos los compuestos de las Tablas 1 a 6 tienen valores de CE_{50} de 500 nM o menos contra la cepa NL4.3 de la integrasa de VIH-1 (SEQ ID NO: 1) según se mide por el ensayo del Ejemplo 48. En la Tabla 7 se proporciona la potencia de compuestos representativos.

TABLAS DE COMPUESTOS

Las siguientes tablas indican compuestos de la invención. Compuestos de la invención son particularmente eficaces en la inhibición de la integrasa de VIH. Los tiempos de retención (t_R) para cada compuesto se miden utilizando las condiciones de HPLC analítica estándares o, en los casos indicados, UPLC descritas en los Ejemplos. Como es bien conocido por un experto en la técnica, los valores del tiempo de retención son sensibles a las condiciones de medición específicas. Por lo tanto, incluso si se utilizan condiciones idénticas de disolvente, caudal, gradiente

lineal, y similares, los valores del tiempo de retención pueden variar cuando se miden, por ejemplo, en diferentes instrumentos de HPLC o UPLC. Incluso cuando se miden en el mismo instrumento, los valores pueden variar cuando se miden, por ejemplo, utilizando diferentes columnas de HPLC o UPLC individuales, o, cuando se miden en el mismo instrumento y en la misma columna individual, los valores pueden variar, por ejemplo, entre mediciones individuales tomadas en diferentes momentos.

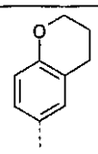
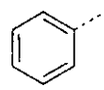
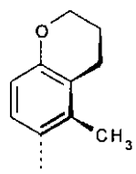
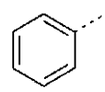
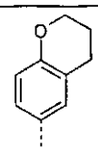
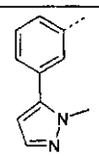
TABLA 1

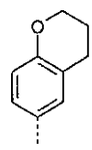
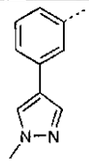
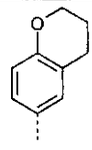
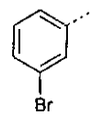
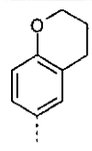
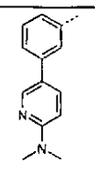
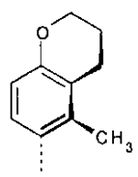
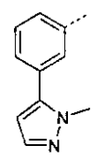
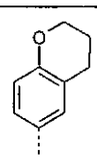
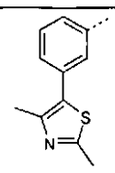
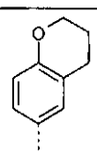
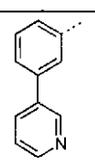
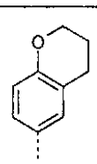
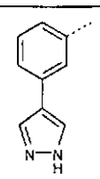
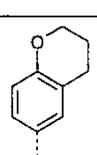
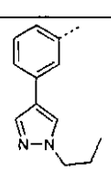


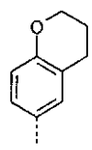
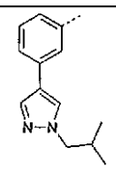
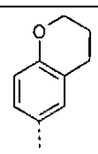
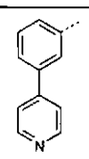
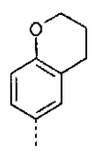
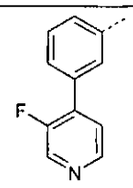
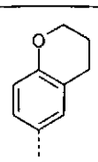
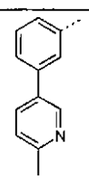
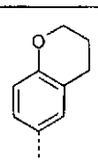
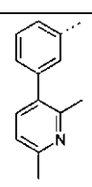
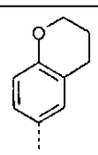
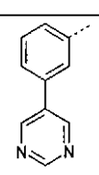
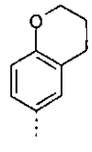
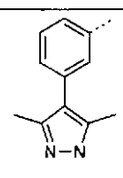
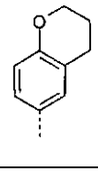
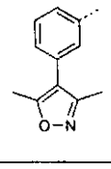
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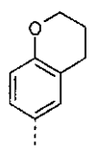
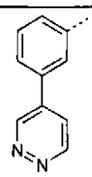
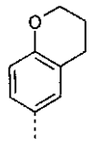
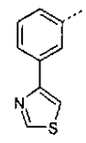
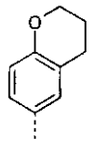
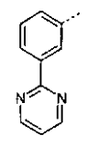
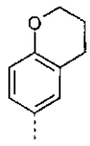
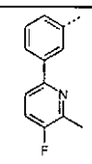
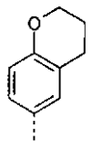
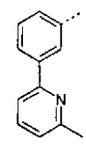
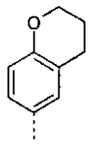
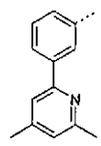
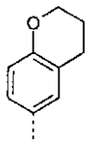
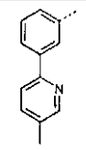
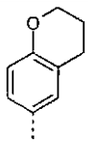
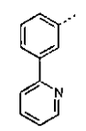
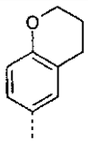
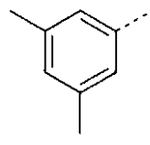
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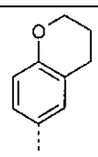
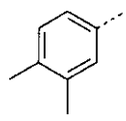
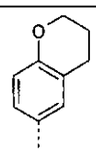
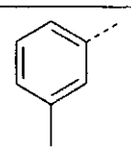
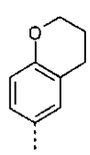
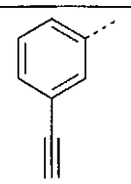
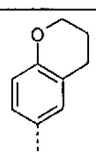
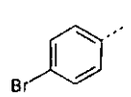
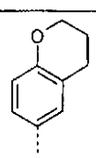
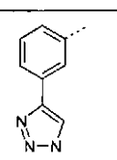
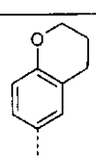
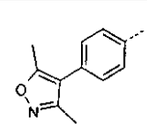
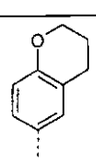
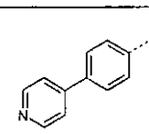
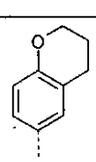
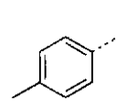
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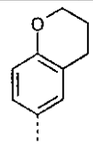
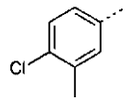
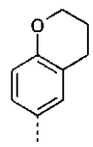
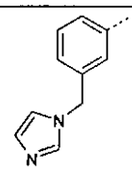
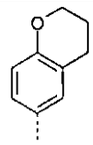
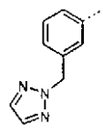
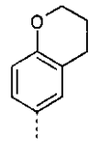
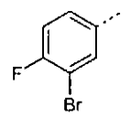
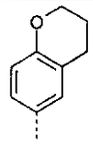
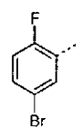
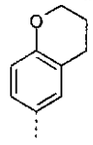
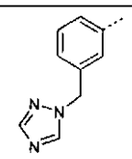
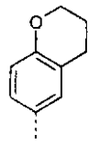
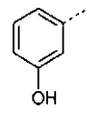
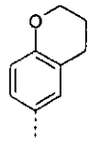
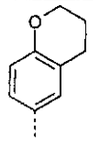
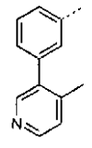
Comp.	R^3	R^5	t_R (min)	EM $(M+H)^+$
1001			5,0/5,1*	446,2
1002			5,2**	460,3
1003			4,9/5,0*	526,3

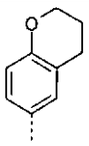
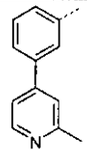
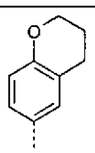
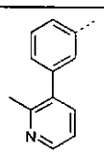
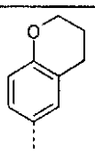
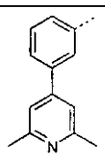
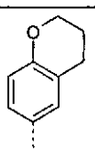
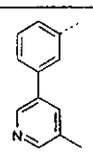
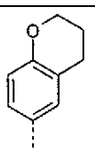
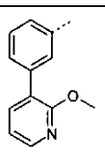
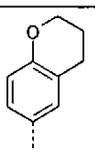
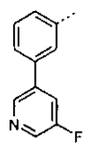
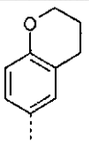
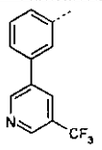
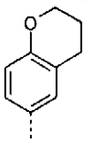
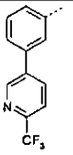
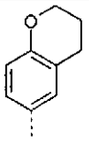
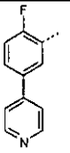
Comp.	R^3	R^5	t_R (min)	EM $(M+H)^+$
1004			4,9/5,0*	526,3
1005			5,4/5,5*	524.1 526,1
1006			4,3/4,4*	566,3
1007			3,6	540,2
1008			3,4	557.2
1009			3,0	523,2
1010			4,8	512,2
1011			5,5	554,3

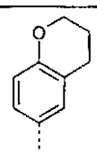
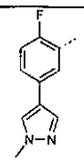
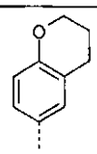
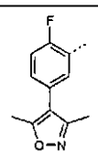
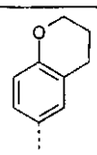
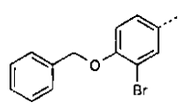
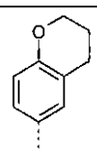
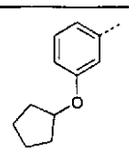
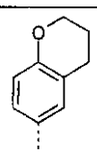
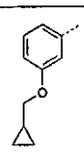
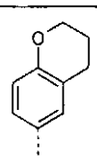
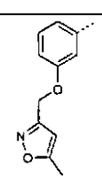
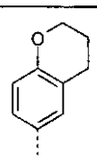
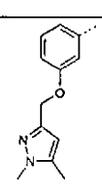
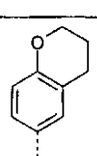
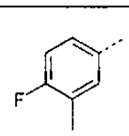
Comp.	R^3	R^5	t_R (min)	EM $(M+H)^+$
1012			5,8	568,3
1013			4,2	523,2
1014			4,8	541.2
1015			4,1/4,2*	537.3
1016			4,2	551,2
1017			4,7/4,8*	524.0
1018			4,5	540,2
1019			5,4	541.2

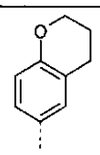
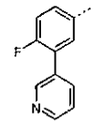
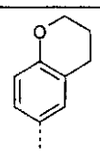
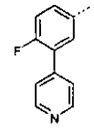
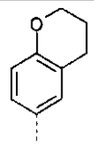
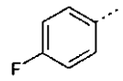
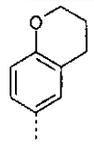
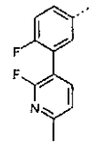
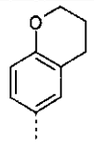
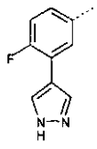
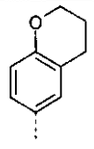
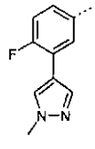
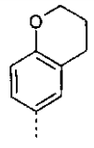
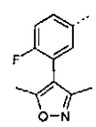
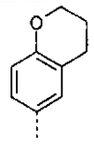
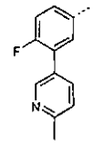
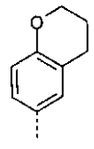
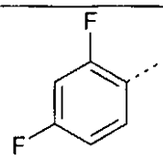
Comp.	R^3	R^5	t_R (min)	EM $(M+H)^+$
1020			4,5/4,6*	524.2
1021			5,2/5,3*	529,2
1022			5,0/5,1*	524.2
1023			5,7/5,8*	555.2
1024			4,2/4,3*	537,2
1025			4,2/4,3*	551,3
1026			4,3/4,4*	537,2
1027			4,3/4,4*	523,2
1028			5,5/5,6*	474.2

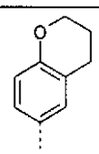
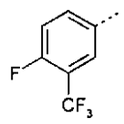
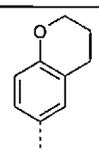
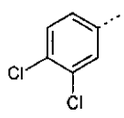
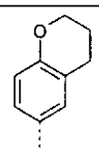
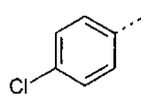
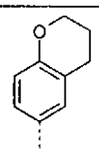
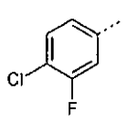
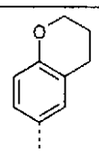
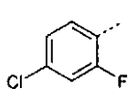
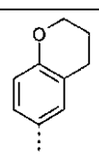
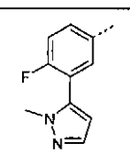
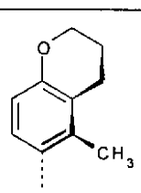
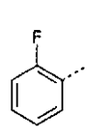
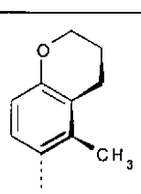
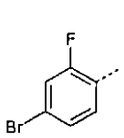
Comp.	R^3	R^5	t_R (min)	EM $(M+H)^+$
1029			5,5/5,6*	474.2
1030			5,3/5,4*	460,1
1031			5,3/5,4*	470,3
1032			5,4/5,5*	524,2/ 526.2
1033			4,7/4,8*	513,3
1034			5,3/5,4*	541.4
1035			4,0/4,1*	523,4
1036			5,4	460,4

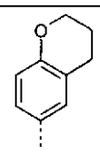
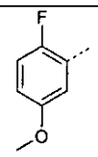
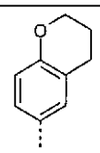
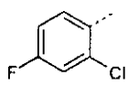
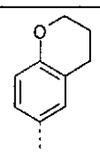
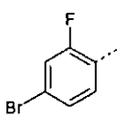
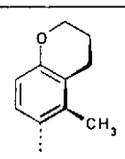
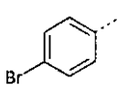
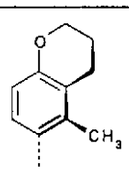
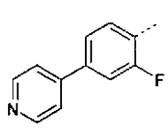
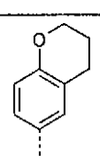
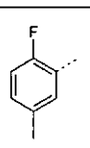
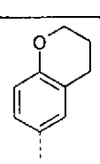
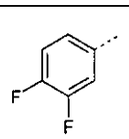
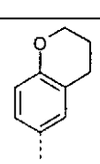
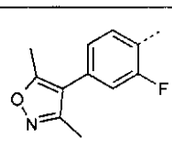
Comp.	R^3	R^5	t_R (min)	EM $(M+H)^+$
1037			5,7	494,3 496,3
1038			4,0	526,3
1039			5,0	527,3
1040			5,5/5,6*	542,1/ 544,1
1041			5,6/5,7*	542,1/ 544,1
1042			4,5	527.4
1043			3,4	462.3
1044			5,0	464,3
1045			4,1/4,2*	537.3

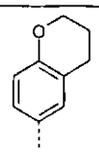
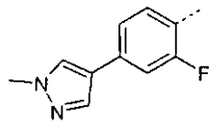
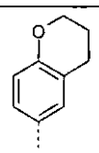
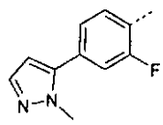
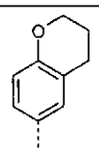
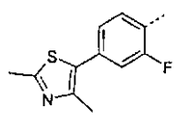
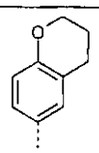
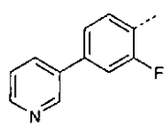
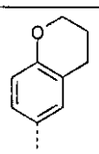
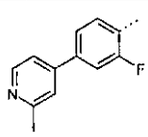
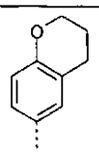
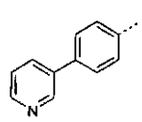
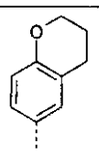
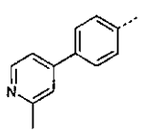
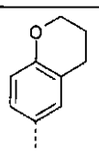
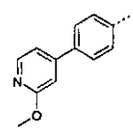
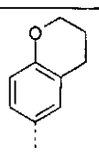
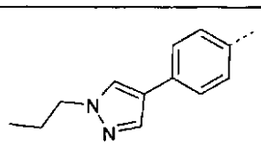
Comp.	R^3	R^5	t_R (min)	EM $(M+H)^+$
1046			4,2	537.3
1047			4,1/4,2*	537.3
1048			4,2/4,3*	551,3
1049			4,2/4,3*	537.3
1050			5,4/5,5*	553,3
1051			5,1/5,2*	541,3
1052			5,7	591,3
1053			5,8	591,3
1054			4,3	541,3

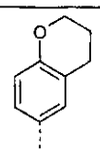
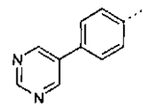
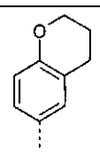
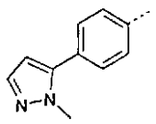
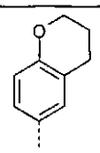
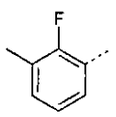
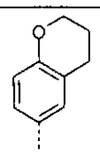
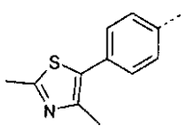
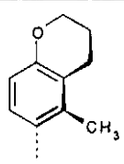
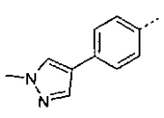
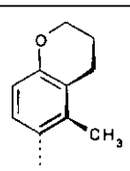
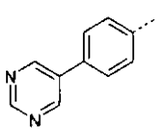
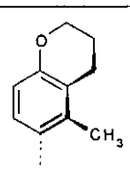
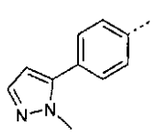
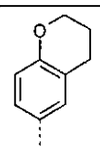
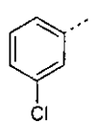
Comp.	R^3	R^5	t_R (min)	EM $(M+H)^+$
1055			5,1/5,2*	544.3
1056			5,4/5,5*	559.3
1057			6,2	630,2/ 632.2
1058			6,0	530,3
1059			5,6	516,3
1060			5,3	557,3
1061			5,0	570,3
1062			5,3/5,4*	478,3

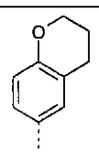
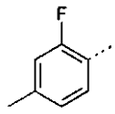
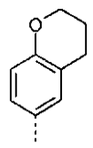
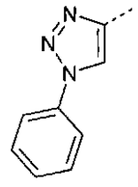
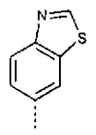
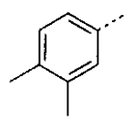
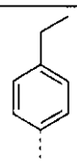
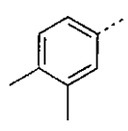
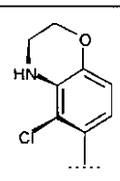
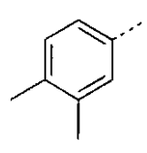
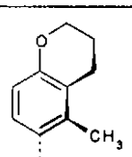
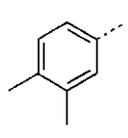
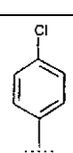
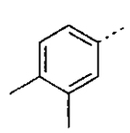
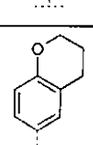
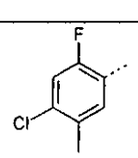
Comp.	R^3	R^5	t_R (min)	EM $(M+H)^+$
1063			4,3	541,3
1064			4,1/4,2*	541,3
1065			5,1/5,2*	464,3
1066			5,5/5,6*	573,3
1067			4,9/5,0*	530,3
1068			5,1/5,2*	544,3
1069			5,4/5,5*	559,3
1070			4,3	555,3
1071			5,0	482,2

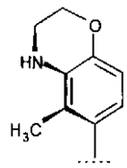
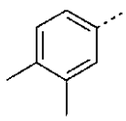
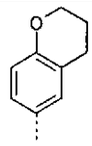
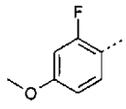
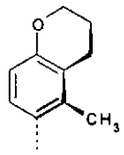
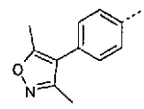
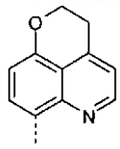
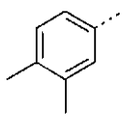
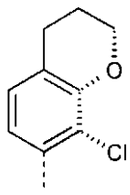
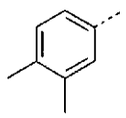
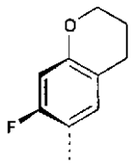
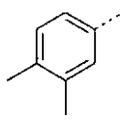
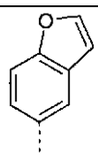
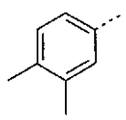
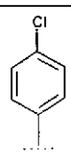
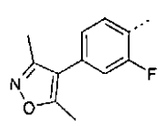
Comp.	R^3	R^5	t_R (min)	EM $(M+H)^+$
1072			5,6	532,2
1073			5,7/5,8*	514,2/ 516,2 518,2
1074			5,3/5,4*	480,2/ 482,2
1075			5,5/5,6*	498,2 500,2
1076			5,4/5,5*	498,2/ 500,2
1077			5,1	544,3
1078			5,3	478,2
1079			5,8	556,2/ 558,2

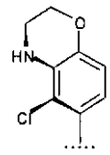
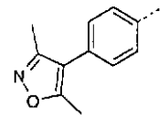
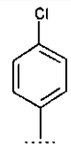
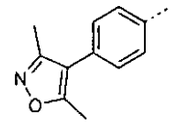
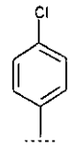
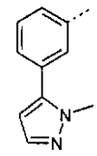
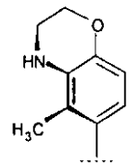
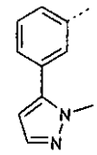
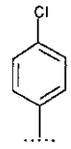
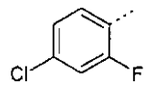
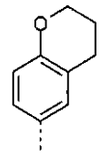
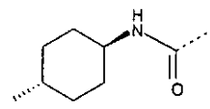
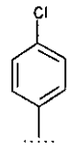
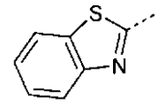
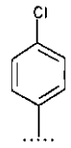
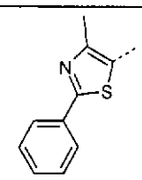
Comp.	R^3	R^5	t_R (min)	EM $(M+H)^+$
1080			6,0/6,1*	494,2
1081			6,2	498,2/ 500,2
1082			5,6/5,7*	542,2/ 544,2
1083			5,6	538,2/ 540,2
1084			4,4	555,2
1085			6,1	478,3
1086			6,0	482,2
1087			5,4/5,5*	559,3

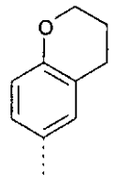
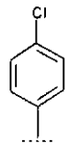
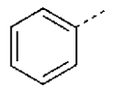
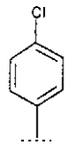
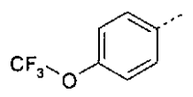
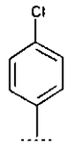
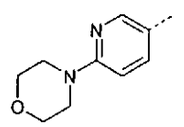
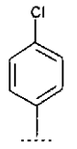
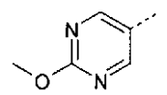
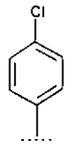
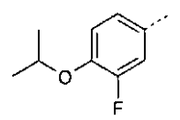
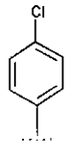
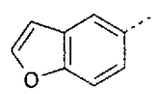
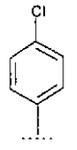
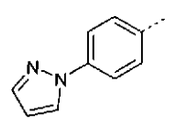
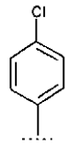
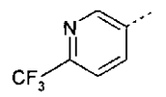
Comp.	R^3	R^5	t_R (min)	EM $(M+H)^+$
1088			5,1/5,2*	544.3
1089			5,1/5,2*	544,3
1090			5,1/5,2*	575,3
1091			4,3	541,3
1092			4,3	555,3
1093			4,1	523,3
1094			4,2	537,3
1095			5,0/5,1*	553,3
1096			5,4/5,5*	554,3

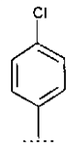
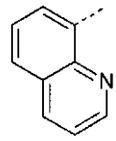
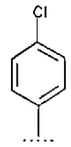
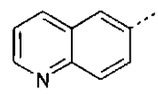
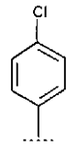
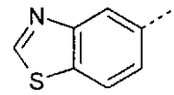
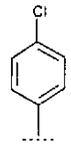
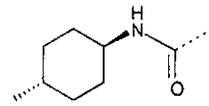
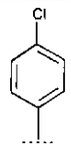
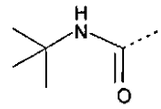
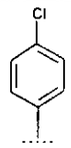
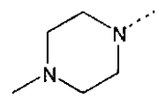
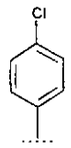
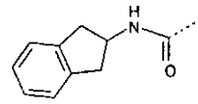
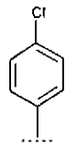
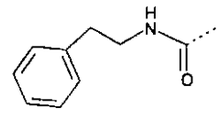
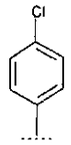
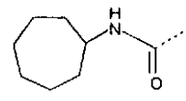
Comp.	R^3	R^5	t_R (min)	EM $(M+H)^+$
1097			4,7/4,8*	524,3
1098			5,6	526,3
1099			6,2	478,3
1100			5,6	557,2
1101			6,0	540,2
1102			5,6	538,3
1103			5,9	540,3
1104			5,1	480,3 482,3

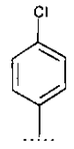
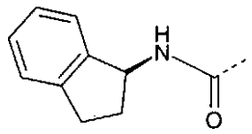
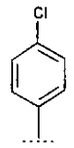
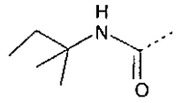
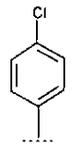
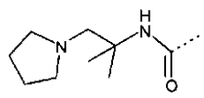
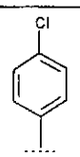
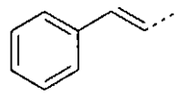
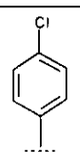
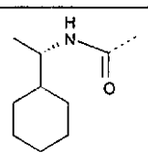
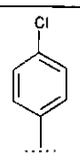
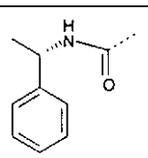
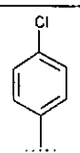
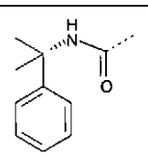
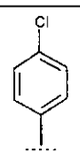
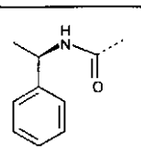
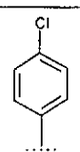
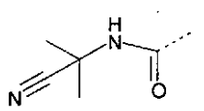
Comp.	R^3	R^5	t_R (min)	EM $(M+H)^+$
1105			6,0	478,3
1106			5,3	513,3
1107			5,2	475,3
1108			6,1	444,3
1109			5,3**	509,3/ 511,3
1110			6,0**	488,4
1111			5,8	452,3/ 454,3
1112			5,7/5,8*	512,2/ 514,2

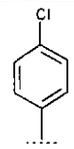
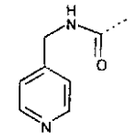
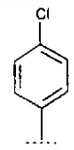
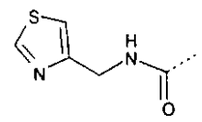
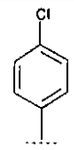
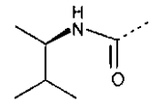
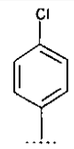
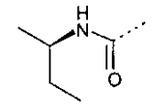
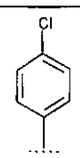
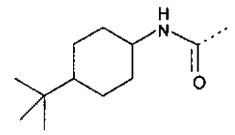
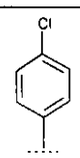
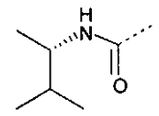
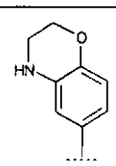
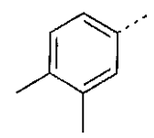
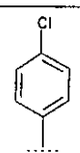
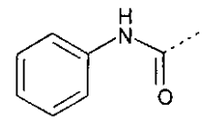
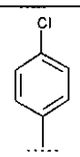
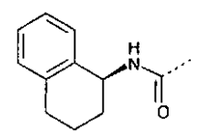
Comp.	R^3	R^5	t_R (min)	EM $(M+H)^+$
1113			6,0**	489,4
1114			6,0	494,4
1115			6,2	555,4
1116			4,7**	511,3
1117			6,5**	508,1 510,1
1118			6,5**	492,4
1119			3,7*	458,4
1120			6,2	537,2/ 539,2

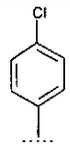
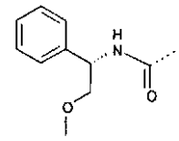
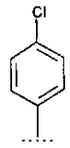
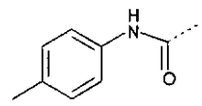
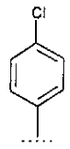
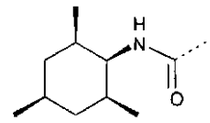
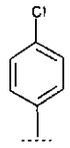
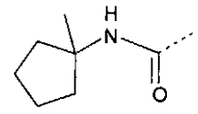
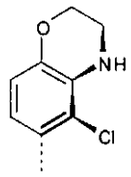
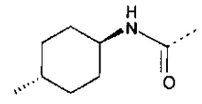
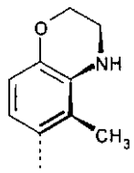
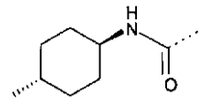
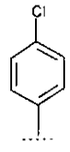
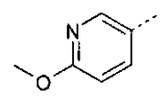
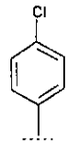
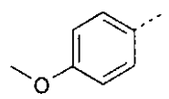
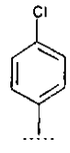
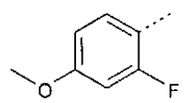
Comp.	R^3	R^5	t_R (min)	EM $(M+H)^+$
1121			3,5**	576,1/ 578,1
1122			3,7	519,1/ 521,1
1124			5,1	504,2/ 506.2
1125			4,6**	541,3
1126			5,9	476,1/ 478,1/ 480,1
1127			6,2*	509,3
1128			7,3	481,1/ 483,1
1129			6,2	521,1/ 523,1

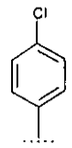
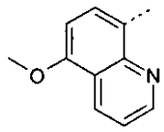
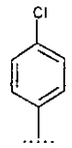
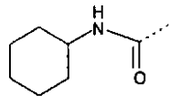
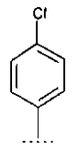
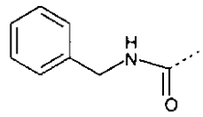
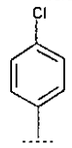
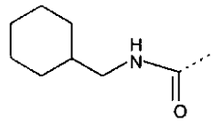
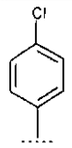
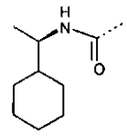
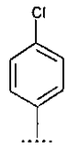
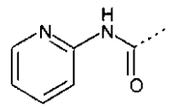
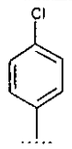
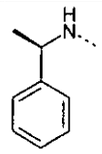
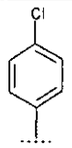
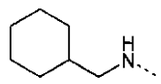
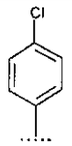
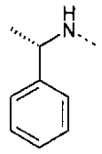
Comp.	R^3	R^5	t_R (min)	EM $(M+H)^+$
1130		$-CH_3$	4,1/4,2*	384,2
1131			5,0	424,2/ 426,2
1132			5,8	508,1/ 510,1
1133			4,4	510,2/ 512,2
1134			4,8,,,,	456,2/ 458,2
1135			5,7,,,	500,2/ 502,2
1136			5,3	464,1/ 466,1
1137			5,2	490,2/ 492,2
1138			5,9	493,1/ 495,1

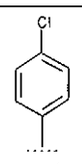
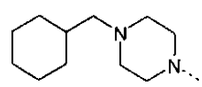
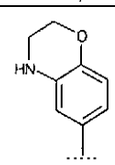
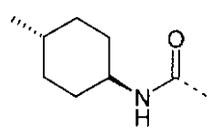
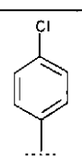
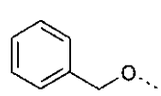
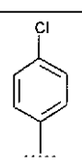
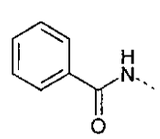
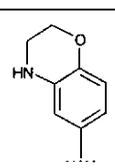
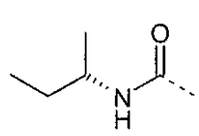
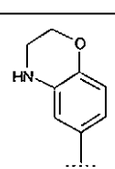
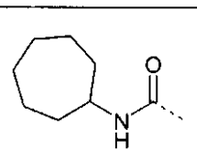
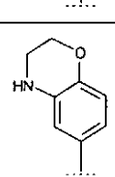
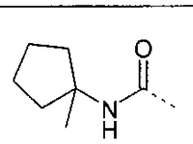
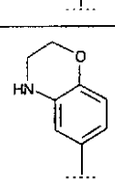
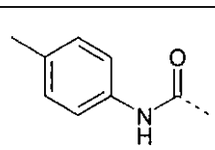
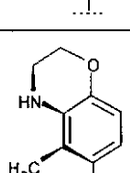
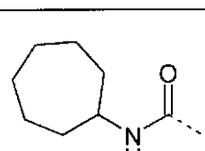
Comp.	R^3	R^5	t_R (min)	EM $(M+H)^+$
1139			4,9	475,1/ 477,2
1140			4,2	475,2/ 477,2
1141			4,9	481,1/ 483,1
1142			6,6	487,2/ 489,2
1143			6,6	447,2/ 449,2
1144			4,1	446,2/ 448,2
1145			6,5	507,1/ 509,1
1146			6,4	495,1/ 497,1
1147			6,5	487,2/ 489,2

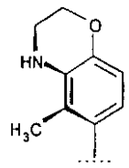
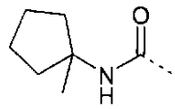
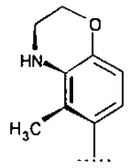
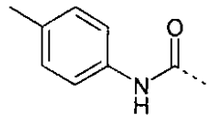
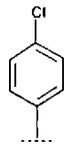
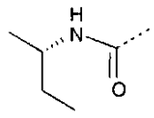
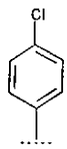
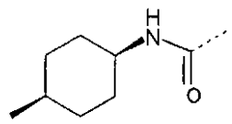
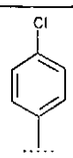
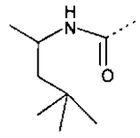
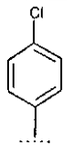
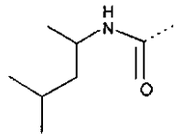
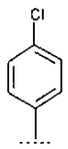
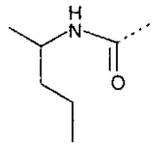
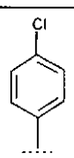
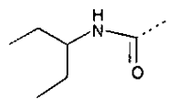
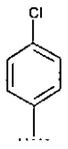
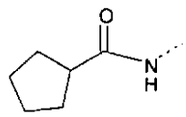
Comp.	R^3	R^5	t_R (min)	EM $(M+H)^+$
1148			6,6	507,1/ 509,1
1149			6,3	461,1/ 463,1
1150			4,8	516,2/ 518,2
1151			5,5	450,1/ 452,1
1152			6,7	501,2/ 503,2
1153			6,5	495,1/ 497,1
1154			6,6	509,2/ 511,2
1155			5,6	495,1/ 497,1
1156			6,1	458,1/ 460,1

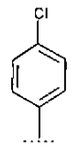
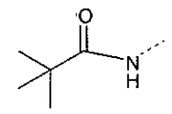
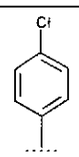
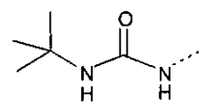
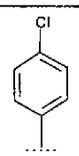
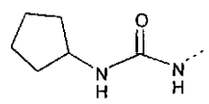
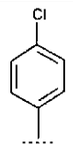
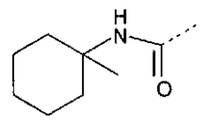
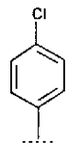
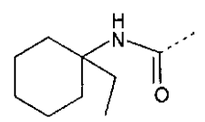
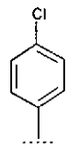
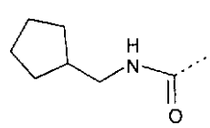
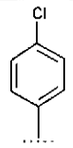
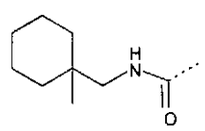
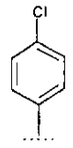
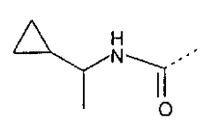
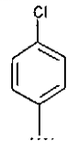
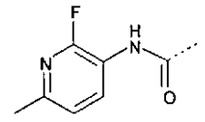
Comp.	R^3	R^5	t_R (min)	EM $(M+H)^+$
1157			4,4	482,2/ 484,2
1158			5,4	488,2/ 490,2
1159			6,3	461,2/ 463,1
1160			6,0	447,1/ 449,1
1161			7,0	529,2/ 531,2
1162			6,2	461,2/ 463,2
1163			4,9/5,5*	475,5
1164			6,7	467,1/ 469,1
1165			6,7	521,1/ 523,2

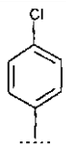
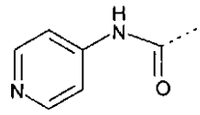
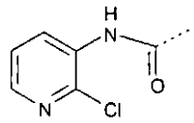
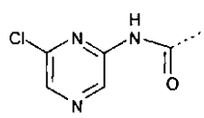
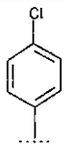
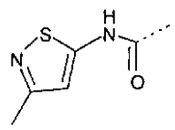
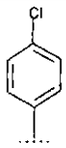
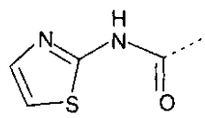
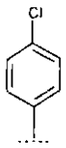
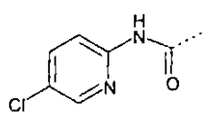
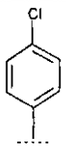
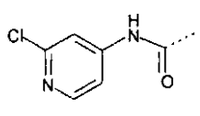
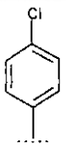
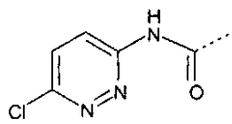
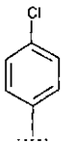
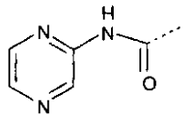
Comp.	R^3	R^5	t_R (min)	EM $(M+H)^+$
1166			6,4	525,1/ 527,1
1167			6,9	481,0/ 483,0
1168			7,1	515,1/ 517,1
1169			6,3	473,1/ 475,1
1170			6,3*	544,3/ 546,3
1171			5,7*	524,2
1172			4,9	455,1/ 457,1
1173			5,2	454,1/ 456,1
1174			5,3	472,1/ 474,1

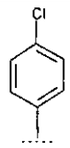
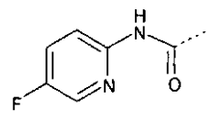
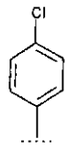
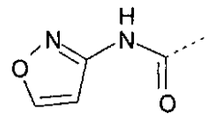
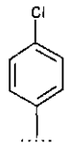
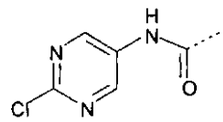
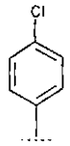
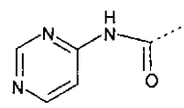
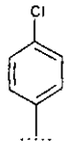
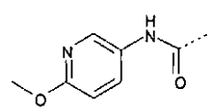
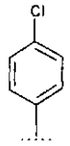
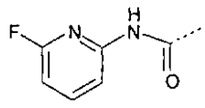
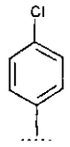
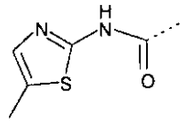
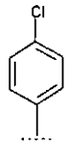
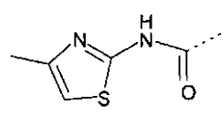
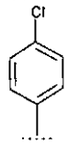
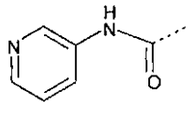
Comp.	R^3	R^5	t_R (min)	EM $(M+H)^+$
1175			5,2	505,1/ 507,1
1176			6,3	473,1/ 475,1
1177			6,4	481,1/ 483,1
1178			6,6	487,1/ 489,1
1179			6,8	501,1/ 503,1
1180			6,6	468,1/ 470,1
1181			5,6	467,3/ 469,3
1182			5,3	459,2/ 461,1
1183			5,2	467,1/ 469,1

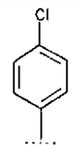
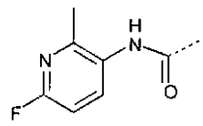
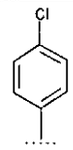
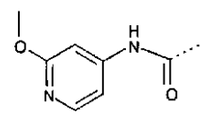
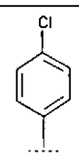
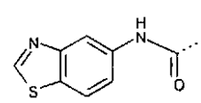
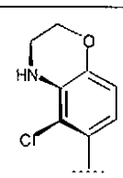
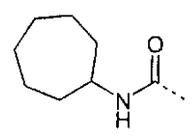
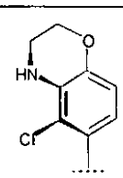
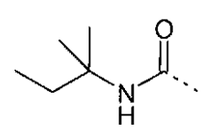
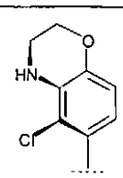
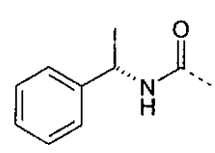
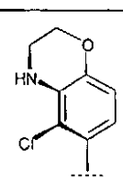
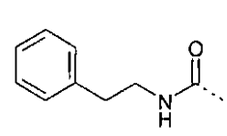
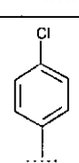
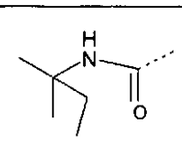
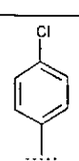
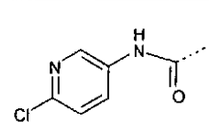
Comp.	R^3	R^5	t_R (min)	EM $(M+H)^+$
1184			5,1	528,3/ 530,2
1185			5,2/5,6*	510,3
1186			7,2	454,1/ 456,1
1187			5,3	467,1/ 469,1
1188			4,3/4,7*	470,3
1189			5,1/5,5*	510,3
1190			4,7/5,1*	496,3
1191			5,6/6,2*	504,3
1192			5,6**	524,2

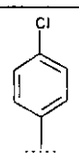
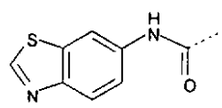
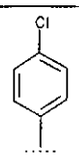
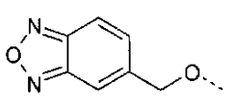
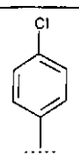
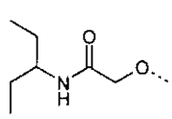
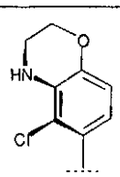
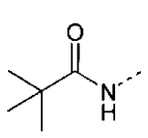
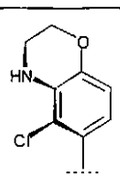
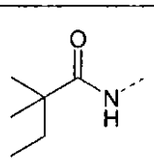
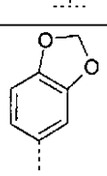
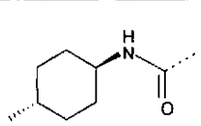
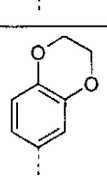
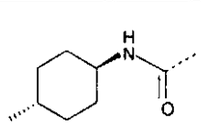
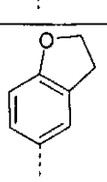
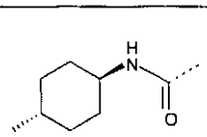
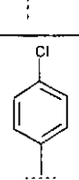
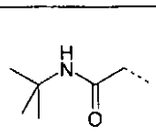
Comp.	R^3	R^5	t_R (min)	EM $(M+H)^+$
1193			5,2**	510,2
1194			6,2**	518,2
1195			5,3	447,1/ 449,1
1196			6,6	487,1/ 489,1
1197			9,0	489,2/ 491,2
1198			8,3	475,2/ 477,2
1199			7,7	461,1/ 463,1
1200			7,6	461,1/ 463,1
1201			5,1	459,1/ 461,1

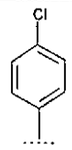
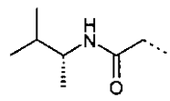
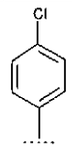
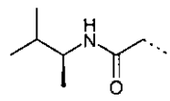
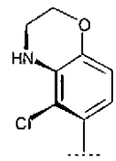
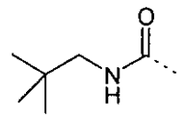
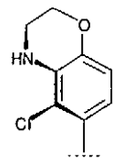
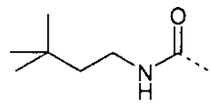
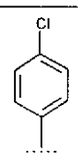
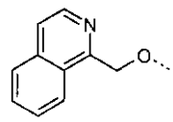
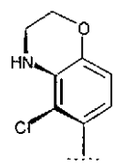
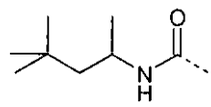
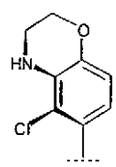
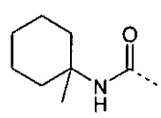
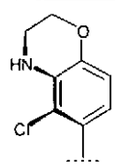
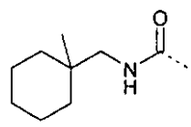
Comp.	R^3	R^5	t_R (min)	EM $(M+H)^+$
1202			5,1	447,1/ 449,1
1203			5,2	462,1/ 464,1
1205			5,3	474,1/ 476,1
1206			8,5	487,1/ 489,1
1207			9,4	501,1/ 503,1
1208			8,1	473,1/ 475,1
1209			9.2	501,2/ 503,1
1210			7,1	459,1/ 461,1
1211			4,6	500,1/ 502,1

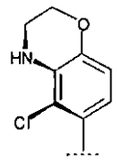
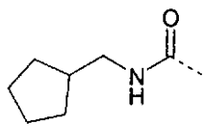
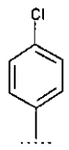
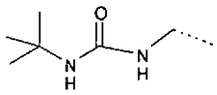
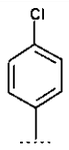
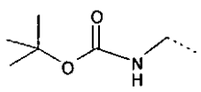
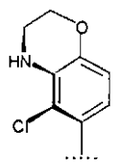
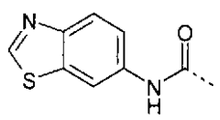
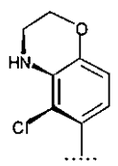
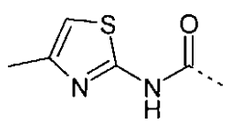
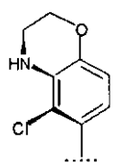
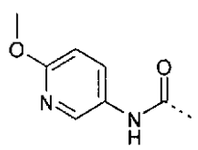
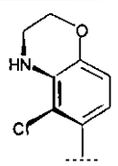
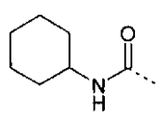
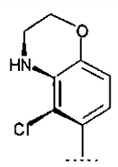
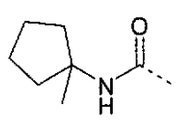
Comp.	R^3	R^5	t_R (min)	EM $(M+H)^+$
1212			3,5	468,1/ 470,1
1213			4,6	502,0/ 504,0/ 506.0
1214			4,7	503,0/ 505,0/ 507,0
1215			4,3	488,0/ 490,0
1216			4,4	474,0/ 476,0
1217			4,7	502,0/ 504,0/ 506.0
1218			4,5	502,0/ 504,0/ 506,0
1219			4,5	503,0/ 505,0/ 507,0
1220			4,4	469,1/ 471,1

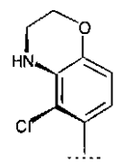
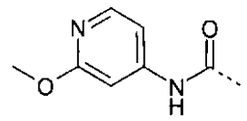
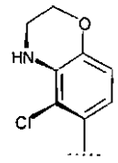
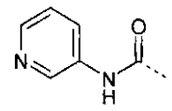
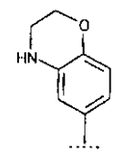
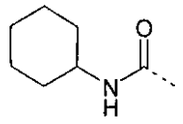
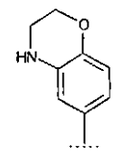
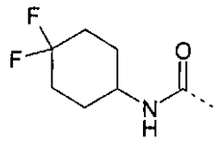
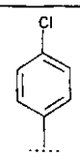
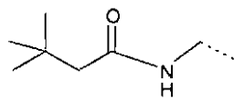
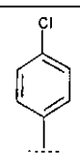
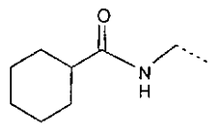
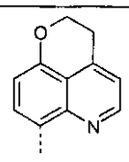
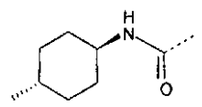
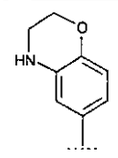
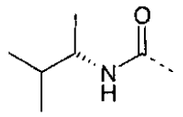
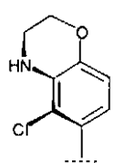
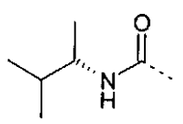
Comp.	R^3	R^5	t_R (min)	EM $(M+H)^+$
1221			4,6	486,1/ 488,1
1222			4,4	458,1/ 460,1
1223			4,5	503,0/ 505,0/ 507,0
1224			4,2	469,1/ 471,1
1225			4,3	498,1/ 500,1
1226			4,6	486,0/ 488,0
1227			4,4	488,0/ 490,0
1228			4,4	488,0/ 490,0
1229			3,4	468,1/ 470,1

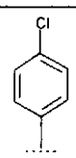
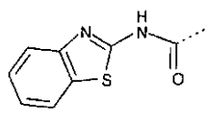
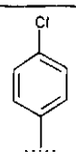
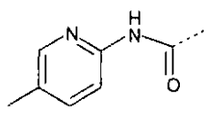
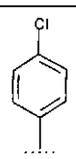
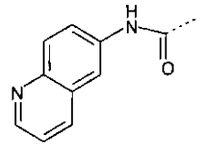
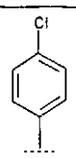
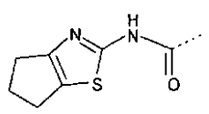
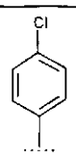
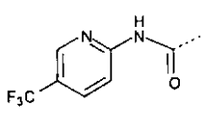
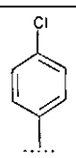
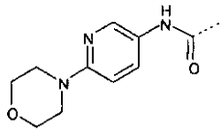
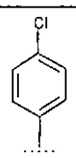
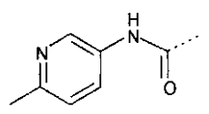
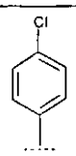
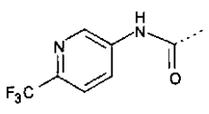
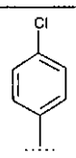
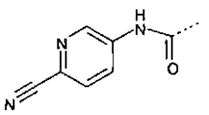
Comp.	R^3	R^5	t_R (min)	EM $(M+H)^+$
1230			4,5	500,1/ 502,1
1231			3,9	498,1/ 500,1
1232			4,4	524,0/ 526,0
1233			6,2**	544,1/ 546,1
1234			5,8**	518,1/ 520,1
1235			6,1**	552,1/ 554,1
1236			6,0**	552,1/ 554,1
1237			5,4	461,1/ 463,1
1238			4,5	502,0/ 504,0/ 506,0

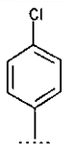
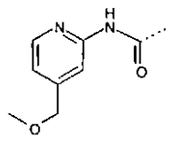
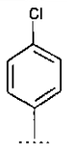
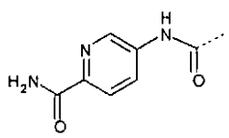
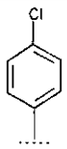
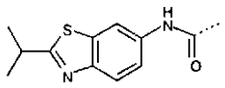
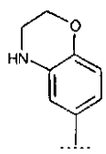
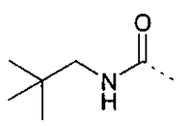
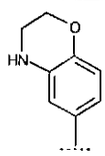
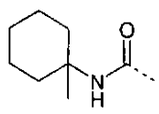
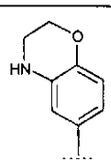
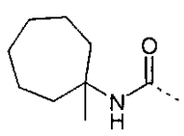
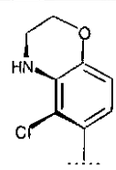
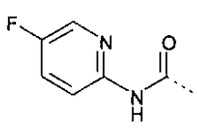
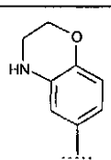
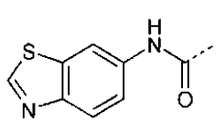
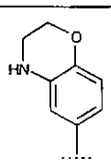
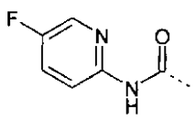
Comp.	R^3	R^5	t_R (min)	EM $(M+H)^+$
1239			4,4	524,0/ 526,0
1240			7,2	496,0/ 498,0
1241			6,7	491,1/ 493,1
1242			4,7**	504,1/ 506,1
1243			4,9**	518,1/ 520,1
1244			4,2*	497,2
1245			4,2*	511,2
1246			4,2*	495,1
1247			4,9	461,1/ 463,1

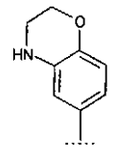
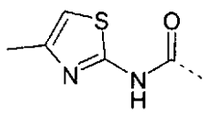
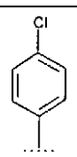
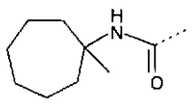
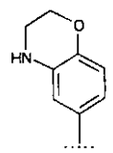
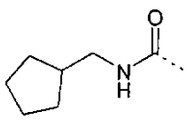
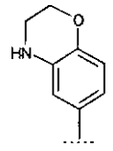
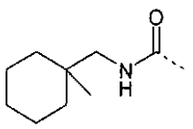
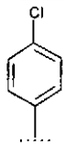
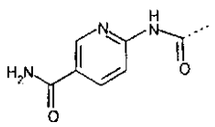
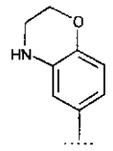
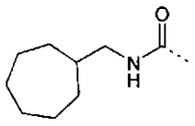
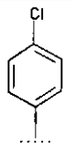
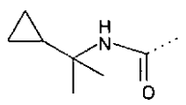
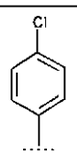
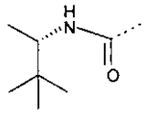
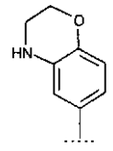
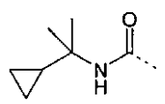
Comp.	R^3	R^5	t_R (min)	EM $(M+H)^+$
1248			5.1	475,1/ 477,1
1249			5,1	475,1/ 447,1
1250			7,0**	518,2/ 520,2
1251			7,6**	532,1/ 534,1
1252			5,3	505,1/ 507,1
1253			8,2**	546,1/ 548,1
1254			7,6**	544,1/ 546,1
1255			8,5**	558,1/ 560,1

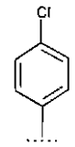
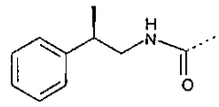
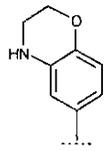
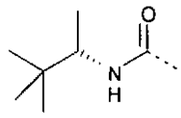
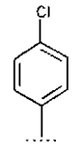
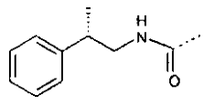
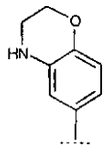
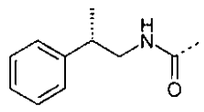
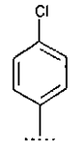
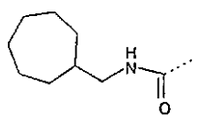
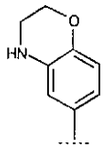
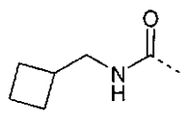
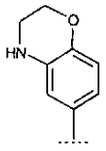
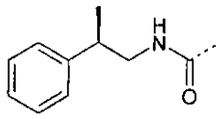
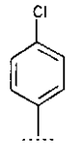
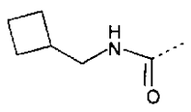
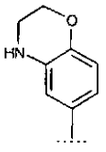
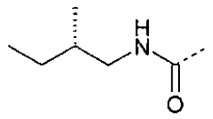
Comp.	R^3	R^5	t_R (min)	EM $(M+H)^+$
1256			7,1**	530,1/ 532,1
1257			4,7	476,1/ 478,1
1258			4,9	477,2/ 479,2
1259			6,3**	581,1/ 583,0
1260			6,3**	545,1/ 547,1
1261			6,0**	555,1/ 557,1
1262			5,8**	530,2/ 532,2
1263			5,7**	530,2/ 532,2

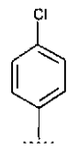
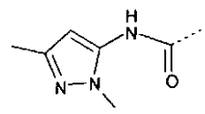
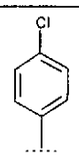
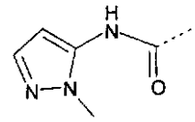
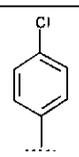
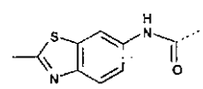
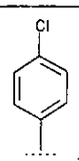
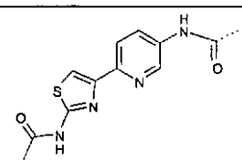
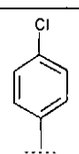
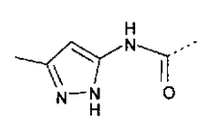
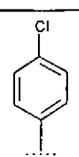
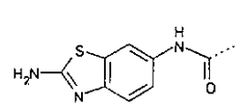
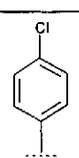
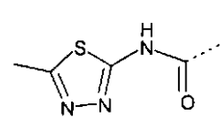
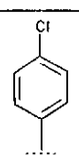
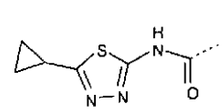
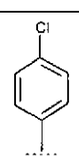
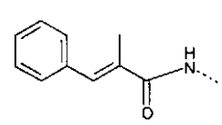
Comp.	R^3	R^5	t_R (min)	EM $(M+H)^+$
1264			5,1**	555,1/ 557,1
1265			4,4**	525,1/ 527,2
1266			4,7/5,2*	496,3
1267			5,3/5,8*	532,3
1268			4,8	475,2/ 477,2
1269			4,9	487,2/ 489,2
1270			5,3**	546,2
1271			4,6/5,1*	484,3
1272			5,7**	518,2/ 520,2

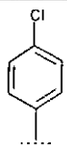
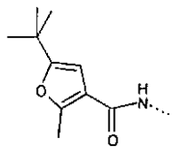
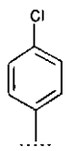
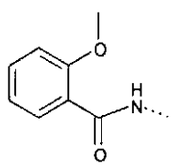
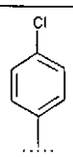
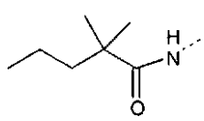
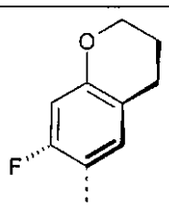
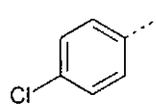
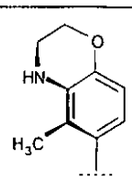
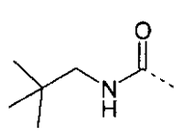
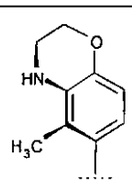
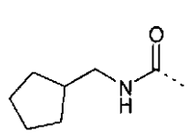
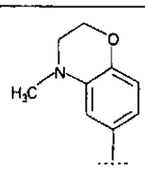
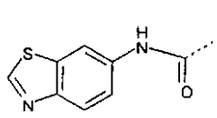
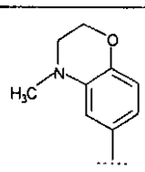
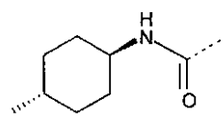
Comp.	R^3	R^5	t_R (min)	EM $(M+H)^+$
1273			7,1	524,1/ 526,1
1274			5,8	482,2/ 484,2
1275			5,1	518,2/ 520,2
1276			6,9	514,1/ 516,1
1277			7,2	536,1/ 538,1
1278			4,9	553,2/ 555,2
1279			4,8	482,2/ 484,2
1280			6,9	536,1/ 538,1
1281			6,7	493,1/ 495,1

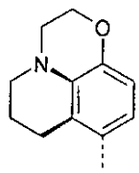
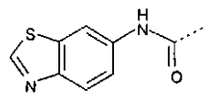
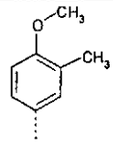
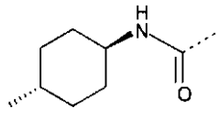
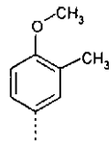
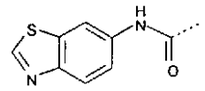
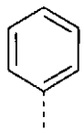
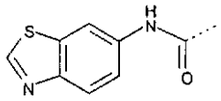
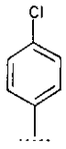
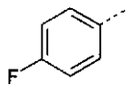
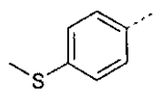
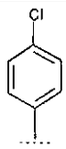
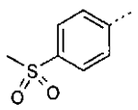
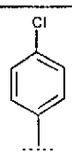
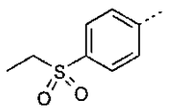
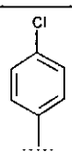
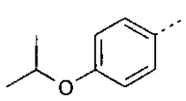
Comp.	R^3	R^5	t_R (min)	EM $(M+H)^+$
1282			5,8	512,2/ 514,2
1283			5,9	511,2/ 513,2
1284			7,1	566,2/ 568,2
1285			5,8/6,4*	484,3
1286			6,2/6,8*	510,3
1287			6,5/7,3*	524,3
1288			4,4**	543,2/ 545,2
1289			3,8/4,1*	547,2
1290			4,0/4,3*	509,2

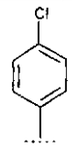
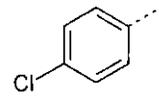
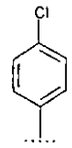
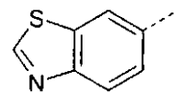
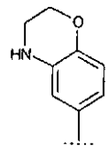
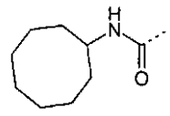
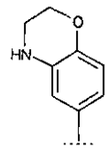
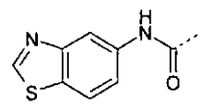
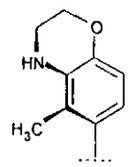
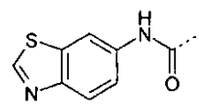
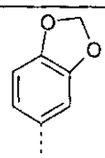
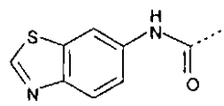
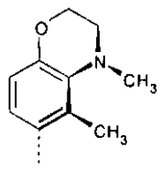
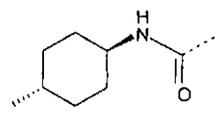
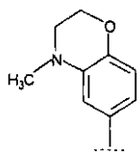
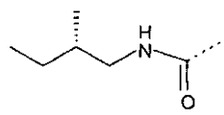
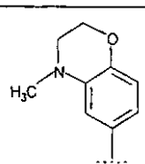
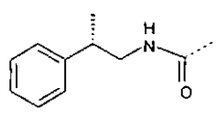
Comp.	R^3	R^5	t_R (min)	EM $(M+H)^+$
1291			3,8/4,1*	511,2
1292			9,3	501,1/ 503,1
1293			5,9/6,5*	496,2
1294			6,8/7,7*	524,2
1295			5,9	511,2/ 513,2
1296			5,6/6,0*	524,2
1297			6,2	473,1/ 475,1
1298			6,5	475,3/ 477,2
1299			4,7/5,1*	496,3

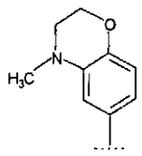
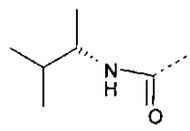
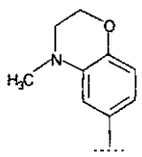
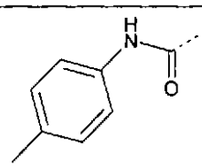
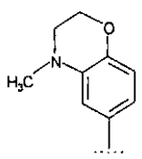
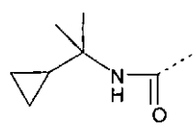
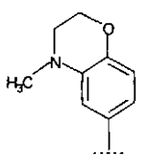
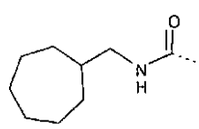
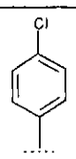
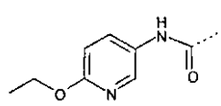
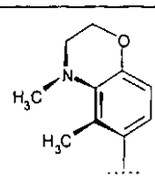
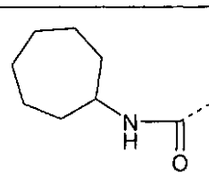
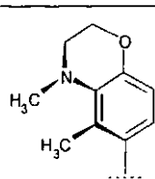
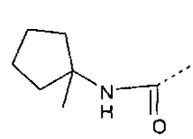
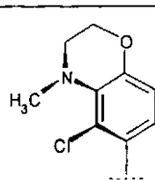
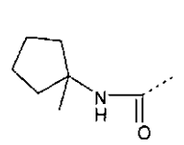
Comp.	R^3	R^5	t_R (min)	EM $(M+H)^+$
1300			6,5	509,0/ 511,0
1301			4,9/5,4*	498,1
1302			6,5	509,0 511,0
1303			5,1/5,6*	532,3
1304			6,8	501,1/ 503,1
1305			4,5/5,0*	482,3
1306			5,1/5,5*	532,3
1307			6,2	459,1/ 461,0
1308			4,8/5,2*	484,3

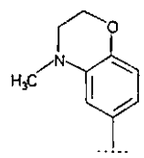
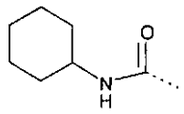
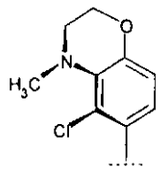
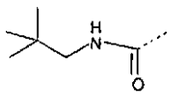
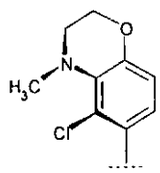
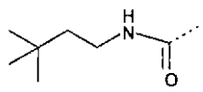
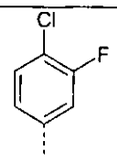
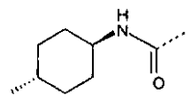
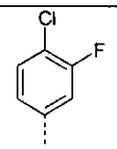
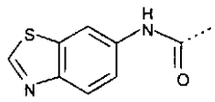
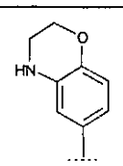
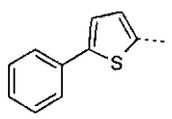
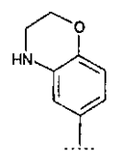
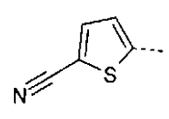
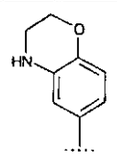
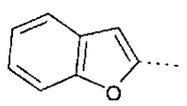
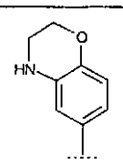
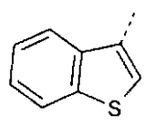
Comp.	R^3	R^5	t_R (min)	EM $(M+H)^+$
1309			6,0	485,2/ 487,2
1310			6,0	471,2/ 473,2
1311			6,7	538,1/ 540,2
1312			5,4	608,2/ 610,2
1313			5,6	471,1/ 473,1
1314			5,0	539,1/ 541,1
1315			6,4	489,0/ 491,0
1316			6,7	515,0/ 517,0
1317			6,2	507,0/ 509,0

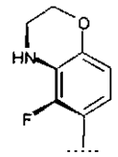
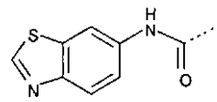
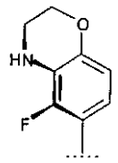
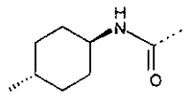
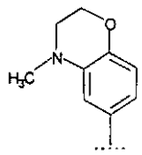
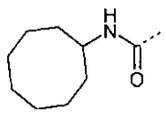
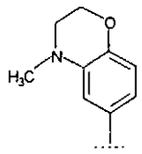
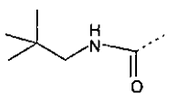
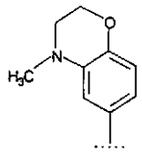
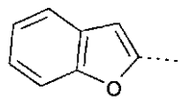
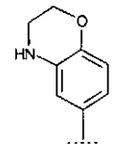
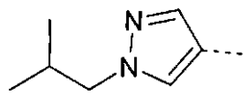
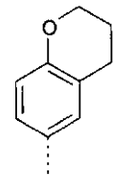
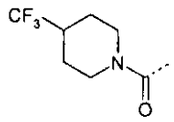
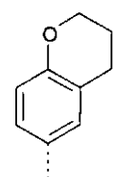
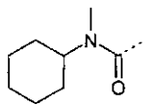
Comp.	R^3	R^5	t_R (min)	EM $(M+H)^+$
1318			6,2	527,1/ 529,1
1319			5,3	497,0/ 499,0
1320			6,1	475,1/ 477,1
1321			5,6**	498,1 500,1
1322			6,1**	498,3
1323			6,2**	510,3
1324			4,2/4,3*	561,2
1325			4,1/4,2*	524,3

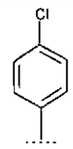
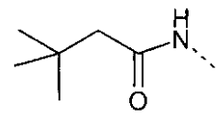
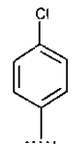
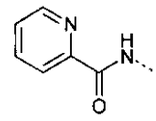
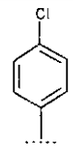
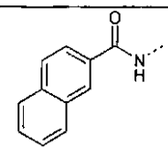
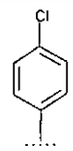
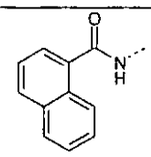
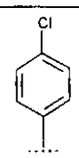
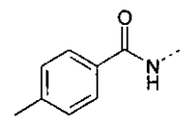
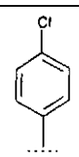
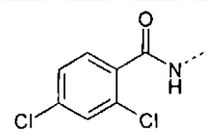
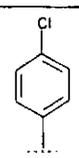
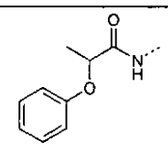
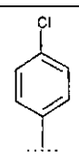
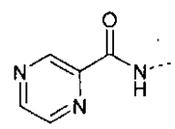
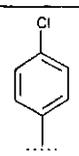
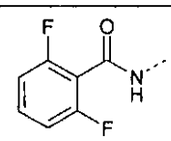
Comp.	R^3	R^5	t_R (min)	EM $(M+H)^+$
1326			7,9**	587,3
1327			7,5/7,8*	497,2
1328			7,8/8,2*	534,1
1329			7,5	490,1
1330			5,2	442,1/ 444,1
1331			5,5	470,2/ 472,1
1332			4,9	502,2/ 504,1
1333			5,1	516,2/ 518,1
1335			5,7	482,2/ 484,2

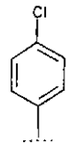
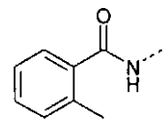
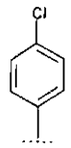
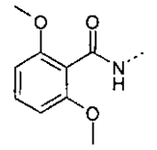
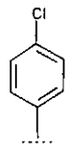
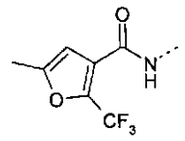
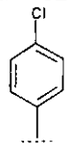
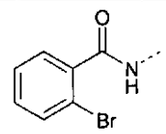
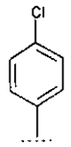
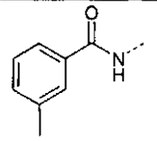
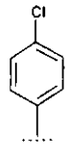
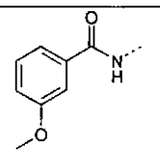
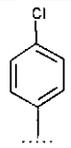
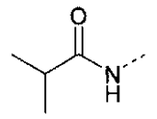
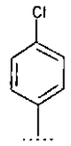
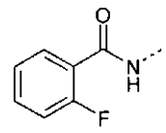
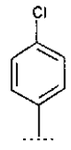
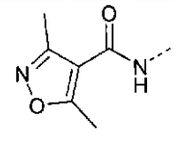
Comp.	R^3	R^5	t_R (min)	EM $(M+H)^+$
1336			5,5	458,1/ 460,1/ 462,1
1337			4,9	481,1/ 483,1
1338			6,1/6,7*	524,3
1339			3,7/4,0*	547,2
1340			4,1**	561,2
1341			4,2	534,2
1342			5,7**	538,2
1343			5,5/5,7*	498,1
1344			5,8/6,0*	546,1

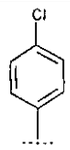
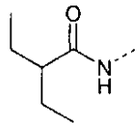
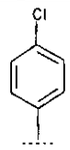
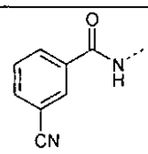
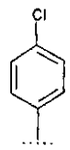
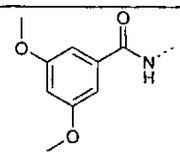
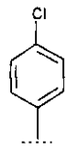
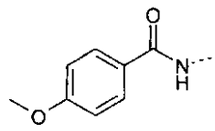
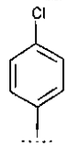
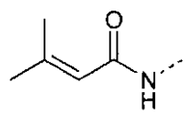
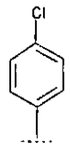
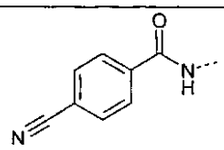
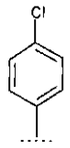
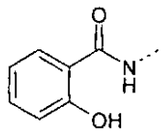
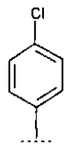
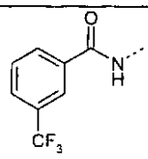
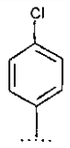
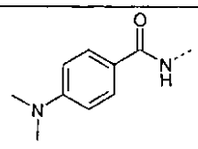
Comp.	R^3	R^5	t_R (min)	EM $(M+H)^+$
1345			5,3/5,5*	498,1
1346			6,4/6,5*	518,1
1347			5,4/5,5*	510,1
1348			6,2/6,4*	538,2
1349			6,6	512,2/ 514,2
1350			5,6**	538,3
1351			5,2**	524,3
1352			5,8**	544,3/ 546,3

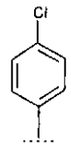
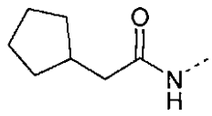
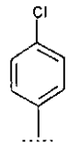
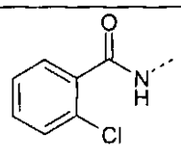
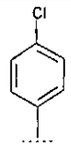
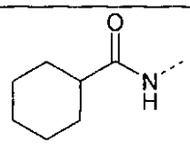
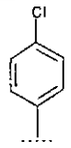
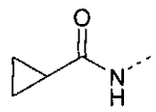
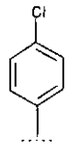
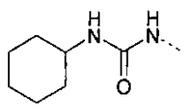
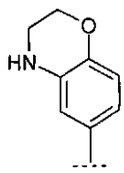
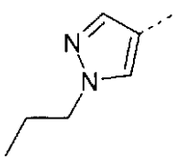
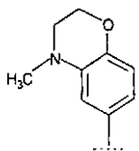
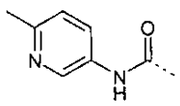
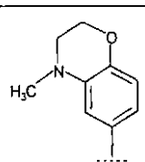
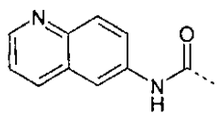
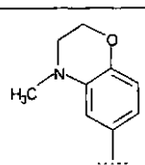
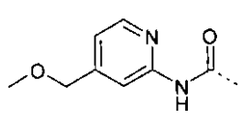
Comp.	R^3	R^5	t_R (min)	EM $(M+H)^+$
1353			5,4/5,6*	510,3
1354			7,1**	532,2/ 534,2
1355			7,8**	546,2/ 548,2
1356			8,9	505,1/ 507,1
1357			8,6	542,0/ 544,0
1358			5,4/5,9*	529,2
1359			5,2/5,8*	478,2
1360			4,7/5,2*	487,2
1361			4,7/5,1*	503,2

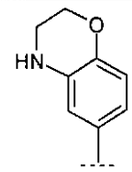
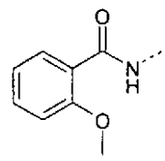
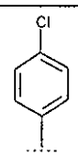
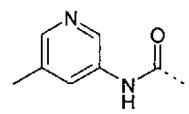
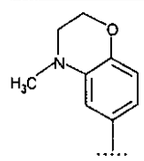
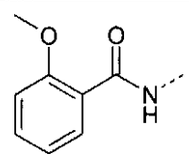
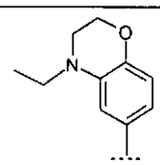
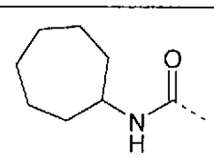
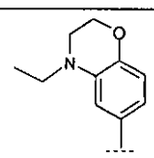
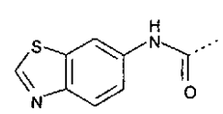
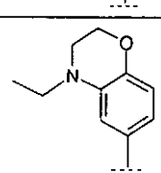
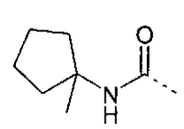
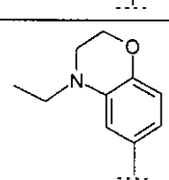
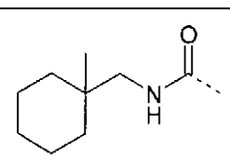
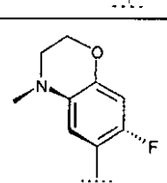
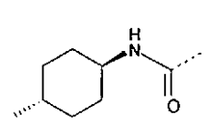
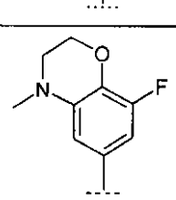
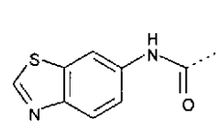
Comp.	R^3	R^5	t_R (min)	EM $(M+H)^+$
1362			7,1**	565,2
1363			7,3**	528,3
1364			7,1/7,4*	538,3
1365			6,3/6,6*	498,3
1366			5,3/5,5*	501,2
1367			4,3/4,7*	493,3
1368			5,6	549,3
1369			4,6	509,3

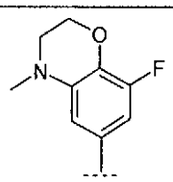
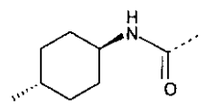
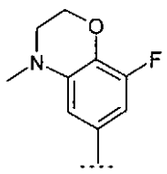
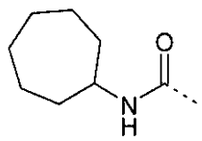
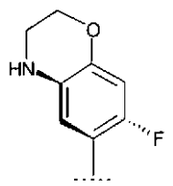
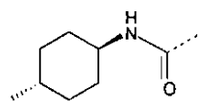
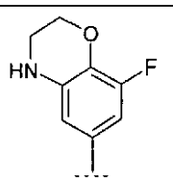
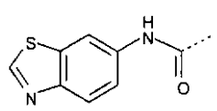
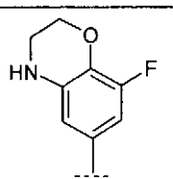
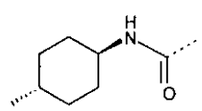
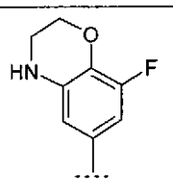
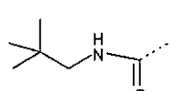
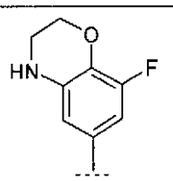
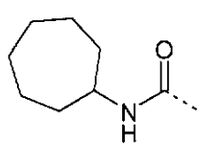
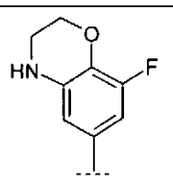
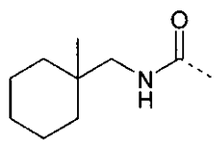
Comp.	R^3	R^5	t_R (min)	EM $(M+H)^+$
1370			1,9$	461,2/ 463,2
1371			1,9$	468,1/ 470,1
1372			2,1$	517,2/ 519,2
1373			2,1$	517,2/ 519,2
1374			2,0$	481,2/ 483,1
1375			2,2$	537,0/ 539,0
1376			2,1$	511,2/ 513,1
1377			1,8$	469,1/ 471,1
1378			2,0$	503,1/ 505,1

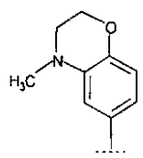
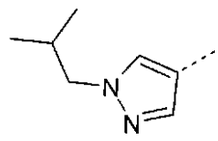
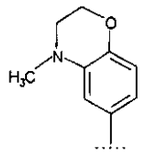
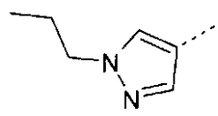
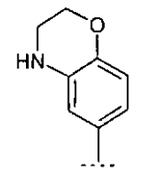
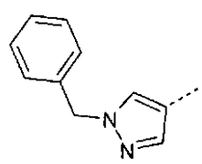
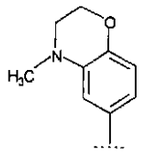
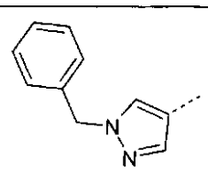
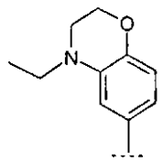
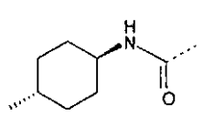
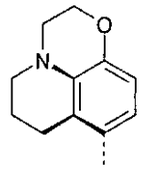
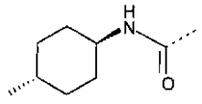
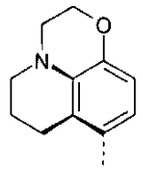
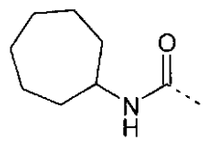
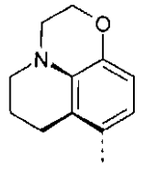
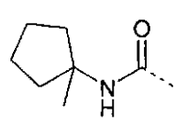
Comp.	R^3	R^5	t_R (min)	EM $(M+H)^+$
1379			2,0$	481,1/ 483,1
1380			1,9$	527,1/ 529,1
1381			2,1$	539,1/ 541,1
1382			2,0$	546,0/ 548,0
1383			2,0$	481,2/ 483,1
1384			2,0$	497,1/ 499,1
1385			1,7$	433,2/ 435,1
1386			2,0$	485,1/ 487,1
1387			1,9$	486,1/ 488,1

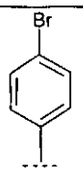
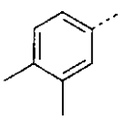
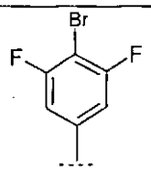
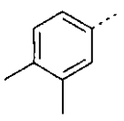
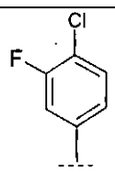
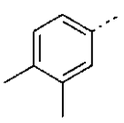
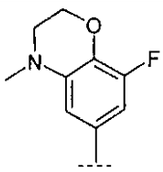
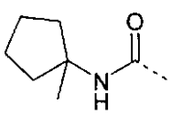
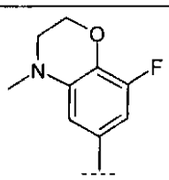
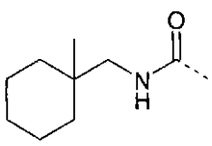
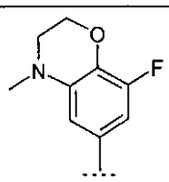
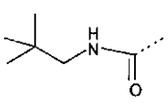
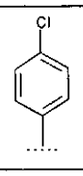
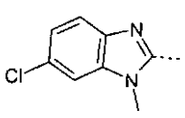
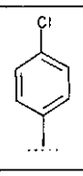
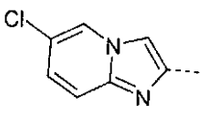
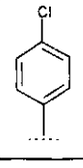
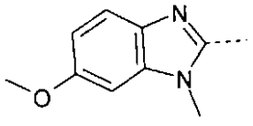
Comp.	R^3	R^5	t_R (min)	EM $(M+H)^+$
1388			1,9$	461,2/ 463,2
1389			2,0$	492,1/ 494,1
1390			2,0$	527,1/ 529,1
1391			1,9$	497,1/ 499,1
1392			1,8$	445,2/ 447,2
1393			2,0$	492,1/ 494,1
1394			1,9$	483,1/ 485,1
1395			2,1$	535,1/ 537.1
1396			2,0$	510,2/ 512,1

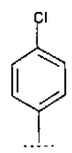
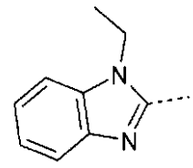
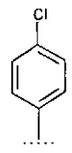
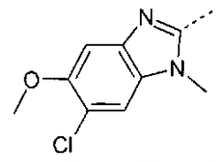
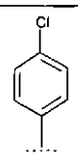
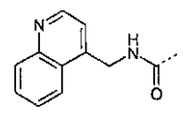
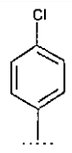
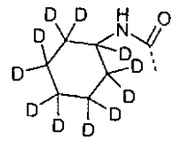
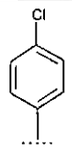
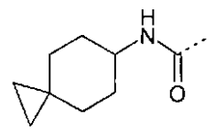
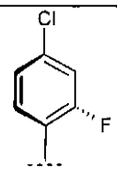
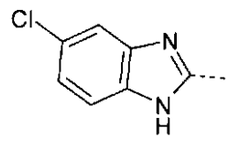
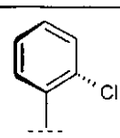
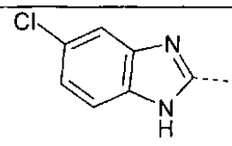
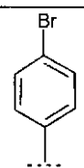
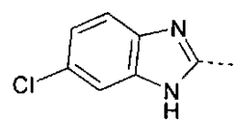
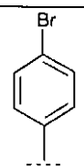
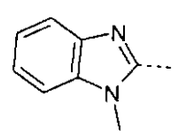
Comp.	R^3	R^5	t_R (min)	EM $(M+H)^+$
1397			2,0$	473,2/ 475,2
1398			2,0$	501,1/ 503,1
1399			2,0$	473,2/ 475,2
1400			1,7$	431,2/ 433,1
1401			2,0$	488,2/ 490,2
1402			4,0/4,4*	479,1
1403			4,4/4,5*	519,2
1404			4,7/4,8*	555,2
1405			5,2/5,4*	549,3

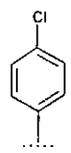
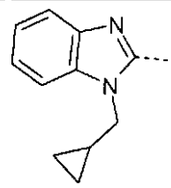
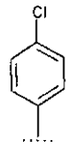
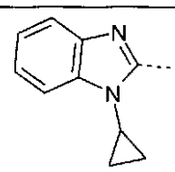
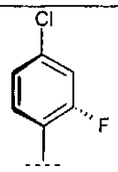
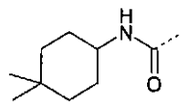
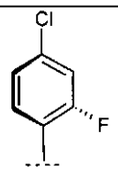
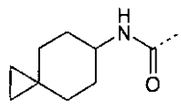
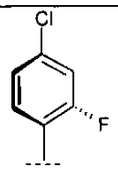
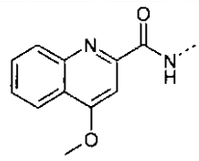
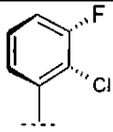
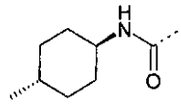
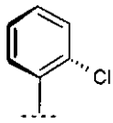
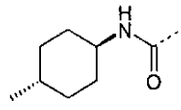
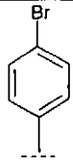
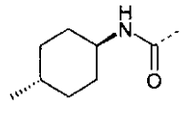
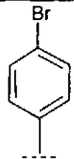
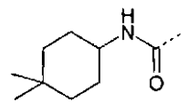
Comp.	R^3	R^5	t_R (min)	EM $(M+H)^+$
1406			4,5/4,8*	520,2
1407			4,9	482,2/ 484,2
1408			4,9/5,1*	534,3
1409			6,1/6,2*	538,4
1410			6,3/6,4*	575,3
1411			5,7/5,8*	524,4
1412			6,6	552,4
1413			6,5**	542,4
1414			6,3/6,4*	579,3

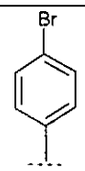
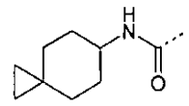
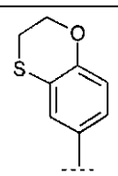
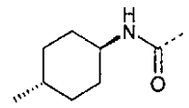
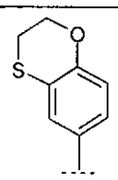
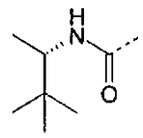
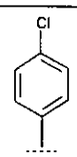
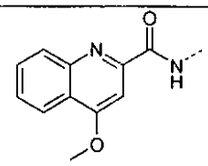
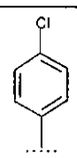
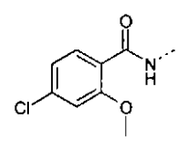
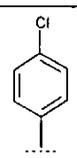
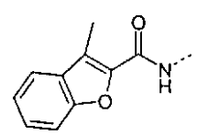
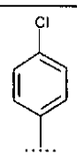
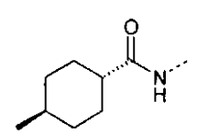
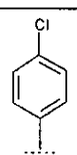
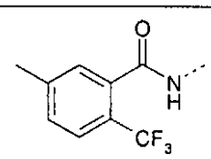
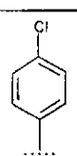
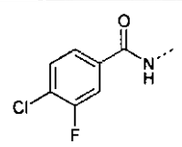
Comp.	R^3	R^5	t_R (min)	EM $(M+H)^+$
1415			6,3/6,4*	542,2
1416			6,2/6,3*	542,2
1417			6,2**	528,3
1418			4,0/4,2*	565,1
1419			4,0/4,2*	528,2
1420			3,8/4,0*	502,3
1421			3,9/4,1*	528,3
1422			4,2/4,3*	542,3

Comp.	R^3	R^5	t_R (min)	EM $(M+H)^+$
1423			4,8/5,0*	507,3
1424			4,6/4,7*	493,3
1425			4,5/4,8*	527,3
1426			5,0/5,1*	541,3
1427			6,3	538,4
1428			2,2$	550,4
1429			2,2$	550,2
1430			2,1$	536,2

Comp.	R^3	R^5	t_R (min)	EM $(M+H)^+$
1431			5,5	496,1/ 498,1
1432			6,6	532,0/ 534,0
1433			6,0	470,1/ 472,1
1434			5,8/5,9*	528,2
1435			6,6	556,3
1436			6,0/6,1	516,2
1437			2,0$	512,2/ 514,2/ 516,2
1438			4,9	498,1/ 500,1
1439			2,1$	508,0/ 510,0

Comp.	R^3	R^5	t_R (min)	EM $(M+H)^+$
1440			2,8$	492,1/ 494,1
1441			1,5$	542,2/ 544,2/ 546,2
1442			4,8	532,2/ 534,2
1443			6,4	484,3/ 486,3
1444			4,4	499,2/ 500,2
1445			4,2**	516,0/ 518,0/ 520,0
1446			4,1**	498,0/ 500,0/ 502,0
1447			4,2	542,0/ 544,0/ 546,0
1448			3,5	522,1/ 524,1

Comp.	R^3	R^5	t_R (min)	EM $(M+H)^+$
1449			2,2[$]	518,2/ 520,2
1450			2,1[$]	504,0/ 506,0
1451			7,0**	519,2/ 521,2
1452			4,6**	517,3/ 519,3
1453			6,6**	566,2/ 568,2
1454			2,9**[$]	505,2/ 507,2
1455			6,7**	487,4/ 489,4
1456			5,4	531,2/ 533,2
1457			7,6	545,2/ 547,2

Comp.	R^3	R^5	t_R (min)	EM $(M+H)^+$
1458			7,4	543,2/ 545,2
1459			6,8	527,3
1460			6,6	512,2
1461			6,7	548,3/ 550,2
1462			2,0[$]	531,2/ 533,1/ 535,1
1463			2,2[$]	521,3/ 523,3
1464			2,0[$]	487,3/ 489,3
1465			2,7[$]	549,0/ 551,0
1466			2,2[$]	519,1/ 521,1/ 523,1

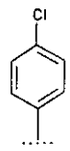
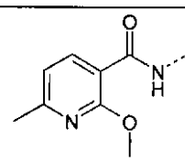
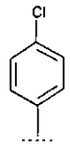
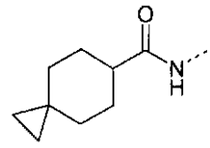
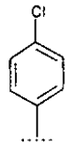
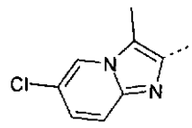
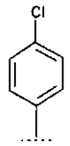
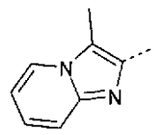
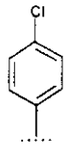
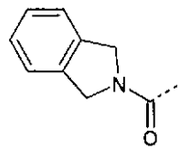
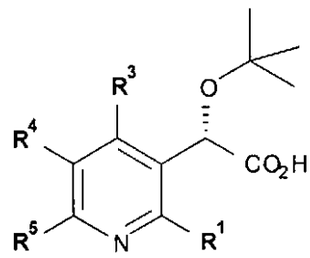
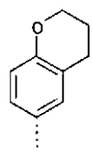
Comp.	R^3	R^5	t_R (min)	EM $(M+H)^+$
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1468			4,0	499,3/ 501,3
1469			4,8	511,9/ 513,9
1470			4,5	487,0/ 480,0
1471			6,3	493,1/ 495,1

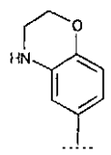
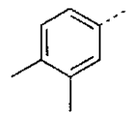
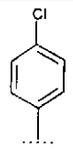
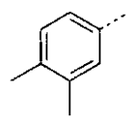
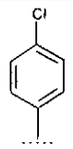
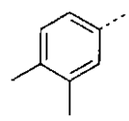
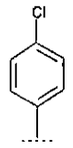
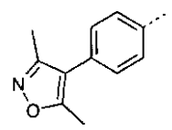
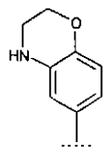
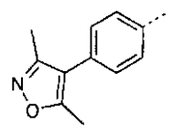
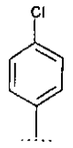
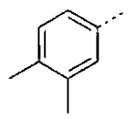
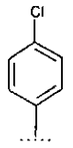
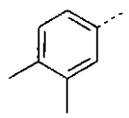
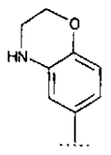
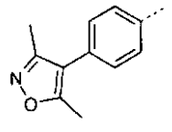
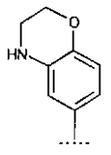
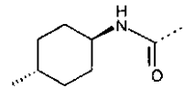
TABLA 2



*presencia de 2 conformadores inter-convertidores por HPLC

**atropisómero más activo

Comp.	R^1	R^3	R^4	R^5	t_R (min)	EM $(M+H)^+$
2001	$-CH_3$		-CN	$-CH_3$	5,9	395,1

Comp.	R^1	R^3	R^4	R^5	t_R (min)	EM $(M+H)^+$
2002	$-CH_2SMe$		$-CH_3$		5,1/5,6*	521,2
2003	$-CH_2OMe$		$-CH_3$		5,7	482,0/ 484,0
2004	$-CH_2OEt$		$-CH_3$		5,8	496,2/ 498,2
2005	$-CH_3$		-CN		8,5	530,2/ 532,2
2006	$-CH_3$		-CN		7,2*	553,2
2007	$-CH=CH_2$		$-CH_3$		5,6	464,2/ 466,2
2008			$-CH_3$		5,8	478,2/ 480,2
2009	$-CH_3$		-F		6,2	546,1
2010	$-CH_2OMe$		$-CH_3$		4,4/5,0*	540,4

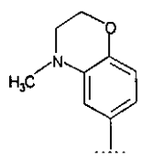
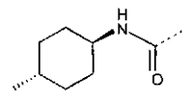
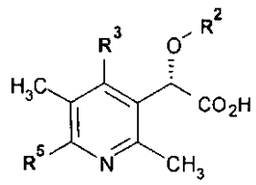
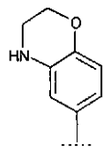
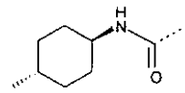
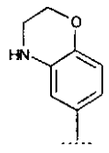
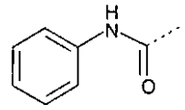
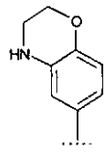
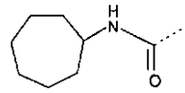
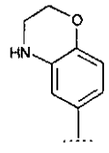
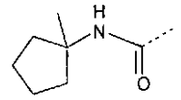
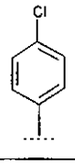
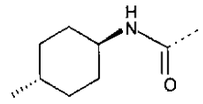
Comp.	R^1	R^3	R^4	R^5	t_R (min)	EM $(M+H)^+$
2011	$-CH_2OMe$		$-CH_3$		5,3/5,5*	554,4

TABLA 3



*presencia de 2 conformadores inter-convertidores por HPLC

**atropisómero más activo

Comp.	R^2	R^3	R^5	t_R (min)	EM $(M+H)^+$
3001				5,7/6,2*	524,3
3002				5,9/6,4*	504,3
3003				5,6/6,1*	524,3
3004				5,1/6,6*	510,2
3005				6,8	501,1/ 503,1

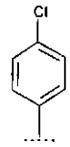
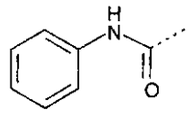
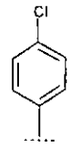
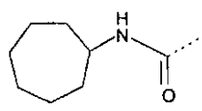
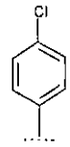
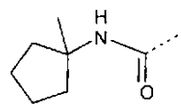
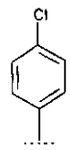
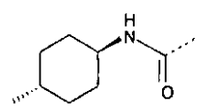
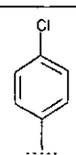
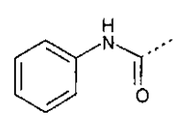
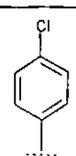
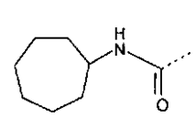
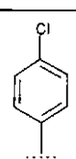
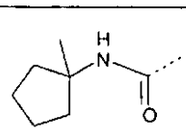
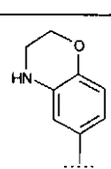
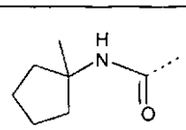
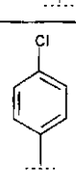
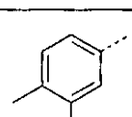
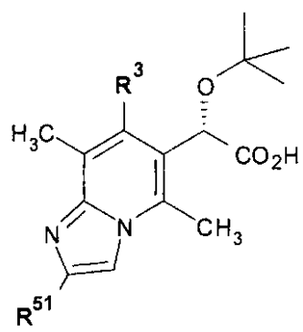
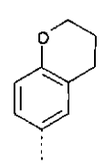
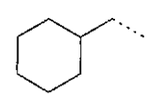
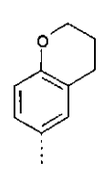
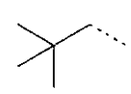
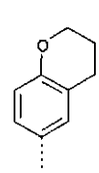
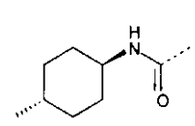
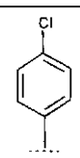
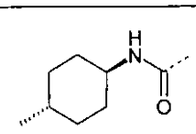
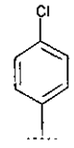
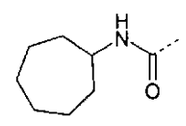
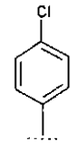
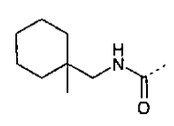
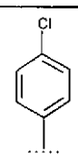
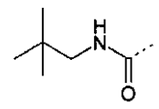
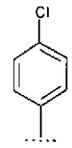
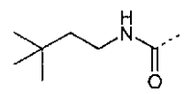
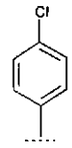
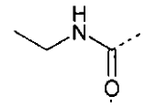
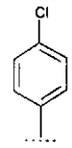
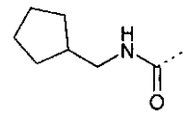
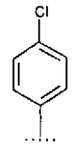
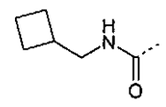
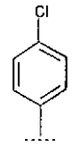
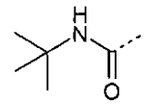
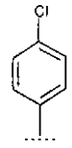
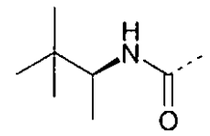
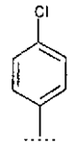
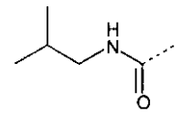
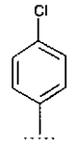
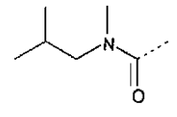
Comp.	R^2	R^3	R^5	t_R (min)	EM $(M+H)^+$
3006				6,9	481,1/ 483,1
3007				6,8	501,1/ 503,1
3008				6,6	487,1/ 489,1
3009				6,8	499,1/ 501,1
3010				6,8	479,1/ 481,1
3011				6,7	499,1/ 501,1
3012				6,5	485,1/ 487,1
3013				4,9/5,0*	508,2
3014				5,5	464,2 466,2

TABLA 4



Comp.	R^3	R^{51}	t_R (min)	EM $(M+H)^+$
4001			6,3	505,2
4002			5,4	479,2
4003			6,3	548,2
4004			7,1	526,1/ 528,1
4005			6,9	526,1/ 528,1
4006			7,9	540,1/ 542,1

Comp.	R^3	R^{51}	t_R (min)	EM $(M+H)^+$
4007			6,6	500,1/ 502,1
4008			7,0	514,1/ 516,1
4009			5,3	458,1/ 460,1
4010			6,7	512,1/ 514,1
4011			6,3	498,1/ 500,1
4012			6,1	486,1/ 488,1
4013			7,0	514,2/ 516,2
4014			6,1	486,1/ 488.1
4015			5,5	500,1/ 502,1

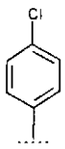
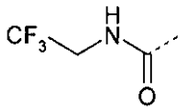
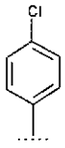
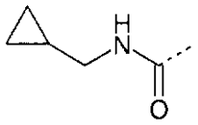
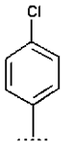
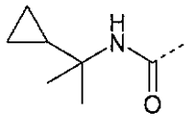
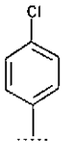
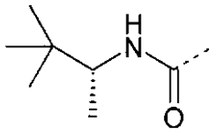
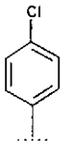
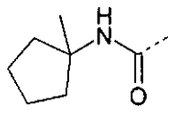
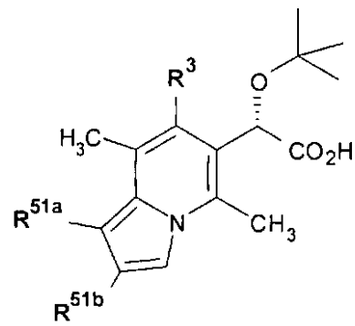
Comp.	R^3	R^{51}	t_R (min)	EM $(M+H)^+$
4016			4,7	512,2/ 514,2
4017			4,5	484,3/ 486,3
4018			5,0	512,3/ 514,3
4019			5,1	514,2/ 516,2
4020			5,0	512,2/ 514,2

TABLA 5



*presencia de 2 conformadores inter-convertidores por HPLC

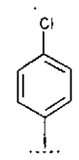
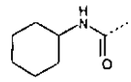
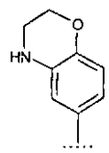
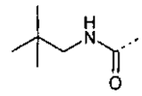
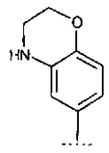
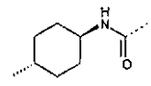
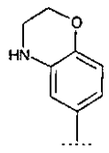
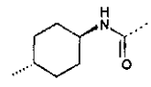
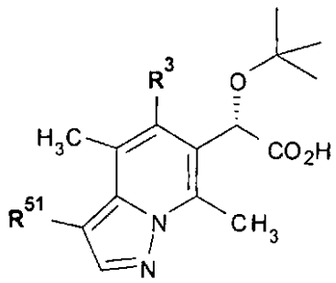
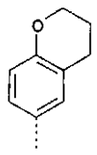
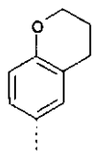
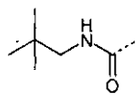
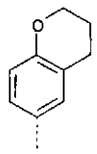
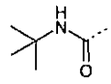
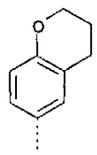
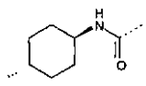
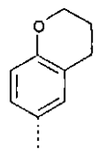
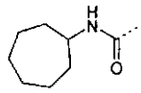
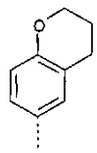
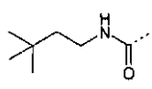
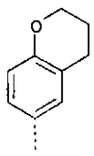
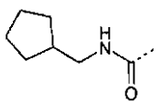
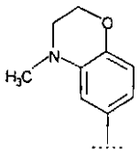
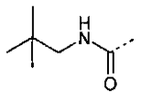
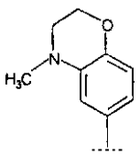
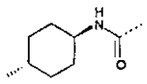
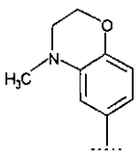
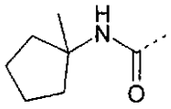
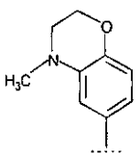
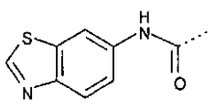
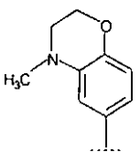
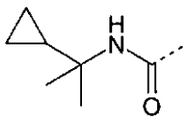
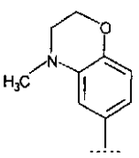
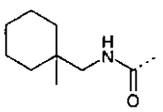
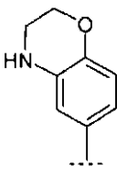
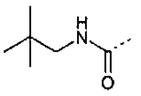
Comp.	R^3	R^{51a}	R^{51b}	t_R (min)	EM $(M+H)^+$
5001			H	8,8	511,2/ 513,2
5002			H	6,0/6,6*	522,3
5003			H	6,5/7,3*	548,4
5004			-CF_3	7,9/8,7*	616,3

TABLA 6



*presencia de 2 conformadores inter-convertidores por HPLC

Comp.	R^3	R^{51}	t_R (min)	EM $(M+H)^+$
6001		-COOMe	8,2	467,1
6002			7,8	522,2
6003			7.4/7.5*	506.2
6004			8.5/8.6	548,2
6005			8,5	548,2
6006			8,4	536,2

Comp.	R^3	R^{51}	t_R (min)	EM $(M+H)^+$
6007			8,1	534,2
6008			6,2/6,4*	537,3
6009			6,5/6,6*	563,2
6010			6,3/6,5*	549,2
6011			6,0/6,2*	600,1
6012			6,3/6,5*	549,2
6013			6,7/6,8*	577,2
6014			5,3/5,8*	523,2

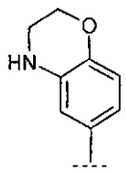
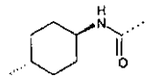
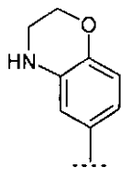
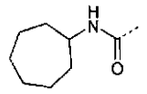
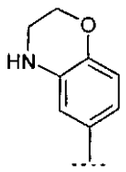
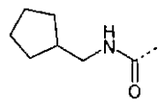
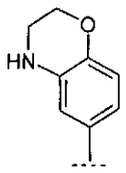
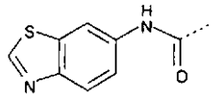
Comp.	R^3	R^{51}	t_R (min)	EM $(M+H)^+$
6015			5,6/5,8*	549,2
6016			5,7/6,2*	549,2
6017			5,4/5,9*	535,2
6018			5,0/5,6*	586,1

TABLA 7:

Potencia antiviral

Compuesto nº	CE_{50} nM
1005	19
1009	20
1011	59
1017	21
1018	180
1020	49
1102	17
1111	15
1113	7,7
1116	13
1119	17

Compuesto nº	CE_{50} nM
1437	0,75
1438	0,94
1439	4,0
1440	2.4
1441	4,9
1442	16
1443	7.1
1444	9.2
1445	1,9
1446	1,9
1447	0,38

1124	81
1127	4,5
1132	9,4
1141	26
1142	7,9
1143	21
1145	35
1146	17
1147	6,9
1152	15
1153	22
1154	27
1160	16
1161	27
1167	9.3
1192	8,3
1202	31
1208	8,9
1242	220
1256	8.1
1275	4,5
1276	68
1280	22
1283	140
1290	11
1293	24
1307	17
1311	26
1316	47

1448	1,4
1449	1,8
1450	7,7
1451	1.7
1452	5,7
1453	2,1
1454	3,7
1455	4,0
1456	4,2
1457	4,0
1458	6,9
1459	4,0
1460	1.7
1461	2,5
1462	1,2
1463	2,1
1464	6,2
1465	11
1466	4,9
1467	4,3
1468	15
1469	0.61
1470	5,9
1471	2.4
2003	17
2005	19
3005	9.3
3009	24
4002	73
6001	89

Cada una de las referencias que incluyen todas las patentes, solicitudes de patente y publicaciones citadas en la presente solicitud se incorporan en la presente

memoria como referencia en su totalidad como si se incorporara cada una de ellas individualmente. Además, debe apreciarse que, en las enseñanzas anteriores de la invención, el experto en la materia podría realizar ciertos cambios o modificaciones a la invención, y estos equivalentes aún estarían dentro del alcance de la invención definido por las reivindicaciones adjuntas de la solicitud.

LISTADO DE SECUENCIAS

<110> Boehringer Ingelheim International GmbH

<120> Inhibidores de la replicación del virus de la inmunodeficiencia humana

<130> 13/157PV2

<160> 1

70> FastSEQ para Windows Versión 4.0

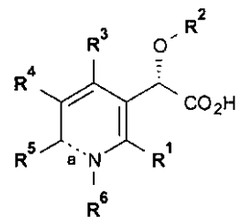
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            20                  25                  30
Ala Lys Glu Ile Val Ala Ser Cys Asp Lys Cys Gln Leu Lys Gly Glu
        35                  40                  45
Ala Met His Gly Gln Val Asp Cys Ser Pro Gly Ile Trp Gln Leu Asp
    50                  55                  60
Cys Thr His Leu Glu Gly Lys Val Ile Leu Val Ala Val His Val Ala
65                  70                  75                  80
Ser Gly Tyr Ile Glu Ala Glu Val Ile Pro Ala Glu Thr Gly Gln Glu
                85                  90                  95
Thr Ala Tyr Phe Leu Leu Lys Leu Ala Gly Arg Trp Pro Val Lys Thr
            100                 105                 110
Val His Thr Asp Asn Gly Ser Asn Phe Thr Ser Thr Thr Val Lys Ala
        115                 120                 125
Ala Cys Trp Trp Ala Gly Ile Lys Gln Glu Phe Gly Ile Pro Tyr Asn
    130                 135                 140
Pro Gln Ser Gln Gly Val Ile Glu Ser Met Asn Lys Glu Leu Lys Lys
145                 150                 155                 160
Ile Ile Gly Gln Val Arg Asp Gln Ala Glu His Leu Lys Thr Ala Val
                165                 170                 175
Gln Met Ala Val Phe Ile His Asn Phe Lys Arg Lys Gly Gly Ile Gly
            180                 185                 190
Gly Tyr Ser Ala Gly Glu Arg Ile Val Asp Ile Ile Ala Thr Asp Ile
        195                 200                 205
Gln Thr Lys Glu Leu Gln Lys Gln Ile Thr Lys Ile Gln Asn Phe Arg
    210                 215                 220
Val Tyr Tyr Arg Asp Ser Arg Asp Pro Val Trp Lys Gly Pro Ala Lys
225                 230                 235                 240
Leu Leu Trp Lys Gly Glu Gly Ala Val Val Ile Gln Asp Asn Ser Asp
                245                 250                 255
Ile Lys Val Val Pro Arg Arg Lys Ala Lys Ile Ile Arg Asp Tyr Gly
            260                 265                 270
Lys Gln Met Ala Gly Asp Asp Cys Val Ala Ser Arg Gln Asp Glu Asp
        275                 280                 285
```

REIVINDICACIONES

1. Un compuesto de fórmula I y un racemato, enantiómero o diastereoisómero de un compuesto de fórmula (I):



(I)

en la que

R^1 es alquilo (C_{1-6}), alquenilo (C_{2-6}) o cicloalquilo (C_{3-6}), en donde el alquilo (C_{1-6}) está opcionalmente sustituido con –Oalquilo (C_{1-6}) o -Salquilo (C_{1-6});

R^2 es alquilo (C_{1-8}) o cicloalquilo (C_{3-8}), en donde el cicloalquilo (C_{3-8}) está opcionalmente sustituido con alquilo (C_{1-6});

R^3 es arilo, en donde el arilo está opcionalmente condensado a uno o más ciclos, al menos uno de los cuales es un heterociclo, para formar un heteropoliciclo, y en donde el arilo o heteropoliciclo está opcionalmente sustituido con 1 a 4 sustituyentes, cada uno independientemente seleccionado de alquilo (C_{1-6}), halo y -Oalquilo (C_{1-6});

R^4 es alquilo (C_{1-6}), -CN, halo, haloalquilo (C_{1-6}), cicloalquilo (C_{3-5}) o -Oalquilo (C_{1-6}); y

a es un doble enlace, R^6 está ausente y R^5 es R^{51} o -alquil (C_{1-3})-R^{51}; o

a es un enlace sencillo y R^5 y R^6 están unidos, junto con los átomos a los que están unidos, para formar un anillo de 5 miembros que tiene, opcionalmente 1 a 3 heteroátomos adicionales, cada uno independientemente seleccionado de O, N y S, en donde el anillo de 5 miembros está opcionalmente sustituido con 1 a 3 sustituyentes R^{51};

en donde R^{51} se selecciona, en cada caso independientemente, de R^{52}, $-OR^{53}$, $-N(R^{54})R^{53}$, $-C(=O)R^{52}$, $-C(=O)OR^{53}$, $-C(=O)N(R^{54})R^{53}$, $-OC(=O)N(R^{54})R^{53}$, $-N(R^{54})C(=O)R^{52}$, $-N(R^{54})C(=O)N(R^{54})R^{53}$ y $-N(R^{54})C(=O)OR^{53}$; en la que

R^{52} se selecciona, en cada caso independientemente, de R^{53}, alquenilo (C_{2-8}) y alquinilo (C_{2-8}),

R^{53} se selecciona, en cada caso independientemente, de alquilo (C_{1-6}), cicloalquilo (C_{3-8}), cicloalquil (C_{3-8})-alquilo (C_{1-6}), arilo, aril-alquilo (C_{1-6}), **Het** y **Het**-alquilo (C_{1-6}), y

R^{54} se selecciona, en cada caso independientemente, de H y alquilo (C_{1-3});

en donde cada uno de R^{52} y R^{53} está opcionalmente sustituido con 1 a 3 sustituyentes seleccionados, en cada caso independientemente, de R^{55}, halo, -CN, $-OR^{56}$, $-SR^{56}$, $-SOR^{56}$, $-SO_2R^{56}$, $-N(R^{54})R^{56}$, $-N(R^{54})C(=O)R^{55}$, $-N(R^{54})C(=O)N(R^{54})R^{56}$, $-N(R^{54})C(=O)OR^{56}$, $-OC(=O)N(R^{54})R^{56}$, $-C(=O)R^{55}$, $-C(=O)OR^{56}$ y $-CON(R^{54})R^{56}$, en donde

R^{55} se selecciona, en cada caso independientemente, de R^{56}, alquenilo (C_{2-8}) y alquinilo (C_{2-8}), y

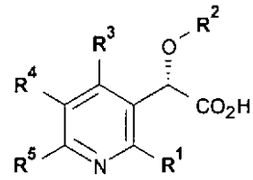
R^{56} se selecciona, en cada caso independientemente, de H, alquilo (C_{1-8}), cicloalquilo (C_{3-8}), cicloalquil (C_{3-8})-alquilo (C_{1-6}), arilo, aril-alquilo (C_{1-6}), **Het** y **Het**-alquilo (C_{1-6}),

en donde cada uno de R^{55} y R^{56} está, siempre que sea posible, en cada caso independientemente, opcionalmente sustituido con 1 a 3 sustituyentes seleccionados, en cada caso independientemente, de alquilo (C_{1-6}), haloalquilo (C_{1-6}), halo, -OH, -Oalquilo (C_{1-6}), $-NH_2$, -NHalquilo (C_{1-6}), -N(alquilo (C_{1-6}))$_2$ y -NH(C=O)alquilo (C_{1-6});

en donde **Het** es un heterociclo de 4 a 7 miembros saturado, insaturado o aromático que tiene de 1 a 4 heteroátomos, cada uno de ellos seleccionado independientemente entre O, N y S, o un heteropoliciclo de 7 a 14 miembros, saturado, insaturado o aromático que tiene, siempre que sea posible, de 1 a 5 heteroátomos, cada uno de ellos seleccionado independientemente entre O, N y S;

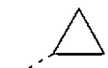
o una de sus sales.

2. El compuesto de acuerdo con la reivindicación 1, o una sal farmacéuticamente del mismo que tiene la fórmula:

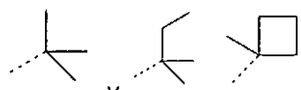


en la que R^1, R^2, R^3, R^4 y R^5 son como se definen en la reivindicación 1.

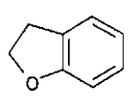
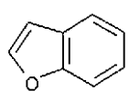
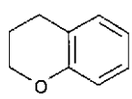
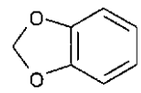
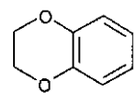
3. El compuesto de acuerdo con la reivindicación 1 ó 2, o una sal farmacéuticamente del mismo, en donde R^1 se selecciona de:

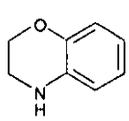
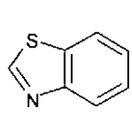
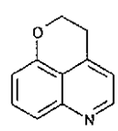
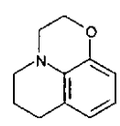
$-CH_3$, $-CH_2OMe$, $-CH_2OEt$, $-CH_2SMe$, $-CH=CH_2$ y  .

4. El compuesto de acuerdo con una cualquiera de las reivindicaciones 1 a 3, o una sal farmacéuticamente del mismo, en donde R^2 se selecciona de:

 y

5. El compuesto de acuerdo con una cualquiera de las reivindicaciones 1 a 4, o una sal farmacéuticamente del mismo, en donde R^3 es fenilo o un heteropoliciclo seleccionado de:

 ,  ,  ,  ,  ,

 ,  ,  y  ; en donde el fenilo o heteropoliciclo está opcionalmente sustituido con 1 a 4 sustituyentes, cada uno independientemente seleccionado de alquilo (C_{1-6}), halo y -Oalquilo (C_{1-6}).

6. El compuesto de acuerdo con una cualquiera de las reivindicaciones 1 a 5, o una sal farmacéuticamente del mismo, en donde R^4 es alquilo (C_{1-6}), -CN,

halo o haloalquilo (C_{1-6}).

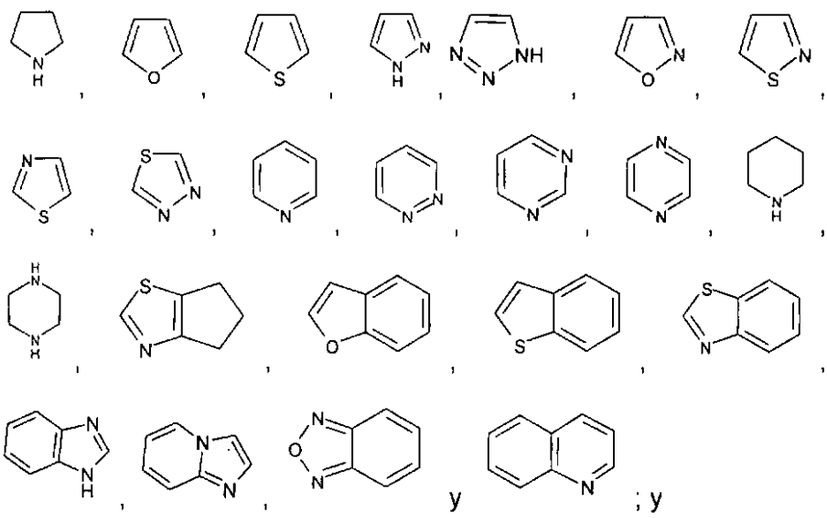
7. El compuesto de acuerdo con una cualquiera de las reivindicaciones 1 a 6, o una sal farmacéuticamente del mismo, en donde R^4 es $-CH_3$.

8. El compuesto de acuerdo con una cualquiera de las reivindicaciones 1 a 7, o una sal farmacéuticamente del mismo, en donde **a** es un doble enlace, R^6 está ausente y R^5 es R^{51} o -alquil (C_{1-3})-R^{51};

en donde R^{51} se selecciona de R^{52}, $-OR^{53}$, $-C(=O)R^{52}$, $-C(=O)OR^{53}$, $-C(=O)N(R^{54})R^{53}$, $-N(R^{54})C(=O)R^{52}$, $-N(R^{54})C(=O)N(R^{54})R^{53}$ y $-N(R^{54})C(=O)OR^{53}$; en la que

R^{52} se selecciona de R^{53} y alquenilo (C_{2-8}), y

R^{53} se selecciona de alquilo (C_{1-8}), cicloalquilo (C_{3-8}), cicloalquil (C_{3-8})-alquilo (C_{1-6})-, arilo, aril-alquilo (C_{1-6})-, **Het** y **Het**-alquilo (C_{1-6})-, en donde **Het** y la porción de **Het** de **Het**-alquilo (C_{1-6})- se seleccionan, en cada caso independientemente, de:



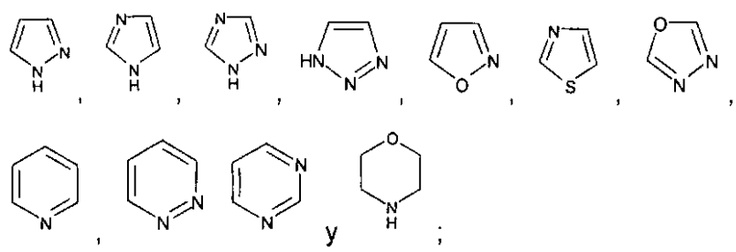
; y

R^{54} se selecciona, en cada caso independientemente, de H y alquilo (C_{1-3});

en donde cada uno de R^{52} y R^{53} está opcionalmente sustituido con 1 a 3 sustituyentes, cada uno independientemente seleccionado de R^{56}, halo, -CN, $-OR^{56}$, $-SR^{56}$, $-SO_2R^{56}$, $-N(R^{54})R^{56}$ y $-CON(R^{54})R^{56}$, en donde

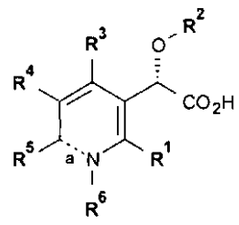
R^{56} se selecciona, en cada caso independientemente, de H, alquilo

(C_{1-8}), cicloalquilo (C_{3-8}), cicloalquil (C_{3-8})-alquilo (C_{1-6})-, arilo, aril-alquilo (C_{1-6})-, **Het** y **Het**-alquilo (C_{1-6})-, en donde **Het** y la porción de **Het** de **Het**-alquilo (C_{1-6})- se seleccionan, en cada caso independientemente, de:



en donde R^{56} está, siempre que sea posible, en cada caso independientemente, opcionalmente sustituido con 1 a 3 sustituyentes, cada uno independientemente seleccionado de alquilo (C_{1-6}), haloalquilo (C_{1-6}), halo, -Oalquilo (C_{1-6}), -N(alquilo (C_{1-6}))$_2$ y -NH(C=O)alquilo (C_{1-6}).

9. Un compuesto y un racemato, enantiómero o diastereoisómero de un compuesto que tiene la fórmula:



en la que

R^1 es alquilo (C_{1-6}), alquenilo (C_{2-6}) o cicloalquilo (C_{3-6}), en donde el alquilo (C_{1-6}) está opcionalmente sustituido con –Oalquilo (C_{1-6}) o -Salquilo (C_{1-6});

R^2 es alquilo (C_{1-8}) o cicloalquilo (C_{3-8}), en donde el cicloalquilo (C_{3-8}) está opcionalmente sustituido con alquilo (C_{1-6});

R^3 es arilo, en donde el arilo está opcionalmente condensado a uno o más ciclos, al menos uno de los cuales es un heterociclo, para formar un heteropoliciclo, y en donde el arilo o heteropoliciclo está opcionalmente sustituido con 1 a 4 sustituyentes, cada uno independientemente seleccionado de alquilo (C_{1-6}), halo y -Oalquilo (C_{1-6});

R^4 es alquilo (C_{1-6}), -CN, halo, haloalquilo (C_{1-6}), cicloalquilo (C_{3-5}) o -Oalquilo (C_{1-6}); y

a es un doble enlace, R^6 está ausente y R^5 es R^{51} o -alquil (C_{1-3})-R^{51}; o

a es un enlace sencillo y R^5 y R^6 están unidos, junto con los átomos a los que están unidos, para formar un anillo de 5 miembros que tiene, opcionalmente 1 a 3 heteroátomos adicionales, cada uno independientemente seleccionado de O, N y S, en donde el anillo de 5 miembros está opcionalmente sustituido con 1 a 3 sustituyentes R^{51};

en donde R^{51} se selecciona, en cada caso independientemente, de R^{52}, $-OR^{53}$, $-N(R^{54})R^{53}$, $-C(=O)R^{52}$, $-C(=O)OR^{53}$, $-C(=O)N(R^{54})R^{53}$, $-OC(=O)N(R^{54})R^{53}$, $-N(R^{54})C(=O)R^{52}$, $-N(R^{54})C(=O)N(R^{54})R^{53}$ y $-N(R^{54})C(=O)OR^{53}$; en la que

R^{52} se selecciona, en cada caso independientemente, de R^{53}, alquenilo (C_{2-8}) y alquinilo (C_{2-8}),

R^{53} se selecciona, en cada caso independientemente, de alquilo (C_{1-8}), cicloalquilo (C_{3-8}), espirocicloalquilo (C_{5-14}), cicloalquil (C_{3-8})-alquilo (C_{1-6}), arilo, aril-alquilo (C_{1-6}), **Het** y **Het**-alquilo (C_{1-6}), y

R^{54} se selecciona, en cada caso independientemente, de H y alquilo (C_{1-3});

en donde cada uno de R^{52} y R^{53} está opcionalmente sustituido con 1 a 3 sustituyentes seleccionados, en cada caso independientemente, de R^{55}, halo, -CN, $-OR^{56}$, $-SR^{56}$, $-SOR^{56}$, $-SO_2R^{56}$, $-N(R^{54})R^{56}$, $-N(R^{54})C(=O)R^{55}$, $-N(R^{54})C(=O)N(R^{54})R^{56}$, $-N(R^{54})C(=O)OR^{56}$, $-OC(=O)N(R^{54})R^{56}$, $-C(=O)R^{55}$, $-C(=O)OR^{56}$ y $-CON(R^{54})R^{56}$, en donde

R^{55} se selecciona, en cada caso independientemente, de R^{56}, alquenilo (C_{2-8}) y alquinilo (C_{2-8}), y

R^{56} se selecciona, en cada caso independientemente, de H, alquilo (C_{1-8}), cicloalquilo (C_{3-8}), cicloalquil (C_{3-8})-alquilo (C_{1-6}), arilo, aril-alquilo (C_{1-6}), **Het** y **Het**-alquilo (C_{1-6}),

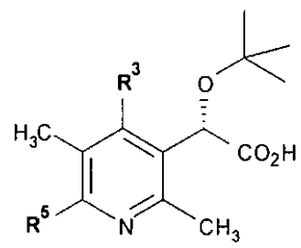
en donde cada uno de R^{55} y R^{56} está, siempre que sea posible, en cada caso independientemente, opcionalmente sustituido con 1 a 3 sustituyentes seleccionados, en cada caso independientemente, de alquilo (C_{1-6}), haloalquilo (C_{1-6}), halo, -OH, -Oalquilo (C_{1-6}), $-NH_2$, -NHalquilo (C_{1-6}), -N(alquilo

$(C_{1-6}))_2$ y -NH(C=O)alquilo (C_{1-6});

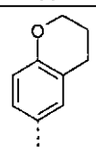
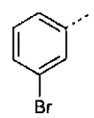
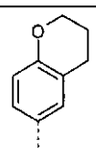
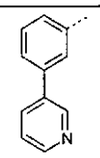
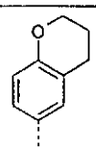
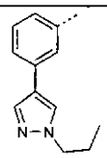
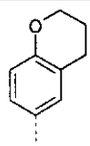
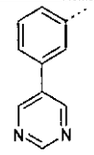
en donde **Het** es un heterociclo de 4 a 7 miembros saturado, insaturado o aromático que tiene de 1 a 4 heteroátomos, cada uno de ellos seleccionado independientemente entre O, N y S, o un heteropoliciclo de 7 a 14 miembros, saturado, insaturado o aromático que tiene, siempre que sea posible, de 1 a 5 heteroátomos, cada uno de ellos seleccionado independientemente entre O, N y S;

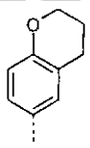
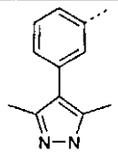
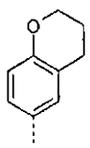
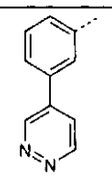
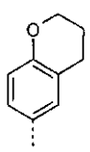
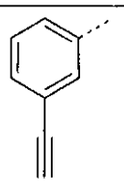
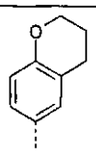
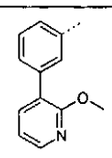
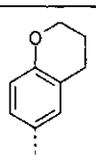
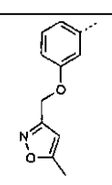
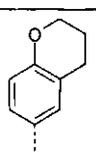
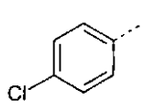
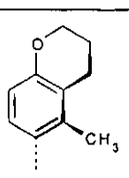
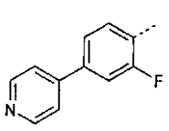
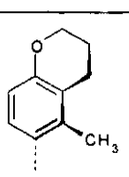
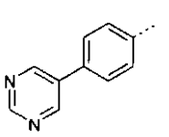
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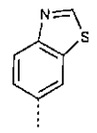
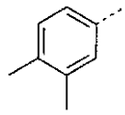
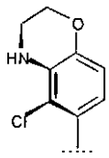
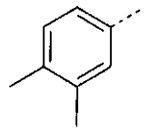
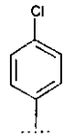
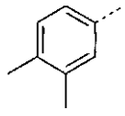
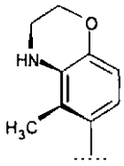
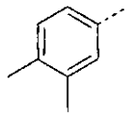
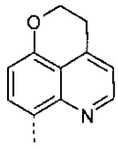
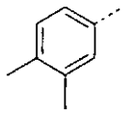
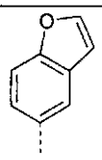
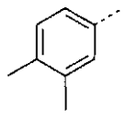
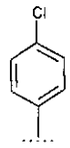
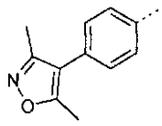
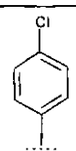
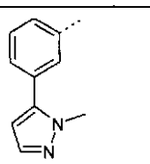
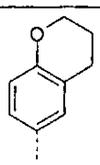
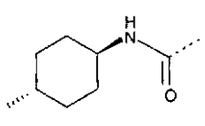
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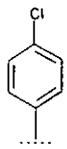
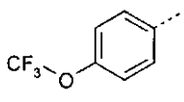
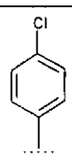
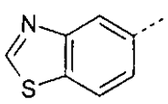
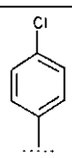
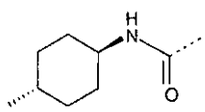
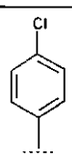
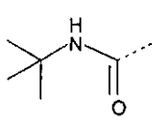
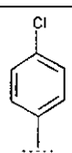
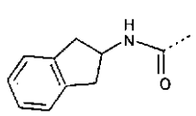
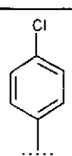
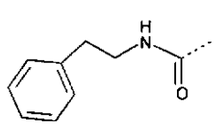
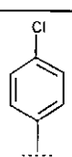
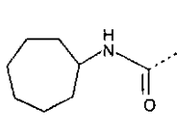
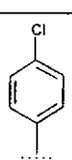
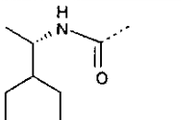
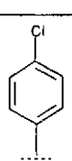
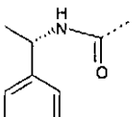


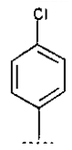
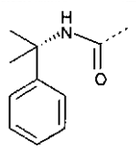
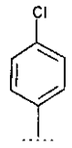
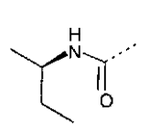
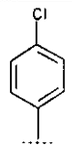
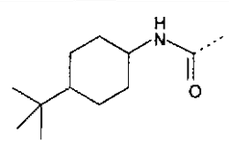
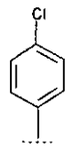
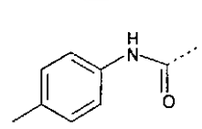
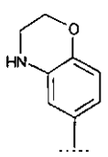
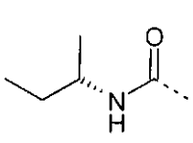
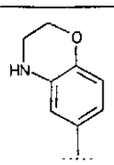
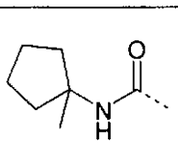
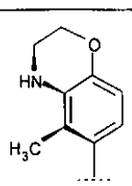
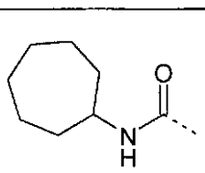
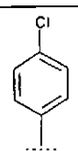
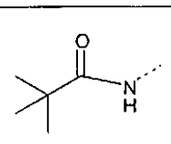
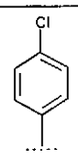
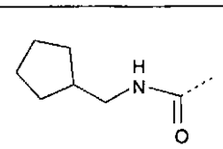
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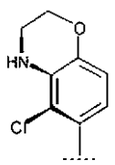
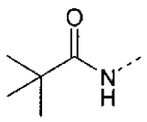
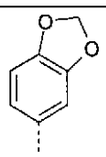
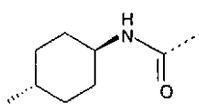
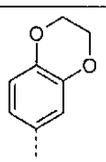
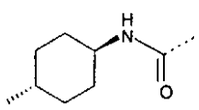
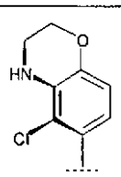
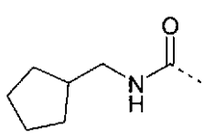
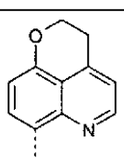
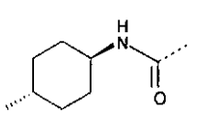
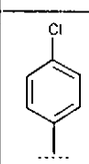
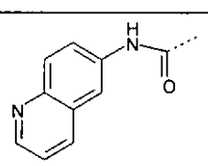
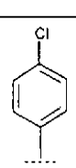
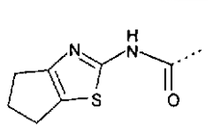
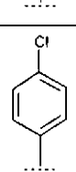
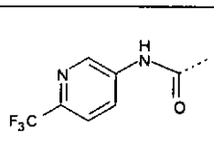
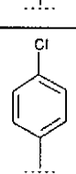
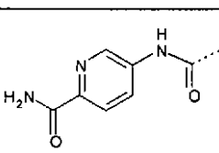
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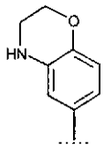
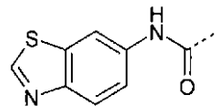
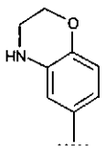
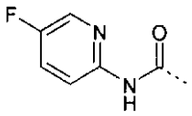
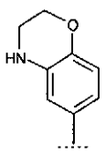
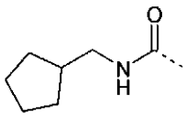
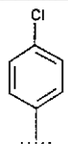
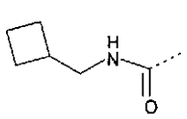
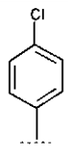
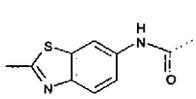
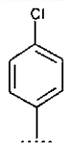
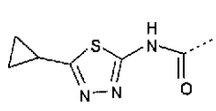
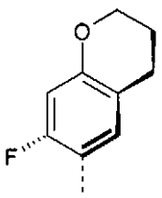
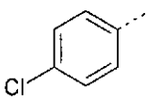
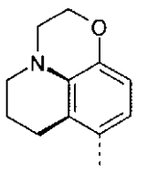
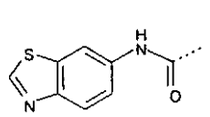
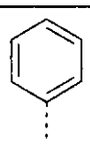
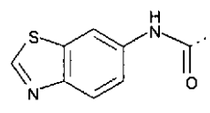
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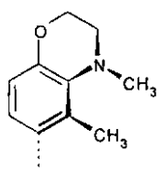
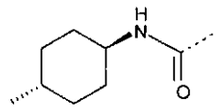
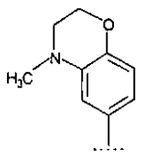
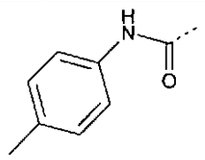
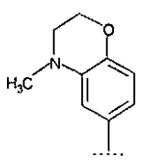
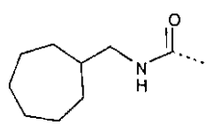
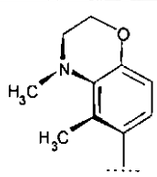
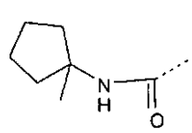
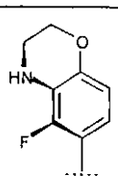
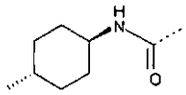
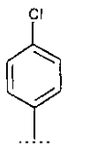
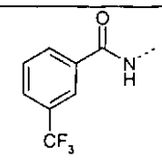
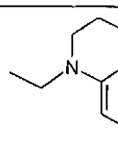
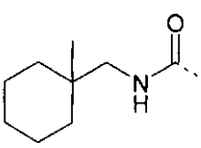
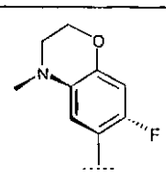
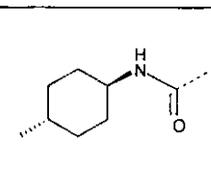
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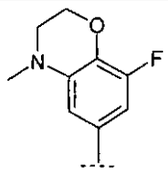
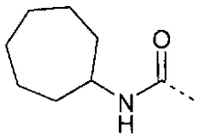
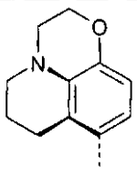
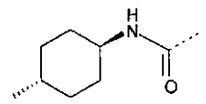
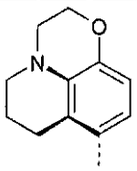
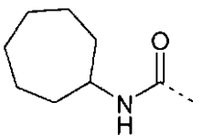
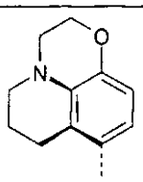
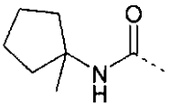
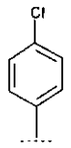
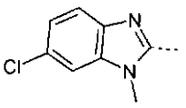
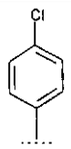
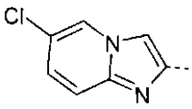
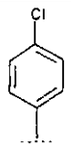
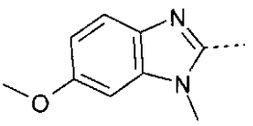
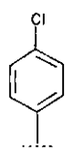
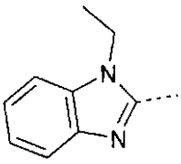
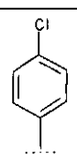
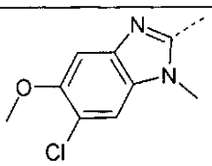
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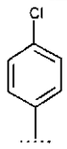
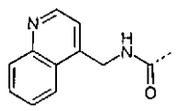
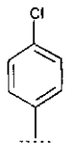
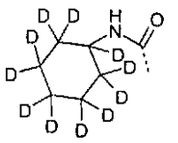
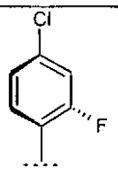
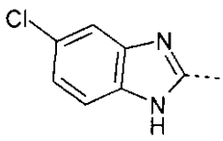
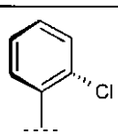
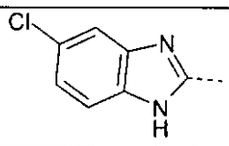
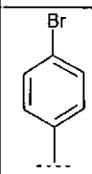
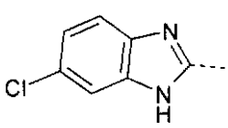
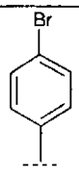
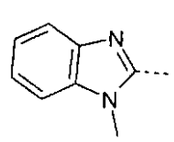
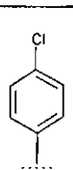
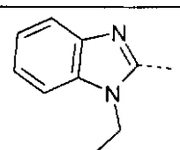
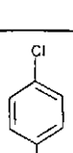
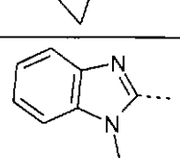
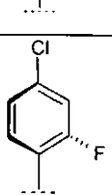
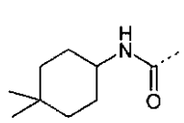
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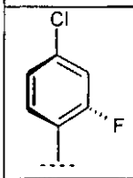
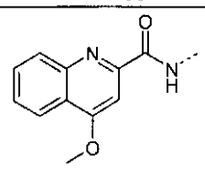
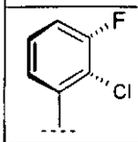
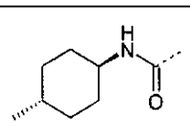
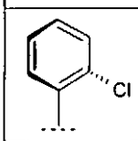
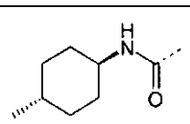
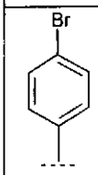
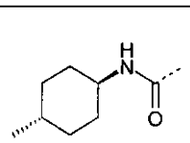
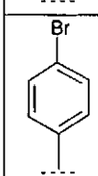
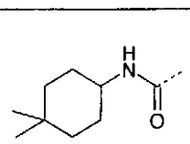
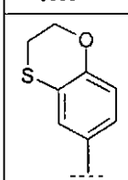
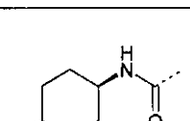
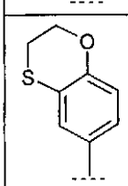
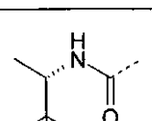
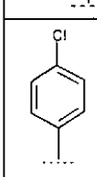
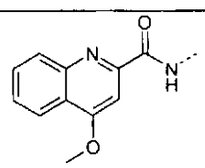
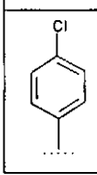
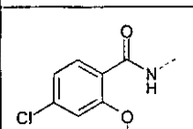
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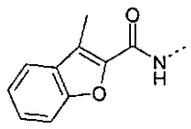
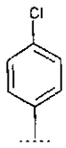
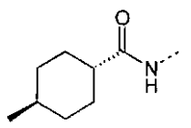
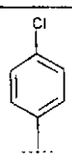
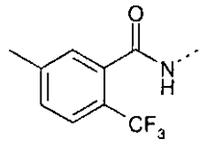
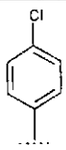
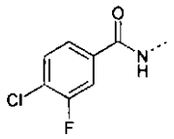
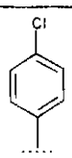
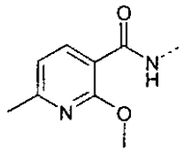
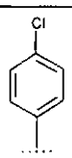
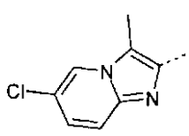
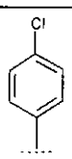
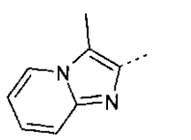
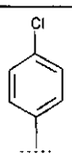
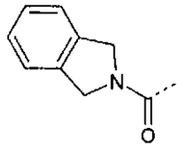
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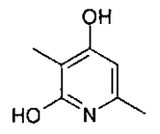
R^3	R^5
	 ;
	 ;
	 ;
	 ;
	 ;
	 ;
	 ;
	 ;
	 ;

R^3	R^5
	 ;
	 ;
	 ;
	 ;
	 ;
	 ;
	 ;
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	 ;

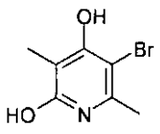
R^3	R^5	
		;
		;
		;
		;
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		;
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		;
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R^3	R^5	
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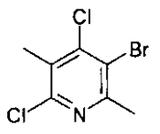
11. Un compuesto representado por una fórmula seleccionada del grupo que consiste en:



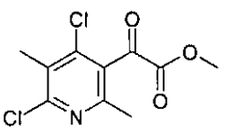
2c ,



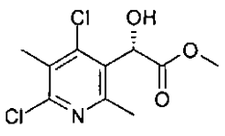
2d ,



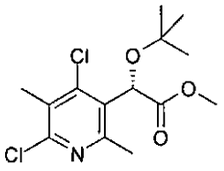
2e ,



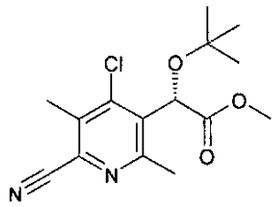
2f ,



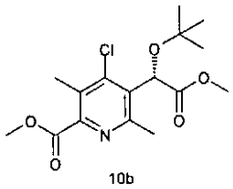
2g ,



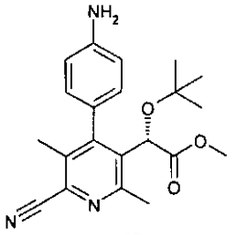
2h ,



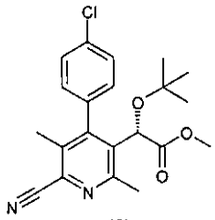
10a



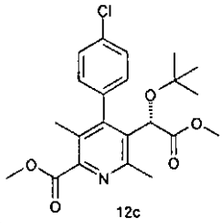
10b



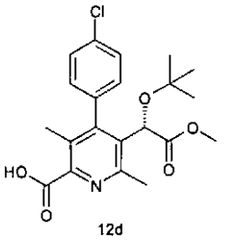
12a



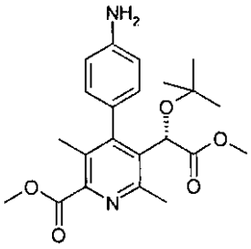
12b



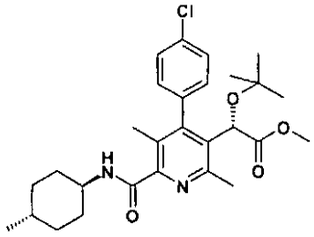
12c



12d



36a y



37a

12. El compuesto de fórmula (I) de acuerdo con una cualquiera de las reivindicaciones 1 a 10, o una sal farmacéuticamente aceptable del mismo, como un medicamento.

13. Una composición farmacéutica que comprende una cantidad terapéuticamente eficaz de un compuesto de fórmula (I) de acuerdo con una cualquiera de las reivindicaciones 1 a 10, o una sal farmacéuticamente aceptable del mismo; y uno o más vehículos farmacéuticamente aceptables.

14. La composición farmacéutica de acuerdo con la reivindicación 13, que comprende, además, al menos otro agente antiviral.

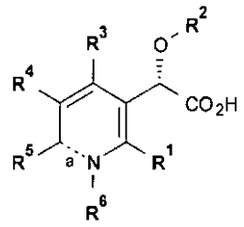
15. Uso de un compuesto de fórmula (I) de acuerdo con una cualquiera de las

reivindicaciones 1 a 10, o una sal farmacéuticamente aceptable del mismo, para el tratamiento de una infección por VIH en un ser humano que tiene o está en riesgo de tener la infección.

5

RESUMEN

Compuestos de fórmula I:



(I)

en donde **a**, R^1, R^2, R^3, R^4, R^5 y R^6 son como se definen en esta memoria, son útiles como inhibidores de la replicación del VIH.

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF THE RECORDING OF A CHANGE

(PCT Rule 92*bis*.1 and Administrative Instructions, Section 422)

To:

LOOPER, Ywe, J.
c/o Boehringer Ingelheim (Canada) Ltd.
2100 Cunard Street
Laval, Québec H7S 2G5
CANADA

Date of mailing *(day/month/year)* 14 November 2011 (14.11.2011)	
Applicant's or agent's file reference 13-157-WO	IMPORTANT NOTIFICATION
International application No. PCT/CA2010/000707	International filing date *(day/month/year)* 13 May 2010 (13.05.2010)

1. The following indications appeared on record concerning:

☒ the applicant ☐ the inventor ☐ the agent ☐ the common representative

Name and Address	State of Nationality	State of Residence
BOEHRINGER INGELHEIM INTERNATIONAL GMBH Binger Strasse 173 55216 Ingelheim Germany	DE	DE
	Telephone No. 011 49 6132 77 2326	
	Facsimile No. 011 49 6132 77 3000	
	E-mail address	

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

☒ the person ☐ the name ☐ the address ☐ the nationality ☐ the residence

Name and Address	State of Nationality	State of Residence
GILEAD SCIENCES LIMITED IDA Business & Technology Park Carrigtohill Co. Cork Ireland		
	Telephone No.	
	Facsimile No.	
	E-mail address ☐ Notifications by e-mail authorized	

3. Further observations, if necessary:
Following an assignment, the applicant in Box 2 should be recorded as applicant for all designated States except the United States of America.

4. A copy of this notification has been sent to:

☒ the receiving Office
☐ the International Searching Authority
☐ the Authority(ies) specified for supplementary search
☐ the International Preliminary Examining Authority
☒ the designated Offices concerned
☐ the elected Offices concerned
☒ other: BOEHRINGER INGELHEIM INTERNATIONAL

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Facsimile No. +41 22 338 89 95	Authorized officer Doherty Fiona e-mail pt04.pct@wipo.int Telephone No. +41 22 338 74 04

PATENT COOPERATION TREATY PCT/CA2010/000707

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF THE RECORDING OF A CHANGE

(PCT Rule 92*bis*.1 and Administrative Instructions, Section 422)

To:

LOOPER, Ywe, J.
c/o Boehringer Ingelheim (Canada) Ltd .
2100 Cunard Street
Laval, Québec H7S 2G5
CANADA

Date of mailing *(day/month/year)*
05 September 2011 (05.09.2011)

Applicant's or agent's file reference
13-157-WO

IMPORTANT NOTIFICATION

International application No.
PCT/CA2010/000707

International filing date *(day/month/year)*
13 May 2010 (13.05.2010)

1. The following indications appeared on record concerning:

☒ the applicant ☒ the inventor ☐ the agent ☐ the common representative

Name and Address	State of Nationality	State of Residence
	Telephone No.	
	Facsimile No.	
	E-mail address	

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

☒ the person ☐ the name ☐ the address ☐ the nationality ☐ the residence

Name and Address	State of Nationality	State of Residence
MORIN, Sebastien Boehringer Ingelheim (Canada) Ltd ., 2100 Cunard Street Laval, Quebec H7S 2G5 Canada	CA	CA
	Telephone No.	
	Facsimile No.	
	E-mail address ☐ Notifications by e-mail authorized	

3. Further observations, if necessary:
The person identified in Box 2 has been added as applicant for US only and inventor for all designated States.

4. A copy of this notification has been sent to:

☒ the receiving Office
☐ the International Searching Authority
☐ the Authority(ies) specified for supplementary search
☐ the International Preliminary Examining Authority
☒ the designated Offices concerned
☐ the elected Offices concerned
☐ other:

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No. +41 22 338 89 95

Authorized officer
Vernhes Thierry
e-mail pt04.pct@wipo.int
Telephone No. +41 22 338 74 04

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter I of the Patent Cooperation Treaty)

(PCT Rule 44*bis*)

Applicant's or agent's file reference 13-157-WO	**FOR FURTHER ACTION**	See item 4 below
International application No. PCT/CA2010/000707	International filing date *(day/month/year)* 13 May 2010 (13.05.2010)	Priority date *(day/month/year)* 15 May 2009 (15.05.2009)
International Patent Classification (8th edition unless older edition indicated) See relevant information in Form PCT/ISA/237		
Applicant GILEAD SCIENCES LIMITED		

1. This international preliminary report on patentability (Chapter I) is issued by the International Bureau on behalf of the International Searching Authority under Rule 44 *bis*.1(a).

2. This REPORT consists of a total of 6 sheets, including this cover sheet.

   In the attached sheets, any reference to the written opinion of the International Searching Authority should be read as a reference to the international preliminary report on patentability (Chapter I) instead.

3. This report contains indications relating to the following items:

☒	Box No. I	Basis of the report
☐	Box No. II	Priority
☐	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☐	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☐	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☒	Box No. VIII	Certain observations on the international application

4. The International Bureau will communicate this report to designated Offices in accordance with Rules 44*bis*.3(c) and 93*bis*.1 but not, except where the applicant makes an express request under Article 23(2), before the expiration of 30 months from the priority date (Rule 44*bis* .2).

	Date of issuance of this report 15 November 2011 (15.11.2011)
The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland	Authorized officer Athina Nickitas-Etienne
Facsimile No. +41 22 338 82 70	e-mail: pt04.pct@wipo.int

Form PCT/IB/373 (January 2004)

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:
LOOPER, YWE J.
c/o Boehringer Ingelheim (Canada) Ltd.
Research and Development
2100 Cunard Street
LAVAL, Quebec
Canada, H7S 2G5

PCT

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing *(day/month/year)*	11 August 2010 (11-08-2010)
Applicant's or agent's file reference 13-157-WO	**FOR FURTHER ACTION** See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/CA2010/000707	13 May 2010 (13-05-2010)	15 May 2009 (15-05-2009)

International Patent Classification (IPC) or both national classification and IPC
IPC: ***C07D 213/55*** (2006.01), ***A61K 31/44*** (2006.01), ***A61K 31/5375*** (2006.01), ***A61K 31/54*** (2006.01), ***A61P 31/18*** (2006.01), ***C07D 213/60*** (2006.01) (more IPCs on the last page)

Applicant
BOEHRINGER INGELHEIM INTERNATIONAL GMBH ET AL

1. This opinion contains indications relating to the following items :

[X]	Box No. I	Basis of the opinion
[ ]	Box No. II	Priority
[ ]	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
[ ]	Box No. IV	Lack of unity of invention
[X]	Box No. V	Reasoned statement under Rule 43*bis*.1(a)(I) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
[ ]	Box No. VI	Certain documents cited
[ ]	Box No. VII	Certain defects in the international application
[X]	Box No. VIII	Certain observations on the international application

2. **FURTHER ACTION**
If a demand for international preliminary examination is made, this opinion will be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA/CA	Date of completion of this opinion	Authorized officer
Canadian Intellectual Property Office Place du Portage I, C114 - 1st Floor, Box PCT 50 Victoria Street Gatineau, Quebec K1A 0C9 Facsimile No.: 001-819-953-2476	29 July 2010 (29-07-2010)	Ursula Wronska (819) 997-6666

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/CA2010/000707

Box No. I Basis of this opinion

1. With regard to the **language**, this opinion has been established on the basis of:

   [x] the international application in the language in which it was filed

   [ ] a translation of the international application into , which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b)).

2. [ ] This opinion has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43*bis*.1(a))

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, this opinion has been established on the basis of a sequence listing filed or furnished:

   a. (means)

      [ ] on paper

      [x] in electronic form

   b. (time)

      [x] the international application as filed.

      [ ] together with the international application in electronic form

      [ ] subsequently to this Authority for the purposes of search

4. [ ] In addition, in the case that more than one version or copy of a sequence listing has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

5. Additional comments :

Box No. V **Reasoned statement under Rule 43*bis*.1(a)(I) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. Statement

Novelty (N)	Claims	1-10, 12-15	YES
	Claims	11	NO
Inventive step (IS)	Claims	1-10, 12-15	YES
	Claims	11	NO
Industrial applicability (IA)	Claims	1-15	YES
	Claims	none	NO

2. Citations and explanations :

PRIOR ART

The following document is considered to be relevant:

D1 CA2262252 A1 (PFIZER PRODUCTS INC.) 17-08-1999

The present application discloses a compound of general formula (I) and the use of the same for inhibiting HIV replication and treatment of HIVinfections. Another aspect of the invention provides intermediate compounds used in the preparation of a compound (I)

NOVELTY Article 33(2) and INVENTIVE STEP Article 33(3)

D1 discloses 2,4-dihydroxy-3,6-dimethylpyridine (see preparation A , page 16) which corresponds to instantly claimed intermediate 2c.

Claim 11 lacks novelty and does not comply with Article 33(2) of the PCT. Given the above objection claim 11 is also considered to lack an inventive step and fail to comply with Article 33(3) of the PCT.

Claims 1-10, 12-15 are considered to be novel under PCT Article 33(2) and the subject matter of these claims is considered to involve an inventive step under Article 33(3) because the prior art does not disclose or fairly suggests the subject compound of formula (I) for the treatment of HIV infections.

INDUSTRIAL APPLICABILITY Article 33(4)

The subject matter of claims 1-15 is considered to be industrially applicable.

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/CA2010/000707

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made :

Claims 1, 9 lack clarity under Article 6 . The term "cycles" is unclear in scope .

Supplemental Box

In case the space in any of the preceding boxes is not sufficient.

Continuation of:

C07D 401/00 (2006.01) , ***C07D 405/00*** (2006.01) , ***C07D 413/00*** (2006.01) , ***C07D 417/00*** (2006.01) , ***C07D 471/04*** (2006.01) , ***C07D 491/06*** (2006.01) , ***C07D 498/06*** (2006.01)

213

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:
LOOPER, YWE J.
c/o Boehringer Ingelheim (Canada) Ltd.
Research and Development
2100 Cunard Street
LAVAL, Quebec
Canada, H7S 2G5

PCT

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing *(day month year)*	11 August 2010 (11-08-2010)
Applicant's or agent's file reference 13-157-WO	**FOR FURTHER ACTION** See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/CA2010/000707	13 May 2010 (13-05-2010)	15 May 2009 (15-05-2009)

International Patent Classification (IPC) or both national classification and IPC
IPC: ***C07D 213/55*** (2006.01), ***A61K 31/44*** (2006.01), ***A61K 31/5375*** (2006.01), ***A61K 31/54*** (2006.01), ***A61P 31/18*** (2006.01), ***C07D 213/60*** (2006.01) (more IPCs on the last page)

Applicant
BOEHRINGER INGELHEIM INTERNATIONAL GMBH ET AL

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- [ ] Box No. II Priority
- [ ] Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- [ ] Box No. IV Lack of unity of invention
- [x] Box No. V Reasoned statement under Rule 43*bis*.1(a)(I) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- [ ] Box No. VI Certain documents cited
- [ ] Box No. VII Certain defects in the international application
- [x] Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**
If a demand for international preliminary examination is made, this opinion will be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

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For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA/CA	Date of completion of this opinion	Authorized officer
Canadian Intellectual Property Office Place du Portage I, C114 - 1st Floor, Box PCT 50 Victoria Street Gatineau, Quebec K1A 0C9 Facsimile No.: 001-819-953-2476	29 July 2010 (29-07-2010)	Ursula Wronska (819) 997-6666

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/CA2010/000707

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2. [ ] This opinion has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43*bis*.1(a))

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, this opinion has been established on the basis of a sequence listing filed or furnished:

   a. (means)

      [ ] on paper

      [x] in electronic form

   b. (time)

      [x] the international application as filed.

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4. [ ] In addition, in the case that more than one version or copy of a sequence listing has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

5. Additional comments :

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/CA2010/000707

Box No. V **Reasoned statement under Rule 43*bis*.1(a)(I) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. Statement

Novelty (N)	Claims	1-10, 12-15	YES
	Claims	11	NO
Inventive step (IS)	Claims	1-10, 12-15	YES
	Claims	11	NO
Industrial applicability (IA)	Claims	1-15	YES
	Claims	none	NO

2. Citations and explanations :

PRIOR ART

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D1 CA2262252 A1 (PFIZER PRODUCTS INC.) 17 -08-1999

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WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/CA2010/000707

Supplemental Box

In case the space in any of the preceding boxes is not sufficient.

Continuation of:

C07D 401/00 (2006.01), *C07D 405/00* (2006.01), *C07D 413/00* (2006.01), *C07D 417/00* (2006.01), *C07D 471/04* (2006.01), *C07D 491/06* (2006.01), *C07D 498/06* (2006.01)

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference 13-157-WO	**FOR FURTHER ACTION**	see Form PCT/ISA/220 as well as, where applicable, item 5 below
International application No. **PCT/CA2010/000707**	International filing date *(day·month·year)* 13 May 2010 (13-05-2010)	(Earliest)Priority date *(day·month·year)* 15 May 2009 (15-05-2009)
Applicant BOEHRINGER INGELHEIM INTERNATIONAL GMBH ET AL		

This international search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This international search report consists of a total of 5 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

   a. With regard to the **language**, the international search was carried out on the basis of:

      [x] the international application in the language in which it was filed

      [ ] a translation of the international application into , which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b))

   b. [ ] This international search report has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43.6*bis*(a)).

   c. [x] With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, see Box No. I

2. [ ] **Certain claims were found unsearchable** (see Box No. II)

3. [ ] **Unity of invention is lacking** (see Box No. III)

4. With regard to the **title**,

   [x] the text is approved as submitted by the applicant

   [ ] the text has been established by this Authority to read as follows :

5. With regard to the **abstract**,

   [x] the text is approved as submitted by the applicant

   [ ] the text has been established, according to Rule 38.2, by this Authority as it appears in Box No. IV. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority

6. With regard to the **drawings**,

   a. the figure of the **drawings** to be published with the abstract is Figure No.

      [ ] as suggested by the applicant

      [ ] as selected by this Authority, because the applicant failed to suggest a figure

      [ ] as selected by this Authority, because this figure better characterizes the invention

   b. [ ] none of the figures is to be published with the abstract

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CA2010/000707

Box No. I Nucleotide and/or amino acid sequence(s) (Continuation of item 1.c of the first sheet)

1. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international search was carried out on the basis of a sequence listing filed or furnished:

   a. (means)

   [ ] on paper

   [x] in electronic form

   b. (time)

   [x] in the international application as filed

   [ ] together with the international application in electronic form

   [ ] subsequently to this Authority for the purposes of search

2. [ ] In addition, in the case that more than one version or copy of a sequence listing has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

3. Additional comments :

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CA2010/000707

A. CLASSIFICATION OF SUBJECT MATTER
IPC: ***C07D 213/55*** (2006.01) , ***A61K 31/44*** (2006.01) , ***A61K 31/5375*** (2006.01) , ***A61K 31/54*** (2006.01) , ***A61P 31/18*** (2006.01) , ***C07D 213/60*** (2006.01) (more IPCs on the last page)
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC: ***C07D 213/55*** (2006.01) , ***A61K 31/44*** (2006.01) , ***A61K 31/5375*** (2006.01) , ***A61K 31/54*** (2006.01) , ***A61P 31/18*** (2006.01) , ***C07D 213/60*** (2006.01)

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

Electronic database(s) consulted during the international search (name of database(s) and, where practicable, search terms used)
STN CAPlus chemical structure search, Canadian Patent Database , Esp@net
keywords: HIV, AIDS, integrase, antiviral, pyridine

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	CA2262252 A1 (PFIZER PRODUCTS INC.) 17 August 1999 (17-08-1999) * page 16, line 4*	11
P, A	WO 2009/062285 (BOEHRINGER INGELHEIM INTERNATIONAL GmbH) 22 May 2009 (22-05-2009) *entire document*	1-15

[ ] Further documents are listed in the continuation of Box C. [x] 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
22 July 2010 (22-07-2010)	11 August 2010 (11-08-2010)
Name and mailing address of the ISA/CA Canadian Intellectual Property Office Place du Portage I, C114 - 1st Floor, Box PCT 50 Victoria Street Gatineau, Quebec K1A 0C9 Facsimile No.: 001-819-953-2476	Authorized officer Ursula Wronska (819) 997-6666

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/CA2010/000707

Patent Document Cited in Search Report	Publication Date	Patent Family Member(s)	Publication Date
CA2262252A1	17 August 1999 (17-08-1999)	AP9901464D0	31 March 1999 (31-03-1999)
		AU1732999A	02 September 1999 (02-09-1999)
		BG103180A	30 September 1999 (30-09-1999)
		BR9900653A	17 October 2000 (17-10-2000)
		CA2262252C	10 January 2006 (10-01-2006)
		CN1231176A	13 October 1999 (13-10-1999)
		EA199900124A3	29 December 1999 (29-12-1999)
		EP0951906A1	27 October 1999 (27-10-1999)
		HR990054A2	29 February 2000 (29-02-2000)
		HU9900386D0	28 April 1999 (28-04-1999)
		HU9900386A2	29 November 1999 (29-11-1999)
		HU9900386A3	28 December 1999 (28-12-1999)
		ID23218A	30 March 2000 (30-03-2000)
		IL128531D0	31 January 2000 (31-01-2000)
		IS4975A	18 August 1999 (18-08-1999)
		JP11292766A	26 October 1999 (26-10-1999)
		MA26608A1	20 December 2004 (20-12-2004)
		NO990722D0	16 February 1999 (16-02-1999)
		NO990722A	18 August 1999 (18-08-1999)
		OA10976A	05 November 2001 (05-11-2001)
		PA8467401A1	29 September 2000 (29-09-2000)
		PL331507A1	30 August 1999 (30-08-1999)
		SG81261A1	19 June 2001 (19-06-2001)
		TR9900328A2	21 October 1999 (21-10-1999)
		US6043260A	28 March 2000 (28-03-2000)
		ZA9901220A	16 August 2000 (16-08-2000)
WO2009062285A1	22 May 2009 (22-05-2009)	AR069335A1	13 January 2010 (13-01-2010)
		AU2008323558A1	22 May 2009 (22-05-2009)
		PE10002009A1	14 August 2009 (14-08-2009)
		UY31472A1	17 July 2009 (17-07-2009)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CA2010/000707

C07D 401/00 (2006.01) . *C07D 405/00* (2006.01) . *C07D 413/00* (2006.01) . *C07D 417/00* (2006.01) .
C07D 471/04 (2006.01) . *C07D 491/06* (2006.01) . *C07D 498/06* (2006.01)

Industria y Comercio
SUPERINTENDENCIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

No. 11-156143- -00000-0000

Fecha: 2011-11-16 16:58:27 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 218

PATENTE DE INVENCIÓN ☐ MODELO DE UTILIDAD ☐ Art 33 Decisión 486/00

- ☐ Indicación que se solicita una patente.
- ☐ Datos de identificación del solicitante o de la persona que presenta la solicitud
- ☐ Descripción de la invención
- ☐ Dibujos de ser estos pertinentes
- ☐ Comprobante de pago de las tasas establecidas (De ser el caso formato de descuento)

Completa ☐ Incompleta ☐

PATENTE DE INVENCIÓN PCT ☑ MODELO DE UTILIDAD PCT ☐ Art.33 Decisión 486/00, Circular Única

- ☑ Indicación que se solicita una PCT
- ☑ Copia de la solicitud en español, tal como fue presentada inicialmente (capítulo descriptivo, reivindicatorio, resumen)
- ☑ Dibujos de ser estos pertinentes
- ☑ Comprobante de pago de las tasas establecidas (de ser el caso formato de descuento)

Completa ☑ Incompleta ☐

DISEÑO INDUSTRIAL ☐ (Art. 119 Decisión 486/00)

- ☐ Indicación que se solicita Diseño industrial
- ☐ Datos de identificación del solicitante o de la persona que presenta la solicitud
- ☐ Representación gráfica y fotográfica del Diseño industrial o muestra del material que incorpora el diseño
- ☐ Comprobante de pago de las tasas establecidas

Completa ☐ Incompleta ☐

ESQUEMA DE TRAZADO ☐ (Art. 92 Decisión 486/00)

- ☐ Indicación que se solicita un esquema de trazado
- ☐ Datos de identificación del solicitante o de la persona que presenta la solicitud
- ☐ Representación gráfica de un esquema de trazado
- ☐ Comprobante de pago de las tasas establecidas

Completa ☐ Incompleta ☐