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División de Nuevas Creaciones

SOLICITUD DE PCT

PATENTE DE INVENCION
PCT ENTRADA EN FASE NACIONAL

21. EXPEDIENTE No. 07-136073

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
INVENTARIO

54. TITULO: **DERIVADOS DE ISOQUINOLINA**

52. CLASIFICACION INTERNACIONAL: **C07D 401/12** ; A61K 31/4725 A61P 11/00 / 27/00

71. SOLICITANTE: **SANOFI-AVENTIS**

DOMICILIO: **174, Avenue de France, 75013 Paris, FRANCIA**

74. APODERADO: **DR. LUIS PATIÑO LEYVA**

22. BOGOTA, D.C., 26 DIC. 2007

PETITORIO

Industria y Comercio
SUPERINTENDENCIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 07-136073- -00000-0000
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Act. 411 PRESENTACION Folios: 259

FORMULARIO UNICO DE SOLICITUD DE PATENTE PCT ENTRADA EN FASE NACIONAL

SOLICITUD DE:

(1)

[X] Patente de Invención. [ ] Patente de Modelo de Utilidad.

[X] Capítulo I [ ] Capítulo II

(2) SOLICITANTE (71)

Nombre: **SANOFI-AVENTIS**

Dirección: **174, avenue de France**
Paris 75013
Francia

Domicilio: **Paris 75013**
Francia

Lugar de Constitución: **Francia**

Teléfono: Fax:
E-mail:

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

(3) REPRESENTANTE O APODERADO (74)

Nombre: **LUIS PATIÑO LEYVA**

Dirección: **Carrera 11A No. 94-76, Of. 308**

Teléfono: **616 1948** Fax: **616 3976**

E-mail: GUSTAVO_HOLLMANN@etb.com

IDENTIFICACIÓN
C.C. [X] NIT [ ]
C.E. [ ] Otro [ ]
Cual
Número **2.930.616** TPA **2698**

(4) INVENTOR (ES) (72)

Ver anexo # 1

(5) PCT (86)

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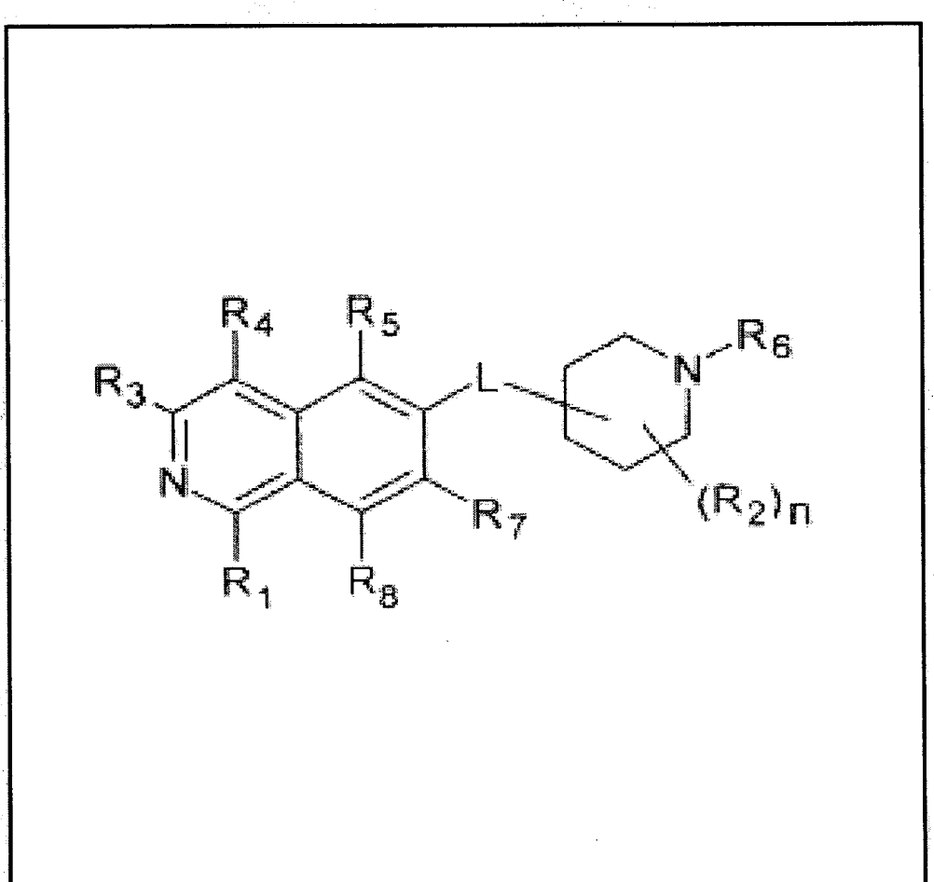
Instrucciones para el diligenciamiento del presente formulario, ver reverso de esta página.

(10) Anexos

- [X] Comprobante de pago de la tasa de presentación de la solicitud.
- [X] Documento que acredita la existencia y representación legal cuando el solicitante sea persona jurídica.
- [X] Poderes, si fuere el caso, junto con la sustitución del mismo a mi favor
- [ ] Documento de cesión del inventor al solicitante o a su causante.
- [ ] Declaraciones.
- [X] Copia de la solicitud internacional (Resumen, descripción, reivindicaciones, dibujos).
- [X] Traducción de la solicitud internacional al castellano (Resumen, descripción, reivindicaciones, dibujos).
- [ ] Copia del examen preliminar 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.
- [X] Arte final 12x12
- [ ] De ser el caso, información sobre otras solicitudes de patente o títulos obtenidos en el extranjero por el mismo titular o su causante, relacionadas parcial o totalmente con la invención de esta solicitud.
- [ ] De ser el caso, modificaciones efectuadas a la solicitud internacional.
- [X] Otros **Tarjeta Propietario, Extracto para la Publicación, Formato PCT/IB/306**

(11) FIGURA CARACTERISTICA:



(12) Solicito la concesión de la patente,

NOMBRE: LUIS PATIÑO LEYVA

FIRMA:

C.C. No. 2.930.616 de Bogotá - T.P.A. 2698 CSJ

ANEXO # 1

INVENTORES

Oliver PLETTENBURG
Sanofi-Aventis Deutschland GmbH
65926 Frankfurt am Main
Alemania

Armin HOFMEISTER
Sanofi-Aventis Deutschland GmbH
65926 Frankfurt am Main
Alemania

Dieter KADEREIT
Sanofi-Aventis Deutschland GmbH
65926 Frankfurt am Main
Alemania

Stefan PEUKERT
19 Albermarle Street
Arlington
MA 02476
Estados Unidos de América

Sven RUF
Sanofi-Aventis Deutschland GmbH
65926 Frankfurt am Main
Alemania

Kurt RITTER
Sanofi-Aventis Deutschland GmbH
65926 Frankfurt am Main
Alemania

Matthias LÖHN
Sanofi-Aventis Deutschland GmbH
65926 Frankfurt am Main
Alemania

Yuri IVASHCHENKO
Sanofi-Aventis Deutschland GmbH
65926 Frankfurt am Main
Alemania

Peter MONECKE
Sanofi-Aventis Deutschland GmbH
65926 Frankfurt am Main
Alemania

Matthias DREYER
Sanofi-Aventis Deutschland GmbH
65926 Frankfurt am Main
Alemania

Aimo KANNT
Sanofi-Aventis Deutschland GmbH
65926 Frankfurt am Main
Alemania

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

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FECHA : DICIEMBRE 18 DE 2007

***** C O N S I G N A C I O N *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
JAIRO SANCHEZ	CONSIGNACION	BANCO POPULAR	050-00110-6	72391247	18/12/2007	3,586,000.00

***** C O N C E P T O *****

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-01 SOLICITUDES	1 TRAMITES DE SOL. DE PATENTE DE IN	482,000.00
		TOTAL : $	482,000.00

SON: CUATROCIENTOS OCHENTA Y DOS MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No._____

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P-8008
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G.HOLLMANN RESTREPO
ABOGADOS LTDA

The undersigned SANOFI AVENTIS....., acting on behalf of and representing of ...., domiciled in 174 Avenue de France, 75013 PARIS, FRANCE, hereby appoint(s) **LUIS PATIÑO LEYVA** and/or **GUSTAVO HOLLMANN RESTREPO**, domiciled in Bogotá D.C., Republic of Colombia, as our true and legal attorney with the necessary powers:

1) To apply to the administrative, judicial and police authorities of the Republic of Colombia, in any instance or appeal, for obtaining registration of patents~~, utility models, industrial designs and models, commercial ensigns and names, trademarks, slogans, health licenses, copyrights and domain names~~ as well as their assignments, extensions, renewals and changes of name; 2) To prepare, apply for, obtain, execute and register contracts, licenses, authorizations and registrations of any kind; 3) To intervene as plaintiff or defendant, in any instance or appeal, before any judge, court, tribunal, corporation, public officer or authority in any judicial, administrative or police action, such as: action dealing with commercial ensigns and names; oppositions against trademark registrations; caducity and nullity actions; recovery actions, actions arising from obtainment and working of license agreements; actions dealing with unfair competition; criminal actions; actions claiming indemnity for damages, complaints or remarks on all sort of industrial property matters; the performance of precautionary measures, and in any other similar action, measure or appeal related to intellectual property matters.

To this effect, I (we) hereby authorize him to file applications, make descriptions, protests, amendments, declarations, oppositions, cancellations, appeals and claims; to pay taxes, quotas and liens as provided by Law; to waive or abandon granted rights or rights in process of being granted, to receive all kind of documents and securities; to issue the respective releases and, in general, to take, before said authorities, pertinent steps to the above mentioned purposes and take all measures they may deem advisable to protect my (our) interests, with all other necessary legal faculties, and I (we) hereby declare as good and valid whatever the attorneys should do to my (our) benefit.

This power comprises the authority to ratify or confirm on my (our) behalf any action, as well as the faculty of receiving, desisting, transacting, compromising, substituting and revoking substitutions, taking notifications, and appointing judicial or extra-judicial attorneys.

Signed in Paris on this 14day of December of 2006.

[signature]

MERLIER Josiane, Director Patent Administration

G. HOLLMANN RESTREPO
ABOGADOS LTDA

Yo (nosotros) , obrando en nombre propio y representación de, con domicilio en , nombro(amos) a **LUIS PATIÑO LEYVA y/o GUSTAVO HOLLMANN RESTREPO**, con domicilio en Bogotá D.C., República de Colombia, apoderado verdadero y legal, con poder especial, amplio y suficiente:

1) Para recabar de las oficinas y autoridades colombianas administrativas, judiciales y de policía en cualquier instancia o recurso, la obtención de patentes de invención, modelos de utilidad, dibujos y modelos industriales, registro de marcas, registro de lemas comerciales, depósito de nombres y enseñas comerciales, registros sanitarios, derechos de autor y nombres de dominio así como sus traspasos, prórrogas, renovaciones y cambios de nombre; 2) Elaborar, tramitar, solicitar, obtener, realizar, ejecutar y registrar contratos, licencias, autorizaciones y registros de cualesquiera clases; 3) Intervenir como demandante o como demandado en cualquier instancia y recurso y ante cualquier juez, entidad, corporación, funcionario público o autoridad en acciones judiciales, administrativas y de policía, tales como acciones derivadas de nombre o enseña comerciales; acciones reivindicatorias; acciones derivadas de la obtención o explotación de licencias; acciones de competencia desleal, demandas penales y civiles; acciones de indemnización de perjuicios, reclamos, u observaciones a cualquier asunto sobre propiedad intelectual; al ejercicio de medidas cautelares y cualesquiera otras acciones, medidas o recursos similares relacionados con la propiedad intelectual.

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Firmado en Paris el de de .

Je soussigné Me **Hervé POMMERY**
Notaire à Paris, certifie matériellement la signature de Madame Josiane MERLIER apposée sur le présent document.
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2. a été signé par Maître POMMERY

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5. à PARIS

6. le 20/12/06

7. *par le Procureur général près la Cour d'appel de* PARIS

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The undersigned Hervé POMMERY certifies: that the preceding signature(s) reading Jasmine MERLIES (are) authentic; that the signer(s) at present fill(s) the position of Director of Patent administration; that he (they) is (are) empowered to grant this power; and that said company exists, accomplishes its social object and is organized in _____ in accordance with the Laws of FRANCE. All the foregoing facts are known to me, due to my having examined the respective documents to which I attest.

Signed in PARIS on this 19th day of February of 2007.

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2007 JUN 28 A 11: 35

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(71) Applicant *(for all designated States except US)*: **SANOFI-AVENTIS DEUTSCHLAND GMBH** [DE/DE]; Bruningstrasse 50, 65929 Frankfurt am Main (DE).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **PLETTENBURG, Oliver** [DE/DE]; Sanofi-Aventis Deutschland GmbH, 65926 Frankfurt am Main (DE). **HOFMEISTER, Armin** [DE/DE]; Sanofi-Aventis Deutschland GmbH, 65926 Frankfurt am Main (DE). **KADEREIT, Dieter** [DE/DE]; Sanofi-Aventis Deutschland GmbH, 65926 Frankfurt am Main (DE). **PEUKERT, Stefan** [DE/US]; 19 Albermarle Street, Arlington, MA 02476 (US). **RUF, Sven** [DE/DE]; Sanofi-Aventis Deutschland GmbH, 65926 Frankfurt am Main (DE). **RITTER, Kurt** [DE/DE]; Sanofi-Aventis Deutschland GmbH, 65926 Frankfurt am Main (DE). **LÖHN, Matthias** [DE/DE]; Sanofi-Aventis Deutschland GmbH, 65926 Frankfurt am Main (DE). **IVASHCHENKO, Yuri** [US/DE]; Sanofi-Aventis Deutschland GmbH, 65926 Frankfurt am Main (DE). **MONECKE, Peter** [DE/DE]; Sanofi-Aventis Deutschland GmbH, 65926 Frankfurt am Main (DE). **DREYER, Matthias** [DE/DE]; Sanofi-Aventis Deutschland GmbH, 65926 Frankfurt am Main (DE). **KANNT, Aimo** [DE/DE]; Sanofi-Aventis Deutschland GmbH, 65926 Frankfurt am Main (DE).

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

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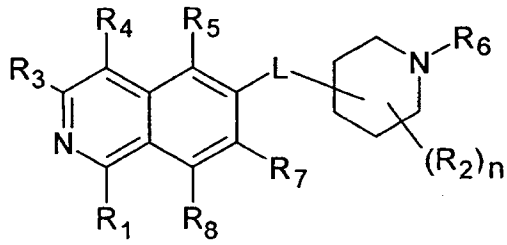
Published:
— *with international search report*

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

(54) Title: ISOQUINOLINE DERIVATIVES AS INHIBITORS OF RHO-KINASE



(I)

(57) Abstract: The invention relates to 6-piperidinyl-substituted isoquinoline derivatives of the formula (I); useful for the treatment and/or prevention of diseases associated with Rho-kinase and/or Rho-kinase mediated phosphorylation of myosin light chain phosphatase, and compositions containing such compounds.

WO 2007/000240 A1

The present invention relates to novel isoquinoline derivatives, their preparation and their use in the treatment and/or prevention of diseases related to the inhibition of Rho-kinase and/or of Rho-kinase mediated phosphorylation of myosin light chain phosphatase.

Activation of a small GTPase RhoA upon agonist stimulation results in conversion of RhoA from the inactive GDP-bound form to the active GTP-bound form with a subsequent binding to and activation of Rho-kinase. Two isoforms, Rho-kinase 1 and Rho-kinase 2, are known. Rho-kinase 2 is expressed in vascular smooth muscle cells and endothelial cells. Activation of Rho-kinase 2 by the active GTP-bound RhoA leads to calcium sensitization of smooth muscle cells through phosphorylation-mediated inhibition of the myosin light chain phosphatase activity and thereby up-regulation of the activity of myosin regulatory light chain (Uehata et al., Nature 1997, 389, 990-994).

It is known that Rho-kinase is involved in vasoconstriction, including the development of myogenic tone (J. Appl. Physiol. 2005, 1940-8, 98), bronchial smooth muscle contraction (Am. J. Resp. Cell Mol. Biol. 20, 1190-1200), hypertension, i.e. pulmonary hypertension (Heart, 91, 391-2, 2005) and ocular hypertension (Invest. Ophthalmol. Visual Sci. 2001, 42, 137-144), endothelial dysfunction (Eur. J. Pharmacol. 2005, 512, 247-249), artherosclerosis, restenosis (Arch. Mal. Coeur 2005, 98, 249-254), glucose utilization, cardiac hypertrophy (Hypertension 2000, 35, 313-318), erectile dysfunction (Nature Medicine 2001, 7, 119-122), retinopathy, inflammation, immune diseases, AIDS, osteoporosis, brain functional disorder, infection of digestive tracts with bacteria (WO 98/06433), cancer development, vascular smooth muscle proliferation and motility (Circ. Res. 1999, 84, 1186-1193; Atherosclerosis 2001, 155, 321-327), endothelial proliferation and motility (Biochem. Biophys. Res. Commun. 2000, 269, 633-640), stress fiber formation (Science 1997, 275, 1308-1311; J. Cell Biol. 2000, 150, 797-806), platelet aggregation (FEBS Lett. 2000, 466, 70-74; Blood 1999, 94, 1665-1672), Na/H exchange transport system activation (EMBO J. 1998, 17, 4712-4722), Alzheimer's disease (Science 2003, 302, 1215-1217), adducin activation (J.

Biol. Chem., 273, 5542-5548, 1998), and in SREB (Sterol response binding element) signalling and its effects on lipid metabolism (Circ. Res., 92,1296-304, 2003).

Therefore, a compound having inhibitory effect on Rho-kinase and/or on Rho-kinase mediated phosphorylation of myosin light chain phosphatase is useful for the treatment and/or prevention of diseases involving Rho-kinase as the primary disease cause, e.g. hypertension, i.e. pulmonary hypertension and ocular hypertension, peripheral circulatory disorder, angina pectoris, cerebral vasospasm, asthma, premature birth, hyperaggregability of platelets, Peripheral Occlusive Arterial Disease (PAOD), Chronic Obstructive Pulmonary Disease (COPD), cancer development, and erectile dysfunction, or as the secondary disease cause, e.g. arteriosclerosis, ischemic organ failure (end organ damage), fibroid lung, fibroid liver, liver failure, fibroid kidney, renal glomerulosclerosis, kidney failure, organ hypertrophy, prostatic hypertrophy, complications of diabetes, blood vessel restenosis, atherosclerosis, cancer, cardiac hypertrophy, heart failure; ischemic diseases; inflammation; autoimmune diseases; AIDS, osteopathy such as osteoporosis, brain functional disorder, infection of digestive tracts with bacteria, sepsis, adult respiratory distress syndrome, retinopathy, glaucoma and Alzheimer's disease.

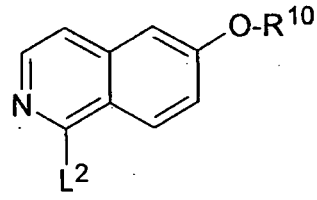
WO 01/64238 describes isoquinoline-5-sulfonamide derivatives optionally substituted by a $-(CH_2)_{1-6}-O-(CH_2)_{0-6}-$, a $-(CH_2)_{0-6}-S-(CH_2)_{0-6}-$ or a $-(CH_2)_{0-6}$-linked heterocyclic group useful as neuroprotective agents.

JP 10087629 A describes isoquinoline derivatives useful for the treatment of infections caused by Heliobacter pylori such as for example gastritis or ulcer. The isoquinoline derivatives are preferably 5-substituted by $X-[(C_1-C_6)alkylene)]_{0-1}-Y$ wherein X may be oxygen and Y may be an aryl or a heterocyclic group.

Hagihara et al. (Bioorg. Med. Chem. 1999, 7, 2647-2666) disclose 6-benzyloxy-isoquinoline for the treatment of infections caused by Heliobacter pylori.
US 5,480,883 generically discloses as EGF and/or PDGF receptor inhibitors useful for inhibiting cell proliferation compounds of the formula "Ar I – X – Ar II" wherein X may

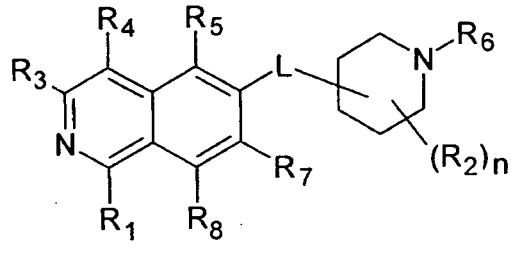
be $(CHR_1)_m$-Z-$(CHR_1)_n$, e.g. Z-CH_2, wherein Z may be O, R_1 is hydrogen or alkyl, Ar I may be among others an optionally substituted C_{5-12} bicyclic heteroaryl ring system and Ar II may be among others an optionally substituted C_{3-7} monocyclic saturated heterocyclic system.

WO 03/053330 describes isoquinoline derivatives of the formula



wherein L^2 is halogen and R^{10} may be C_{1-5}alkylene-C_{5-6}heterocyclic group as intermediates in the synthesis of GSK-3 inhibitors.

An embodiment of the present invention is a compound of the formula (I)



(I)

wherein

R_1 is

H,

$(C_1$-$C_6)$alkyl,

R',

NH-$(C_1$-$C_6)$alkyl,

NH-R', or

N[$(C_1$-$C_6)$alkyl]$_2$;

R_2 is hydrogen, halogen, or $(C_1\text{-}C_6)$alkyl;

R_3 is
H,
halogen,
$(C_1\text{-}C_6)$alkyl,
$(C_1\text{-}C_6)$alkylene-R',
OH,
O-R",
NH_2,
NHR",
NR"R" or
NH-C(O)-R",

R_4 is
H,
halogen,
hydroxy,
CN,
$(C_1\text{-}C_6)$alkyl,
R',
$(C_1\text{-}C_6)$alkylene-R';

R_5 is
H,
halogen,
CN,
NO_2,
$(C_1\text{-}C_6)$alkyl,
$(C_2\text{-}C_6)$alkenyl,
R',

$(C_1\text{-}C_6)$alkylene-$(C_6\text{-}C_{10})$aryl,

$(C_1\text{-}C_6)$alkenylene-$(C_6\text{-}C_{10})$aryl,

$(C_1\text{-}C_6)$alkylene-$(C_5\text{-}C_{10})$heterocyclyl,

CH(OH)-$(C_1\text{-}C_6)$alkyl,

NH_2,

NH-R',

$NH\text{-}SO_2H$,

$NH\text{-}SO_2\text{-}(C_1\text{-}C_6)$alkyl,

$NH\text{-}SO_2\text{-}R'$,

NH-C(O)-$(C_1\text{-}C_6)$alkyl,

NH-C(O)-R',

$C(O)N[(C_1\text{-}C_6)alkyl]_2$,

C(O)OH, or

C(O)O-$(C_1\text{-}C_6)$alkyl;

R_6 is

H,

R',

$(C_1\text{-}C_8)$alkyl,

$(C_1\text{-}C_6)$alkylene-R',

$(C_1\text{-}C_6)$alkylene-O-$(C_1\text{-}C_6)$alkyl,

$(C_1\text{-}C_6)$alkylene-O-R',

$(C_1\text{-}C_6)alkylene\text{-}CH[R']_2$,

$(C_1\text{-}C_6)$alkylene-C(O)-R',

$(C_1\text{-}C_6)alkylene\text{-}C(O)NH_2$,

$(C_1\text{-}C_6)$alkylene-C(O)NH-R', or

$(C_1\text{-}C_6)alkylene\text{-}C(O)N[R']_2$;

R_7 is

H,
halogen,
CN,
NO_2,
$(C_1\text{-}C_6)$alkyl,
$(C_2\text{-}C_6)$alkenyl,
R',
$(C_1\text{-}C_6)$alkenylene-$(C_6\text{-}C_{10})$aryl,
$(C_1\text{-}C_6)$alkylene-R',
CH(OH)-$(C_1\text{-}C_6)$alkyl,
CH(OH)-$(C_6\text{-}C_{10})$aryl,
CH(OH)-$(C_5\text{-}C_{10})$heterocyclyl,
NH_2,
NH-R',
NH-SO_2H,
NH-SO_2-$(C_1\text{-}C_6)$alkyl,
NH-SO_2-R',
SO_2-NH_2,
SO_2-NHR',
NH-C(O)-$(C_1\text{-}C_6)$alkyl,
NH-C(O)-R',
C(O)N[$(C_1\text{-}C_6)$alkyl]$_2$,
C(O)OH, or
C(O)O-$(C_1\text{-}C_6)$alkyl;

R_8 is H, halogen or $(C_1\text{-}C_6)$alkyl;

n is 1, 2, 3 or 4; and

L is O or O-$(C_1\text{-}C_6)$alkylene;

wherein

R' is

(C_3-C_8)cycloalkyl,

(C_5-C_{10})heterocyclyl,

(C_6-C_{10})aryl; and

R" is

(C_3-C_8)cycloalkyl,

(C_5-C_{10})heterocyclyl,

(C_6-C_{10})aryl,

(C_1-C_6)alkyl,

(C_1-C_6)alkylene-R',

(C_1-C_6)alkylene-O-(C_1-C_6)alkyl,

(C_1-C_6)alkylene-O-R', or

(C_1-C_6)alkylene-NR_xR_y; and

wherein R_x and R_y are independently of each other

(C_1-C_6)alkyl,

(C_5-C_{10})heterocyclyl,

(C_6-C_{10})aryl,

(C_1-C_4)alkylene-(C_5-C_{10})heterocyclyl,

(C_1-C_4)alkylene-(C_6-C_{10})aryl,

(C_1-C_4)alkylene-NH(C_1-C_6)alkyl,

(C_1-C_4)alkylene-N$[(C_1-C_6)\text{alkyl}]_2$,

(C_1-C_4)alkylene-N$[(C_6-C_{10})\text{aryl}]_2$, or

(C_1-C_4)alkylene-N$[(C_5-C_{10})\text{heterocyclyl}]_2$;

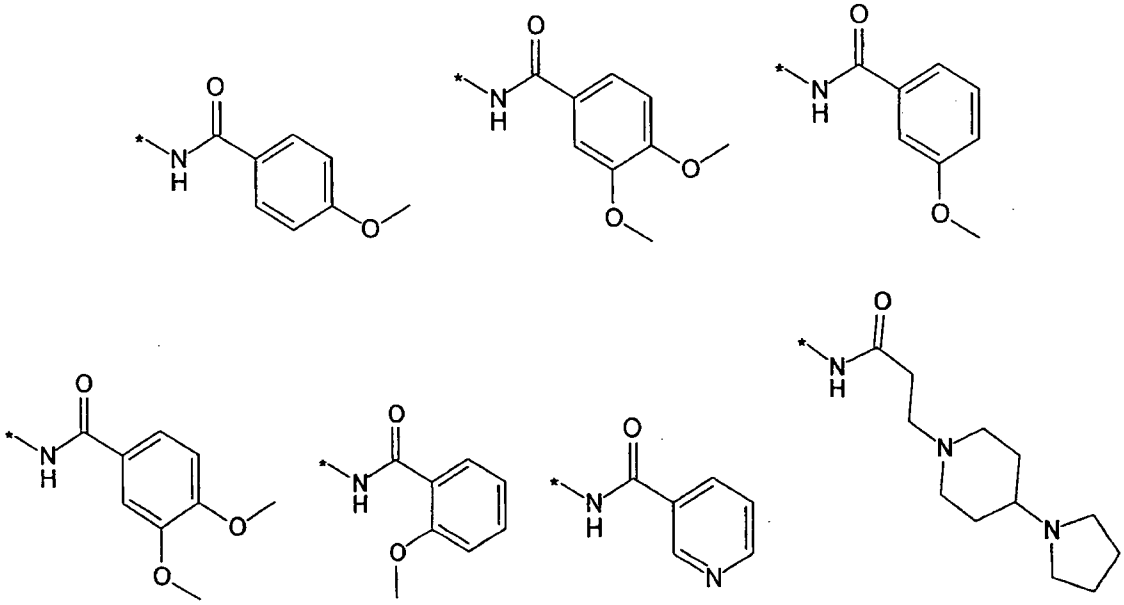
wherein in residues R_4, R_5, R_7 and R_8 one alkyl or alkylene hydrogen atom can optionally be substituted by OH, F, OCH_3, COOH, $COOCH_3$, NH_2, $NHCH_3$, $N(CH_3)_2$, $CONH_2$, $CONHCH_3$ or $CON(CH_3)_2$;

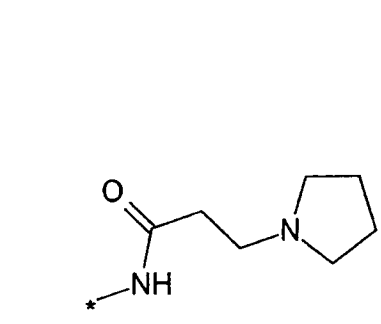
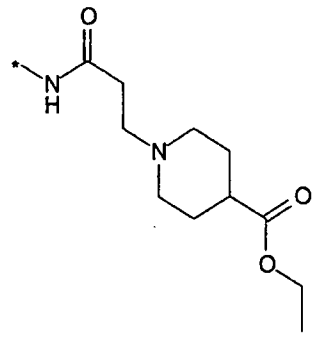
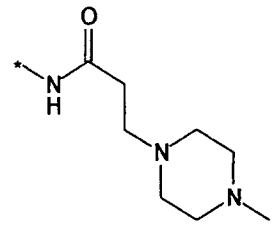
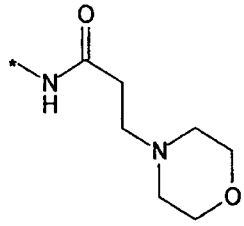
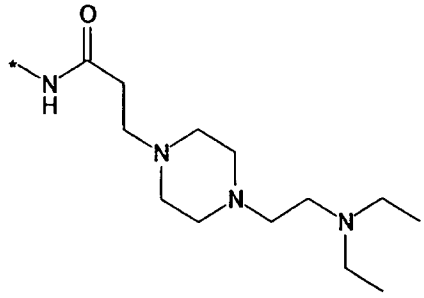
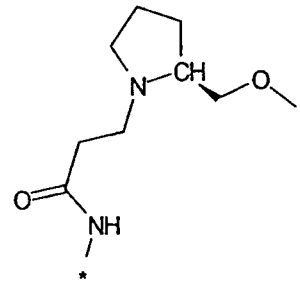
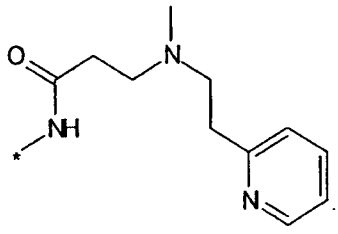
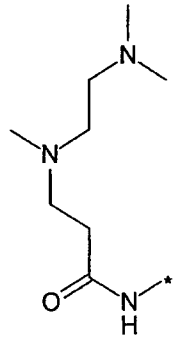
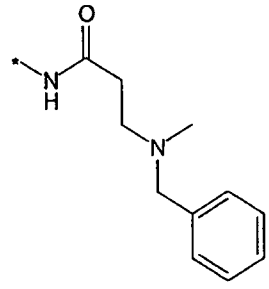
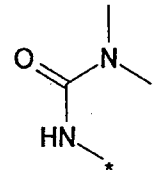
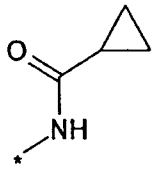
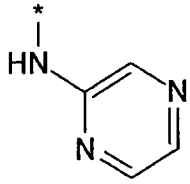
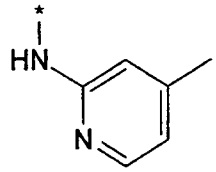
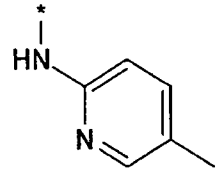
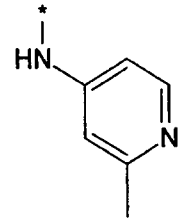
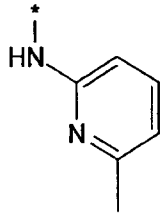
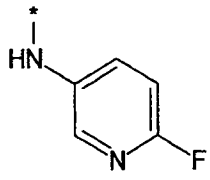
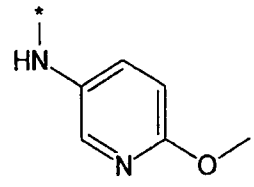
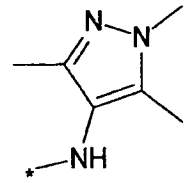
and their pharmaceutically acceptable salts and/or physiologically functional derivatives.

Preferably, R_1 is H, $(C_1\text{-}C_6)$alkyl, $(C_6\text{-}C_{10})$aryl, NH-$(C_1\text{-}C_6)$alkyl, NH-$(C_6\text{-}C_{10})$aryl or N[$(C_1\text{-}C_6)$alkyl]$_2$. More preferably, R_1 is H, halogen, $(C_1\text{-}C_4)$alkyl, NH-$(C_1\text{-}C_4)$alkyl, N[$(C_1\text{-}C_4)$alkyl]$_2$ or NH-phenyl. Most preferably, R_1 is H, $(C_1\text{-}C_2)$alkyl or NH-$(C_1\text{-}C_2)$alkyl, especially preferred H.

Preferably, R_2 is H, halogen or $(C_1\text{-}C_4)$alkyl. Preferably, R_2 is H or $(C_1\text{-}C_4)$alkyl. More preferred, R_2 is H, $(C_1\text{-}C_2)$alkyl. R_2 may be bound to any carbon atom of the piperidine ring including the position where the linker group L is bound.

R_3 is preferably H, halogen, $(C_1\text{-}C_4)$alkylene-R', O-R" or NHR". More preferred, R_3 is H or NHR". Most preferred, R_3 is H, NH-$(C_5\text{-}C_6)$heterocyclyl or NH-phenyl, especially preferred are H, NH-$(C_5\text{-}C_6)$heteroaryl containing one or more N atoms or NH-phenyl. Most especially preferred, R_3 is H. Examples of R_3 substituents are



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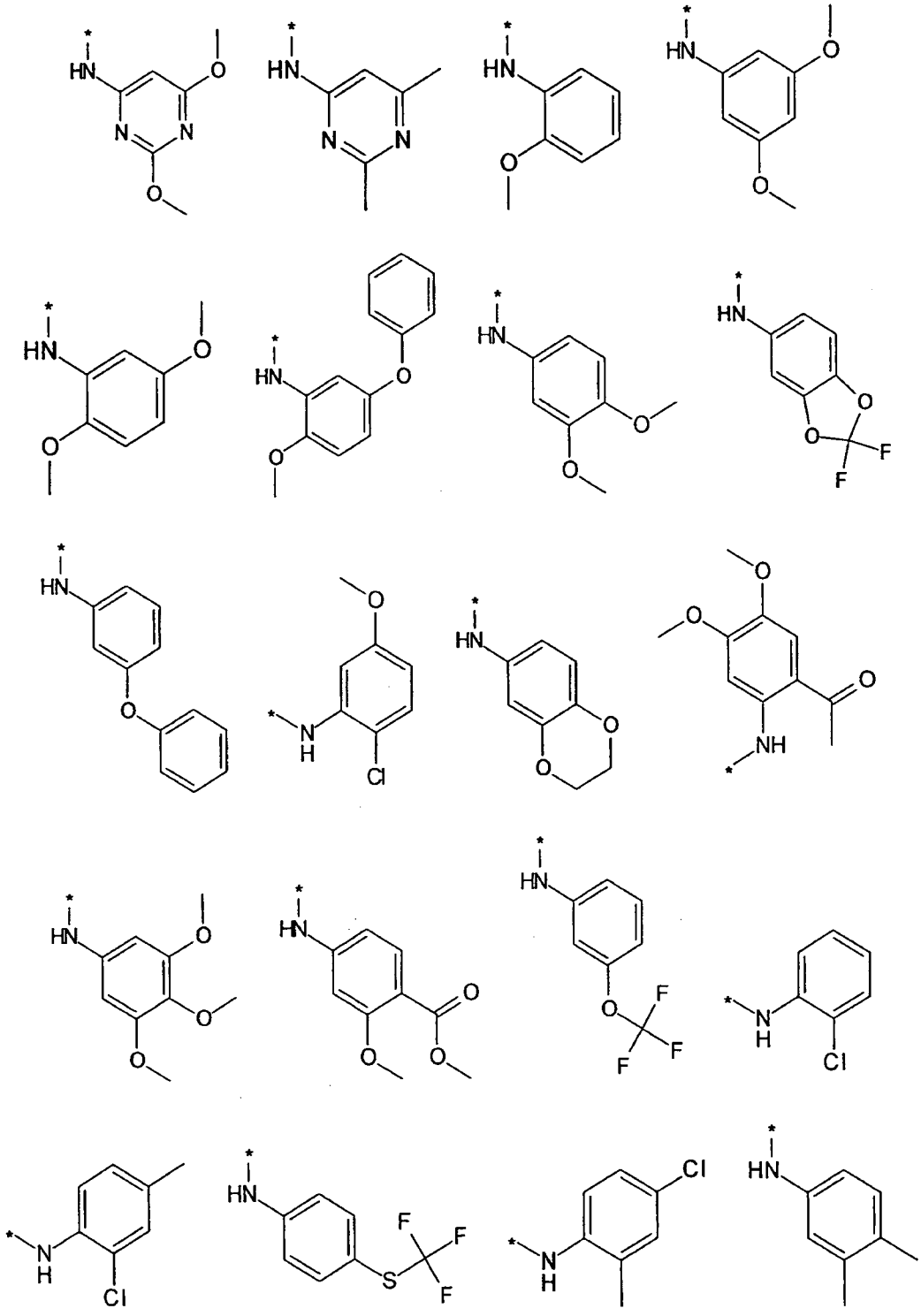

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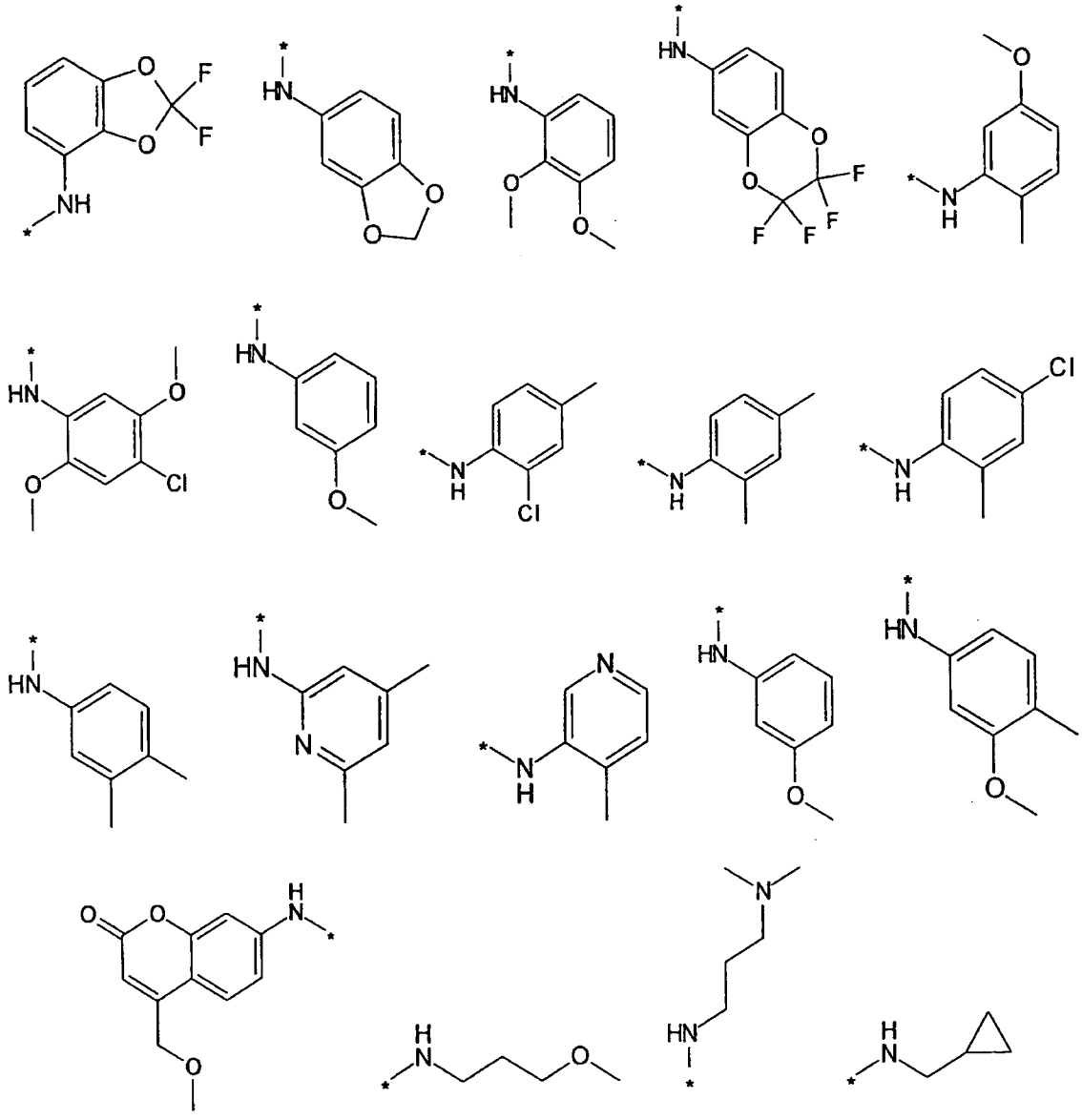
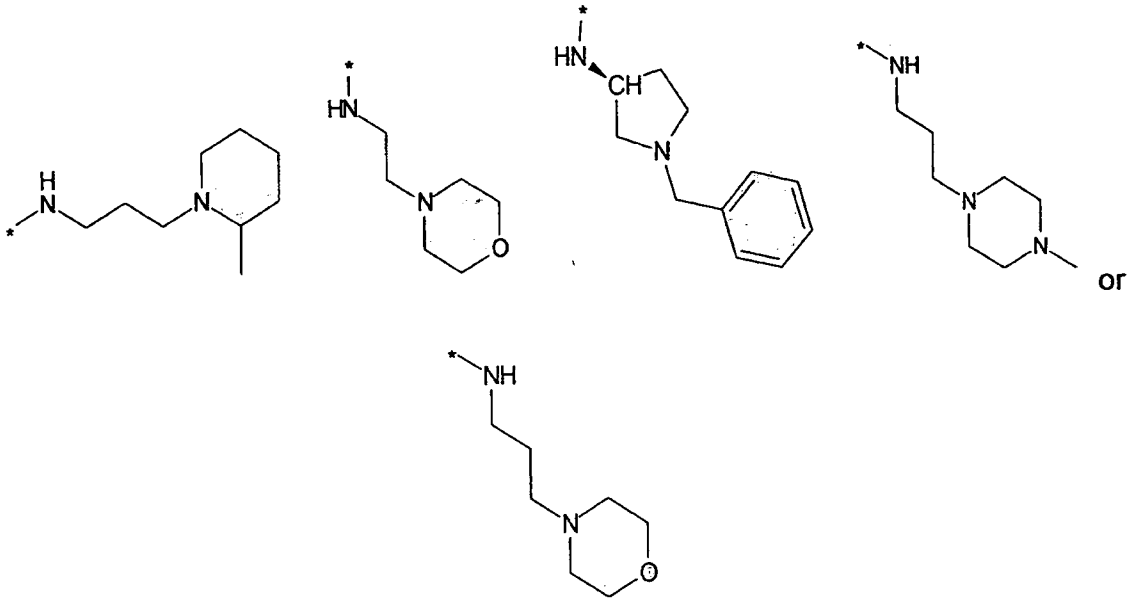
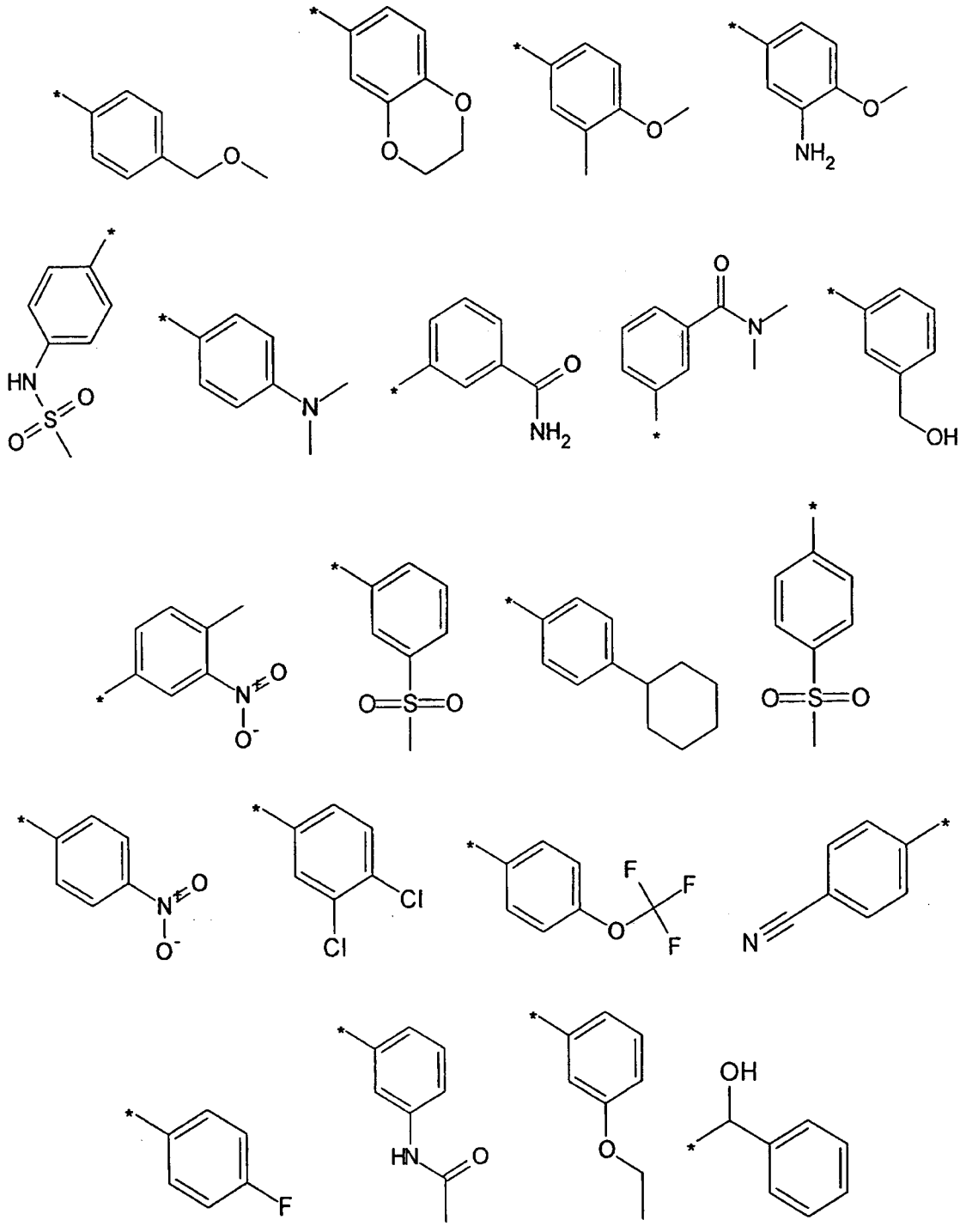




Preferably, R_4 is H, halogen or $(C_1$-$C_6)$alkyl. More preferred, R_4 is H, halogen or $(C_1$-$C_4)$alkyl. Most preferred, R_4 is H.

Preferably, R_5 is H, halogen, CN, $(C_1$-$C_6)$alkyl, R', NH-$(C_6$-$C_{10})$aryl or $(C_1$-$C_6)$alkylene-R'. More preferably, R_5 is H, halogen, $(C_1$-$C_6)$alkyl, R', NH-$(C_6$-$C_{10})$aryl or $(C_1$-$C_6)$alkylene-R'. Most preferably, R_5 is H, halogen, $(C_6$-$C_{10})$aryl, NH-$(C_6$-$C_{10})$aryl, $(C_1$-$C_2)$alkyl-$(C_6$-$C_{10})$aryl, $(C_1$-$C_6)$alkyl or $(C_5$-$C_{10})$heteroaryl. Especially preferred, R_5 is H, halogen, phenyl, $(C_1$-$C_6)$alkyl or $(C_5$-$C_6)$heteroaryl. Examples of R_5 are hydrogen, fluoro, chloro, bromo, iodo, nitrile, nitro, (p-methoxy)-phenyl, N-aniline, phenyl, benzyl, methyl, ethyl, vinyl, 2-propenyl, s-butenyl, cyclopropyl, thienyl, tetrazol, amino, 4-methoxy-anilin, N-acetyl or a substituent of the group consisting of



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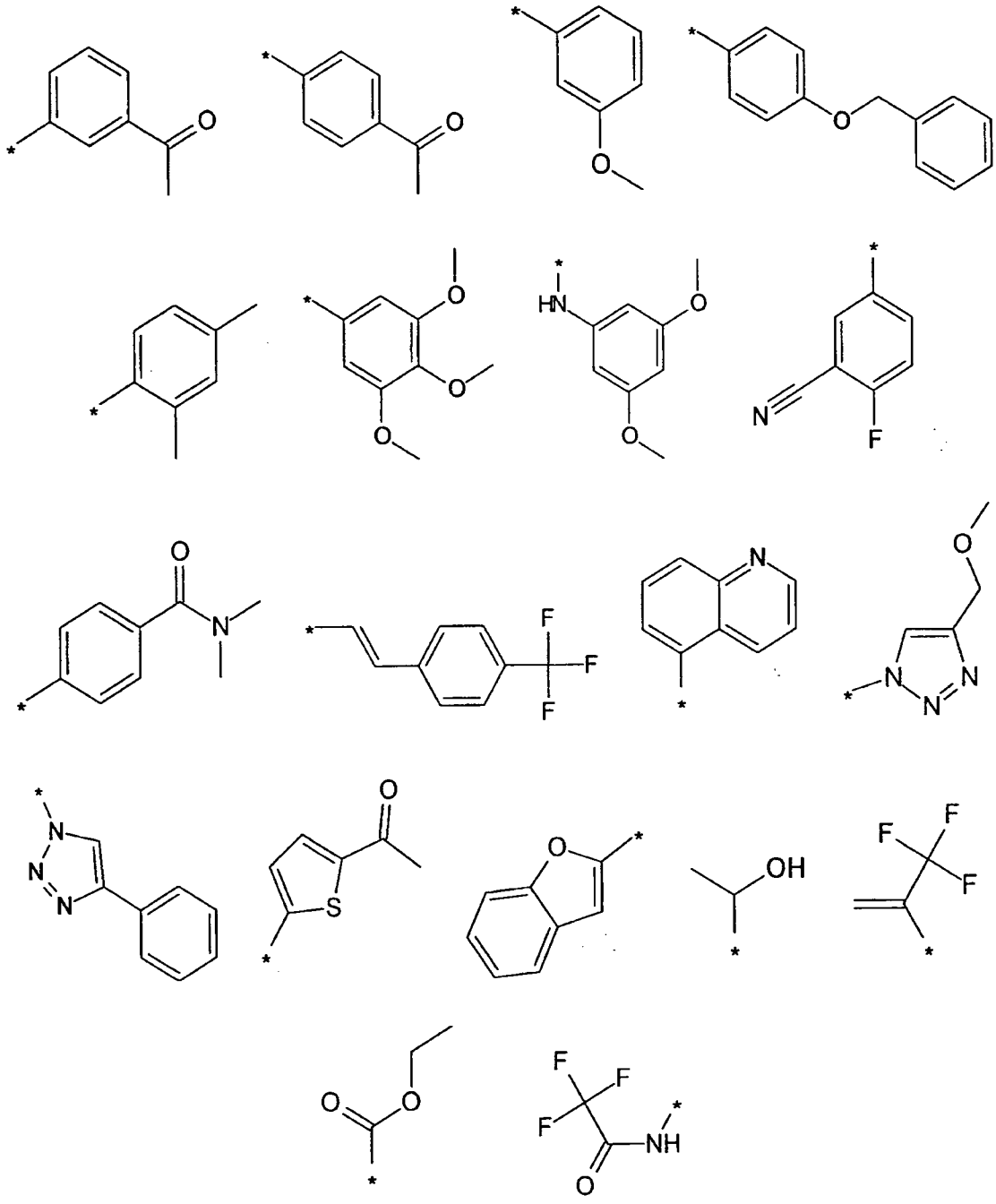
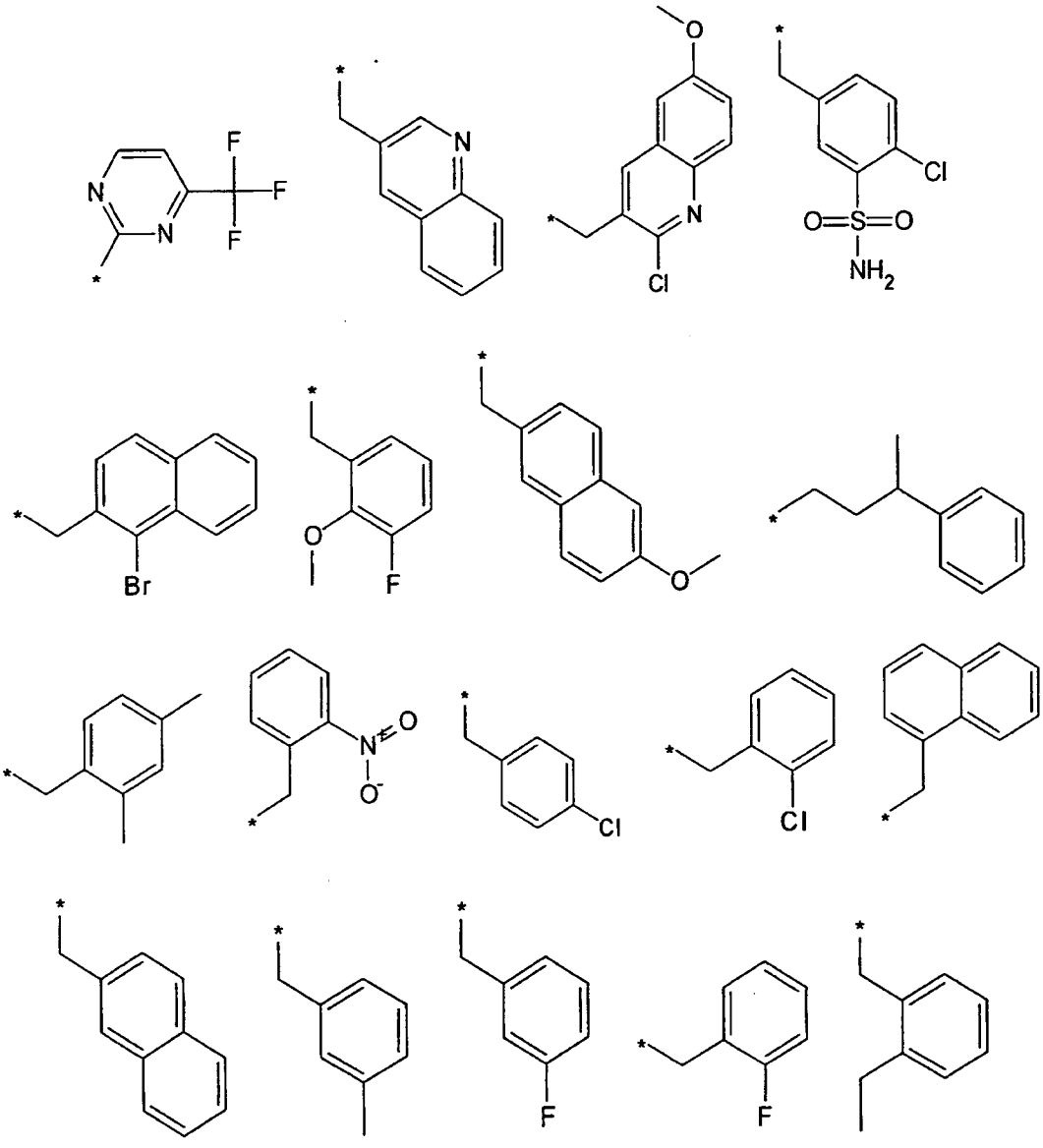
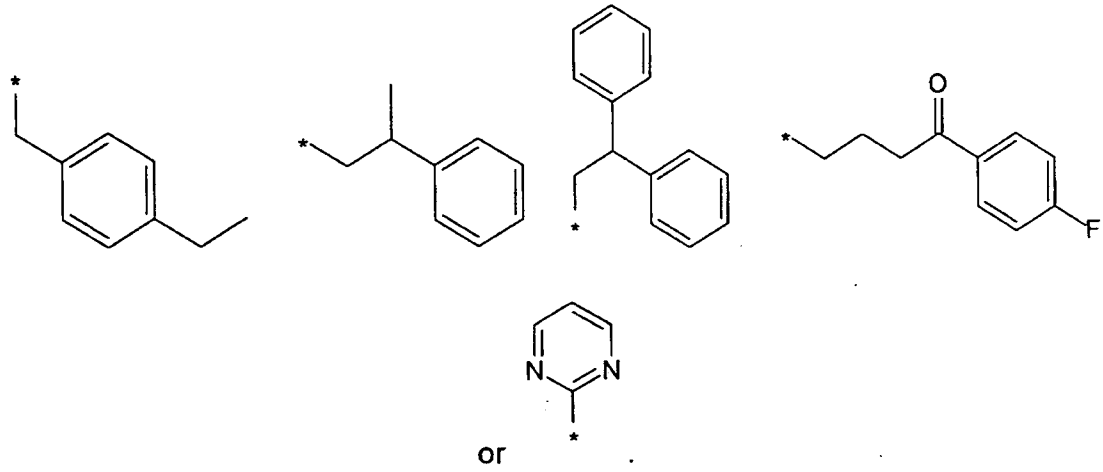


or

Preferably, R_6 is H, $(C_1\text{-}C_6)$alkyl, R', $(C_1\text{-}C_4)$alkylene-$(C_3\text{-}C_8)$cycloalkyl, $(C_1\text{-}C_4)$alkylene-$(C_5\text{-}C_{10})$heterocyclyl, $(C_1\text{-}C_4)$alkylene-C(O)-$(C_5\text{-}C_{10})$heterocyclyl, $(C_1\text{-}C_4)$alkylene-C(O)-$(C_6\text{-}C_{10})$aryl or $(C_1\text{-}C_6)$alkylene-$(C_6\text{-}C_{10})$aryl. More preferred, R_6 is H, $(C_1\text{-}C_6)$alkyl, $(C_5\text{-}C_{10})$heterocyclyl, $(C_1\text{-}C_4)$alkylene-$(C_5\text{-}C_{10})$heterocyclyl or

$(C_1\text{-}C_6)$alkylene-$(C_6\text{-}C_{10})$aryl. Examples of R_6 are H, methyl, ethyl, propyl, butyl, s-butyl, pentyl, 3-methyl-butyl, isopropyl, trifluoromethyl, 3,3,3-trifluorobutyl, cyclopropyl, methylene cyclopropyl, 2-pyrimidinyl, benzyl or a substituent of the group consisting of





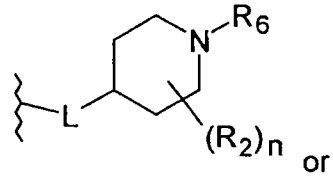
or

Preferably, R_7 is H, halogen, CN, $(C_1\text{-}C_6)$alkyl, $(C_2\text{-}C_6)$alkenyl, R' or $(C_1\text{-}C_6)$alkylene-$(C_3\text{-}C_8)$cycloalkyl. More preferred, R_7 is H, halogen, CN, $(C_1\text{-}C_4)$alkyl, $(C_1\text{-}C_4)$alkenyl, phenyl, cyclopropyl or $(C_5\text{-}C_6)$heteroaryl. Most preferably, R_7 is H, fluoro, chloro, bromo, methyl, ethyl, phenyl, nitrile, cyclopropyl, thienyl or vinyl.

R_8 is preferably H, halogen or $(C_1\text{-}C_4)$alkyl. More preferred, R_8 is H, Cl, F, methyl or ethyl.

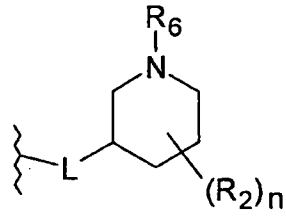
Preferably, n is 1, 2 or 3. More preferred, n is 1.

The linker group L may be bound to the piperidine ring in any position via a piperidine ring carbon atom. In a preferred embodiment, L is attached to the 4-position of the piperidine ring



or

L is attached to the 3-position of the piperidine ring

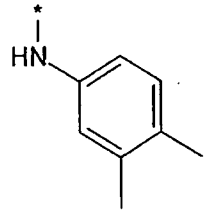


In an especially preferred embodiment, L is attached to the 4-position of the piperidine ring.

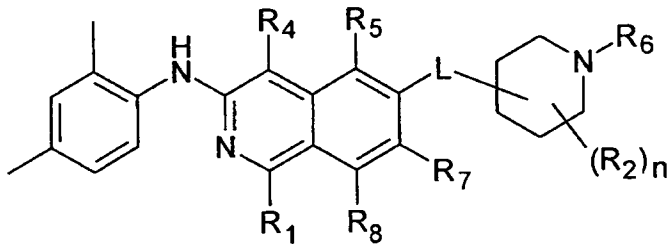
In a further preferred embodiment, L is O-methylene, O-ethylene or preferably O. More preferably, L is O-methylene, O-ethylene or O attached to the 4-position of the piperidine ring.

In preferred embodiments of the present invention one or more or all of the groups contained in the compounds of formula (I) can independently of each other have any of the preferred, more preferred or most preferred definitions of the groups specified above or any one or some of the specific denotations which are comprised by the definitions of the groups and specified above, all combinations of preferred definitions, more preferred or most preferred and/or specific denotations being a subject of the present invention. Also with respect to all preferred embodiments the invention includes the compounds of the formula (I) in all stereoisomeric forms and mixtures of stereoisomeric forms in all ratios, and their physiologically acceptable salts.

The term "*–" in the exemplified substituents *vide supra* marks the point where the substituent is attached, which means, for example, for a R_3 substituent



a compound of the formula



A preferred embodiment is a compound of the formula (I) wherein

R_1 is H, $(C_1\text{-}C_6)$alkyl, $(C_6\text{-}C_{10})$aryl, NH-$(C_1\text{-}C_6)$alkyl, NH-$(C_6\text{-}C_{10})$aryl, or N[$(C_1\text{-}C_6)$alkyl]$_2$;

R_2 is hydrogen, halogen, or $(C_1\text{-}C_6)$alkyl;

R_3 is H, halogen, $(C_1\text{-}C_4)$alkylene-R', O-R" or NHR", wherein R' and R" are defined as above;

R_4 is H, halogen or $(C_1\text{-}C_6)$alkyl;

R_5 is H, halogen, $(C_1\text{-}C_6)$alkyl, CN, $(C_6\text{-}C_{10})$aryl, NH-$(C_6\text{-}C_{10})$aryl, $(C_1\text{-}C_6)$alkylene-$(C_6\text{-}C_{10})$aryl, $(C_5\text{-}C_{10})$heterocyclyl or $(C_1\text{-}C_6)$alkylene-$(C_5\text{-}C_{10})$heterocyclyl;

R_6 is H, R', $(C_1\text{-}C_4)$alkylene-$(C_5\text{-}C_{10})$heterocyclyl, $(C_1\text{-}C_6)$alkylene-C(O)-$(C_6\text{-}C_{10})$aryl, $(C_1\text{-}C_4)$alkylene-C(O)-$(C_5\text{-}C_{10})$heterocyclyl, $(C_1\text{-}C_6)$alkylene-$(C_6\text{-}C_{10})$aryl or $(C_1\text{-}C_6)$alkyl.

R_7 is H, halogen, CN, $(C_1\text{-}C_6)$alkyl, $(C_2\text{-}C_6)$alkenyl or R';

R_8 is H, halogen or $(C_1\text{-}C_6)$alkyl;

n is 1, 2 or 3, and
L is O, O-methylene or O-ethylene;

and their pharmaceutically acceptable salts and/or physiologically functional derivatives.

A further preferred embodiment is a compound of the formula (I) wherein

R_1 is H, $(C_1\text{-}C_6)$alkyl, $(C_6\text{-}C_{10})$aryl, NH-$(C_1\text{-}C_6)$alkyl, NH-$(C_6\text{-}C_{10})$aryl, or $N[(C_1\text{-}C_6)alkyl]_2$;

R_2 is H or $(C_1\text{-}C_4)$alkyl;

R_3 is H, halogen or NHR", wherein R" is defined as above;

R_4 is H, halogen or $(C_1\text{-}C_4)$alkyl;

R_5 is H, halogen, $(C_1\text{-}C_6)$alkyl, $(C_6\text{-}C_{10})$aryl, NH-$(C_6\text{-}C_{10})$aryl, $(C_1\text{-}C_6)$alkylene-$(C_6\text{-}C_{10})$aryl or $(C_5\text{-}C_{10})$heterocyclyl;

R_6 is H, $(C_1\text{-}C_6)$alkyl, R', $(C_1\text{-}C_4)$alkylene-$(C_5\text{-}C_{10})$heterocyclyl or $(C_1\text{-}C_6)$alkylene-$(C_6\text{-}C_{10})$aryl;

R_7 is H, halogen, CN, $(C_1\text{-}C_6)$alkyl, $(C_2\text{-}C_6)$alkenyl or R';

R_8 is H, halogen or $(C_1\text{-}C_6)$alkyl;

n is 1, 2 or 3; and

L is O;

and their pharmaceutically acceptable salts and/or physiologically functional derivatives.

An especially preferred embodiment is a compound of the formula (I) wherein

R_1 is H, $(C_1\text{-}C_4)$alkyl, NH-$(C_1\text{-}C_4)$alkyl, N[$(C_1\text{-}C_4)$alkyl]$_2$ or NH-phenyl;

R_2 is H, $(C_1\text{-}C_4)$alkyl;

R_3 is H, NH-$(C_5\text{-}C_6)$heteroaryl or NH-phenyl;

R_4 is H, halogen or $(C_1\text{-}C_4)$alkyl;

R_5 is H, halogen, $(C_1\text{-}C_4)$alkyl, $(C_6\text{-}C_{10})$aryl, NH-$(C_6\text{-}C_{10})$aryl, $(C_1\text{-}C_2)$alkyl-$(C_6\text{-}C_{10})$aryl or $(C_5\text{-}C_{10})$heteroaryl;

R_6 is H, $(C_1\text{-}C_6)$alkyl, $(C_5\text{-}C_{10})$heterocyclyl, $(C_1\text{-}C_4)$alkylene-$(C_5\text{-}C_{10})$heterocyclyl, $(C_6\text{-}C_{10})$aryl or $(C_1\text{-}C_6)$alkylene-$(C_6\text{-}C_{10})$aryl;

R_7 is H, halogen, CN, $(C_1\text{-}C_4)$alkyl, $(C_1\text{-}C_4)$alkenyl, phenyl, cyclopropyl, $(C_5\text{-}C_6)$heteroaryl;

R_8 is H, halogen or $(C_1\text{-}C_4)$alkyl;

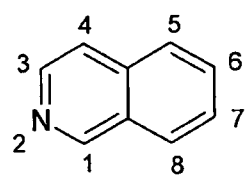
n is 1; and

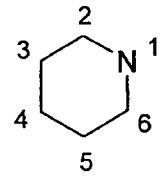
L is O;

and their physiologically acceptable salts and/or physiologically functional derivatives.

As in any embodiment of the invention, in the preceding embodiments which contain preferred, more preferred, most preferred or exemplary definitions of compounds according to the invention, one or more or all of the groups can have any of its preferred, more preferred, most preferred definitions specified above or any one or some of the specific denotations which are comprised by its definitions and are specified above.

Isoquinoline and piperidyl substitution pattern are numbered text according to IUPAC rules:





Physiologically acceptable salts of compounds of the formula (I) mean both their organic and inorganic salts as described in Remington's Pharmaceutical Sciences (17th edition, page 1418 (1985)). Because of the physical and chemical stability and the solubility, preference is given for acidic groups inter alia to sodium, potassium, calcium and ammonium salts; preference is given for basic groups inter alia to salts of maleic acid, fumaric acid, succinic acid, malic acid, tartaric acid, methylsulfonic acid, hydrochloric acid, sulfuric acid, phosphoric acid or of carboxylic acids or sulfonic acids, for example as hydrochlorides, hydrobromides, phosphates, sulfates, methanesulfonates, acetates, lactates, maleates, fumarates, malates, gluconates, and salts of amino acids, of natural bases or carboxylic acids. The preparation of physiologically acceptable salts from compounds of the formula (I) and (II) which are capable of salt formation, including their stereoisomeric forms, takes place in a manner known per se. The compounds of the formula (I) form stable alkali metal, alkaline earth metal or optionally substituted ammonium salts with basic reagents such as hydroxides, carbonates, bicarbonates, alcoholates and ammonia or organic bases, for example trimethyl- or triethylamine, ethanolamine, diethanolamine or triethanolamine, trometamol or else basic amino acids, for example lysine, ornithine or arginine. Where the compounds of the formula (I) have basic groups, stable acid addition salts can also

be prepared with strong acids. Suitable pharmaceutically acceptable acid addition salts of the compounds of the invention are salts of inorganic acids such as hydrochloric acid, hydrobromic, phosphoric, metaphosphoric, nitric and sulfuric acid, and of organic acids such as, for example, acetic acid, benzenesulfonic, benzoic, citric, ethanesulfonic, fumaric, gluconic, glycolic, isethionic, lactic, lactobionic, maleic, malic, methanesulfonic, succinic, p-toluenesulfonic and tartaric acid.

Salts with a physiologically unacceptable anion such as, for example, trifluoroacetate likewise belong within the framework of the invention as useful intermediates for the preparation or purification of pharmaceutically acceptable salts and/or for use in nontherapeutic, for example in vitro, applications.

The term "physiologically functional derivative" used herein refers to any physiologically tolerated derivative of a compound of the formula (I) of the invention, for example an N-oxide, which on administration to a mammal such as, for example, a human is able to form (directly or indirectly) a compound of the formula (I) or an active metabolite thereof.

Physiologically functional derivatives include prodrugs of the compounds of the invention, as described, for example, in H. Okada et al., Chem. Pharm. Bull. 1994, 42, 57-61. Such prodrugs can be metabolized in vivo to a compound of the invention. These prodrugs may themselves be active or not.

The invention relates to compounds of the formula (I) in the form of their racemates, racemic mixtures and pure enantiomers and to their diastereomers and mixtures thereof.

If radicals or substituents may occur more than once in the compounds of the formula (I), they may all, independently of one another, have the stated meaning and be identical or different.

The compounds of the invention may also exist in various polymorphous forms, for example as amorphous and crystalline polymorphous forms. All polymorphous forms of the compounds of the invention belong within the framework of the invention and are a further aspect of the invention.

All references to "compound(s) of formula (I)" hereinafter refer to compound(s) of the formula (I) as described above, and their physiologically acceptable salts, solvates and physiologically functional derivatives as described herein.

The terms $(C_1\text{-}C_2)$alkyl, $(C_1\text{-}C_4)$alkyl, $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_8)$alkyl and the corresposponding alkylene substituents are understood as a hydrocarbon residue which can be linear, i.e. straight-chain, or branched and has 1, 2, 3, 4, 5, 6, 7 or 8 carbon atoms, respectively. This also applies if an alkyl group occurs as a substituent on another group, for example in an alkoxy group (O-alkyl), S-alkyl or a -O$(C_1\text{-}C_6)$alkylene-O-, an alkoxycarbonyl group or an arylalkyl group. Examples of alkyl groups are methyl, ethyl, propyl, butyl, pentyl or hexyl, the n-isomers of all these groups, isopropyl, isobutyl, 1-methylbutyl, isopentyl, neopentyl, 2,2-dimethylbutyl, 2-methylpentyl, 3-methylpentyl, isohexyl, sec-butyl, tert-butyl or tert-pentyl. Alkyl groups may – if not otherwise stated – be halogenated once or more, i.e. alkyl groups may be fluorinated, i.e. perfluorinated. Examples of halogenated alkyl groups are CF_3 and CH_2CF_3, OCF_3, SCF_3, or -O-$(CF_2)_2$-O-.

Alkenyl are, for example, vinyl, 1-propenyl, 2-propenyl (= allyl), 2-butenyl, 3-butenyl, 2-methyl-2-butenyl, 3-methyl-2-butenyl, 5-hexenyl or 1,3-pentadienyl.

Alkynyl are, for example, ethynyl, 1-propynyl, 2-propynyl (= propargyl) or 2-butynyl.

Halogen means fluoro, chloro, bromo or iodo.

$(C_3\text{-}C_8)$cycloalkyl groups are cyclic alkyl groups containing 3, 4, 5, 6, 7 or 8 ring carbon atoms like cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl or cyclooctyl, which

can also be substituted and/or contain 1 or 2 double bounds (unsaturated cycloalkyl groups) like, for example, cyclopentenyl or cyclohexenyl can be bonded via any carbon atom.

A (C_6-C_{10})aryl group means an aromatic ring or a ring system which comprises two aromatic rings which are fused or otherwise linked, for example a phenyl, naphthyl, biphenyl, tetrahydronaphthyl, alpha- or beta-tetralon-, indanyl- or indan-1-on-yl group. A preferred (C_6-C_{10})aryl group is phenyl.

A (C_5-C_{10})heterocyclyl group means a mono- or bicyclic ring system which comprises, apart from carbon, one or more heteroatoms such as, for example, e.g. 1, 2 or 3 nitrogen atoms, 1 or 2 oxygen atoms, 1 or 2 sulfur atoms or combinations of different hetero atoms. The heterocyclyl residues can be bound at any positions, for example on the 1-position, 2-position, 3-position, 4-position, 5-position, 6-position, 7-position or 8-position. (C_5-C_{10})heterocyclyl groups may be (1) aromatic [= heteroaryl groups] or (2) saturated or (3) mixed aromatic/saturated.

Suitable (C_5-C_{10})heterocyclyl group include acridinyl, azocinyl, benzimidazolyl, benzofuryl, benzomorpholinyl, benzothienyl, benzothiophenyl, benzoxazolyl, benzthiazolyl, benztriazolyl, benztetrazolyl, benzisoxazolyl, benzisothiazolyl, carbazolyl, 4aH-carbazolyl, carbolinyl, furanyl, quinazolinyl, quinolinyl, 4H-quinolizinyl, quinoxalinyl, quinuclidinyl, chromanyl, chromenyl, chromen-2-onyl, cinnolinyl, decahydroquinolinyl, 2H,6H-1,5,2-dithiazinyl, dihydrofuro[2,3-b]-tetrahydrofuran, furyl, furazanyl, homomorpholinyl, homopiperazinyl, imidazolidinyl, imidazolinyl, imidazolyl, 1H-indazolyl, indolinyl, indolizinyl, indolyl, 3H-indolyl, isobenzofuranyl, isochromanyl, isoindazolyl, isoindolinyl, isoindolyl, isoquinolinyl (benzimidazolyl), isothiazolyl, isoxazolyl, morpholinyl, naphthyridinyl, octahydroisoquinolinyl, oxadiazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl, oxazolidinyl, oxazolyl, oxazolidinyl, pyrimidinyl, phenanthridinyl, phenanthrolinyl, phenazinyl, phenothiazinyl, phenoxathiinyl, phenoxazinyl, phthalazinyl, piperazinyl, piperidinyl, prolinyl, pteridinyl, purynyl, pyranyl, pyrazinyl, pyroazolidinyl, pyrazolinyl, pyrazolyl, pyridazinyl, pyridonyl, pyridooxazoles, pyridoimidazoles, pyridothiazoles, pyridinyl,

pyridyl, pyrimidinyl, pyrrolidinyl, pyrrolinyl, 2H-pyrrolyl, pyrrolyl, tetrahydrofuranyl, tetrahydroisoquinolinyl, tetrahydroquinolinyl, 6H-1,2,5-thiadazinyl, thiazolyl, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,2,5-thiadiazolyl, 1,3,4-thiadiazolyl, thienyl, triazolyl, tetrazolyl and xanthenyl. Pyridyl stands both for 2-, 3- and 4-pyridyl. Thienyl stands both for 2- and 3-thienyl. Furyl stands both for 2- and 3-furyl. Also included are the corresponding N-oxides of these compounds, for example, 1-oxy-2-, 3- or 4-pyridyl.

Substitutions in (C_5-C_{10})heterocyclyl residues can occur on free carbon atoms or on nitrogen atoms.

Preferred examples of (C_5-C_{10})heterocyclyl residues are pyrazinyl, pyridyl, pyrimidinyl, pyrazolyl, morpholinyl, pyrrolidinyl, piperazinyl, piperidinyl, thienyl, benzofuryl, quinolinyl, tetrazolyl and triazolyl.

(C_6-C_{10})aryl and (C_5-C_{10})heterocyclyl groups are unsubstituted or substituted one or more times by suitable groups independently selected from halogen, CF_3, NO_2, N_3, CN, C(O)-(C_1-C_6)alkyl, C(O)-(C_1-C_6)aryl, COOH, COO(C_1-C_6)alkyl, $CONH_2$, CONH(C_1-C_6)alkyl, CON[(C_1-C_6)alkyl]$_2$, (C_3-C_8)cycloalkyl, (C_1-C_6)alkyl, (C_1-C_6)alkylene-OH, (C_1-C_6)alkylene-NH_2, (C_1-C_6)alkylene-NH(C_1-C_6)alkyl, (C_1-C_6)alkylene-N[(C_1-C_6)alkyl]$_2$, (C_2-C_6)alkenyl, (C_2-C_6)alkynyl, O-(C_1-C_6)alkyl, O-C(O)-(C_1-C_6)alkyl, O-C(O)-(C_6-C_{10})aryl, O-C(O)-(C_5-C_{10})heterocyclyl, PO_3H_2, SO_3H, SO_2-NH_2, SO_2NH(C_1-C_6)alkyl, SO_2N[(C_1-C_6)alkyl]$_2$, S-(C_1-C_6)alkyl; S-(C_1-C_6)alkylene-(C_6-C_{10})aryl, S-(C_1-C_6)alkylene-(C_5-C_{10})heterocyclyl, SO-(C_1-C_6)alkyl, SO-(C_1-C_6)alkylene-(C_6-C_{10})aryl, SO-(C_1-C_6)alkylene-(C_5-C_{10})heterocyclyl, SO_2-(C_1-C_6)alkyl, SO_2-(C_1-C_6)alkylene-(C_6-C_{10})aryl, SO_2-(C_1-C_6)alkylene-(C_5-C_{10})heterocyclyl, SO_2-NH(C_1-C_6)alkylene-(C_6-C_{10})aryl, SO_2-NH(C_1-C_6)alkylene-(C_5-C_{10})heterocyclyl, SO_2-N[(C_1-C_6)alkyl][(C_1-C_6)alkylene-(C_6-C_{10})aryl], SO_2-N[(C_1-C_6)alkyl][(C_1-C_6)alkylene-(C_5-C_{10})heterocyclyl], SO_2-N[(C_1-C_6)alkylene-(C_6-C_{10})aryl]$_2$, SO_2-N[(C_1-C_6)alkylene-(C_5-C_{10})heterocyclyl]$_2$,

$C(NH)(NH_2)$, NH_2, NH-$(C_1$-$C_6)$alkyl, N[$(C_1$-$C_6)$alkyl]$_2$, NH-C(O)-$(C_1$-$C_6)$alkyl, NH-C(O)O-$(C_1$-$C_6)$alkyl, NH-C(O)-$(C_6$-$C_{10})$aryl, NH-C(O)-$(C_5$-$C_{10})$heterocyclyl, NH-C(O)O-$(C_6$-$C_{10})$aryl, NH-C(O)O-$(C_5$-$C_{10})$heterocyclyl, NH-C(O)-NH-$(C_1$-$C_6)$alkyl, NH-C(O)-NH-$(C_6$-$C_{10})$aryl, NH-C(O)-NH-$(C_5$-$C_{10})$heterocyclyl, NH-SO_2-$(C_1$-$C_6)$alkyl, NH-SO_2-$(C_6$-$C_{10})$aryl, NH-SO_2-$(C_5$-$C_{10})$heterocyclyl, N$(C_1$-$C_6)$alkyl-C(O)-$(C_1$-$C_6)$alkyl, N$(C_1$-$C_6)$alkyl-C(O)O-$(C_1$-$C_6)$alkyl, N$(C_1$-$C_6)$alkyl-C(O)-$(C_6$-$C_{10})$aryl, N$(C_1$-$C_6)$alkyl-C(O)-heterocyclyl, N$(C_1$-$C_6)$alkyl-C(O)O-$(C_6$-$C_{10})$aryl, N$(C_1$-$C_6)$alkyl-C(O)O-$(C_5$-$C_{10})$heterocyclyl, N$(C_1$-$C_6)$alkyl-C(O)-NH-$(C_1$-$C_6)$alkyl], N$(C_1$-$C_6)$alkyl-C(O)-NH-$(C_6$-$C_{10})$aryl, N$(C_1$-$C_6)$alkyl-C(O)-NH-$(C_5$-$C_{10})$heterocyclyl, N[$(C_1$-$C_6)$alkyl]-C(O)-N[$(C_1$-$C_6)$alkyl]$_2$, N[$(C_1$-$C_6)$alkyl]-C(O)-N[$(C_1$-$C_6)$alkyl]-$(C_6$-$C_{10})$aryl, N[$(C_1$-$C_6)$alkyl]-C(O)-N[$(C_1$-$C_6)$alkyl]-$(C_5$-$C_{10})$heterocyclyl, N[$(C_1$-$C_6)$alkyl]-C(O)-N[$(C_6$-$C_{10})$aryl]$_2$, N[$(C_1$-$C_6)$alkyl]-C(O)-N[$(C_5$-$C_{10})$heterocyclyl]$_2$, N[$(C_6$-$C_{10})$aryl]-C(O)-$(C_1$-$C_6)$alkyl, N[$(C_5$-$C_{10})$heterocyclyl]-C(O)-$(C_1$-$C_6)$alkyl, N[$(C_6$-$C_{10})$aryl]-C(O)O-$(C_1$-$C_6)$alkyl, N[$(C_5$-$C_{10})$heterocyclyl]-C(O)O-$(C_1$-$C_6)$alkyl, N(aryl)-C(O)-$(C_6$-$C_{10})$aryl, N[$(C_5$-$C_{10})$heterocyclyl]-C(O)-$(C_6$-$C_{10})$aryl, N[$(C_6$-$C_{10})$aryl]-C(O)O-$(C_6$-$C_{10})$aryl, N[$(C_5$-$C_{10})$heterocyclyl]-C(O)O-$(C_6$-$C_{10})$aryl, N[$(C_6$-$C_{10})$aryl]-C(O)-NH-$(C_1$-$C_6)$alkyl, N[$(C_5$-$C_{10})$heterocyclyl]-C(O)-NH-$(C_1$-$C_6)$alkyl, N(aryl)-C(O)-NH-$(C_6$-$C_{10})$aryl, N[$(C_5$-$C_{10})$heterocyclyl]-C(O)-NH-$(C_6$-$C_{10})$aryl, N[$(C_6$-$C_{10})$aryl]-C(O)-N[$(C_1$-$C_6)$alkyl]$_2$, N[$(C_5$-$C_{10})$heterocyclyl]-C(O)-N[$(C_1$-$C_6)$alkyl]$_2$, N[$(C_6$-$C_{10})$aryl]-C(O)-N[$(C_1$-$C_6)$alkyl]-$(C_6$-$C_{10})$aryl, N[$(C_5$-$C_{10})$heterocyclyl]-C(O)-N[$(C_1$-$C_6)$alkyl]- $(C_6$-$C_{10})$aryl, N[$(C_6$-$C_{10})$aryl]-C(O)-N[$(C_6$-$C_{10})$aryl]$_2$, N[$(C_5$-$C_{10})$heterocyclyl]-C(O)-N[$(C_6$-$C_{10})$aryl]$_2$, $(C_6$-$C_{10})$aryl, $(C_1$-$C_6)$alkylene-$(C_6$-$C_{10})$aryl, O-$(C_1$-$C_6)$alkylene-$(C_6$-$C_{10})$aryl, $(C_5$-$C_{10})$heterocyclyl, $(C_1$-$C_6)$alkylene-$(C_5$-$C_{10})$heterocyclyl, O-$(C_1$-$C_6)$alkylene-$(C_5$-$C_{10})$heterocyclyl, wherein the $(C_6$-$C_{10})$aryl or $(C_5$-$C_{10})$heterocyclyl may be substituted one to 3 times

by halogen, OH, NO_2, CN, O-(C_1-C_6)alkyl, (C_1-C_6)alkyl, NH_2, NH(C_1-C_6)alkyl, N[(C_1-C_6)alkyl]$_2$, SO_2CH_3, COOH, C(O)O-(C_1-C_6)alkyl, $CONH_2$, (C_1-C_6)alkylene-O-(C_1-C_6)alkyl, (C_1-C_6)alkylene-O-(C_6-C_{10})aryl, O-(C_1-C_6)alkylene-(C_6-C_{10})aryl; or wherein (C_6-C_{10})aryl is vicinally substituted by a O-(C_1-C_4)alkylene-O group whereby a 5-8-membered ring is formed together with the carbon atoms the oxygen atoms are attached to. Aryl or heterocyclyl substituents of (C_6-C_{10})aryl and (C_5-C_{10})heterocyclyl groups may not be further substituted by an aryl or heterocyclyl containing group.

Preferred substituents for (C_6-C_{10})aryl groups are (C_1-C_4)alkyl, O-(C_1-C_4)alkyl, O-phenyl, C(O)O-(C_1-C_6)alkyl, C(O)OH, C(O)-(C_1-C_4)alkyl, halogen, NO_2, SO_2NH_2, CN, SO_2-(C_1-C_4)alkyl, NH-SO_2-(C_1-C_4)alkyl, NH_2, NH-C(O)-(C_1-C_4)alkyl, (C_3-C_8)cycloalkyl, (C_1-C_4)alkyl-OH, C(O)N[(C_1-C_4)alkyl]$_2$, $C(O)NH_2$, N[(C_1-C_4)alkyl]$_2$, (C_1-C_4)alkenylene-(C_6-C_{10})aryl, wherein the (C_6-C_{10})aryl may be further substituted by (C_1-C_4)alkyl, (C_1-C_4)alkylene-O-(C_1-C_6)alkyl, O-(C_1-C_6)alkyl-(C_6-C_{10})aryl, or may be vicinally substituted by a O-(C_1-C_4)alkylene-O group whereby a 5-8-membered ring is formed together with the carbon atoms the oxygen atoms are attached to.

In monosubstituted phenyl groups the substituent can be located in the 2-position, the 3-position or the 4-position, with the 3-position and the 4-position being preferred. If a phenyl group carries two substituents, they can be located in 2,3-position, 2,4-position, 2,5-position, 2,6-position, 3,4-position or 3,5-position. In phenyl groups carrying three substituents the substituents can be located in 2,3,4-position, 2,3,5-position, 2,3,6-position, 2,4,5-position, 2,4,6-position, or 3,4,5-position.

The above statements relating to phenyl groups correspondingly apply to divalent groups derived from phenyl groups, i.e. phenylene which can be unsubstituted or substituted 1,2-phenylene, 1,3-phenylene or 1,4-phenylene. The above statements also correspondingly apply to the aryl subgroup in arylalkylene groups. Examples of arylalkylene groups which can also be unsubstituted or substituted in the aryl subgroup

as well as in the alkylene subgroup, are benzyl, 1-phenylethylene, 2-phenylethylene, 3-phenylpropylene, 4-phenylbutylene, 1-methyl-3-phenyl-propylene.

Preferred substituents for (C_5-C_{10})heterocyclyl groups are (C_1-C_4)alkyl, O-(C_1-C_4)alkyl, (C_1-C_4)alkylene-phenyl, halogen, (C_1-C_4)alkylene-O-(C_1-C_4)alkyl, (C_5-C_{10})heterocyclyl, (C_1-C_4)alkylene-N[(C_1-C_4)alkyl]$_2$, or (C_6-C_{10})aryl, wherein the (C_6-C_{10})aryl may be further substituted by (C_1-C_4)alkyl, (C_1-C_4)alkylene-O-(C_1-C_6)alkyl, O-(C_1-C_6)alkyl-(C_6-C_{10})aryl, or may be vicinally substituted by a O-(C_1-C_4)alkylene-O group whereby a 5-8-membered ring is formed together with the carbon atoms the oxygen atoms are attached to.

The general and preferred substituents of (C_6-C_{10})aryl and (C_5-C_{10})heterocyclyl groups may be combined with the general and preferred definitions of R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8, n and L as described above.

The present invention therefore also relates to the compounds of the formula (I) and/or their physiologically acceptable salts and/or their prodrugs for use as pharmaceuticals (or medicaments), to the use of the compounds of the formula (I) and/or their physiologically acceptable salts and/or their prodrugs for the production of pharmaceuticals for the treatment and/or prevention of diseases associated with Rho-kinase and/or Rho-kinase mediated phosphorylation of myosin light chain phosphatase, i.e. for the treatment and/or prevention of hypertension, i.e. pulmonary hypertension and ocular hypertension, peripheral circulatory disorder, angina pectoris, cerebral vasospasm, asthma, premature birth, hyperaggregability of platelets, Peripheral Occlusive Arterial Disease (PAOD), Chronic Obstructive Pulmonary Disease (COPD), cancer development, erectile dysfunction, arteriosclerosis, ischemic organ failure (end organ damage), fibroid lung, fibroid liver, liver failure, fibroid kidney, renal glomerulosclerosis, kidney failure, organ hypertrophy, prostatic hypertrophy, complications of diabetes, blood vessel restenosis, atherosclerosis, cancer, cardiac hypertrophy, heart failure; ischemic diseases; inflammation; autoimmune diseases; AIDS, osteopathy such as osteoporosis, brain functional disorder, infection of digestive

tracts with bacteria, sepsis, adult respiratory distress syndrome, retinopathy, glaucoma and Alzheimer's disease.

The present invention furthermore relates to pharmaceutical preparations (or pharmaceutical compositions) which contain an effective amount of at least one compound of the formula (I) and/or its physiologically acceptable salts and/or its prodrugs and a pharmaceutically acceptable carrier, i. e. one or more pharmaceutically acceptable carrier substances (or vehicles) and/or additives (or excipients).

The pharmaceuticals can be administered orally, for example in the form of pills, tablets, lacquered tablets, coated tablets, granules, hard and soft gelatin capsules, solutions, syrups, emulsions, suspensions or aerosol mixtures. Administration, however, can also be carried out rectally, for example in the form of suppositories, or parenterally, for example intravenously, intramuscularly or subcutaneously, in the form of injection solutions or infusion solutions, microcapsules, implants or rods, or percutaneously or topically, for example in the form of ointments, solutions or tinctures, or in other ways, for example in the form of aerosols or nasal sprays.

The pharmaceutical preparations according to the invention are prepared in a manner known per se and familiar to one skilled in the art, pharmaceutically acceptable inert inorganic and/or organic carrier substances and/or additives being used in addition to the compound(s) of the formula (I) and/or its (their) physiologically acceptable salts and/or its (their) prodrugs. For the production of pills, tablets, coated tablets and hard gelatin capsules it is possible to use, for example, lactose, corn starch or derivatives thereof, talc, stearic acid or its salts, etc. Carrier substances for soft gelatin capsules and suppositories are, for example, fats, waxes, semisolid and liquid polyols, natural or hardened oils, etc. Suitable carrier substances for the production of solutions, for example injection solutions, or of emulsions or syrups are, for example, water, saline, alcohols, glycerol, polyols, sucrose, invert sugar, glucose, vegetable oils, etc. Suitable carrier substances for microcapsules, implants or rods are, for example, copolymers of glycolic acid and lactic acid. The pharmaceutical preparations normally contain about 0.5 to about 90 % by weight of the compounds of the formula (I) and/or their

physiologically acceptable salts and/or their prodrugs. The amount of the active ingredient of the formula (I) and/or its physiologically acceptable salts and/or its prodrugs in the pharmaceutical preparations normally is from about 0.5 to about 1000 mg, preferably from about 1 to about 500 mg.

In addition to the active ingredients of the formula (I) and/or their physiologically acceptable salts and/or prodrugs and to carrier substances, the pharmaceutical preparations can contain one or more additives such as, for example, fillers, disintegrants, binders, lubricants, wetting agents, stabilizers, emulsifiers, preservatives, sweeteners, colorants, flavorings, aromatizers, thickeners, diluents, buffer substances, solvents, solubilizers, agents for achieving a depot effect, salts for altering the osmotic pressure, coating agents or antioxidants. They can also contain two or more compounds of the formula (I) and/or their physiologically acceptable salts and/or their prodrugs. In case a pharmaceutical preparation contains two or more compounds of the formula (I) the selection of the individual compounds can aim at a specific overall pharmacological profile of the pharmaceutical preparation. For example, a highly potent compound with a shorter duration of action may be combined with a long-acting compound of lower potency. The flexibility permitted with respect to the choice of substituents in the compounds of the formula (I) allows a great deal of control over the biological and physico-chemical properties of the compounds and thus allows the selection of such desired compounds. Furthermore, in addition to at least one compound of the formula (I) and/or its physiologically acceptable salts and/or its prodrugs, the pharmaceutical preparations can also contain one or more other therapeutically or prophylactically active ingredients.

When using the compounds of the formula (I) the dose can vary within wide limits and, as is customary and is known to the physician, is to be suited to the individual conditions in each individual case. It depends, for example, on the specific compound employed, on the nature and severity of the disease to be treated, on the mode and the schedule of administration, or on whether an acute or chronic condition is treated or whether prophylaxis is carried out. An appropriate dosage can be established using clinical approaches well known in the medical art. In general, the daily dose for

achieving the desired results in an adult weighing about 75 kg is from about 0.01 to about 100 mg/kg, preferably from about 0.1 to about 50 mg/kg, in particular from about 0.1 to about 10 mg/kg, (in each case in mg per kg of body weight). The daily dose can be divided, in particular in the case of the administration of relatively large amounts, into several, for example 2, 3 or 4, part administrations. As usual, depending on individual behavior it may be necessary to deviate upwards or downwards from the daily dose indicated.

Furthermore, the compounds of the formula (I) can be used as synthesis intermediates for the preparation of other compounds, in particular of other pharmaceutical active ingredients, which are obtainable from the compounds of the formula I, for example by introduction of substituents or modification of functional groups.

The compounds of the formula (I) can be prepared according to the following exemplified compounds without limiting the scope of the claims.

In general, protective groups that may still be present in the products obtained in the coupling reaction are then removed by standard procedures. For example, tert-butyl protecting groups, in particular a tert-butoxycarbonyl group which is a protected form of an amidino group, can be deprotected, i. e. converted into the amidino group, by treatment with trifluoroacetic acid. As already explained, after the coupling reaction also functional groups can be generated from suitable precursor groups. In addition, a conversion into a physiologically acceptable salt or a prodrug of a compound of the formula (I) can then be carried out by known processes.

In general, a reaction mixture containing a final compound of the formula (I) or an intermediate is worked up and, if desired, the product is then purified by customary processes known to those skilled in the art. For example, a synthesized compound can be purified using well known methods such as crystallization, chromatography or reverse phase-high performance liquid chromatography (RP-HPLC) or other methods of separation based, for example, on the size, charge or hydrophobicity of the compound. Similarly, well known methods such as amino acid sequence analysis,

NMR, IR and mass spectrometry (MS) can be used for characterizing a compound of the invention.

It is understood that modifications that do not substantially affect the activity of the various embodiments of this invention are included within the invention disclosed herein. Accordingly, the following examples are intended to illustrate but not limit the present invention.

LCMS methods

Method #1

Column: YMC J'shere 33x2 4µm

gradient (AcN+0.05% TFA) : H2O+0.05% TFA; 5:95 (0min) to 95:5 (2.5 min) to 95:5 (3 min)

Method #2

Column: YMC J'shere 33x2 4µm

gradient (AcN+0.05% TFA) : H2O+0.05% TFA, 5:95 (0min) to 95:5 (3.4min) to 95:5 (4.4min)

Method #3

Column: YMC J'shere 33x2 4µm

gradient AcN+0.08%FA : H2O+0.1%FA; 5:95 (0min) to 95:5(2.5min) to 95:5(3min)

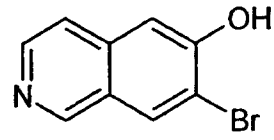
Method #Top

Column: YMC YMC J`sphere ODS H80 20X2 1 4µ

gradient 0 min 96%H2O(0.05%TFA) 2.0min-95%ACN; 95%ACN bis 2.4min;4%ACN 2.45min

Building block syntheses

7-Bromo-isoquinoline-6-ol (1)



25 g (116.3 mmol) of 3-bromo-4-methoxybenzaldehyde, 19.0 mL (18.3 g, 174.5 mmol) of aminoacetaldehyde dimethyl acetal and 250 mL of toluene were heated to reflux for 6 h using a Dean-Stark apparatus. Solvent and excess reagent were distilled off and the crude product (approx. 37 g) was used for the next step without any additional purification.

The imine was dissolved in 240 mL of THF. 11.1 mL (12.6 g, 116.3 mmol) of ethyl chloroformate were added dropwise at 0°C. After stirring for 5 minutes 24.3 mL (23.2 g, 139.2 mmol) triethylphosphite were added dropwise. The mixture was stirred for 18 h at room temperature. Then the solvents were distilled off. Excess reagent was removed by repeated addition of 100 ml toluene and evaporation of the solvents. The P,N–acetal (approx. 62 g) was used for the next step without any additional purification.

The P,N–acetal, 51.3 mL (88.2 g, 465.2 mmol) titanium tetrachloride and 300 mL chloroform were heated to reflux for 48 h. The mixture was poured on ice and the pH was adjusted to 9 by using aqueous ammonia. Repeated extraction with ethyl acetate followed by removal of the solvents gave 14.8 g (53%.) of 7-bromo-6-methoxyisoquinoline.

^{1}H-NMR (d_6-DMSO): δ = 9.16 (1H, s), 8.46 (1H, d, J = 5.9 Hz), 8.46 (1H, s), 7.76 (1H, d, J = 5.9 Hz), 7.51 (1H, s), 4.01 (3H, s).

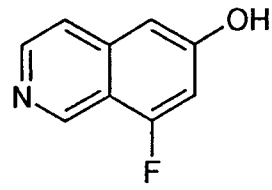
MS: m/z = 238 (MH^+).

3.6 mL (9.5 g, 37.8 mmol) of BBr_3 were added at 0°C to a solution of 4.5 g (18.9 mmol) 7-bromo-6-methoxy isoquinoline in 30 mL dichloromethane and stirred for 18 h at room temperature. Aqueous $NaHCO_3$-solution was added to adjust the pH to 8. Extraction with chloroform/isopropanol (3/1) followed by drying over sodium sulfate and removal of the solvents gave 2,7 g (64%) of compound 1.

^{1}H-NMR (d_6-DMSO): δ = 9.19 (1H, s), 8.49 (1H, s), 8.38 (1H, d, J = 6.1 Hz), 7.78 (1H, d, J = 6.1 Hz), 7.34 (1H, s).
MS: m/z = 224 (MH^+).

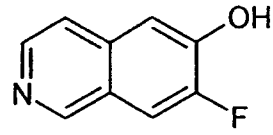
The following intermediates were synthesized using this procedure:

8-Fluoro-isoquinoline-6-ol (2)



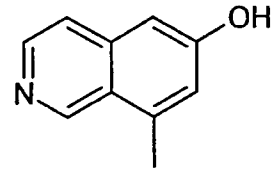
^{1}H-NMR (d_6-DMSO): δ = 10.84 (1H, s), 9.21 (1H, s), 8.40 (1H, d, J = 5.8 Hz), 7.67 (1H, d, J = 5.8 Hz), 7.01 (2H, m).
MS: m/z = 164 (MH^+).

7-Fluoro-isoquinoline-6-ol (3)



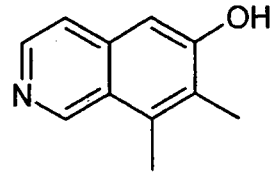
^{1}H-NMR (d_6-DMSO): δ = 11.06 (1H, s), 9.07 (1H, s), 8.33 (1H, d, J = 5.6 Hz), 7.88 (1H, d, J = 11.4 Hz), 7.64 (1H, d, J = 5.6 Hz) , 7.31 (1H, d, J = 8.6 Hz).
MS: m/z = 164 (MH^+).

8-Methyl-isoquinoline-6-ol (4)



^{1}H-NMR (d_6-DMSO): δ = 11.55 (1H, s), 9.47 (1H, s), 8.42 (1H, d, J = 6.5 Hz), 8.11 (1H, d, J = 6.5 Hz), 7.31 (1H, s), 7.25 (1H, s), 2.76 (3H, s).
MS: m/z = 160 (MH^+).

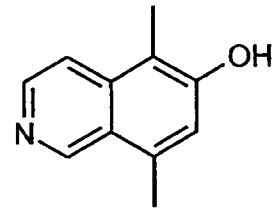
7, 8-Dimethyl-isoquinoline-6-ol (5)



^{1}H-NMR (d_6-DMSO): δ = 11.87 (1H, s), 9.58 (1H, s), 8.41 (1H, d, J = 6.5 Hz), 8.18 (1H, d, J = 6.5 Hz), 7.35 (1H, s), 7.25 (1H, s), 2.71 (3H, s), 2.35 (3H, s).

MS: m/z = 174 (MH^+).

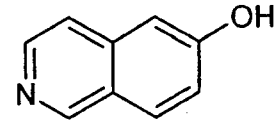
5, 8-Dimethyl-isoquinoline-6-ol (6)



^{1}H-NMR (d_6-DMSO): δ = 11.55 (1H, s), 9.52 (1H, s), 8.47 (1H, d, J = 6.8 Hz), 8.26 (1H, d, J = 6.8Hz), 7.42 (1H, s), 2.76 (3H, s), 2.42 (3H, s).

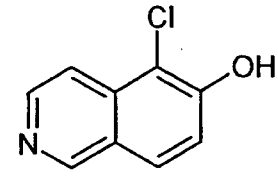
MS: m/z = 174 (MH^+).

6-Hydroxy-isoquinoline (7)



LCMS Method # 1, retention time 0.14 min, detected mass 146.08 $[M+H]^+$

5-Chloroisoquinoline-6-ol (8)



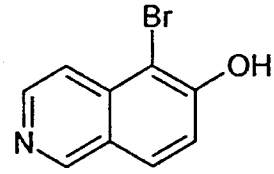
0.61 mL (1.02 g, 7.6 mmol) of sulfuryl chloride were added to a solution of 1.0 g (6,9 mmol) of compound 7 in 30 mL of dichloromethane. Three drops diethyl ether were

added and the reaction was stirred at room temperature for 5 h. The solvents were removed by distillation and the remainder was treated with aqueous $NaHCO_3$ solution. The precipitate was filtered, washed with water and dried to give 1.1 g (89%) of compound 8 as a green-yellow solid.

^{1}H-NMR (d_6-DMSO): δ = 11.37 (1H, s), 9.18 (1H, s), 8.50 (1H, d, J = 6 Hz), 8.00 (1H, d, J= 8.8 Hz), 7.83 (1H, J = 6 Hz), 7.44 (1H, d, J = 8.7 Hz).

MS: m/z = 180 (MH^+).

5-Bromoisoquinoline-6-ol (9)

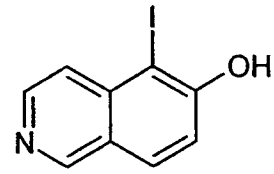


7.9 mL (19.18 g, 120 mmol) of bromine were added dropwise to a suspension of 17.42 g (120 mmol) of compound 7 in 250 mL of chloroform at room temperature. After stirring for 2 h ethyl acetate was added. The precipitate was filtered, washed with ethyl acetate and dried. Aqueous $NaHCO_3$ solution was added carefully. The precipitate was filtered and washed with $NaHCO_3$ solution until the filtrate had a pH of 8. Drying gave 23.78 g (88%) of compound 9 as an off-white solid.

^{1}H-NMR (d_6-DMSO): δ = 11.30 (1H, s), 9.13 (1H, s), 8.48 (1H, d, J = 5.9 Hz), 8.02 (1H, d, J= 8.8 Hz), 7.78 (1H, J = 5.9 Hz), 7.40 (1H, d, J = 8.8 Hz).

MS: m/z = 224 (MH^+).

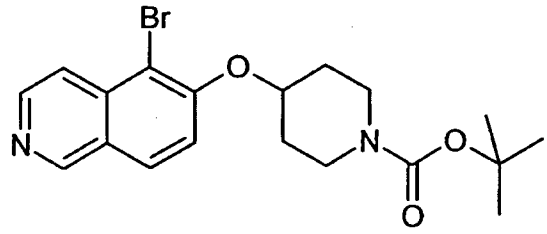
5-Iodoisoquinoline-6-ol (10)



Under argon atmosphere 1.77 g (12.2 mmol) of compound 7 were added to a solution of 5.0 g (13.5 mmol) bis(pyridin)iodonium tetrafluoroborate in 100 mL of dry dichloromethane. A solution of 2.4 mL (4 g, 26.8 mmol) trifluoromethane sulfonic acid in 20 mL dry dichloromethane was added dropwise at 0°C and the mixture was stirred for 3 hours at room temperature. The solvents were removed by distillation and the

remainder was treated with aqueous $NaHCO_3$ solution. The precipitate was filtered, washed with water and dried to yield 3.2 g (97%) of compound 10 as a beige solid.
^{1}H-NMR (d_6-DMSO): δ = 9.09 (1H, s), 8.47 (1H, d, J = 6.1 Hz), 8.04 (1H, d, J= 8.8 Hz), 7.76 (1H, J = 6.1 Hz), 7.37 (1H, d, J = 8.8 Hz).
MS: m/z = 272 (MH^+).

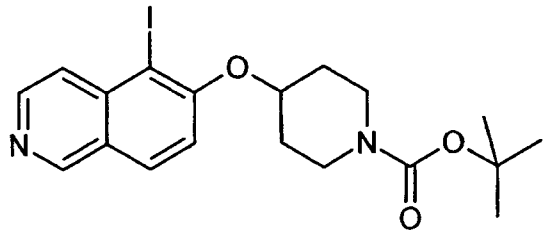
4-(5-Bromo-isoquinolin-6-yloxy)-piperidine-1-carboxylic acid tert-butyl ester (11)



3.75 mL (4.15 g, 23.8 mmol) of diethyl azo dicarboxylate were added to 12.7 g (19.9 mmol) of polymer-bound triphenylphosphine (PS-PPh_3, approx. 1.6 mmol/g, Argonaut) in 250 mL of dichloromethane at 0°C and stirred for 15 min. 4.45 g (19.9 mmol) 5-bromo isoquinoline-6-ol (9), 4.0 g (19.9 mmol) Boc-(4-hydroxy)piperidine and 4.1 mL (3.0 g, 29.8 mmol) triethyl amine were added. The mixture was shaken for 16h. The polymer was removed by filtration through Celite and the solvents were distilled off. 20 mL dichloromethane were added and the precipitate was isolated by filtration. The crude product (8 g) was purified by flash chromatography using ethyl acetate/n-heptane as eluent to give 4.78 g (60%) of compound 11.
^{1}H-NMR (d_6-DMSO): δ = 9.24 (1H, s), 8.97 (1H, s), 8.56 (1H, d, J = 6 Hz), 8.20 (1H, d, J = 9 Hz), 7.85 (1H, d, J= 6 Hz), 7.75 (1H, d, J = 9 Hz), 5.02 (1H, m), 3.58 (2H, m), 3.40 (2H, m), 1.91 (2H, m), 1.70 (2H, m), 1.41 (9H, s).
MS: m/z = 407 (MH^+).

The following building blocks were synthesized according to this method:

4-(5-Iodo-isoquinoline-6-yloxy)-piperidin-1-carboxylic acid tert-butyl ester (12)

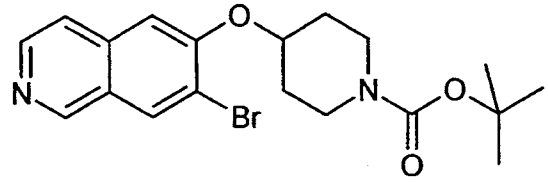


using compound 10 as starting material

^{1}H-NMR ($CDCl_3$): δ = 9.04 (1H, s), 8.55 (1H, d, J = 6 Hz), 7.93 (1H, d, J = 9 Hz), 7.86 (1H, d, J = 6 Hz), 7.27 (1H, d, J= 9 Hz), 4.87 (1H, m), 3.66 (4H, m), 1.93 (4H, m), 1.48 (9H, s).

MS: m/z = 455 (MH^+).

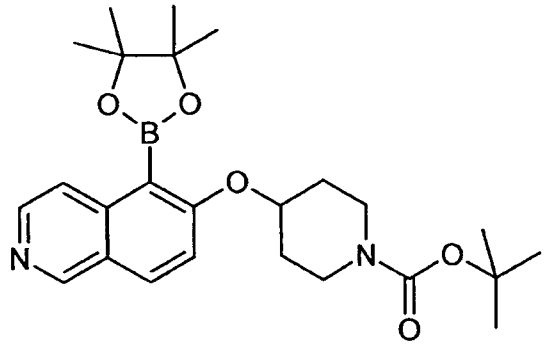
4-(7-Bromo-isoquinoline-6-yloxy)-piperidin-1-carboxylic acid tert-butyl ester (13)



using compound 1 as starting material

LCMS Method # 4, retention time 1.13 min, detected mass 407.4 $[M+H]^+$

4-[5-(4,4,5,5-Tetramethyl-[1,3,2]dioxaborolan-2-yl)-isoquinoline-6-yloxy]-piperidin-1-carboxylic acid tert-butyl ester (14)

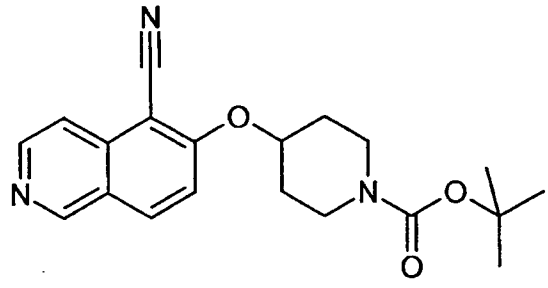


A solution of 0.55 g (1.34 mmol) 4-(5-bromo-isoquinolin-6-yloxy)-piperidine-1-carboxylic acid tert-butyl ester (11) in 14 mL of DMSO was added to a mixture of 1.0 g (4.0 mmol) bis(pinacolato)diboron, 0.78 g (8.0 mmol) K_2CO_3 and 29 mg (0.03 eq.) $Pd(dppf)Cl_2$. Argon was bubbled through the mixture for 30 min and then the reaction

mixture was heated in a microwave reactor (CEM Discovery) to 100°C for 60 min. After cooling to room temperature water was added. The mixture was extracted with ethyl acetate. After removal of the solvent the product was isolated by flash chromatography (ethyl acetate/n-heptane) to yield: 269 mg (44%) of compound 14 as a white solid.

LCMS Method # 4, retention time 1.30 min, detected mass 433.3 $[M+H]^+$

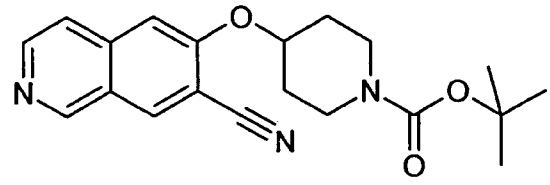
4-(5-Cyano-isoquinolin-6-yloxy)-piperidine-1-carboxylic acid tert-butyl ester (15)



Under argon atmosphere 47 mg (0.4 mmol) of $Zn(CN)_2$ and 23 mg of (0.02 eq) $Pd(PPh_3)_4$ were added to a solution 62 mg (0.4 mmol) of 4-(5-bromo-isoquinolin-6-yloxy)-piperidine-1-carboxylic acid tert-butyl ester (11) in DMF. The reaction was heated for 5 minutes to 150°C in a microwave reactor (CEM Discovery). After cooling to room temperature water and ethyl acetate were added. The mixture was filtered through celite, washed with ethyl acetate and concentrated to yield 176 mg of compound 15.

MS: m/z = 354 (MH^+).

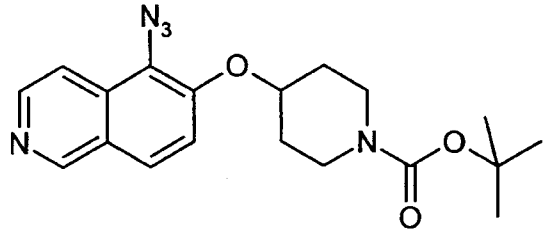
4-(7-Cyano-isoquinolin-6-yloxy)-piperidine-1-carboxylic acid tert-butyl ester (16)



Under argon atmosphere 35 mg (0.3 mmol) of $Zn(CN)_2$ and 17 mg (0.05 eq) of $Pd(PPh_3)_4$ were added to a solution of 122 mg (0.3 mmol) of 4-(7-bromo-isoquinolin-6-yloxy)-piperidine-1-carboxylic acid tert-butyl ester (13) in DMF. The reaction was heated for 5 minutes to 150°C in a microwave reactor (CEM Discovery). After cooling to room temperature water and ethyl acetate were added. The mixture was filtered

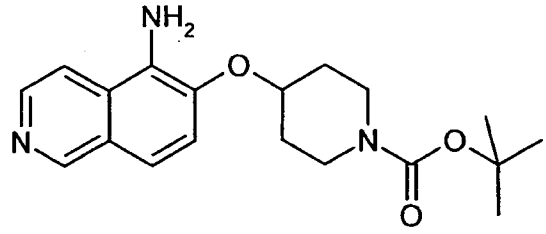
through Celite, washed with ethyl acetate and concentrated. The crude product was purified by preparative HPLC to yield 77 mg of compound 16.
LCMS Method # 4, retention time 1.06 min, detected mass 354.5 $[M+H]^+$

4-(5-Azido-isoquinoline-6-yloxy)- piperidin-1- carboxylic acid tert-butyl ester (17)



Under argon atmosphere 40 µL (0.04 mmol) of 1N NaOH, 4.6 mg (0.04 mmol) of L-proline, 3.8 mg of (0.02 mmol) CuI and 15.6 mg (0.24 mmol) of NaN_3 were added to a solution of 91 mg (0.2 mmol) of 4-(5-iodo-isoquinoline-6-yloxy)-piperidin-1-carboxylic acid tert-butyl ester (12) in 2 mL of DMSO. The mixture was heated to 60°C for 18 h. NaN_3, NaOH and L-proline were added in the same amounts again and the reaction was heated to 60°C for 5 h. After cooling to room temperature water was added. The precipitate was filtered, washed with water and dried in vacuo to give 74 mg of compound 17, which was used without any additional purification.
MS: m/z = 370 (MH^+).

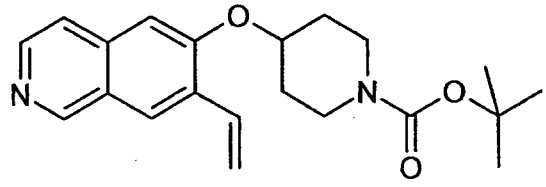
4-(5-Amino-isoquinoline-6-yloxy)- piperidin-1- carboxylic acid tert-butyl ester (18)



Under argon atmosphere 600 µL (0.6 mmol) of 1N NaOH, 13.8 mg (0.12 mmol) L-proline, 7.6 mg (0.04 mmol) of CuI and 52 mg (0.8 mmol) of NaN_3 were added to a solution of 163 mg (0.4 mmol) 4-(5-bromo-isoquinoline-6-yloxy)-piperidin-1-carboxylic acid tert-butyl ester (11) in 0.6 mL of water. The mixture was heated to 95°C for 3 h in a microwave reactor (CEM Discovery). After cooling to room temperature water and ethyl acetate were added. The mixture was filtered through Celite, washed with ethyl

acetate and concentrated. The crude product was purified by preparative HPLC to yield 42 mg of compound 18 (containing some 11 as impurity).
LCMS Method # 4, retention time 0.97 min, detected mass 344.5 $[M+H]^+$

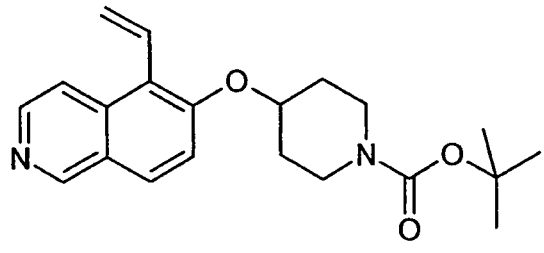
4-(7-Vinyl-isoquinolin-6-yloxy)-piperidine-1-carboxylic acid tert-butyl ester (19)



Under argon atmosphere 340 mg tributyl-vinyl-stannane (1.07 mmol, 1.2 eq.) and 103 mg of $Pd(PPh_3)_4$ (0.1 eq.) were added to a solution of 364 mg of 4-(7-Bromo-isoquinoline-6-yloxy)-piperidin-1-carboxylic acid tert-butyl ester (13) (0.98 mmol) in 4 ml of toluene. The reaction was heated to 100°C in a microwave reactor (CEM Discovery) for 1 h.
After cooling to room temperature water and ethyl acetated were added. The mixture was filtered through a Celite cartridge, washed with ethyl acetate and concentrated. The crude product was purified by preparative HPLC to yield 256 mg (81 %) of compound 19.
LCMS Method # 4, retention time 1.19 min, detected mass 355.5 $[M+H]^+$

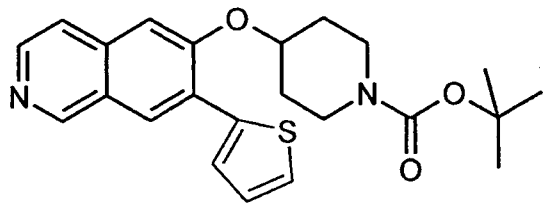
The following building blocks were synthesized according to this method:

4-(5-Vinyl-isoquinolin-6-yloxy)-piperidine-1-carboxylic acid tert-butyl ester (19A)



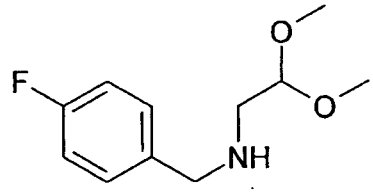
using compound 11 as starting material
LCMS Method # 4, retention time 1.11 min, detected mass 355.4 $[M+H]^+$

4-(7-Thiophen-2-yl-isoquinolin-6-yloxy)-piperidine-1-carboxylic acid tert-butyl ester (20)



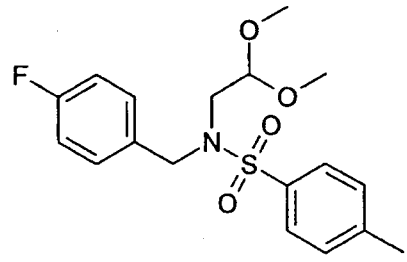
using compound 13 and tributyl-thiophen-2-yl-stannane as starting materials. LCMS Method # 4, retention time 1.26 min, detected mass 411.5 $[M+H]^+$

(2,2-Dimethoxy-ethyl)-(4-fluoro-benzyl)-amine (21)



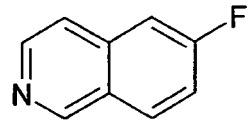
12.4 g of 4-Fluorobenzaldehyde were dissolved in 100 mL of toluene and reacted with 10.5 g 2-Aminoacetaldehyde dimethylacetal and 1.90 g (10 mmol) p-toluenesulfonic acid monohydrate for two hours at a Dean Stark apparatus. The solution was allowed to cool down, extracted with saturated sodium bicarbonate, water and brine, dried over magnesium sulfate and evaporated to dryness. The crude product was dissolved in 100 mL of ethanol. 1.89 g of sodium borohydride were added portionwise. Stirring was continued overnight. For workup, acetic acid was added until no gas evolution could be observed. Then the solution was evaporated to dryness, taken up in dichloromethane and washed twice with water. The organic layer was extracted with brine, dried over magnesium sulfate and evaporated to dryness. The obtained crude product (20 g) was used for further reactions without purification. R_t = 0.86 min (Method #1). Detected mass: 182.1 ($M-OMe^-$), 214.2 ($M+H^+$).

N-(2,2-Dimethoxy-ethyl)-N-(4-fluoro-benzyl)-4-methyl-benzenesulfonamide (22)



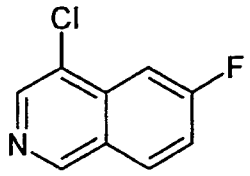
20 g (2,2-Dimethoxy-ethyl)-(4-fluoro-benzyl)-amine (21) were dissolved in 120 ml of dichloromethane. 20 mL of pyridine are added. At 0 °C a solution of 23.8 g p-toluenesulfonic acid chloride in dichloromethane was added dropwise. The reaction was allowed to warm to room temperature and stirring is continued until conversion was completed. For workup, the reaction mixture was extracted twice with 2M hydrochloric acid, twice with sodium bicarbonate and once with brine. The organic layer was dried over magnesium sulfate, evaporated to dryness and the obtained crude product was purified by silica gel chromatography to yield 22.95g of compound 22 as an orange oil. R_t = 1.71 min (Method # 4). Detected mass: 336.1 ($M-OMe^-$).

6-Fluoro-isoquinoline (23)



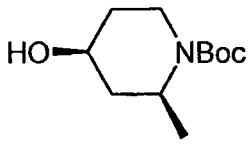
41.6 g of $AlCl_3$ were suspended in 400 mL of dichloromethane. At room temperature, a solution of 22.95 g of N-(2,2-Dimethoxy-ethyl)-N-(4-fluoro-benzyl)-4-methyl-benzenesulfonamide (22) in 150 ml of dichloromethane was added. Stirring was continued at room temperature overnight, the solution was poured on ice, the organic layer was separated, the aqueous phase was extracted twice with dichloromethane and the combined organic layers are then extracted twice with sodium bicarbonate. The organic layer was dried over magnesium sulfate, evaporated to dryness and the obtained crude product (8.75g) is purified by silica gel chromatography to yield 2.74 g of compound 23. R_t = 0.30 min (Method # 4). Detected mass: 148.1 ($M+H^+$).

4-Chloro-6-fluoro-isoquinoline (24)



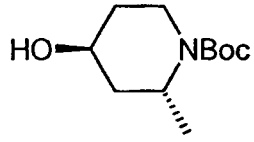
A solution of 1.5 g 6-fluoro-isoquinoline (23) in 4.5 ml sulfuryl chloride was heated to 60 °C in a microwave reactor (CEM Discovery) for 8 h. After cooling to room temperature the mixture was poured on ice and extracted three times with $CHCl_3$. After drying over Na_2SO_4 the solvent was distilled off and the crude product was purified by flash chromatography to yield 930 mg of compound 24.
LCMS Method # 1, retention time 1.37 min, detected mass 182.01 $[M+H]^+$

Cis and trans N-Boc-2-methyl-piperidin-4-ol (25 and 26)



racemic - cis

25



racemic - trans

26

213 mg (5.6 mmol) of $NaBH_4$ were added portionwise at 0°C to a solution of 1.0 g (4.7 mmol) 1-Boc-2-methyl-piperidin-4-on in 10 mL EtOH. The mixture was stirred at room temperature for another 2 h. The solvent was removed by distillation and the remainder was dissolved in water and ethyl acetate. The aqueous layer was extracted twice with ethyl acetated and the combined organic layers were dried over Na_2SO_4. After filtration the solvent was removed by distillation and the crude product was purified by column chromatography n-heptane/ethyl acetate (1/1) to yield 367 mg (36%) of the cis-isomer 25 and 205 mg (20%) of the trans-isomer 26 in addition to 97 mg (10%) mixture of both isomers.

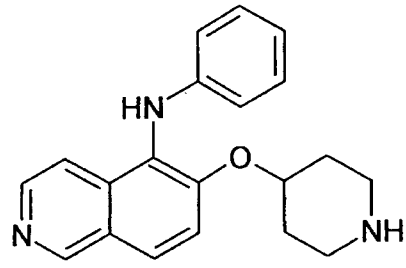
Cis-Isomer (25):

^{1}H-NMR ($CDCl_3$): δ= 4.28 (1H, m), 4.17 (1H, m), 3.82 (1H, m), 3.26 (1H, m), 1.85 (1H, ddd, J= 14.7, 6.6, und 3.4 Hz), 1.77 (1H, m), 1.66 (2H, m), 1.33 (3H, d, J = 7.1 Hz).

Trans-Isomer (26):

^{1}H-NMR ($CDCl_3$): δ = 4.50 (1H, m), 4.04 (1H, m), 3.95 (1H, m), 2.87 (1H, dt, J = 2.9 und 13.6 Hz), 1.93 (1H, m), 1.83 (1H, m), 1.53 (1H, m), 1.32 (1H, m), 1.14 (3H, d, J = 7.1 Hz).

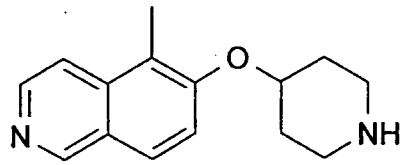
Phenyl-[6-(piperidin-4-yloxy)-isoquinolin-5-yl]-amine (27)



Under an argon atmosphere 81 mg (0.2 mmol) of 4-(5-bromo-isoquinolin-6-yloxy)-piperidine-1-carboxylic acid tert-butyl ester (11) and 24 mg (0.26 mmol) of aniline were added to a solution of 27 mg (0.28 mmol) of NaO*t*Bu in 3 mL of toluene. After stirring at room temperature for 10 min., 9 mg (0.05 eq) of Pd_2dba_3 were added and the mixture was heated to 100°C in a microwave reactor (CEM Discovery) for 1h. After cooling to room temperature water and ethyl acetate were added. The organic layer was separated, dried over Na_2SO_4 and concentrated. HPLC purification gave the Boc protected intermediate which was treated with 2 mL 5-6 N HCl in isopropanol for 2 h. The hydrochloride was filtered and subjected to another HPLC chromatography to yield compound 27 as trifluoroacetate (31.3 mg).

LCMS Method # 2, retention time 0.78 min, detected mass 320.26 $[M+H]^+$

5-Methyl-6-(piperidin-4-yloxy)-isoquinoline hydrochloride (28)

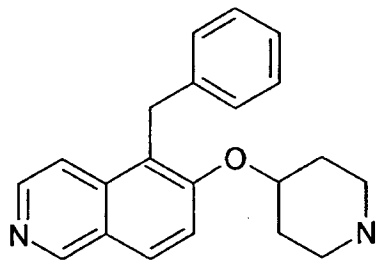


ClH

Under an argon atmosphere a 2 M solution of dimethyl zinc (0.5 mL, 93.7 mg, 4 eq.) in toluene was added to a solution of 100 mg (0.24 mmol) 4-(5-bromo-isoquinoline-6-yloxy)-piperidin-1-carboxylic acid tert-butyl ester (11) and 10 mg (1,1'-bis(diphenylphosphino)ferrocen)palladium(II)chlorid (0.056 eq. $Pd(dppf)Cl_2$) in 3 mL of dioxane. The mixture was heated to 100 °C for 5 h. After cooling the solvents were distilled off and the remainder was subjected to preparative HPLC to give the Boc-protected intermediate which was treated with 5-6 N HCl in isopropanol for 2 h at room temperature. Removal of the solvents gave 13.7 mg (18%) of compound 28.

LCMS Method # 1, retention time 0.67 min, detected mass 243.24 $[M+H]^+$

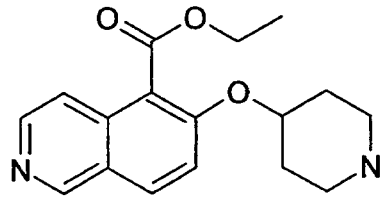
5-Benzyl-6-(piperidin-4-yloxy)-isoquinoline (29)



0.3 mL of water were added to a solution of 81 mg (0.2 mmol) of 4-(5-bromo-isoquinoline-6-yloxy)-piperidin-1- carboxylic acid tert-butyl ester (11), 195 mg (0.6 mmol) of Cs_2CO_3, 14.6 mg (0.02 mmol) of $Pd(dppf)Cl_2$ and 51 mg (0.26 mmol) of potassium benzyltrifluoroborate in 3 mL of THF. Argon was bubbled through the mixture for 10 minutes and then the reaction was heated to reflux for 16 h (incomplete conversion). After cooling to room temperature water and ethyl acetate were added. The organic layer was separated, dried over Na_2SO_4. After removal of the solvents 2 mL 5-6 N HCl in isopropanol was added. After 2 h the solvents were distilled off and the remainder was subjected twice to preparative HPLC to give 3.5 mg compound 29 as trifluoroacetate.

LCMS Method # 3, retention time 0.56 min, detected mass 319.23 $[M+H]^+$

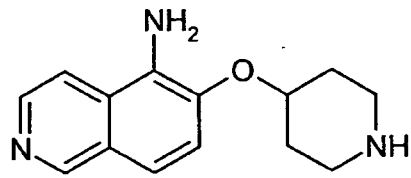
6-(Piperidin-4-yloxy)-isoquinoline-5-carboxylic acid ethyl ester (30)



A solution of 200 mg (0.44 mmol) 4-(5-iodo-isoquinoline-6-yloxy)-piperidin-1-carboxylic acid tert-butyl ester (12), 107 mg (0.88 mmol) of DMAP, 4.7 mg (0.1 eq) of Pd on charcoal (10%), 150 µL (0.88 mmol) of triethyl amine and 58 mg (0.22 mmol) of $Mo(CO)_6$ in 3 mL of ethanol was heated to 135°C for 1 h in a microwave reactor (CEM Discovery). Then water and ethyl acetate were added and the mixture was filtered through a Celite cartridge. After removal of the solvents the remainder was subjected to preparative HPLC to give the 7.4 mg Boc-protected intermediate. To remove the Boc group the intermediate was treated with 2 mL 5-6 N HCl in isopropanol at room temperature for 2 h. Purification by preparative HPLC gave 2.5 mg of compound 30 as TFA salt.

LCMS Method # 3, retention time 0.14 min, detected mass 301.29 $[M+H]^+$

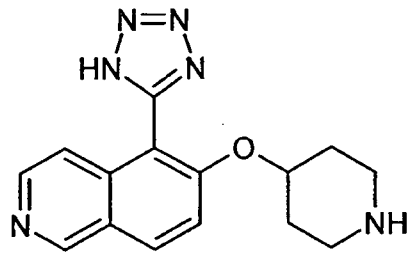
6-(Piperidin-4-yloxy)-isoquinolin-5-ylamine (31)



60 µL of 1N NaOH-solution, 6.9 mg (0.3 eq) of L-proline, 3.8 mg (0.1 eq) of CuI and 26 mg (0.4 mmol) of NaN_3 were added to a solution of 82 mg (0.2 mmol) of 4-(5-Bromo-isoquinolin-6-yloxy)-piperidine-1-carboxylic acid tert-butyl ester (11) in 2 mL of ethanol/water (7/3). The mixture was heated to 95°C for 3 h in a microwave reactor (CEM Discover). After cooling water and ethyl acetate were added and the mixture was filtered through a celite cartridge. After removal of the solvents by distillation the remainder was subjected to preparative HPLC. The N-Boc-protected intermediate was deprotected by treatment with 2 mL 5-6 N HCl in isopropanol for 2 h at room temperature. Then water was added and all solvents were removed by freeze drying to yield 18 mg of compound 31 as hydrochloride.

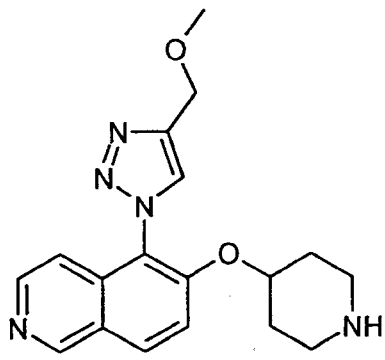
^{1}H-NMR (d_6-DMSO): δ = 9.60 (1H, s), 8.95 (2H, br s), 8.56 (1H, d, J = 7.1 Hz), 8.41 (1H, d, J = 7.1 Hz), 7.85 (1H, d, J = 9.0 Hz), 7.81(1H, d, J = 9.0 Hz), 5.03 (1H, m), 3.13 (1H, m), 2.92 (1H, m), 2.15 (2H, m), 1.99 (2H, m), 1.84 (1H, m), 1.55 (1H, m).
LCMS Method # 1, retention time 0.35 min, detected mass 244.25 $[M+H]^+$

6-(Piperidin-4-yloxy)-5-(1H-tetrazol-5-yl)-isoquinoline (32)



Under argon atmosphere 78 mg (1.2 mmol) of NaN_3 and 64 mg (1.2 mmol) of NH_4Cl were added to a solution of 35 mg (0.1 mmol) 4-(5-Cyano-isoquinolin-6-yloxy)-piperidine-1-carboxylic acid tert-butyl ester (15) in 1 mL of DMF. The mixture was heated to approximately 160°C and 7 bar pressure for 3 h in a microwave reactor (CEM Discovery). After cooling to room temperature aqueous NH_4Cl-solution and dichloromethane was added. The mixture was filtered through a phase separation cartridge and the aqueous layer was washed twice with dichloromethane. The organic layers were combined and the solvents were distilled off. The remainder was subjected to preparative HPLC to yield 4 mg (8%) of compound 32 as trifluoroacetate. LCMS Method # 3, retention time 0.90 min, detected mass 297.04 $[M+H]^+$

5-(4-Methoxymethyl-[1,2,3]triazol-1-yl)-6-(piperidin-4-yloxy)-isoquinoline (33)

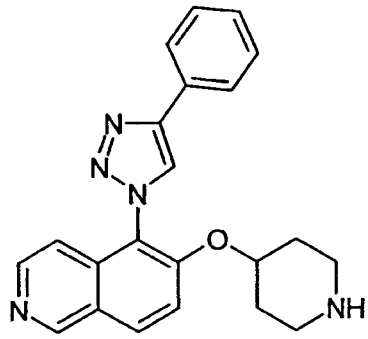


4 mg (0.1 eq.) of sodium ascorbate and 0.5 mg (0.01 eq.) of Copper(II)sulfate-hydrate were added to a solution of 73 mg (0.2 mmol) of 4-(5-Azido-isoquinoline-6-yloxy)-

piperidin-1- carboxylic acid tert-butyl ester (17) and 14 mg (0.2 mmol) of methyl propargyl ether in 4 ml of water/tert-butanol (1/1). The mixture was stirred for 18 h at room temperature. Then ethyl acetate was added and the mixture was filtered through a Celite cartridge. After removal of the solvents the remainder was subjected to preparative HPLC. The N-Boc-protected intermediate was deprotected by treatment with 2 mL 5-6 N HCl in isopropanol for 2 h at room temperature. Then the solvent was evaporated and the product was isolated by preparative HPLC to yield 2.8 mg compound 33 as trifluoroacetate.

LCMS Method # 3, retention time 0.08 min, detected mass 340.17 $[M+H]^+$

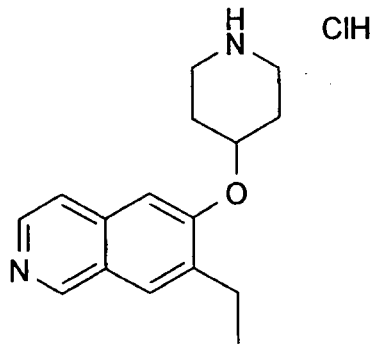
5-(4-Phenyl-[1,2,3]triazol-1-yl)-6-(piperidin-4-yloxy)-isoquinoline (34)



According to the procedure described for compound 33 the title compound was obtained using 20 mg (0.2 mmol) phenylacetylene. Yield 2.5 mg of compound 34 as trifluoroacetate.

LCMS Method # 3, retention time 0.14 min, detected mass 372.2 $[M+H]^+$

7-Ethyl-6-(piperidin-4-yloxy)-isoquinoline hydrochloride (35)



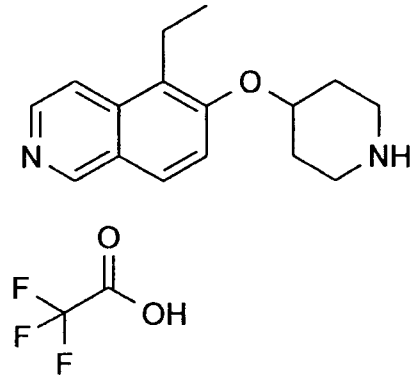
1 mg of 5 % Palladium on charcoal (0.02 eq.) was added to a solution of 174 mg 4-(7-Vinyl-isoquinolin-6-yloxy)-piperidine-1-carboxylic acid tert-butyl ester (19) (0.49 mmol, 1 eq.) in 15 mL of methanol. The olefin was hydrogenated under 5 bar H_2 at ambient temperature over night. Only partial conversion was observed, thus the catalyst was removed by filtration and fresh catalyst was added. Another treatment under the same hydrogenation conditions completed the reaction. Then the catalyst was removed by filtration and the crude product was purified by preparative HPLC to give 97 mg of the Boc protected intermediate.

The protecting group was removed by treatment with 5-6 N HCl in isopropanol for 2 h at room temperature. The solvent was distilled of and water and acetonitrile were added. Freeze drying of the mixture gave 53 mg of compound 35.

LCMS Method # 1, retention time 0.71 min, detected mass 257.18 $[M+H]^+$

The following example compound was synthesized according to this method:

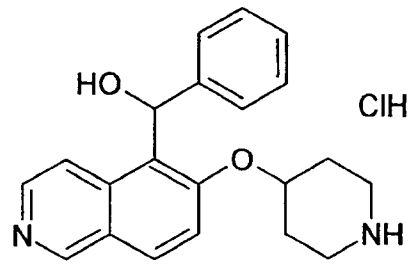
5-Ethyl-6-(piperidin-4-yloxy)-isoquinoline trifluoroacetate (36)



using compound 19A as the starting material

LCMS Method # 2, retention time 0.17 min, detected mass 257.21 $[M+H]^+$

Phenyl-[6-(piperidin-4-yloxy)-isoquinolin-5-yl]-methanol hydrochloride (37)



At –78°C 0.6 mL (0.98 mmol, 1.6 M in hexane) n-butyl lithium were added to a solution of 200 mg (0.49 mmol, 1 eq.) 4-(5-Bromo-isoquinolin-6-yloxy)-piperidine-1-carboxylic acid tert-butyl ester (11) in 3 mL of THF. After 30 min 110 µL (115 mg, 1.08 mmol) of benzaldehyde were added and the mixture was allowed to warm to ambient temperature. After 2 h of stirring at room temperature water and ethyl acetate were added. The layers were separated and the organic layer was washed with water and brine. After drying over Na_2SO_4 and evaporation of the solvent the remainder was subjected to preparative HPLC to yield the Boc protected intermediate.

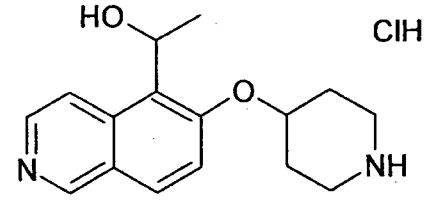
The Boc group was removed by dissolving the intermediate in isopropanol and addition of 5-6 N HCl in isopropanol. The precipitated hydrochloride was isolated by filtration to yield 5.2 mg of compound 37 (3 %).

^{1}H-NMR (d_6-DMSO): δ = 9.43 (1H, s), 8.50 (1H, br s), 8.40 (1H, br s), 8.30 (3H, m), 7.87 (1H, d, J = 9.2 Hz), 7.33 (2H, d, J = 7.4 Hz), 7.28 (2H, t, J= 7.4 Hz), 7.19 (1H, t, J = 7.4 Hz), 6.74 (1H, s), 6.34 (1H, s), 5.10 (1H, m), 3.25 (2H, m), 3.15 (2H, m), 2.19 (2H, m), 1.93 (2H, m).

LCMS Method # 1, retention time 0.80 min, detected mass 335.22 $[M+H]^+$

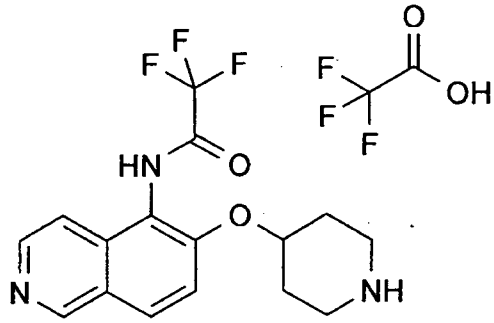
The following example compound was also synthesized according to this method:

1-[6-(Piperidin-4-yloxy)-isoquinolin-5-yl]-ethanol hydrochloride (38)



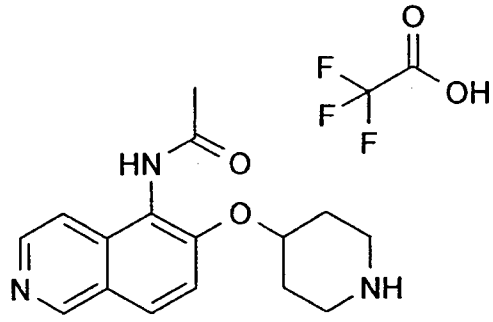
LCMS Method # 1, retention time 0.55 min, detected mass 273.2 $[M+H]^+$

2,2,2-Trifluoro-N-[6-(piperidin-4-yloxy)-isoquinolin-5-yl]-acetamide trifluoro-acetate (39)



62.8 mg of potassium carbonate (0.46 mmol, 4 eq.) and 10.7 µL of methanesulfonyl chloride (0.13 mmol, 1.2 eq.) were added to a solution of 39 mg (0.11 mmol) of 4-(5-Amino-isoquinoline-6-yloxy)- piperidin-1- carboxylic acid tert-butyl ester (18) (containing some compound 11) in 3 mL DMF. The reaction was stirred for 4 h at room temperature. Then water and ethyl acetate were added. The mixture was filtered through Celite, washed with ethyl acetate and concentrated to yield a single product. The N-Boc-protected intermediate was deprotected by treatment with 2 mL 5-6 N HCl in isopropanol for 2 h at room temperature. Then the solvent was evaporated and the product was isolated by preparative HPLC to yield 18.5 mg of compound 39.
LCMS Method # 1, retention time 0.39 min, detected mass 340.15 $[M+H]^+$

N-[6-(Piperidin-4-yloxy)-isoquinolin-5-yl]-acetamide trifluoro-acetate (40)

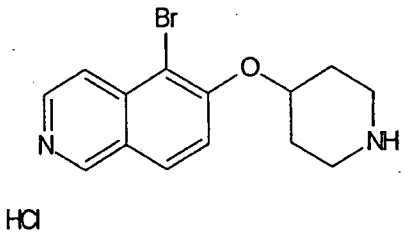
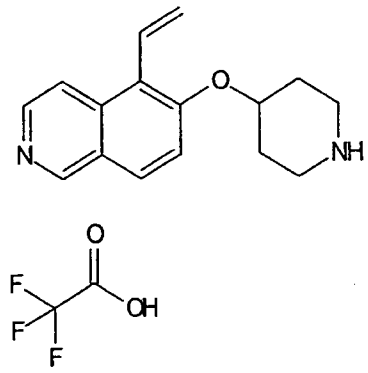


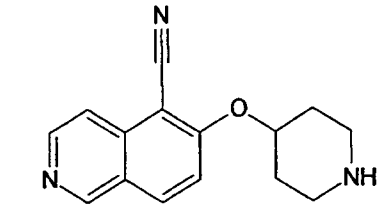
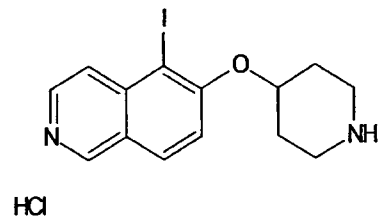
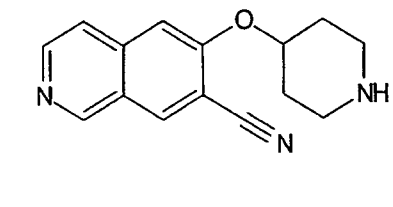
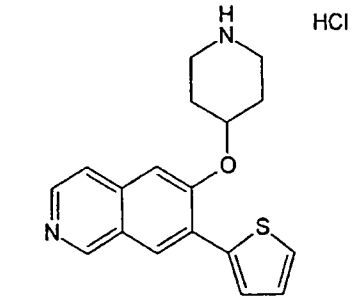
Under argon atmosphere 81.5 mg (0.2 mmol) of 4-(5-bromo-isoquinoline-6-yloxy)-piperidin-1-carboxylic acid tert-butyl ester (11) and 14.2 mg of acetamide (0.24 mmol, 1.2 eq.) were added to a solution of 27 mg (0.28 mmol, 1.4 eq) of NaOtBu in 3 mL toluene. After stirring for 10 minutes at room temperature 9.1 mg (0.01 mmol, 0.05 eq) $Pd_2(dba)_3$ and 11.9 mg (0.04 mmol, 0.2 eq) of 2-(dt-butylphosphino)biphenyl were added. The reaction was heated to 120 °C for 2 h in a microwave reactor (CEM Discovery). Then water and ethyl acetate were added. The mixture was filtered

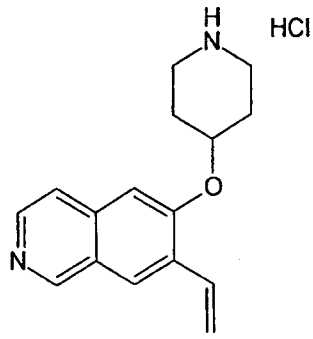
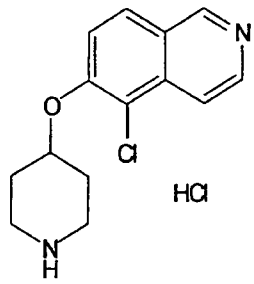
through Celite, washed with ethyl acetate and concentrated. The remainder was subjected twice to preparative HPLC to yield the N-Boc-protected intermediate. The N-Boc-protected intermediate was deprotected by treatment with 2 mL 5-6 N HCl in isopropanol for 2 h at room temperature. Then the solvent was evaporated and the product was isolated by preparative HPLC to yield 2.5 mg of compound 40.
LCMS Method # 3, retention time 0.15 min, detected mass 286.15 $[M+H]^+$

General procedure for Boc-deprotection of building blocks:

The corresponding N-Boc-protected compounds were treated with 5-6 N HCl in isopropanol for 2 h at room temperature. The precipitated hydrochlorides were isolated by filtration and dried. If necessary, additional purification by preparative HPLC was performed.

No.	Compound	Starting material	LCMS Method #	Retention time	Detected mass $[M+H]^+$
41		11	2	0.57	307.13
42		19A	2	0.64	255.19

No.	Compound	Starting material	LCMS Method #	Retention time	Detected mass $[M+H]^+$
43	 HCl	15	2	0.46	254.15
44	 HCl	12	1	0.67	355.04
45	 HCl	16	1	0.64	254.13
46	 HCl	20	1	0.87	311.12

No.	Compound	Starting material	LCMS Method #	Retention time	Detected mass $[M+H]^+$
47		19	1	0.72	255.19
48		8	1	0.52	263.10

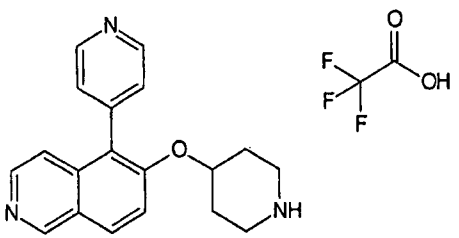
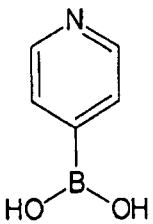
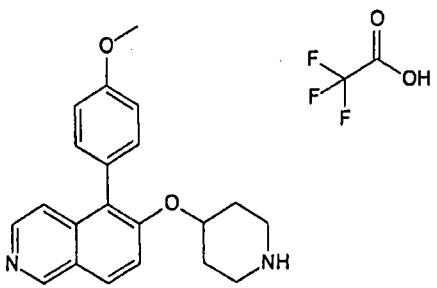
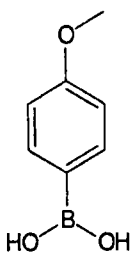
General procedure for Suzuki-coupling with 4-(5-Bromo-isoquinoline-6-yloxy)-piperidin-1- carboxylic acid tert-butyl ester (11)

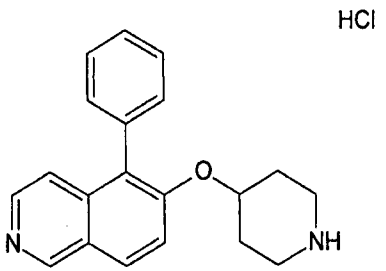
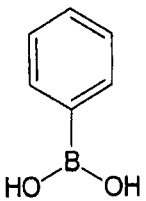
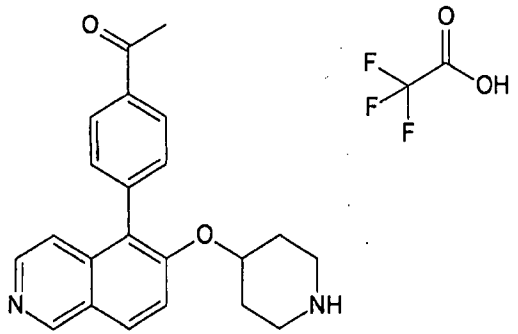
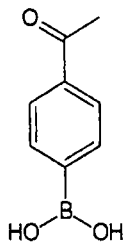
Aqueous Na_2CO_3 solution (0.2 ml, 0.4 mmol, 2 eq. 2M) was added to a solution of 81 mg (0.2 mmol, 1 eq.) of 4-(5-Bromo-isoquinoline-6-yloxy)-piperidin-1- carboxylic acid tert-butyl ester (11) and 1.5 eq. (0.3 mmol) of the corresponding boronic acid (reagent 2) in 3 mL of DME. Argon was bubbled through the reaction mixture for 10 min. Then 23 mg (0.1 eq.) $Pd(PPh_3)_4$ were added and the reaction was stirred at 95 °C overnight under Argon atmosphere. After cooling 2 mL of water and 10 mL of ethyl acetate were added. The organic layer was separated, dried and the solvent was distilled off. The remainder was subjected to preparative HPLC.

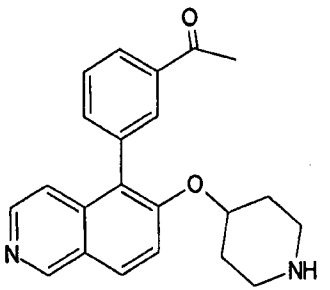
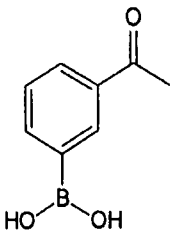
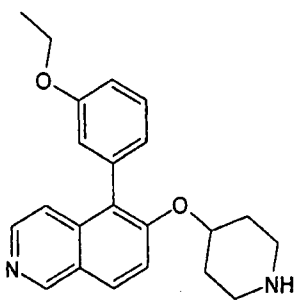
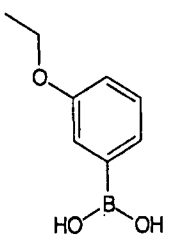
The Boc group was removed by dissolving the intermediate in isopropanol and addition of 5-6 N HCl in isopropanol. The precipitate was isolated by filtration.

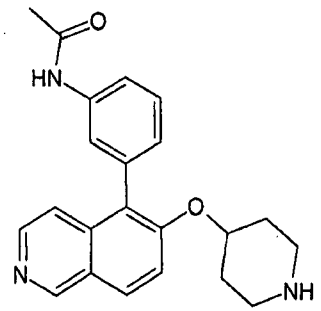
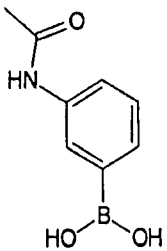
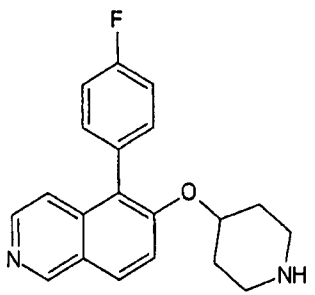
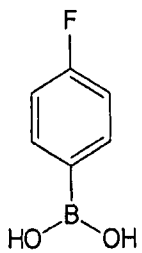
In some reactions no hydrochloride precipitated or the purity of the precipitate was unsatisfactory. In these cases the solvent was distilled off and the remainder was purified by preparative HPLC.

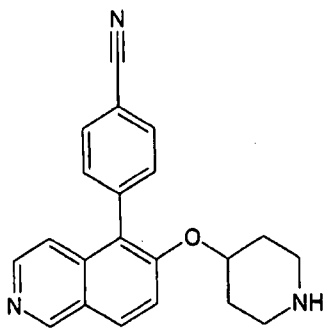
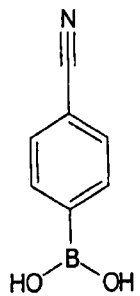
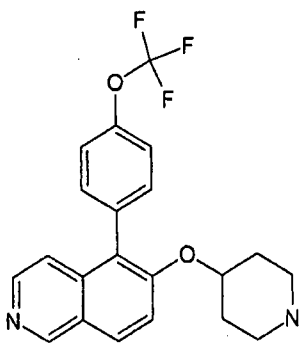
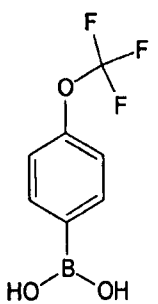
The following examples were synthesized using this method:

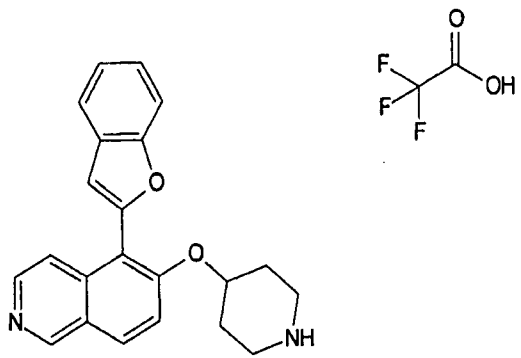
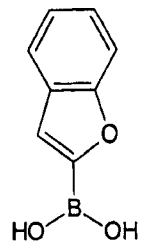
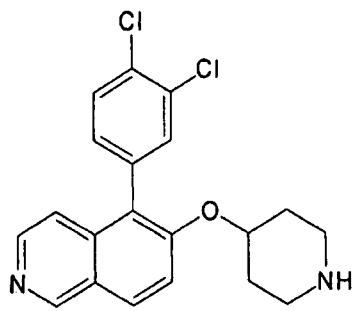
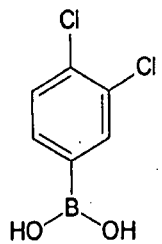
No.	Compound	Reagent 1	Reagent 2	Method #	retention time	detected mass $[M+H]^+$
49		11		2	0.15	306.22
50		11		4	0.75	335.20

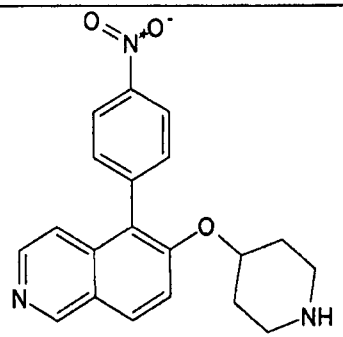
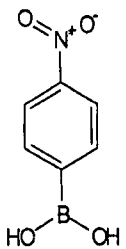
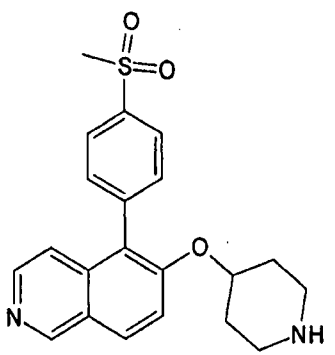
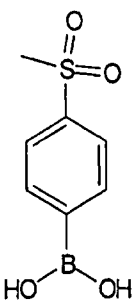
No.	Compound	Reagent 1	Reagent 2	Method #	retention time	detected mass $[M+H]^+$
51		11		4	0.76	305.15
52		11		1	0.81	347.18

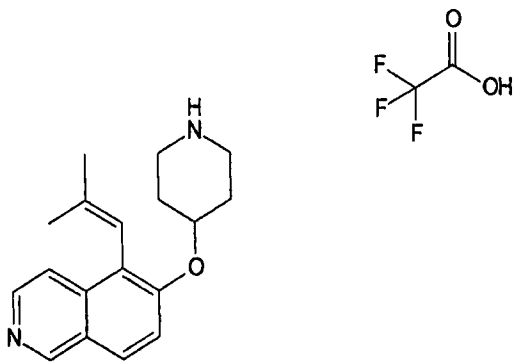
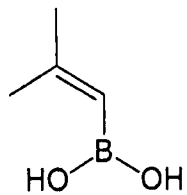
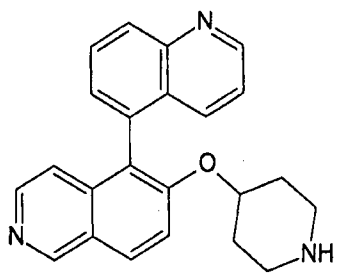
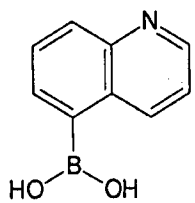
No.	Compound	Reagent 1	Reagent 2	Method #	retention time	detected mass $[M+H]^+$
53	 HCl	11		1	0.84	347.17
54	 HCl	11		1	0.90	349.24

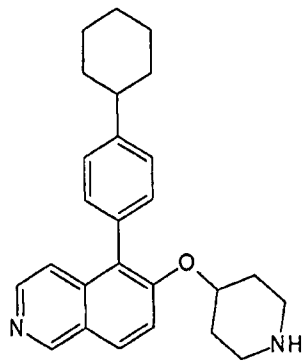
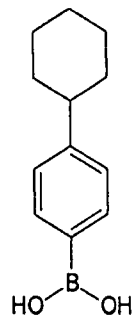
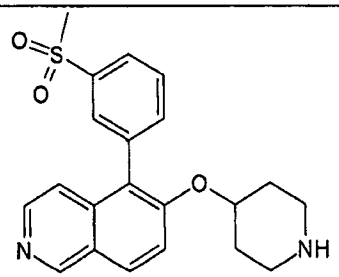
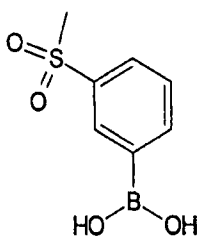
No.	Compound	Reagent 1	Reagent 2	Method #	retention time	detected mass $[M+H]^+$
55	 HCl	11		1	0.75	362.22
56	 HCl	11		1	0.88	323.20

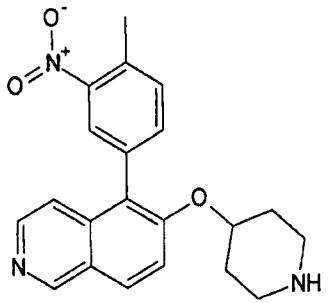
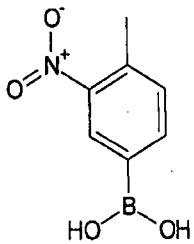
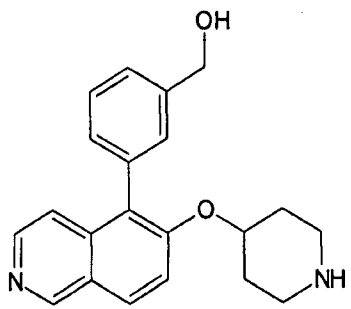
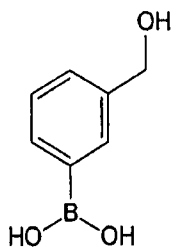
No.	Compound	Reagent 1	Reagent 2	Method #	retention time	detected mass $[M+H]^+$
57	 TFA	11		3	0.44	371.24 $[M+MeCN+H]^+$
58	 TFA	11		3	1.09	389.13

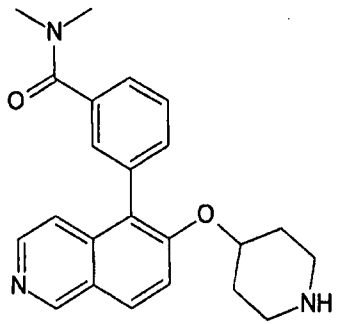
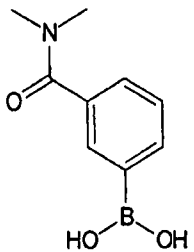
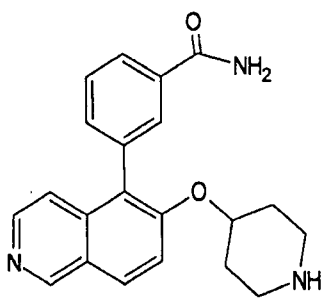
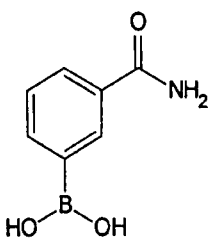
No.	Compound	Reagent 1	Reagent 2	Method #	retention time	detected mass $[M+H]^+$
59		11		3	1.02	345.14
60	 TFA	11		3	1.06	373.03

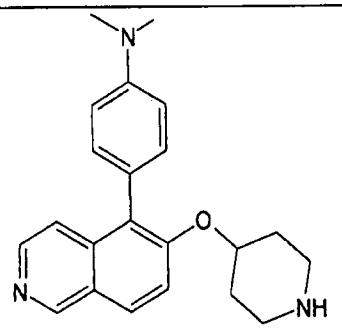
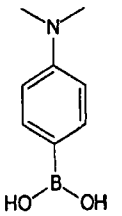
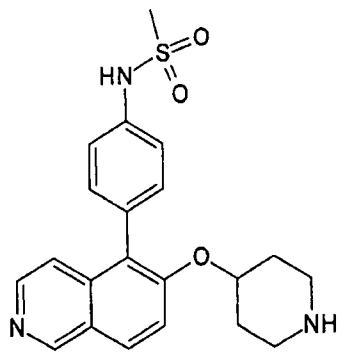
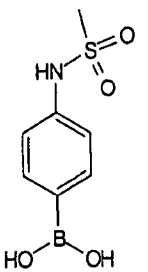
No.	Compound	Reagent 1	Reagent 2	Method #	retention time	detected mass $[M+H]^+$
61	 TFA	11		1	0.87	350.16
62	 HCl	11		1	0.72	383.14

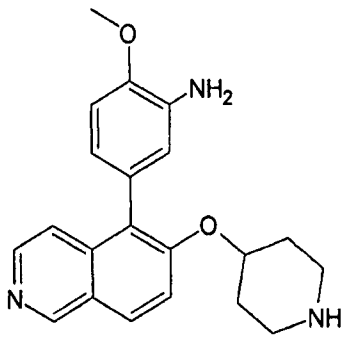
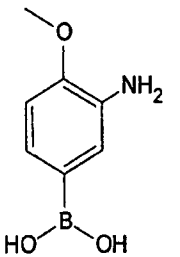
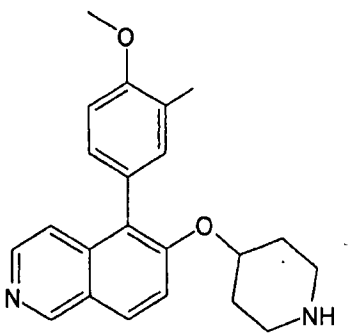
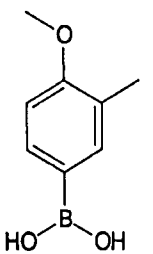
No.	Compound	Reagent 1	Reagent 2	Method #	retention time	detected mass $[M+H]^+$
62A		11		1	0.79	283.18
63	 TFA	11		2	0.18 0.47	356.21 356.23

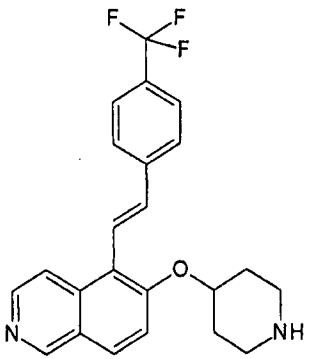
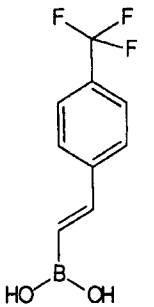
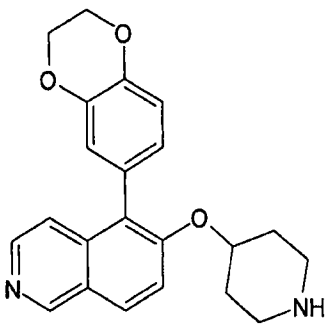
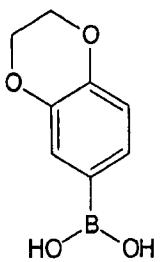
No.	Compound	Reagent 1	Reagent 2	Method #	retention time	detected mass $[M+H]^+$
64	 TFA	11		2	1.31	387.30
65	 HCl	11		2	0.73	383.21

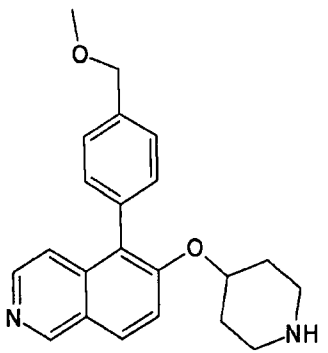
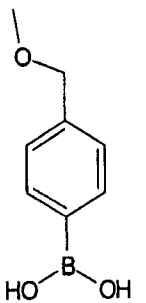
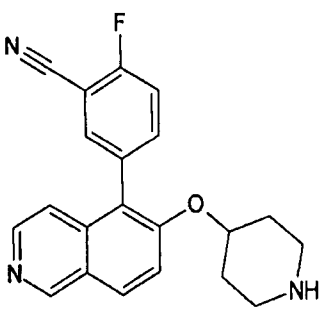
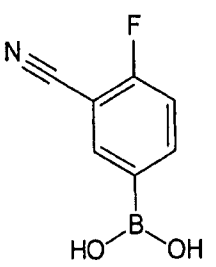
No.	Compound	Reagent 1	Reagent 2	Method #	retention time	detected mass $[M+H]^+$
66	 TFA	11		1	0.90	364.15
67	 TFA	11		1	0.76	335.17

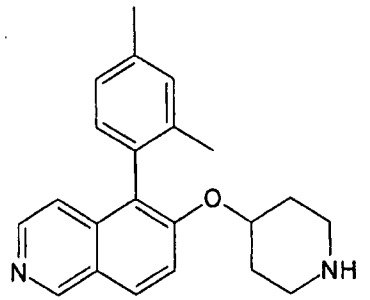
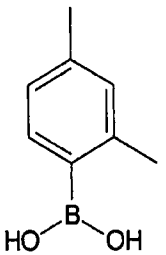
No.	Compound	Reagent 1	Reagent 2	Method #	retention time	detected mass $[M+H]^+$
68	 TFA	11		3	0.42	376.18
69	 HCl	11		2	0.61	348.23

No.	Compound	Reagent 1	Reagent 2	Method #	retention time	detected mass $[M+H]^+$
70	 HCl	11		1	0.61	348.21
71	 HCl	11		4	0.75	398.15

No.	Compound	Reagent 1	Reagent 2	Method #	retention time	detected mass $[M+H]^+$
72	 TFA	11		2	0.64	350.24
73	 TFA	11		2	0.93	349.24

No.	Compound	Reagent 1	Reagent 2	Method #	retention time	detected mass $[M+H]^+$
74	 TFA	11		2	1.22	399.23
75	 TFA	11		2	0.75	363.23

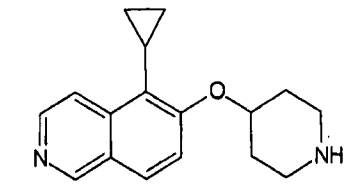
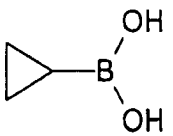
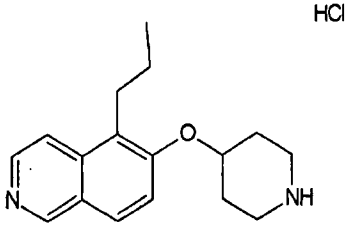
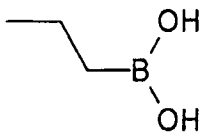
No.	Compound	Reagent 1	Reagent 2	Method #	retention time	detected mass $[M+H]^+$
76	 TFA	11		2	0.87	349.25
77	 TFA	11		2	0.81	348.20

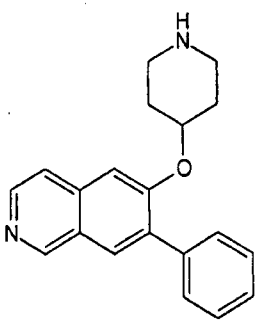
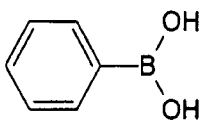
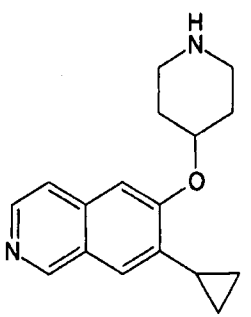
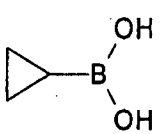
No.	Compound	Reagent 1	Reagent 2	Method #	retention time	detected mass $[M+H]^+$
78	 TFA	11		2	1.00	333.25

Suzuki coupling procedure for variation in the 5- and 7-position

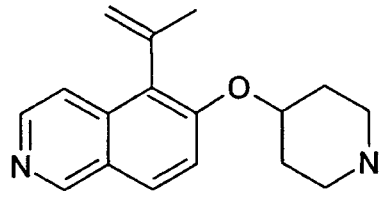
The base was added to a solution of reagent 1 (typically 0.2 mmol) and reagent 2 in DME. Argon was bubbled through the reaction mixture for 10 min. Then the catalyst was added and the reaction was stirred at reflux temperature overnight under Argon atmosphere. After cooling 2 mL of water and 10 mL of ethyl acetate were added. The mixture was filtered through a celite cartridge. The solvents were removed by distillation and the remainder was subjected to preparative HPLC.
The isolated intermediate was deprotected by treatment with 2 mL 5-6 N HCl in isopropanol for 2 h at room temperature. The solvent was distilled of and the precipitate was isolated by filtration. In some reactions no hydrochloride precipitated or the purity of the precipitate was unsatisfactory. In these cases the solvent was distilled off and the remainder was purified by preparative HPLC.

Using this method the following examples were prepared:

No.	Compound	Reagent 1	Reagent 2	Catalyst	Base	LCMS Method #	Retention time	Detected mass $[M+H]^+$
79	 HCl	12		0.05 eq. $PdOAc_2$ 0.1 eq. $P(Cy)_3$	3.5 eq. K_3PO_4	2	0.66	269.17
80	HCl 	12		0.05 eq. $PdOAc_2$ 0.1 eq. $P(Cy)_3$	3.5 eq. K_3PO_4	1	0.81	271.19

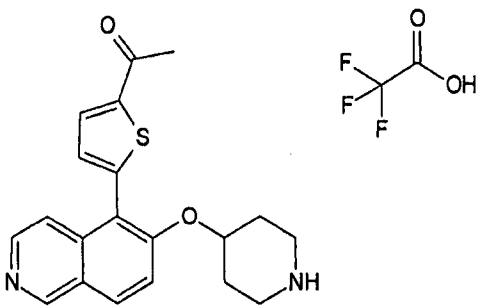
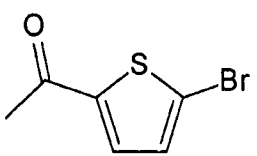
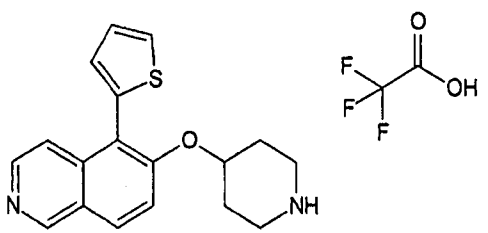
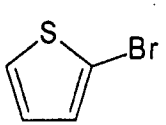
No.	Compound	Reagent 1	Reagent 2	Catalyst	Base	LCMS Method #	Retention time	Detected mass $[M+H]^+$
81	 TFA	13		0.15 eq. $Pd(PPh_3)_4$	2 eq. K_2CO_3	1	0.87	305.16
82	 TFA	13		0.15 eq. $Pd(PPh_3)_4$	2 eq. K_2CO_3	1	0.85	269.2

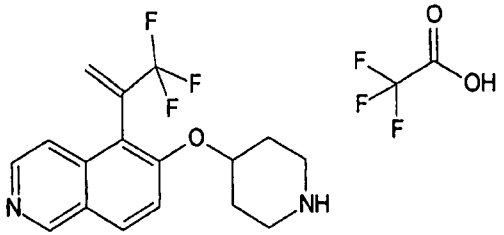
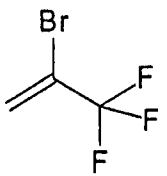
5-Isopropenyl-6-(piperidin-4-yloxy)-isoquinoline (83)



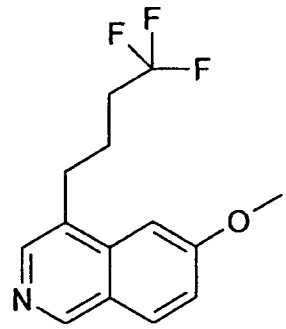
85 mg (0.62 mmol) of K_2CO_3 and 70 mg (0.15 mmol) of 4-[5-(4,4,5,5-Tetramethyl-[1,3,2]dioxaborolan-2-yl)-isoquinoline-6-yloxy]-piperidin-1- carboxylic acid tert-butyl ester (14) were added to a solution of 22 mg (0.18 mmol) 2-Bromo-propene in 2mL of DMF. Under argon atmosphere 5.6 mg (0.05 eq) of $Pd(dppf)Cl_2$ were added and the mixture was heated to 100°C for 16 h. After cooling to room temperature water and dichloromethane were added. The mixture was filtered through a Celite cartridge. The solvents were removed by distillation and the remainder was subjected to preparative HPLC. The isolated intermediate was deprotected by treatment with 2 mL 5-6 N HCl in isopropanol for 2 h at room temperature. The solvent was distilled of and compound 83 was isolated by preparative HPLC to give 3.2 mg as the trifluoroacetate.
LCMS Method # 3, retention time 0.15 min, detected mass 269.15 $[M+H]^+$

Using this method the following examples were prepared:

No.	Compound	Reagent	LCMS Method #	retention time	detected mass $[M+H]^+$
84			3	0.14	353.16
85			3	0.41	311.22

No.	Compound	Reagent	LCMS Method #	retention time	detected mass $[M+H]^+$
86			3	0.56	323.15

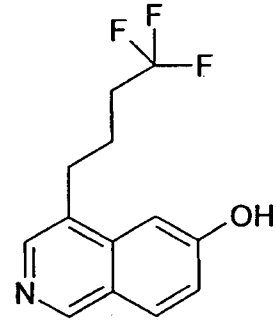
6-Methoxy-4-(4,4,4-trifluoro-butyl)-isoquinoline (87)



2 g 6-Methoxy-isoquinoline were dissolved in 25 mL of dry tetrahydrofuran. 12.56 mL of a 1 M solution of potassium triethyl borohydrate were added dropwise. The solution was allowed to stir at room temperature for 2 h, then 3,29 g of 4,4,4-Trifluoro-1-iodobutane were added dropwise. The solution was allowed to stir overnight, then 32 mL of 1M sodium hydroxide and 12 mL of sodium peroxide solution (35%) were added. Stirring was continued for another 3 hrs, then the solution was diluted with dichloromethane, extracted with water and brine and the organic layer was dried over sodium sulfate and evaporated to dryness. Silica gel chromatography yields 1.03 g of the desired product.

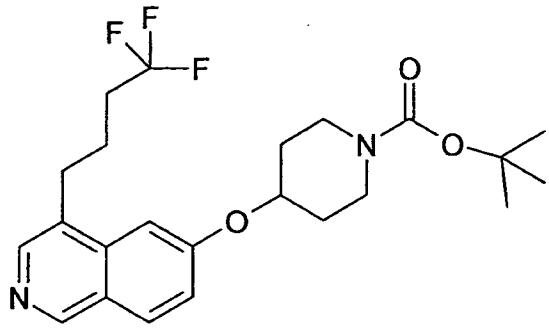
LCMS Method # 1, retention time 1.20 min, detected mass 270.06 $[M+H]^+$

6-Hydroxy-4-(4,4,4-trifluoro-butyl)-isoquinoline (88)



1.02 g of 6-Methoxy-4-(4,4,4-trifluoro-butyl)-isoquinoline (87) were treated with boron tribromide as described for the synthesis of compound 1 to give 410 mg of the desired product 88. LCMS Method # 1, retention time 1.04 min, detected mass 256.00 $[M+H]^+$

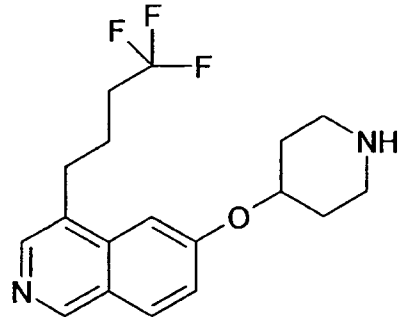
4-[4-(4,4,4-Trifluoro-butyl)-isoquinolin-6-yloxy]-piperidine-1-carboxylic acid tert- butyl ester (89)



100 mg of compound 88, 118 mg of Boc-(4-hydroxy)piperidine and 416 mg of Diphenyl-[4-[1H,1H,2H,2H-perfluorodecyl]phenyl]phosphine were dissolved in 5 mL of dry tetrahydrofurane. 208 mg of Bis (1H, 2H, 2H, 3H, 3H-perflourononyl)-azodicarboxylate were added and the reaction was allowed to stir overnight. The mixture was evaporated to dryness and filtered over a 5 g Fluoro-Flash cartridge. The obtained crude product was purified by preparative HPLC to yield 46 mg of the desired product.

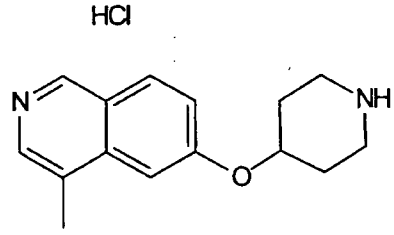
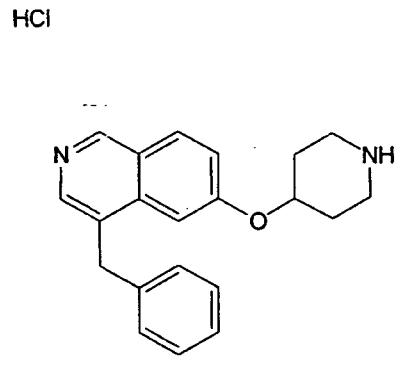
LCMS Method # 1, retention time 1.51 min, detected mass 439.13 $[M+H]^+$

6-(Piperidin-4-yloxy)-4-(4,4,4-trifluoro-butyl)-isoquinoline (90)



42 mg of compound 89 were dissolved in 5M hydrochloric acid in isopropanol. The solution was stirred at room temperature for 2hrs and another 2 hrs at 40°C, evaporated to dryness and taken up in water and lyophilized three times to give 32 mg of the desired product as the hydrochloride salt. LCMS Method # 1, retention time 0.98 min, detected mass 338.16 $[M+H]^+$

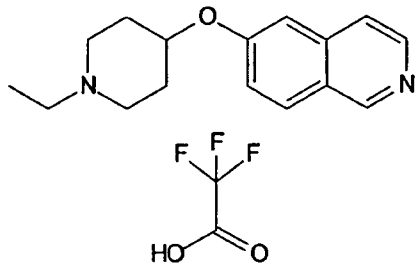
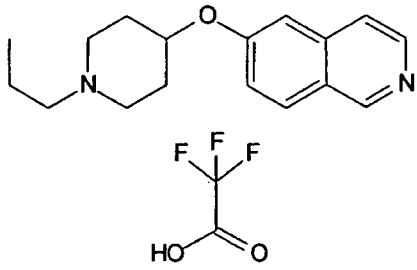
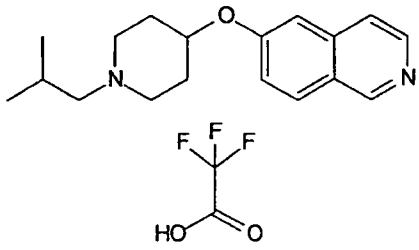
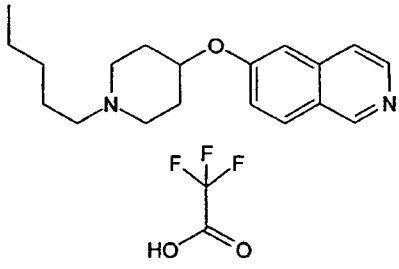
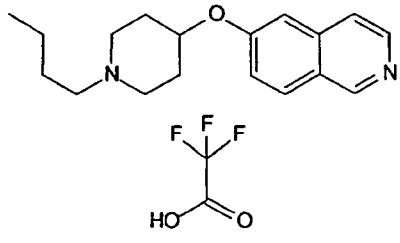
The following isoquinolines were synthesized in a similar fashion as described for compound 90, using appropriate alkyl halides:

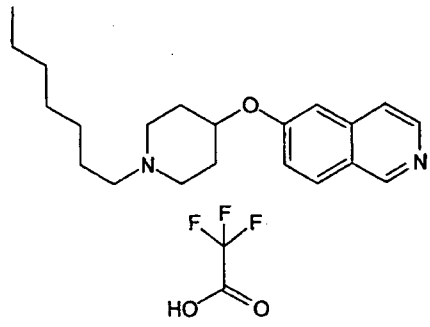
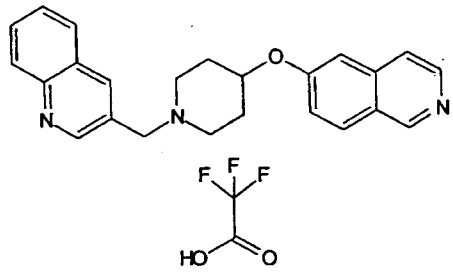
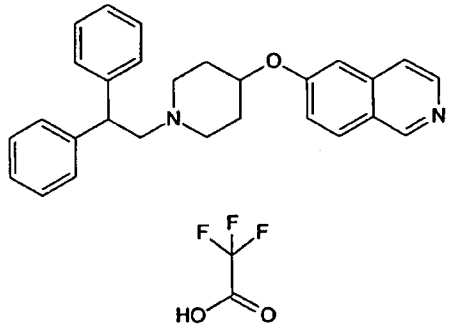
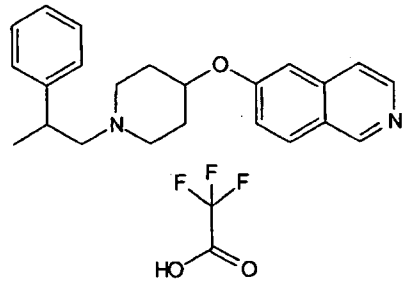
No.	Compound	Weight	Method	RT [min]	Detected Mass [MH^+]
91		242.14	1	0.56	243.13
92		318.17	1	0.84	319.17

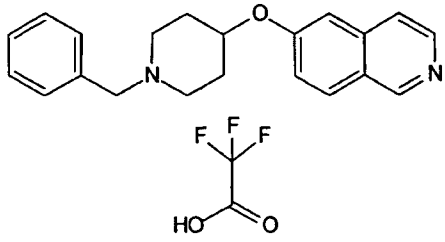
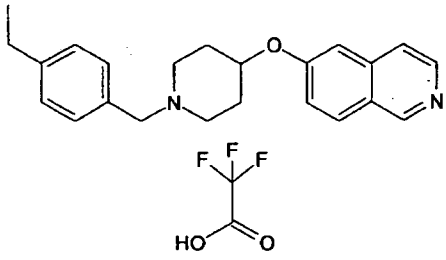
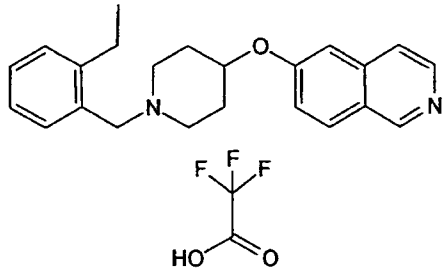
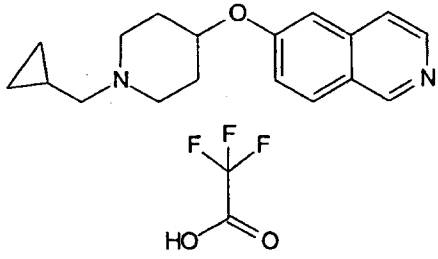
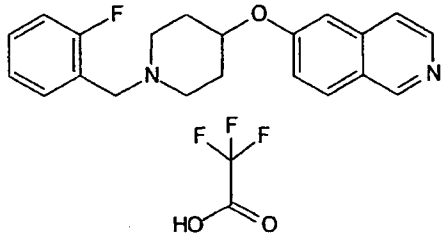
General procedure for reductive amination:

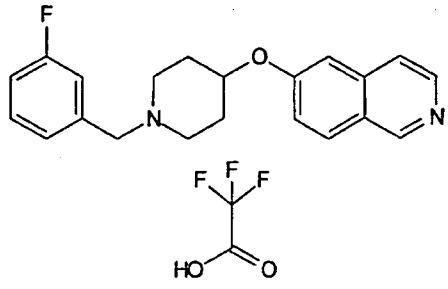
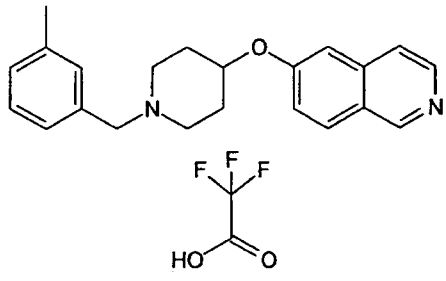
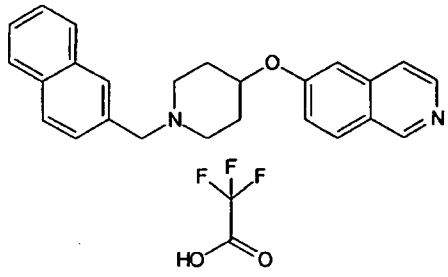
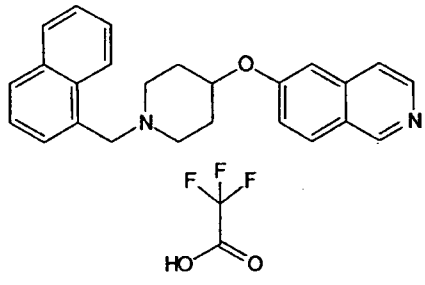
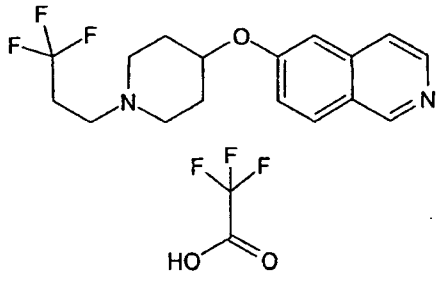
1.5 eq of aldehyde was dissolved in 1 mL of methanol and 50 mg of compound 124 and 27 mg of anhydrous sodium acetate, dissolved in methanol, were added. 0.250 mL of a solution of 1M sodium cyanoborohydride in THF was added. The reaction was allowed to run overnight, then the solution was filtered, evaporated to dryness and the residue was taken up in ethyl acetate. The organic layer was extracted with a solution of 5% sodium carbonate in water, then with 5% sodium chloride in water. The organic layer was dried, evaporated to dryness and purified by RP chromatography.

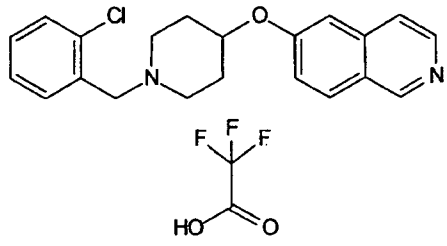
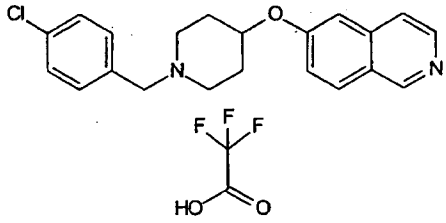
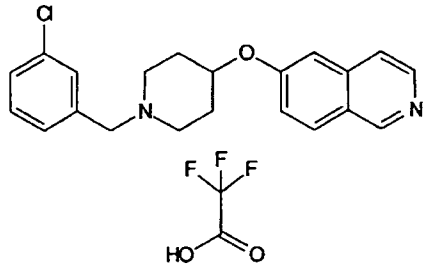
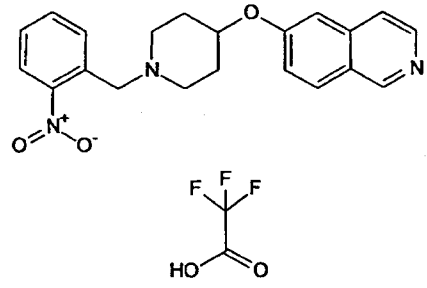
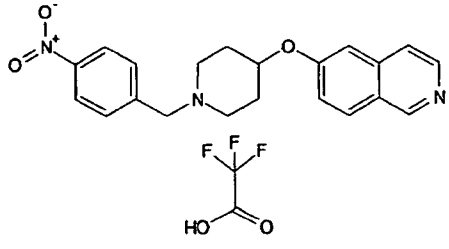
This procedure was used to obtain compounds 93 to 123:

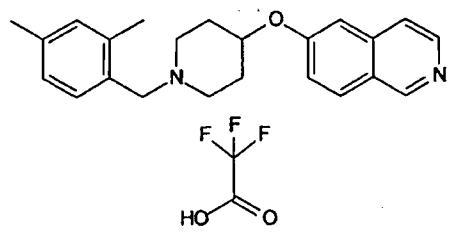
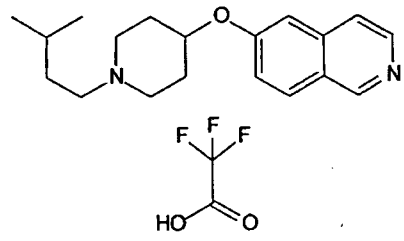
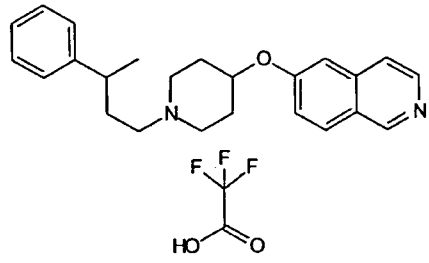
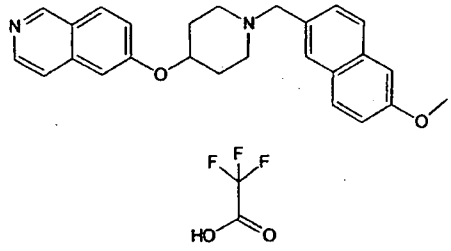
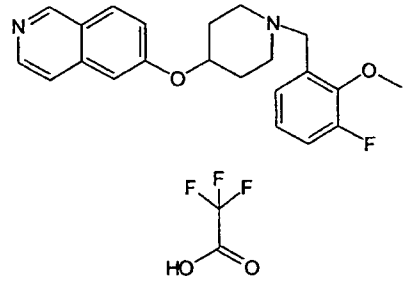
No.	Compound	RT	Mass $[MH]^+$
93		0.13	257.23
94		0.53	271.26
95		0.79	285.27
96		0.92	299.29
97		0.74	285.27

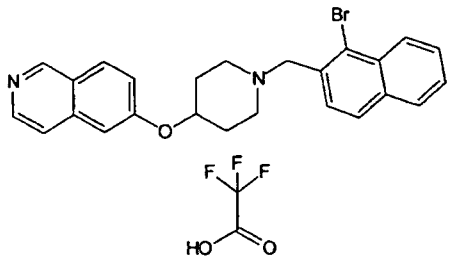
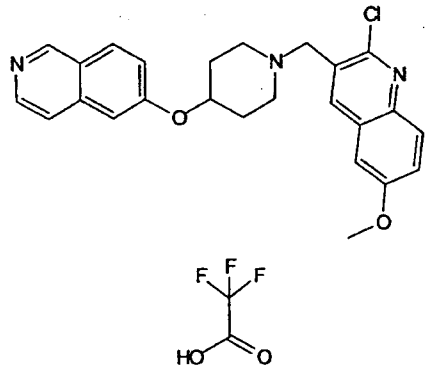
No.	Compound	RT	Mass $[MH]^+$
98		1.22	327.30
99		0.89	370.29
100		1.25	409.34
101		1.06	347.29

No.	Compound	RT	Mass $[MH]^+$
102		0.89	319.26
103		0.99	347.32
104		0.96	347.29
105		0.60	283.15
106		0.74	337.26

No.	Compound	RT	Mass $[MH]^+$
107		0.95	337.24
108		1.01	333.28
109		1.04	369.29
110		1.14	369.30
111		0.58/0.74	325.23

No.	Compound	RT	Mass $[MH]^+$
112		1.00	353.22/355.23
113		0.91	353.23/355.23
114		0.88	353.24/355.24
115		0.87	364.20
116		0.92	364.26

No.	Compound	RT	Mass $[MH]^+$
117		1.10	347.31
118		0.77	299.28
119		1.13	361.31
120		1.07	399.30
121		0.86	367.27

No.	Compound	RT	Mass $[MH]^+$
122		1.15	447.22/449.68
123		1.13	434.16

All LCMS in this table were obtained using LCMS method #2.

General procedure for the reaction of boc-protected aminoalcohols with 6-hydroxy isoquinolines (Mitsunobu-reaction):

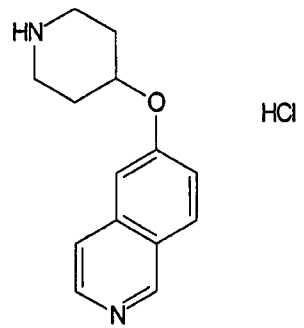
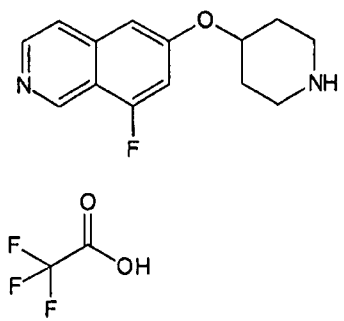
AAV1:

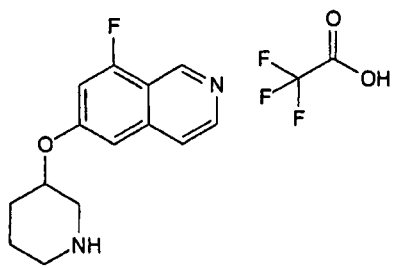
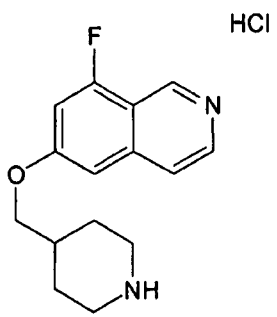
To 500 mg (1.5 mmol) of triphenylphosphine (bound to polystyrene, 3mmol/g) and 10 ml of dichloromethane 0.195 mL (1.2 mmol) of diethylazodicarboxylate (or alternatively diisopropylazodicarboxylate) were added. The reaction mixture was allowed to shake for 10 min. and then 0.14 mL of triethylamine, 145 mg of 6-hydroxyisoquinoline (7) (or an equivalent amount of a different suitable isoquinol) (reagent 1) and 1 mmol of the desired, boc-protected aminoalcohol (reagent 2) was added. The reaction was shaken at room temperature until no further conversion could be observed by LCMS. For workup, the solution was filtered, the residue was washed with dichloromethane and

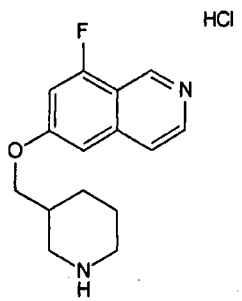
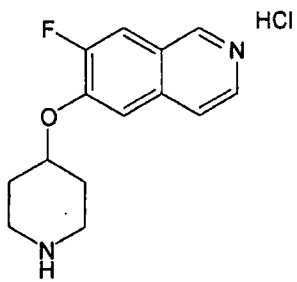
the organic layer was washed twice with 1N sodium hydroxide, twice with water and once with brine, dried over magnesium sulfate and evaporated. The crude product was purified by preparative HPLC to yield the boc protected coupled product.

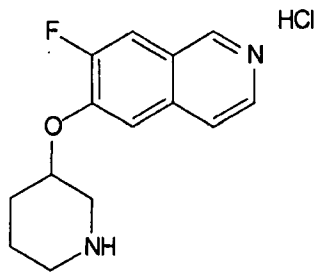
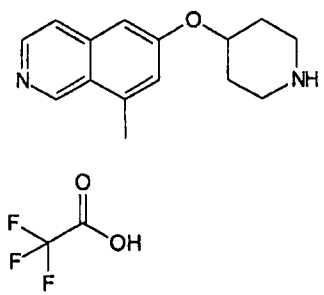
General procedure for removal of the boc-group (AAV2):

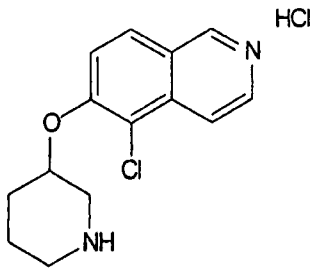
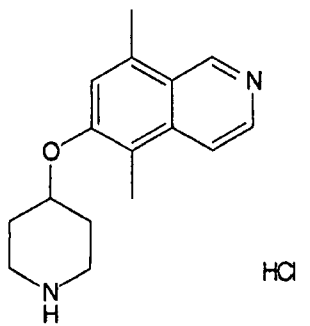
The starting material was dissolved in 2M hydrochloric acid and reacted overnight. To compounds with poor aqueous solubility, methanol or dioxane was added until a homogenous solution was obtained. Alternatively, 4M hydrochloric acid in isopropanol was used to react the compound. The reaction mixture was lyophilised and the deprotected product is obtained as the corresponding hydrochloride of the free amine.

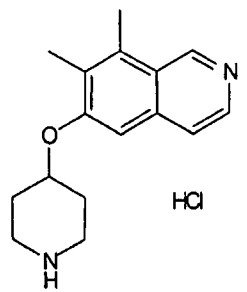
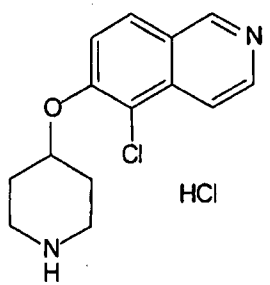
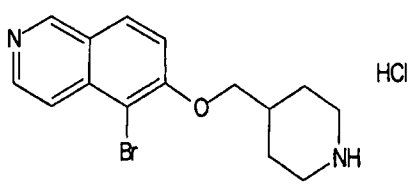
No.	Compound	Reagent 1	Reagent 2	LCMS Method #	Retention time	Detected mass [M+H]+
124		7	4-Hydroxypiperidine-1-carboxylic acid tert-butyl ester	1	0.47	229.21
125		2	4-Hydroxypiperidine-1-carboxylic acid tert-butyl ester	4	0.37	247.4

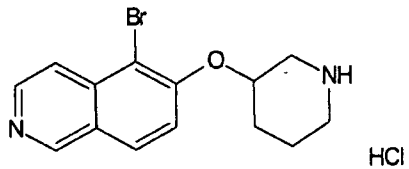
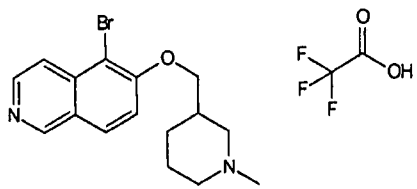
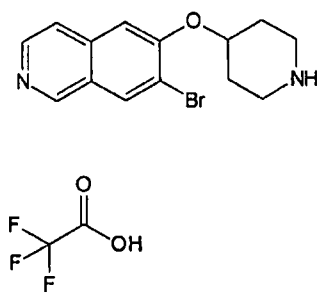
No.	Compound	Reagent 1	Reagent 2	LCMS Method #	Retention time	Detected mass [M+H]+
126		2	3-Hydroxypiperidine-1-carboxylic acid tert-butyl ester	4	0.34	247.35
127		2	4-Piperidylmethanol-1-carboxylic acid tert-butyl ester	4	0.53	261.20

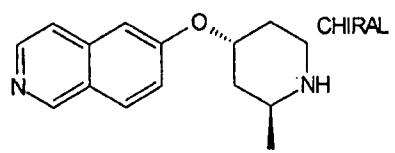
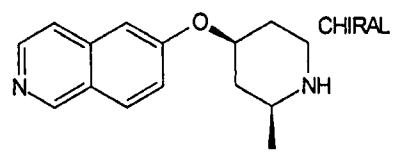
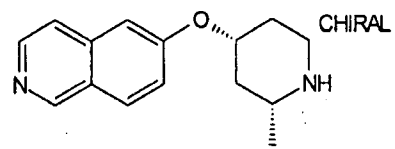
No.	Compound	Reagent 1	Reagent 2	LCMS Method #	Retention time	Detected mass [M+H]+
128		2	3-Piperidylmethanol-1-carboxylic acid tert-butyl ester	4	0.57	261.20
129		3	4-Hydroxypiperidine-1-carboxylic acid tert-butyl ester	4	0.35	247.10

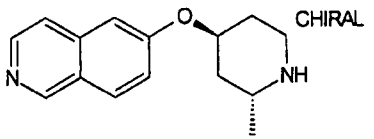
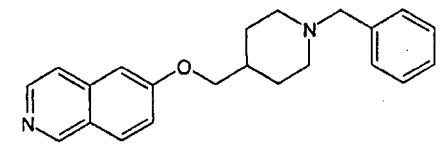
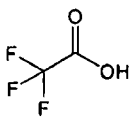
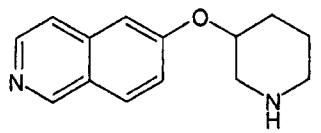
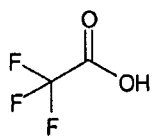
No.	Compound	Reagent 1	Reagent 2	LCMS Method #	Retention time	Detected mass [M+H]+
130		3	3-Hydroxypiperidine-1-carboxylic acid tert-butyl ester	4	0.35	247.10
131		4	4-Hydroxypiperidine-1-carboxylic acid tert-butyl ester	3	0.14	243.12

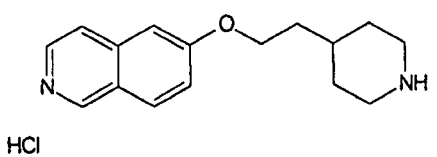
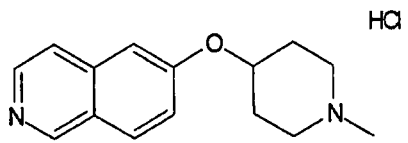
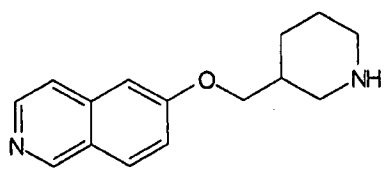
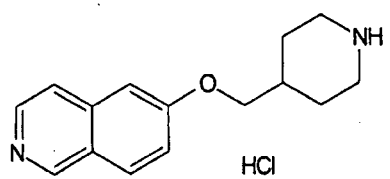
No.	Compound	Reagent 1	Reagent 2	LCMS Method #	Retention time	Detected mass [M+H]+
132		8	3-Hydroxypiperidine-1-carboxylic acid tert-butyl ester	4	0.60	263.15
133		6	4-Hydroxypiperidine-1-carboxylic acid tert-butyl ester	4	0.67	257.15

No.	Compound	Reagent 1	Reagent 2	LCMS Method #	Retention time	Detected mass [M+H]+
134		5	4-Hydroxypiperidine-1-carboxylic acid tert-butyl ester	1	0.68	257.20
135		8	4-Hydroxypiperidine-1-carboxylic acid tert-butyl ester	1	0.52	263.10
136		9	4-Hydroxymethyl-piperidine-1-carboxylic acid tert-butyl ester	2	0.33	321.14/323.15

No.	Compound	Reagent 1	Reagent 2	LCMS Method #	Retention time	Detected mass [M+H]+
137		9	3-Hydroxy-piperidine-1-carboxylic acid tert-butyl ester	2	0.31	307.12/309.12
138		9	N-Methyl-3-piperidylmethanol	1	0.75	335.12
139		1	4-Hydroxypiperidine-1-carboxylic acid tert-butyl ester	2	0.62	307.06

No.	Compound	Reagent 1	Reagent 2	LCMS Method #	Retention time	Detected mass [M+H]+
140	 HCl	7	26	1	0.60	243.22
141	 HCl	7	25	1	0.60	243.19
142	 HCl	7	25	1	0.60	243.29

No.	Compound	Reagent 1	Reagent 2	LCMS Method #	Retention time	Detected mass [M+H]+
143	 HCl	7	26	3	0.12	243.13
144	 	7	(1-Benzyl-piperidin-4-yl)-methanol	2	0.17	333.2
145	 	7	3-Hydroxy-piperidine-1-carboxylic acid tert-butyl ester	2	0.2	229.2

No.	Compound	Reagent 1	Reagent 2	LCMS Method #	Retention time	Detected mass [M+H]+
146	 HCl	7	4-(2-Hydroxy-ethyl)-piperidine-1-carboxylic acid tert-butyl ester	2	0.18	257.2
147	 HCl	7	1-Methyl-piperidin-4-ol	1	0.45	243.2
148	 HCl	7	3-Hydroxymethyl-piperidine-1-carboxylic acid tert-butyl ester	2	0.17	243.2
149	 HCl	7	4-Hydroxymethyl-piperidine-1-carboxylic acid tert-butyl ester	2	0.17	243.2

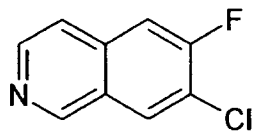
Chromatographic resolution of compounds 140 and 143:

The N-Boc protected intermediate, obtained as an enantiomeric mixture of compound 140 and compound 143, was separated into the enantiomers on a chiral column (Chiralcel OD-H/56 250 x 4.6 mm). The removal of the protection group as the final step was performed as described in the general procedure.
The absolute configuration of the stereo centers has not been determined.
Compound 140: earlier eluting Boc-protected intermediate;
Compound 143: later eluting Boc-protected intermediate

Chromatographic resolution of compounds 141 and 142:

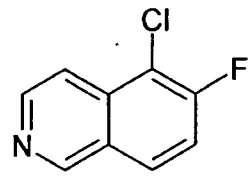
The N-Boc protected intermediate, obtained as an enantiomeric mixture of compound 141 and compound 142, was separated into the enantiomers on a chiral column (Chiralpak AD-H/40 250 x 4.6 mm). The removal of the protection group as the final step was performed as described in the general procedure.
The absolute configuration of the stereo centers has not been determined.
Compound 141: earlier eluting Boc-protected intermediate;
Compound 142: later eluting Boc-protected intermediate.

7-Chloro-6-fluoro-isoquinoline (150)



7-Chloro-6-fluoro-isoquinoline is obtained by the same reaction sequence, used for the synthesis of 6-Fluoro-isoquinoline (23), starting from 3-Chloro-4-fluoro-benzaldehyde. R_t = 0.77 min (Method #2). Detected mass: 182.1/184.1 ($M+H^+$).

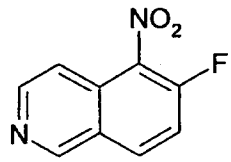
5-Chloro-6-fluoro-isoquinoline-trifluoro acetate (151)



TFA

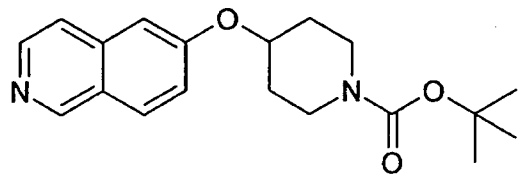
7.0 g (38.1 mmol) of 6-Fluoroisoquinoline (23) are dissolved in 60 mL of concentrated sulfuric acid. At 0°C 10.18 g of N-Chlorosuccinimide are added. After 1h another 5.2g of N-Chlorosucciminide are added and the solution is warmed to 50°C. Two more portions of 5.2 g N-Chlorosuccinimide are added successively and stirring is continued at 50 °C until the reaction is complete. The reaction mixture is cooled to room temperature, is poured on ice and adOPJusted to pH 10 by addition of sodium hydroxide. The precipitate is filtered off, taken up in dichloromethane and washed with aqueous sodium hydroxide. The organic layer is dried over magnesium sulfate, evaporated and the crude product is purified by preparative HPLC to yield 4.04 g of 5-Chlor-6-fluor-isoquinoline (151) as trifluoroacetate. R_t = 0.97 min (Method #2). Detected mass: 182.0/184.0 ($M+H^+$).

6-Fluoro-5-nitro-isoquinoline (152)



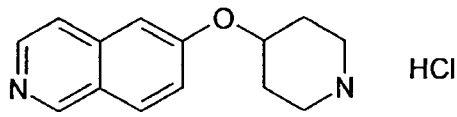
Under cooling 2.0 mL of concentrated nitric acid are added to 2.8 mL of sulphuric acid. Subsequently 350 mg of 6-fluoroisoquinoline (23) are added, the reaction is warmed up to room temperature and allowed to stir overnight. The reaction mixture is poured on ice, extracted with dichloromethane and adOPJusted to alkaline pH by addition of sodium hydroxide. The aqueous layer is extracted again with dichloromethane. The dichloromethane layer is dried over magnesium sulfate and evaporated to give 90 mg of 6-Fluoro-5-nitro-isoquinoline, which can be used without further purification. R_t = 1.03 min (Method #1). Detected mass: 193.0 ($M+H^+$).

4-(Isoquinolin-6-yloxy)-piperidine-1-carbocyclic acid-tert-butylester (154)



7.49 g of 4-Hydroxy-piperidine-1-carboyclic acid-tert-butylester are dissolved in 20 mL of dry dimethyl acetamide. 1.49 g of sodium hydride (60%) are added. Then a solution of 3.65 g 6-Fluoroisoquinoline (23) is added dropwise. The solution is heated at 80 °C for 2 hours, then the solvent is removed and the residue is taken up in dichloromethane. The organic layer is extracted twice with water and then with brine, dried over magnesium sulfate and evaporated to dryness. The crude product is purified by silica gel chromatography to yield 6.22g of 4-(Isoquinolin-6-yloxy)-piperidine-1-carbocyclic acid-tert-butylester. R_t = 1.32 min (Method #1). Detected mass: 329.1 ($M+H^+$).

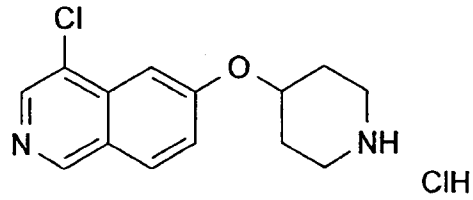
6-(Piperidin-4-yloxy)-isoquinoline hydrochloride (124)



4-(Isoquinolin-6-yloxy)-piperidine-1-carbocyclic acid-tert-butylester (154) is deprotected by the general procedure described in AAV2 to yield the title compound as HCl-salt. R_t = 0.20 min (Method #2). Detected mass: 229.1 ($M+H^+$).

The following example was synthesized according to this method:

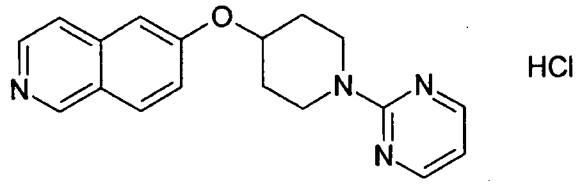
4-Chloro-6-(piperidin-4-yloxy)-isoquinoline hydrochloride (156)



using 4-chloro-6-fluoro-isoquinoline (24) as starting material

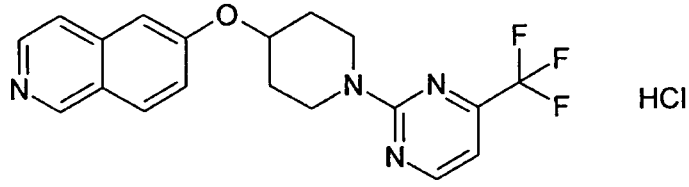
LCMS Method # 2, retention time 0.56 min, detected mass 263.12 $[M+H]^+$

6-(1-Pyrimidin-2-yl-piperidin-4-yloxy)-isoquinoline-hydrochloride (157)



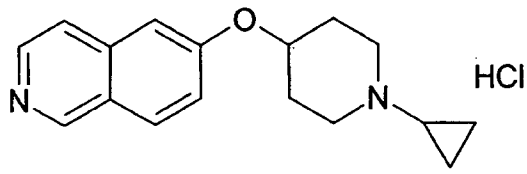
150 mg of 6-(Piperidine-4-yloxy)-isoquinoline hydrochloride (124) are dissolved in 10 mL of dry pyridine. 177 mg of triethylamine and 69 mg of 4-chloropyrimidine are added and the solution is stirred at 65°C for 6 hours. The reaction mixture is poured on brine and extracted three times with ethyl acetate. The combined organic layers are dried over magnesium sulfate, evaporated to dryness and the crude product is purified by preparative HPLC. The product is converted into the corresponding HCl salt by taking up the product in 20 mL of 1 N hydrochloric acid followed by lyophilization. Yield: 47 mg. R_t = 1.05 min (Method #2). Detected mass: 307.1 ($M+H^+$).

6-[1-(4-Trifluoromethyl-pyrimidin-2-yl)-piperidin-4-yloxy]-isoquinoline hydrochloride (158)



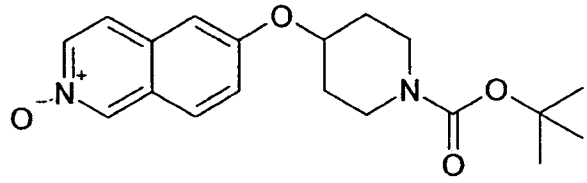
75 mg of 6-(Piperidine-4-yloxy)-isoquinoline-Hydrochloride (124) are dissolved in 5 mL of dry pyridine and 5 mL of DMF. 55 mg 2-Chlor-4-trifluoromethyl-pyrimidine are added and the solution is stirred at 60°C for 3 hours. The solvents are removed in vacuo and the residue is taken up in brine and extracted three times with ethyl acetate. The combined organic layers are dried over magnesium sulfate, evaporated to dryness and the crude product is purified by preparative HPLC. The product is converted into the corresponding HCl salt by taking up the product in 20 mL of 1 N hydrochloric acid followed by lyophilization. Yield: 29 mg. R_t = 1.69 min (Method #2). Detected mass: 375.1 ($M+H^+$).

6-(1-Cyclopropyl-piperidin-4-yloxy)-isoquinoline-hydrochloride (159)



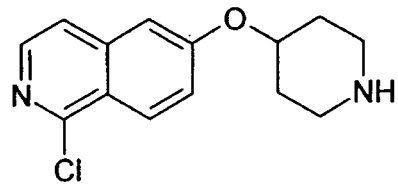
300 mg (1,13 mmol) 6-(Piperidine-4-yloxy)-isoquinoline hydrochloride (124) are dissolved in 10 mL of methanol. 202 mg of triethylamine, molecular sieves 4A, 600 mg of glacial acetic acid, 871 mg of (1-Ethoxy-cyclopropyloxy)-trimethyl-silane and 101 mg of sodium cyanoborohydrate are added successively and the reaction mixture is heated under reflux for 6 hours. The reaction mixture is cooled to room temperature, 6 mL of 2N sodium hydroxide are added and the reaction mixture is filtered. The filtrate is evaporated, the residue is taken up in dichloromethane, extracted with 2 N sodium hydroxide and brine, dried with sodium sulfate, evaporated to dryness and the crude material is purified by preparative HPLC. The product fractions are evaporated, the product is taken up in 2 N hydrochloric acid and lyophilized.
Yield: 60 mg. R_t = 0.50 min (Method #1).Detected mass: 269.2 ($M+H^+$).

4-(2-Oxy-isoquinolin-6-yloxy)-piperidine-1-carboxylic acid tert-butyl ester (160)



3.97 g (12.1 mmol) of 4-(Isoquinolin-6-yloxy)-piperidine-1-carboxylic acid tert-butyl ester (154) are dissolved in 100 ml of dichloromethane and 4.47 g (18.1 mmol) of 3-chloro-perbenzoic acid (70 %) are added at room temperature. The reaction mixture is stirred for 1 h and then washed with saturated sodium bicarbonate-solution. The aqueous phase is separated and extracted with dichloromethane. The combined organic layers are dried over magnesium sulfate and evaporated, to yield 4.19 g of crude material, which can be used for further conversion without purification. R_t = 1.46 min (Method #1). Detected mass: 345.2 ($M+H^+$).

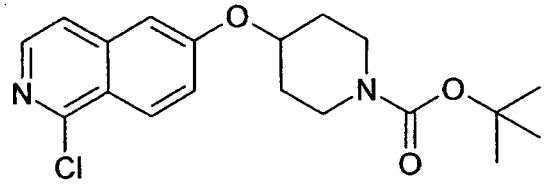
1-Chloro-6-(piperidin-4-yloxy)-isoquinoline-hydrochloride (161)



HCl

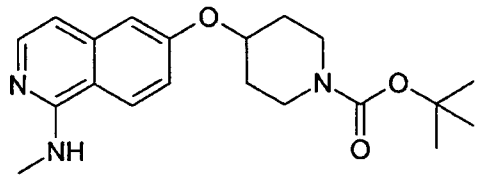
3.5 g (10.16 mmol) 4-(2-Oxy-isoquinolin-6-yloxy)-piperidine-1-carboxylic acid tert-butyl ester (160) were dissolved in 250 ml of HCl-saturated ethanol at 50 °C. The clear solution was concentrated i. vac. and the residue was refluxed in 50 ml $POCl_3$. After 3 h the $POCl_3$ was removed i. vac. and the residue was taken up in H_2O. The pH was adOPJusted to 11, by adding sodium hydroxide and the aqueous solution was extracted twice with dichloromethane. The combined organic layers were dried over magnesium sulfate and evaporated to dryness. The residue was purified by preparative HPLC, by which the title compound was obtained as trifluoroacetate. This was converted to the corresponding HCl-salt by dissolving the product in 2 N HCl, followed by lyophilization. Yield: 950 mg. R_t = 1.03 min (Method #1). Detected mass: 263.1/265.1 ($M+H^+$).

4-(1-Chloro-isoquinolin-6-yloxy)-piperidine-1-carboyclic acid tert-butyl ester (162)



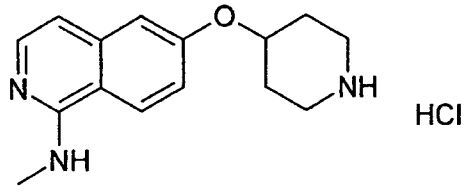
1.23 g (4.11 mmol) of 1-Chloro-6-(piperidin-4-yloxy)-isoquinoline hydrochloride (161) were dissolved in 50 ml of dichloromethane and 0.85 ml (6.15 mmol) of triethylamine were added. At 0 °C a solution of 1.09 g (5.0 mmol) of tert-butyl-carbonate in 10 ml dichloromethane was added dropwise and the mixture was allowed to stand at room temperature overnight. For working up, the mixture was washed twice with H_2O, dried over magnesium sulfate and evaporated, to yield 1.1 g of the desired product, which could be used without further purification. R_t = 1.86 min (Method # 4). Detected mass: 363.1/365.2 ($M+H^+$).

4-(1-Methylamino-isoquinolin-6-yloxy)-piperidine-1-carboxylic acid tert-butyl ester (163)



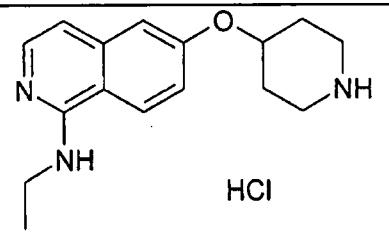
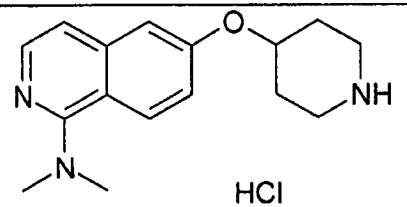
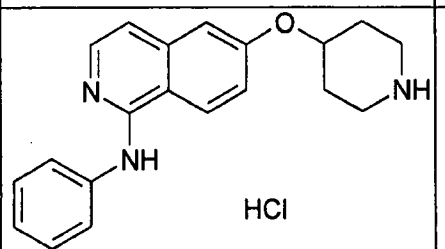
154 mg (0.42 mmol) of 4-(1-Chloro-isoquinolin-6-yloxy)-piperidine-1-carboyclic acid tert-butyl ester (162) were heated in 15 ml of an aqueous methylamine-solution (41 %) at 110 °C in a sealed tube. After 7h the reaction mixture was evaporated and the residue was taken up in saturated sodium bicarbonate solution and extracted with ethyl acetate. The organic layer was separated, dried over magnesium sulfate and the solvent was removed i. vac. The residue was purified by silica gel chromatography (ethyl acetate/methanol 5:1). Yield: 45 mg. R_t = 1.14 min (Method # 4). Detected mass: 358.3 ($M+H^+$).

Methyl-[6-(piperidin-4-yloxy)-isoquinolin-1-yl]-amine-hydrochloride (164)

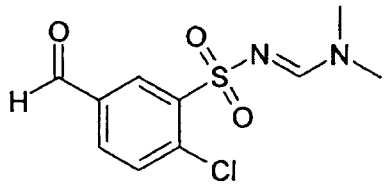


4-(1-Methylamino-isoquinolin-6-yloxy)-piperidine-1-carboxylic acid tert-butyl ester (163) was converted to the deprotected title compound by the general procedure, described in AAV2, by which 34 mg of the corresponding HCl-salt could be obtained. R_t = 0,69 min (Method #1). Detected mass: 258.3 ($M+H^+$).

Following the synthetic route, described for compound 164, the following compounds were prepared starting from 4-(1-Chloro-isoquinolin-6-yloxy)-piperidine-1-carboyclic acid tert-butyl ester (162) and the corresponding amines:

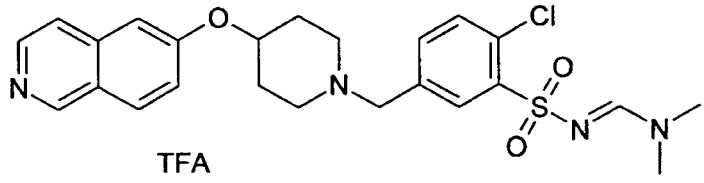
No.	Compound	Amine	T [°C]	Mass [MH^+]	Retention time [min]	Method
165	 HCl	Ethylamine; 70 % in H_2O	110 °C	272.28	0.72	1
166	 HCl	Dimethylamine; 2 M in THF	110 °C	272.29	0.68	1
167	 HCl	Aniline; 1:1 in dioxan (v/v)	120 °C	320.20	0.88	1

2-Chloro-N-dimethylaminomethylene-5-formyl-benzenesulfonamide (168)



5.0 g (22,8 mmol) of 2-Chloro-5-formyl-benzenesulfonamide were dissolved in 50 ml of dichloromethane. 4.08 g (34.3 mmol) of dimethylformamide dimethylacetal were added and the mixture was refluxed for 2 h. After cooling to room temperature, the solution was washed twice with H_2O, dried over magnesium sulfate and evaporated. 5.16 g of the crude product were obtained and used in the next step without further purification. R_t = 1.14 min (Method #1). Detected mass: 275.1/277.1 ($M+H^+$).

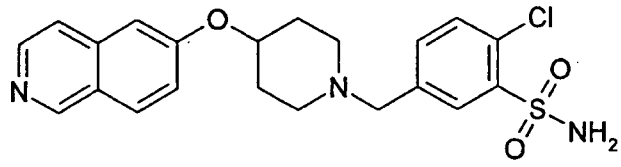
2-Chloro-N-dimethylaminomethylene-5-[4-(isoquinolin-6-yloxy)-piperidin-1-ylmethyl]-benzenesulfonamide-trifluoro acetate (169)



TFA

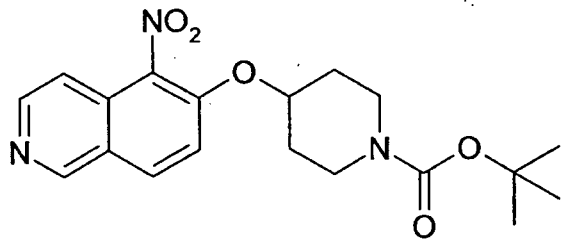
200 mg (0.88 mmol) of 6-(piperidine-4-yloxy)-isoquinoline hydrochloride (124) were dissolved in 20 ml of methanol and 158 mg (1.56 mmol) of triethylamine were added. After stirring for 15 minutes at room temperature 467 mg (7.78 mmol) of glacial acetic acid, 482 mg (1.76 mmol) of 2-Chloro-N-dimethylaminomethylene-5-formyl-benzenesulfonamide (168), 166 mg (2.64 mmol) of sodium cyanoborohydride and freshly dried molecular sieves were added and the mixture was refluxed for 3 h. After stirring overnight at room temperature, the mixture was filtered and the filtrate was evaporated. The residue was dissolved in dichloromethane and washed twice with saturated sodium bicarbonate solution and brine. After drying over magnesium sulfate and evaporation of the solvent, the crude product was purified by preparative HPLC, by which 133 mg of the desired product could be isolated as trifluoroacetate. R_t = 0.87 min (Method #2), Detected mass: 487.2/489.2 ($M+H^+$).

2-Chloro-5-[4-(isoquinolin-6-yloxy)-piperidin-1-ylmethyl]-benzenesulfonamide (170)



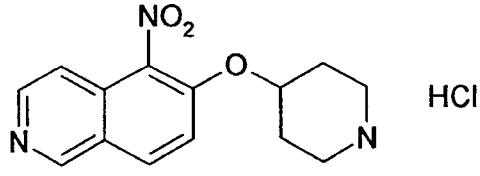
133 mg (0.27 mmol) of 2-Chloro-N-dimethylaminomethylene-5-[4-(isoquinolin-6-yloxy)-piperidin-1-ylmethyl]-benzenesulfonamide (169) were dissolved in ethanol. After adding 50 ml of 2N NaOH, the solution was heated to 60 °C for 6 h. After cooling to room temperature, the mixture was neutralized by addition of aqueous HCl and the solvent was removed i. vac. The residue was stirred with ethanol, the inorganic salts were filtered off and the filtrate was evaporated. R_t = 0.78 min (Method #2), Detected mass: 432.1 ($M+H^+$).

4-(5-Nitro-isoquinolin-6-yloxy)-piperidine-1-carboxylic acid tert-butyl ester (171)



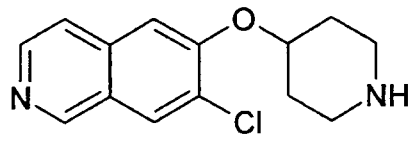
90 mg (0.47 mmol) 6-Fluoro-5-nitro-isoquinoline (152) were treated with 4-Hydroxy-piperidine-1-carboxylic acid tert-butyl ester following the method described for the preparation of compound 154.

5-Nitro-6-(piperidin-4-yloxy)-isoquinoline-hydrochloride (172)



18.5 mg (0.05 mmol) 4-(5-Nitro-isoquinolin-6-yloxy)-piperidine-1-carboxylic acid tert-butyl ester (171) were deprotected following the procedure, described in AAV2, by which 12.5 mg of the title compound could be isolated as HCl-salt. R_t = 0.57 min (Method #1). Detected mass: 274.2 ($M+H^+$).

7-Chloro-6-(piperidin-4-yloxy)-isoquinoline-hydrochloride (173)

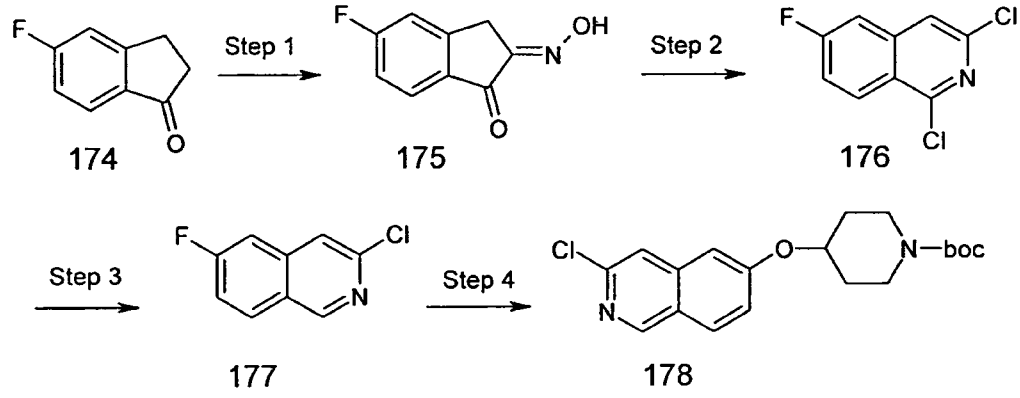


HCl

Starting from 7-Chloro-6-fluoro-isoquinoline (150), the title compound was prepared by the same synthetic route as for compound 124. R_t = 0.66 min (Method #1), detected mass: 263.1/265.1 ($M+H^+$).

Synthetic procedure for the generation of 3,6-disubstituted isoquinolines.

General reaction scheme:



Step 1:

188 g of 5-Fluro-indanone-1 (174) were dissolved in 1.8l of diethyl ether, 50ml of EtOH saturated with HCl are added at 0°C and 1.1 l of a 15% ethyl nitrite solution in ether is added over 1 hour.

The solution is allowed to stir for an additional 3 hours to reach room temperature, then the solvent is removed partially and the precipitated product is collected by filtration.

Step 2

129 g of the product from Step 1 was added to a mixture of 170g of PCl_5 in 2l of $POCl_3$. Then gaseous HCl was added at 0°C until saturation of the solution was reached. The remaining mixture was heated to 60°C for 6h, the solvent partially removed in vacuo

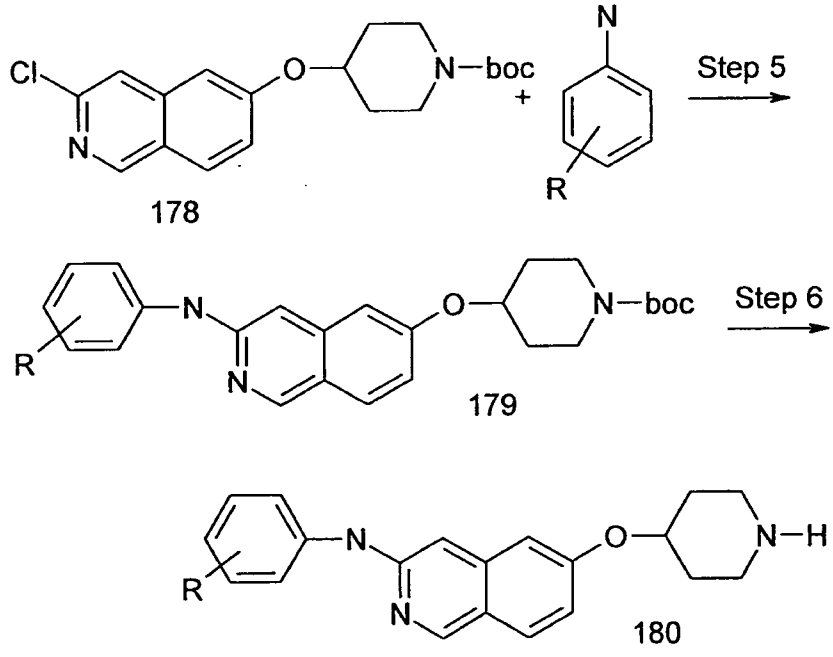
and the residue was hydrolyzed on a crushed ice/water mixture. The precipitated product is isolated by filtration.

Step 3

155g of product from Step 2 were added to a mixture of 740ml HOAc and 330 ml HI (57%) containing 53g of red phosphorous. After heating to reflux for 4 hours, the solution was treated with concentrated NaOH (until pH = 8) and the precipitated product is isolated by filtration.

Step 4:

16.5 g of N-Boc-4-hydroxypiperidine were dissolved in 210ml of diglyme and treated with 4.1g 50% NaH under nitrogen. The resulting mixture was stirred for 1h at room temperature, then 14.8 g of the product from Step 4 was added. The mixture was allowed to stir for 1 day at room temperature, then 100 ml of toluene were added and the resulting mixture was washed with water 3 times. The organic phases were collected and the solvent was removed in vacuo.



Step 5:

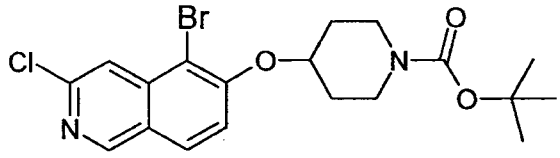
100 mg of compound 178 and 1.1 equivalents of the corresponding aniline are dissolved in 5 ml of dioxane, 350 mg of Cs_2CO_3, 20mg of $Pd(OAc)_2$ and 60 mg of XANTHPHOS are added and the resulting mixture is heated to reflux under nitrogen until the starting material is consumed. (reaction is monitored by LCMS) The solvent is removed in vacuo and the residue is subOPJected to chromatography on a HPLC system.

Step 6:

The products of Step 5 are dissolved in 5 ml of ethanol saturated with gaseous HCl. After stirring for 5h the desired product is isolated by removal of the solvent in vacuo.

All 3,5,6-trisubstituted derivatives were synthesized according to the procedure illustrated by the synthesis of compound 184. For synthesis of compound 185, acetamide was used as amine component in the Pd coupling step.

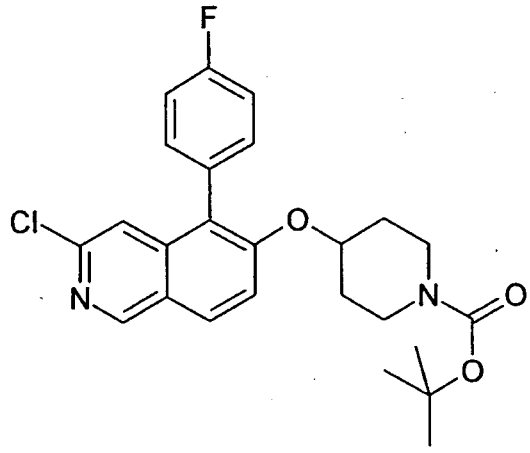
Synthesis of 4-(5-Bromo-3-chloro-isoquinolin-6-yloxy)-piperidine-1-carboxylic acid tert-butyl ester (181)



200 mg of 4-(3-Chloro-isoquinolin-6-yloxy)-piperidine-1-carboxylic acid tert-butyl ester (178) were dissolved in 5 ml of CH_3CN and heated to 85°C. Then a mixture of 148 mg of N-bromosuccinimide and 9 mg of AIBN was added as solid and the resulting mixture was heated to reflux for 1h. The solvent was removed in vacuo and the residue subOPJected to flash column chromatography. The yield of the isolated product was 41%

LCMS : detected mass :441.03, R_t= 2.41 min (Method #1)

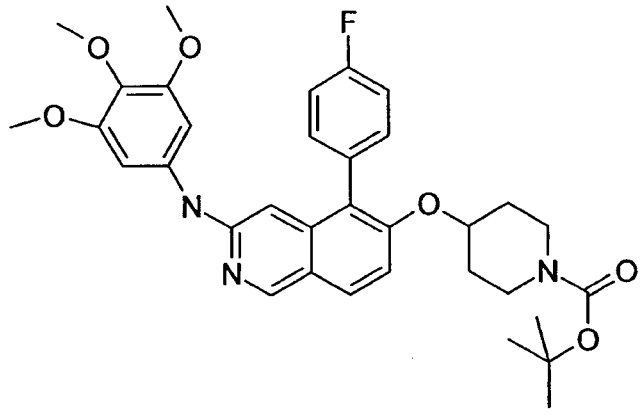
Synthesis of of 4-[3-Chloro-5-(4-fluoro-phenyl)-isoquinolin-6-yloxy]-piperidine-1-carboxylic acid tert- butyl ester (182)



150 mg of 4-(5-Bromo-3-chloro-isoquinolin-6-yloxy)-piperidine-1-carboxylic acid tert-butyl ester (181) were dissolved in a mixture of 9 ml of dioxane and 3ml of water, 47mg of 4-fluoro-benzene-boronic acid, 47mg of Na_2CO_3 and 40mg of $Pd(PPh_3)_4$ were added and the resulting mixture was heated to 100°C for 6h. The solvent was removed in vacuo and the residue subOPJected to chromatography on a HPLC system. Yield: 44%

LCMS : detected mass :457.22, R_t = 2.45 min (Method #1)

Synthesis of 4-[5-(4-Fluoro-phenyl)-3-(3,4,5-trimethoxy-phenylamino)-isoquinolin-6-yloxy]-piperidine-1- carboxylic acid tert-butyl ester (183)

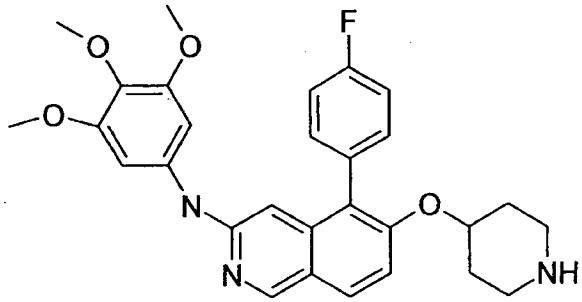


70 mg of 4-[3-Chloro-5-(4-fluoro-phenyl)-isoquinolin-6-yloxy]-piperidine-1-carboxylic acid tert- butyl ester(182) were dissolved in 7ml of toluene, 20mg of $Pd(OAc)_2$, 60 mg of XANTHPHOS, 400mg of Cs_2CO_3 and 30 mg of 3,4,5 trimethoxyaniline were added and the resulting mixture was heated to 100°C for 6h. Then the solvent was removed

in vacuo and the residue subOPJected to chromatography on a HPLC system. The yield of isolated product was 24%

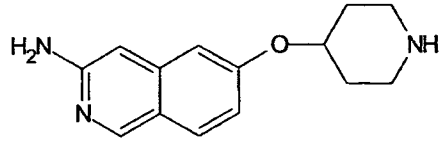
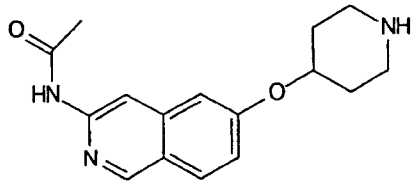
LCMS : detected mass :604.17, RT = 1.81 min (Method #1)

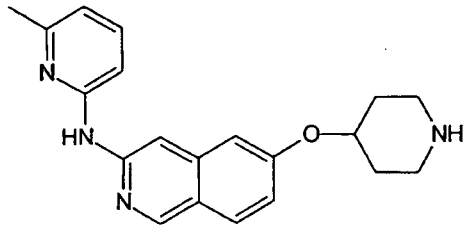
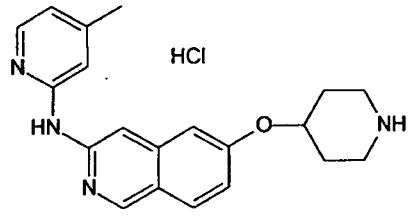
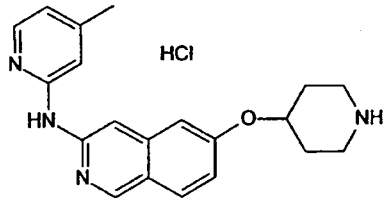
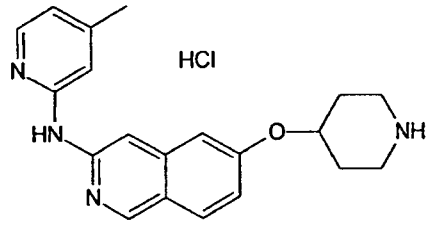
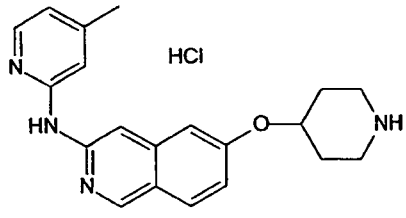
Synthesis of [5-(4-Fluoro-phenyl)-6-(piperidin-4-yloxy)-isoquinolin-3-yl]-(3,4,5-trimethoxy-phenyl)- amine (184)

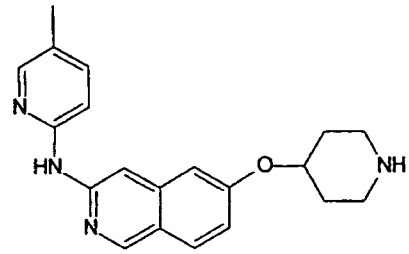
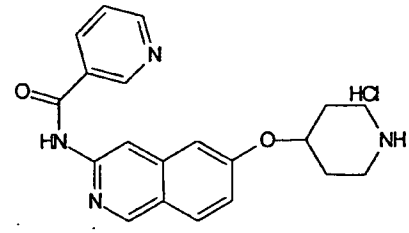
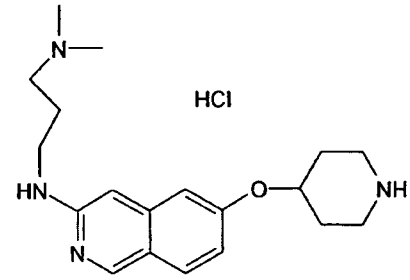
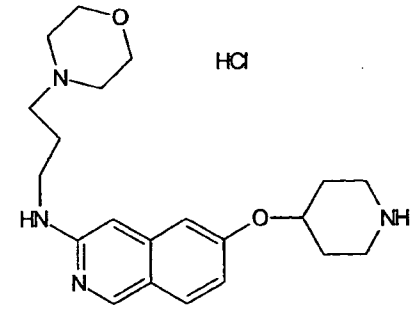


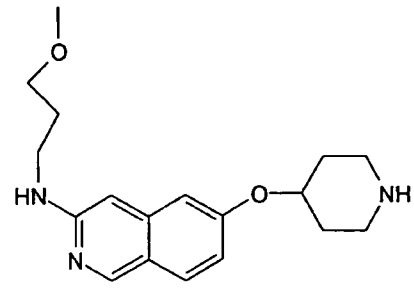
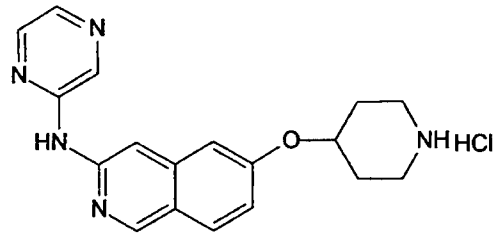
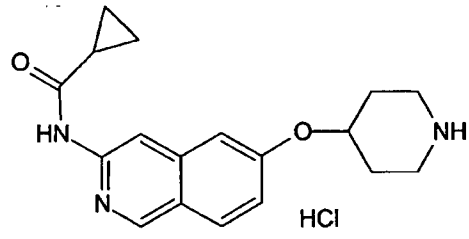
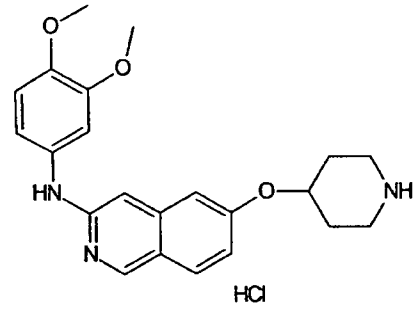
20 mg of 4-[5-(4-Fluoro-phenyl)-3-(3,4,5-trimethoxy-phenylamino)-isoquinolin-6-yloxy]-piperidine-1- carboxylic acid tert-butyl ester (183) were dissolved in 5 ml of ethanol saturated with HCl (gaseous). The resulting mixture was stirred for 1h, then the solvent was evaporated and the product collected. Yield: 85%

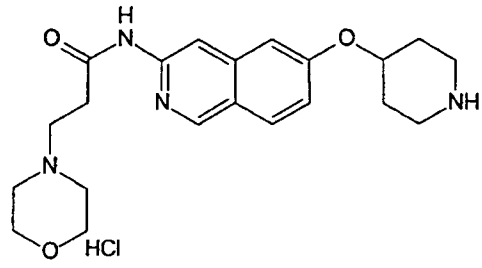
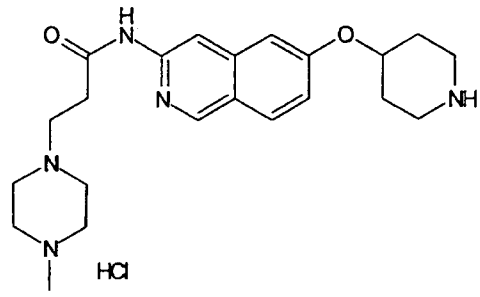
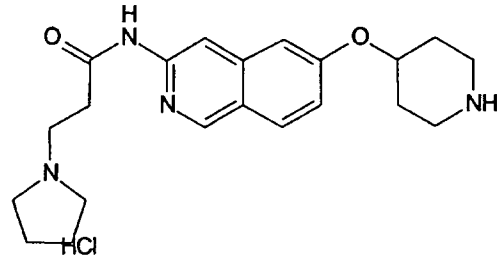
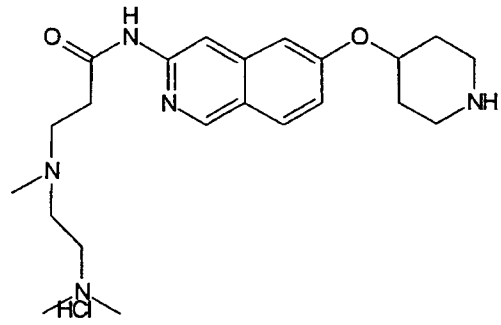
LCMS : detected mass :503.22, R_t = 1.22 min (Method #1)

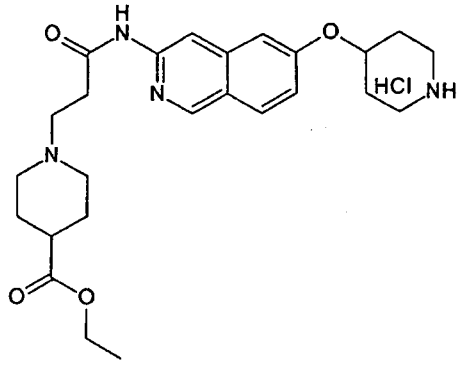
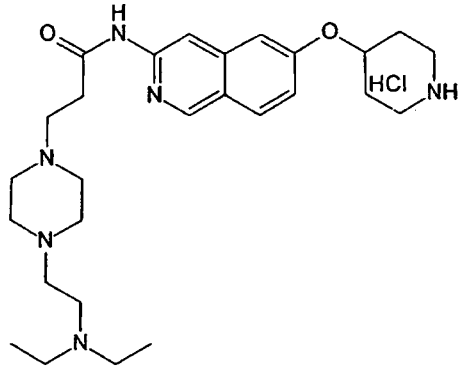
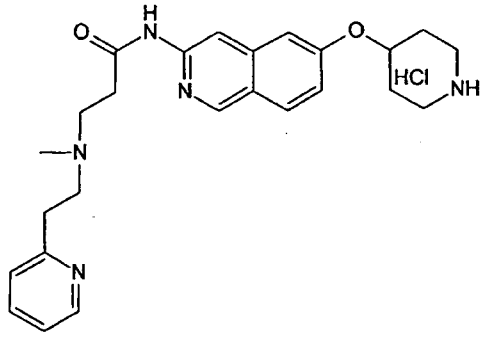
No.	Compound	RT	Method	Detected Mass [MH^+]
185		0.12	#2	244.14
186	HCl 	0.19	#2	286.18

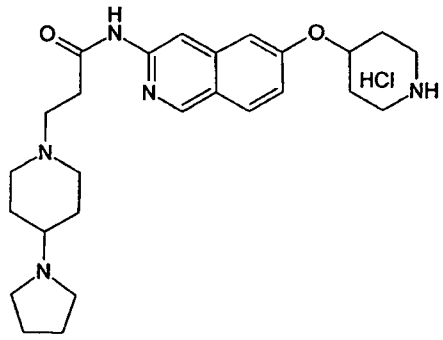
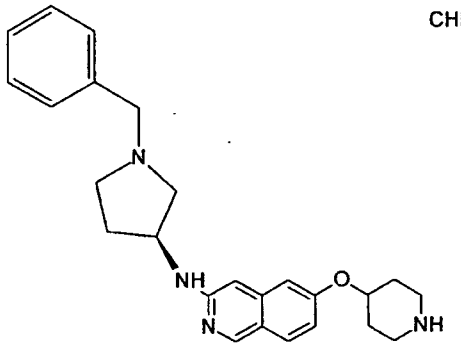
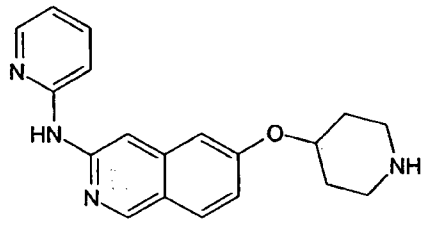
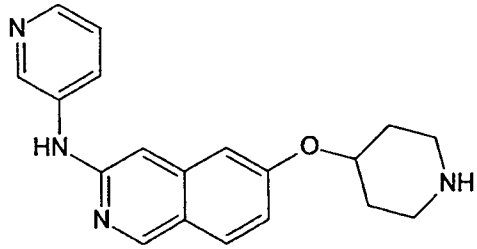
No.	Compound	RT	Method	Detected Mass [MH^+]
187		0.17	#2	335.21
188		1.02	#2	335.21
189		1.02	#2	335.21
190		1.02	#2	335.21
191		1.02	#2	335.21

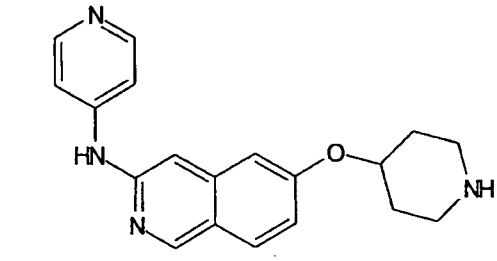
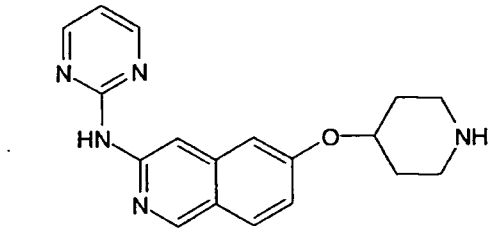
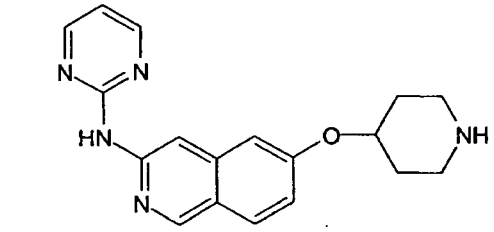
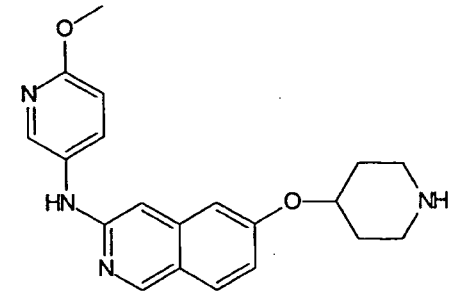
No.	Compound	RT	Method	Detected Mass [MH^+]
192		1.32	#2	335.20
193		1.21	#2	349.21
194		0.11	#2	329.34
195		0.17	#2	371.32

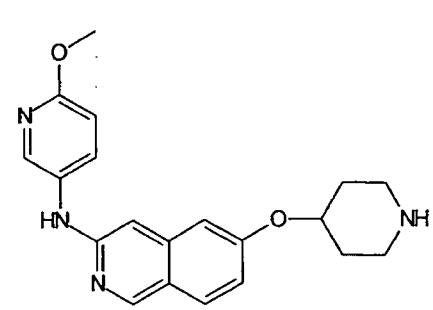
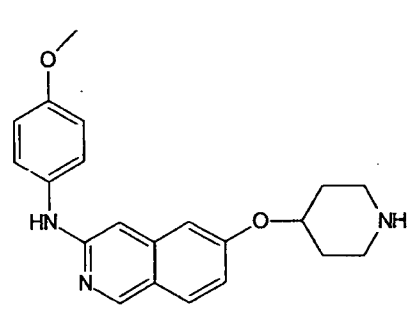
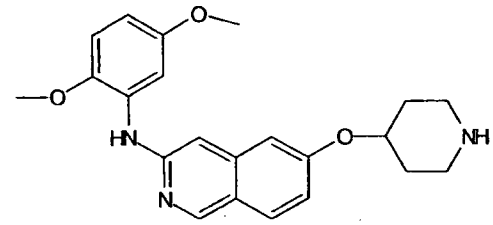
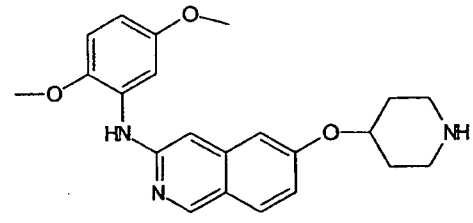
No.	Compound	RT	Method	Detected Mass [MH^+]
196		0.15	#2	316,21
197		1.18	#2	322.25
198		1..18	#2	312.18
199		1.29	#2	380.30

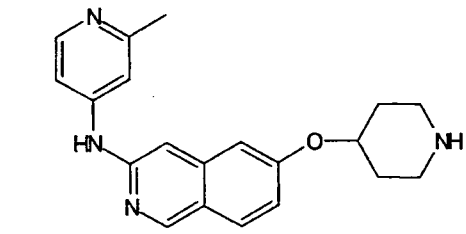
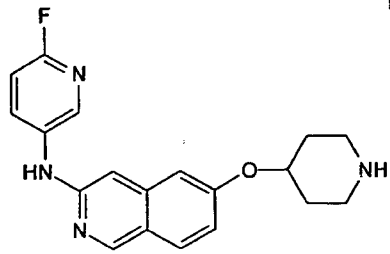
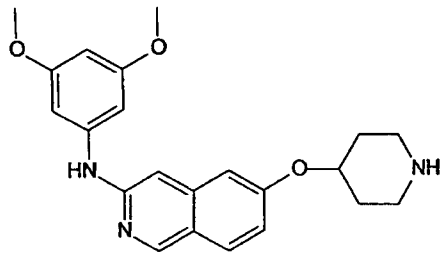
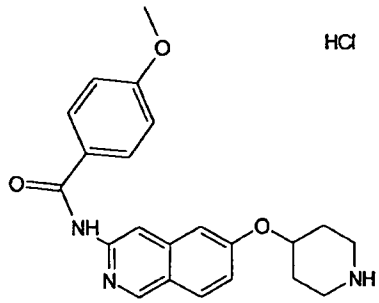
No.	Compound	RT	Method	Detected Mass [MH^+]
200		0.63	#2	385.29
201		0.2	#2	398.34
202		0.18	#2	369.30
203		0.2	#2	400.27

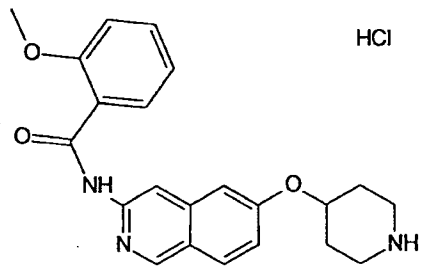
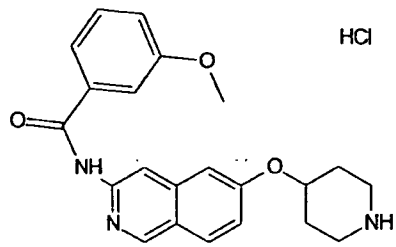
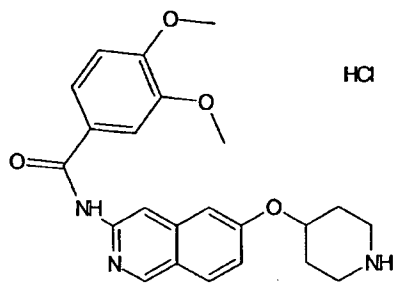
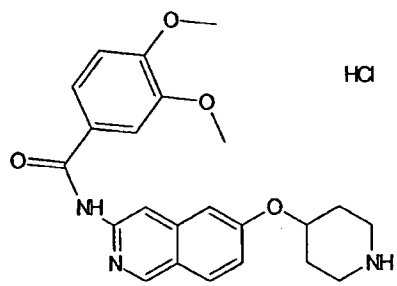
No.	Compound	RT	Method	Detected Mass [MH+]
204		0.16	#2	455.27
205		0.16	#2	483.34
206		0.16	#2	434.26

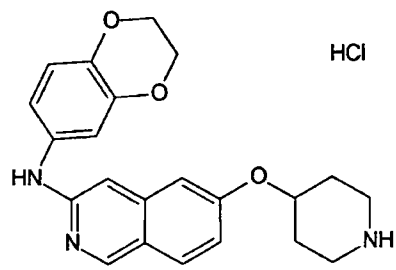
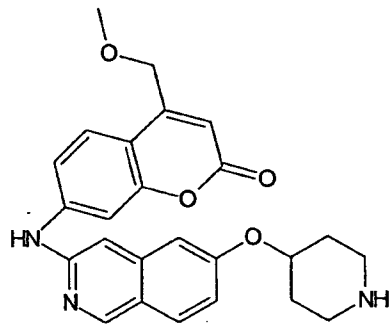
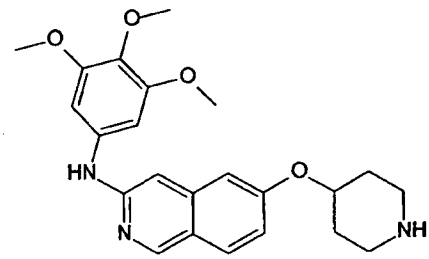
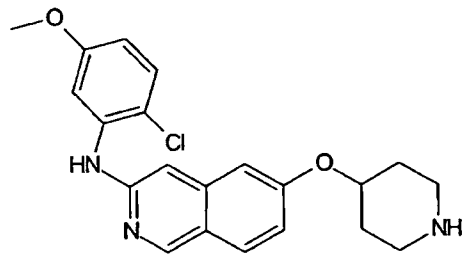
No.	Compound	RT	Method	Detected Mass [MH^+]
206A		0.15	#2	452.30
207	 CHIRAL	0.15	#2	403.25
208	 HCl	1.02	#2	321.17
209		1.02	#2	321.17

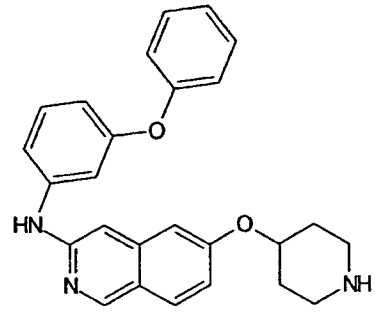
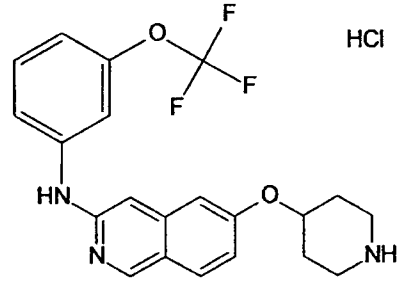
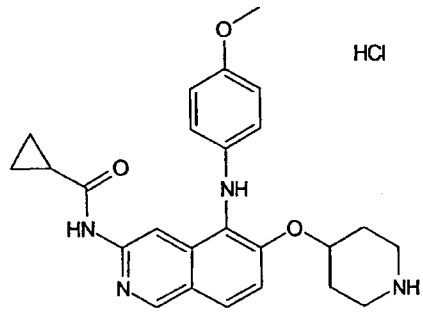
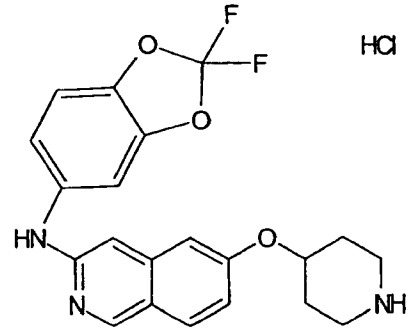
No.	Compound	RT	Method	Detected Mass [MH^+]
210	 HCl	1.06	#2	321.17
211	 HCl	0.85	#2	322.17
212	 HCl	0.85	#2	322.17
213	 HCl	0.89	#2	351.18

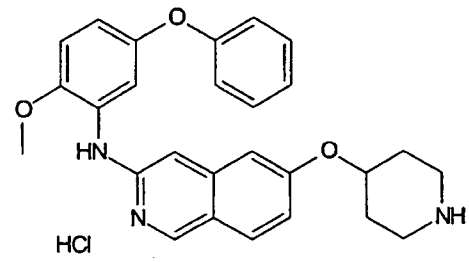
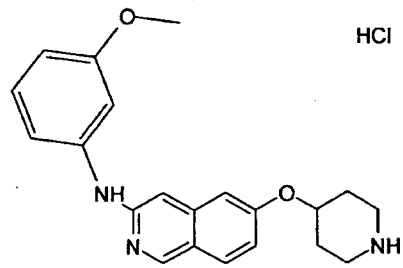
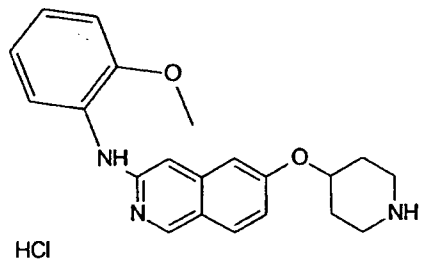
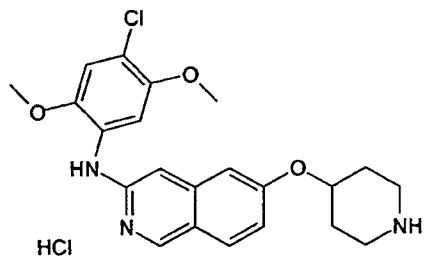
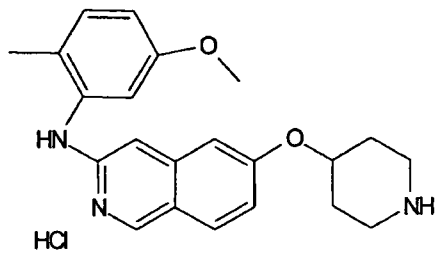
No.	Compound	RT	Method	Detected Mass [MH^+]
214		0.89	#2	351.18
215		1.03	#2	350.19
216		1	#2	380.20
217		1	#2	380.20

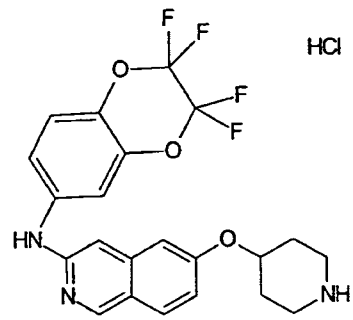
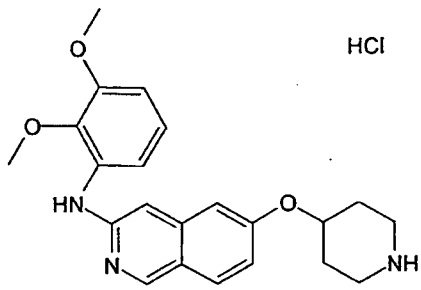
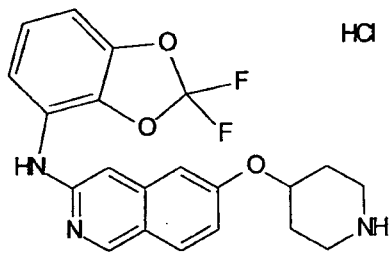
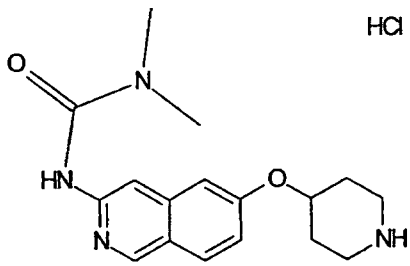
No.	Compound	RT	Method	Detected Mass [MH^+]
218	 HCl	0.95	#2	335.19
219	HCl 	1	#2	339.16
220		1.05	#1	380.20
221	HCl 	1.06	#1	378.18

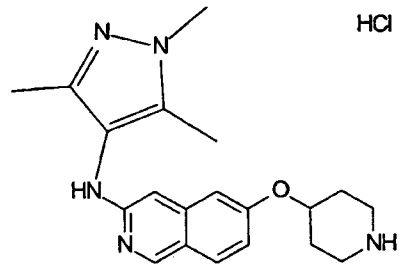
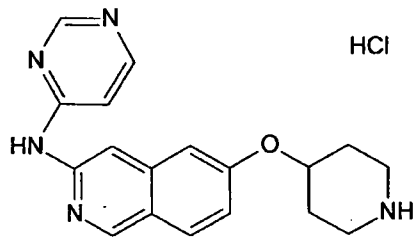
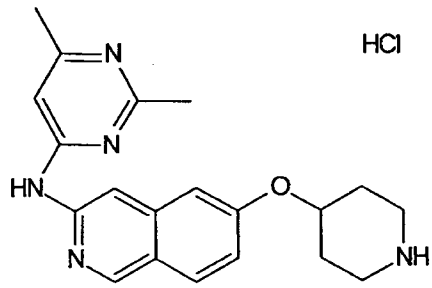
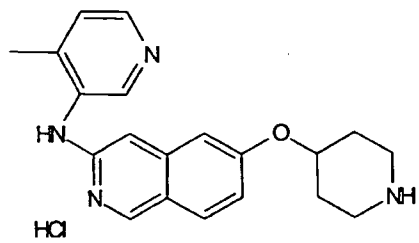
No.	Compound	RT	Method	Detected Mass [MH^+]
222		1.17	#1	378.18
223		1.12	#1	378.18
224		1.04	#1	408.19
225		1.04	#1	408.19

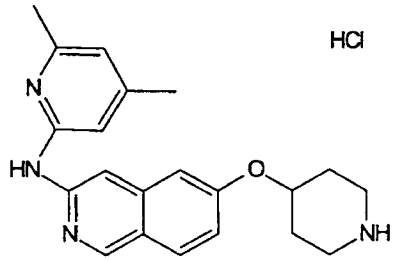
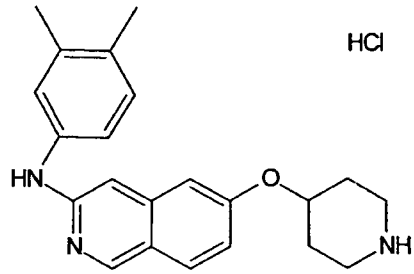
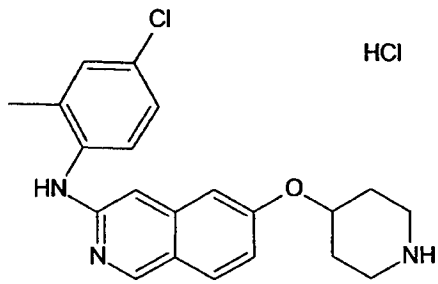
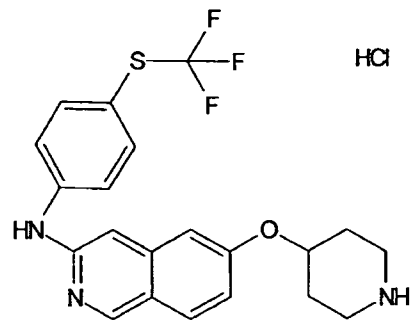
No.	Compound	RT	Method	Detected Mass [MH+]
226		0.95	#1	378.18
227		1.1	#1	432.19
228		1.02	#1	410.21
230		1.12	#1	384.15

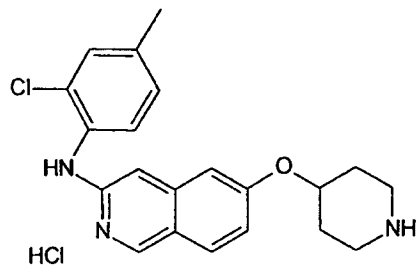
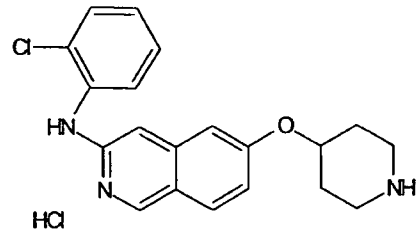
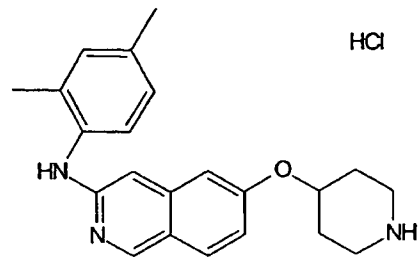
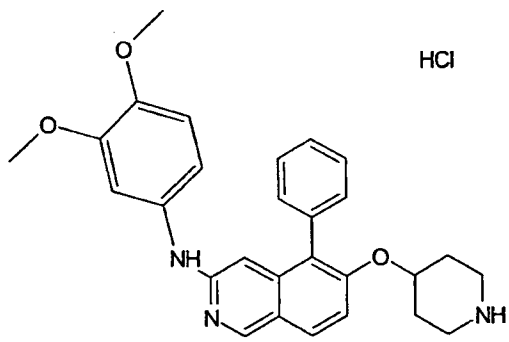
No.	Compound	RT	Method	Detected Mass [MH+]
231		1.28	#1	412.20
232		1.31	#1	404.16
233		1.15	#1	433.22
234		1.25	#1	400.15

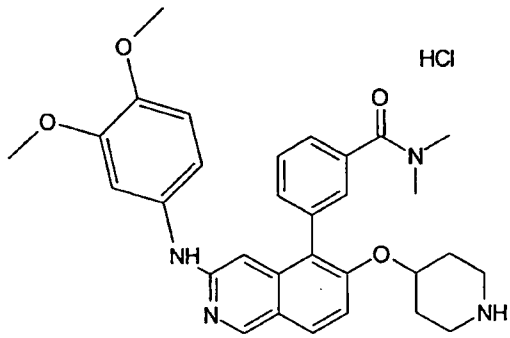
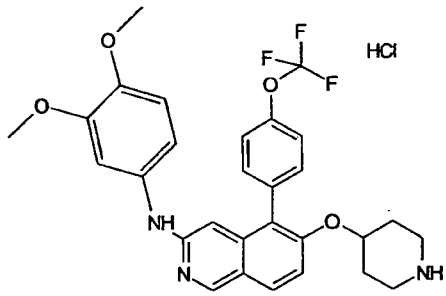
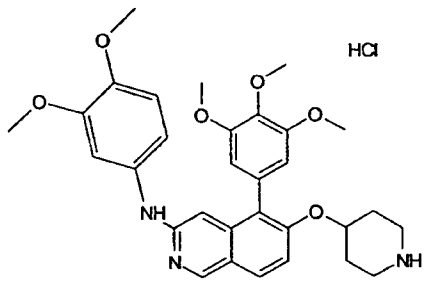
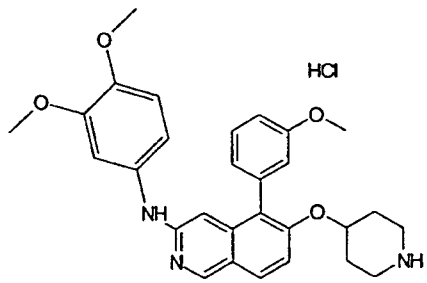
No.	Compound	RT	Method	Detected Mass [MH^+]
235		1.39	#1	442.21
236		1	#1	350.19
237		0.99	#1	350.19
238		1.13	#1	414.16
239		1.03	#1	364.20

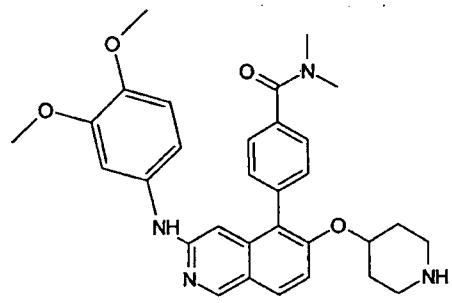
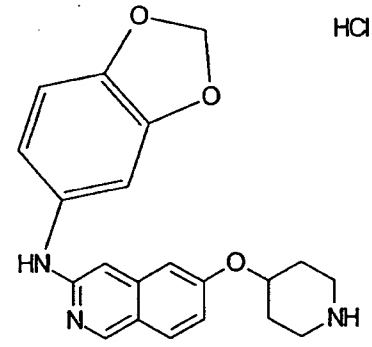
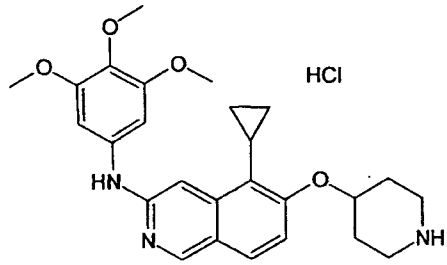
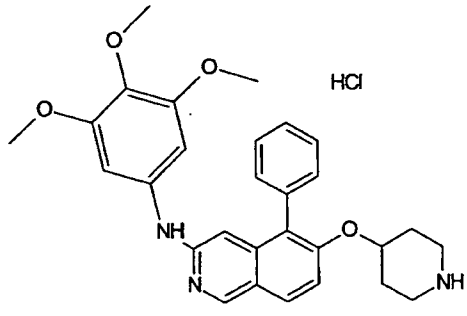
No.	Compound	RT	Method	Detected Mass [MH^+]
240		1.5	#1	450.14
241		0.99	#1	380.20
242		1.25	#1	400.15
243		0.75	#1	315.18

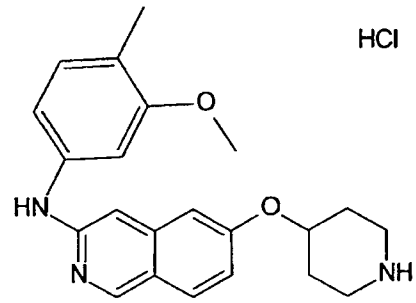
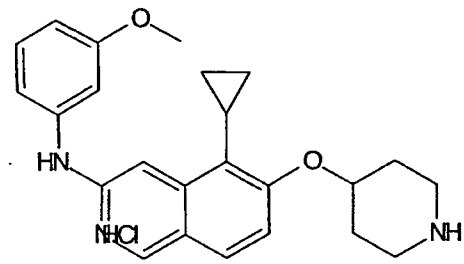
No.	Compound	RT	Method	Detected Mass [MH+]
244		0.83	#1	352.21
245		0.73	#1	322.17
246		0.84	#1	350.20
247		0.85	#1	335.19

No.	Compound	RT	Method	Detected Mass [MH^+]
248		1.05	#1	349.20
249		1.1	#1	348.21
250		1.1	#1	368.15
251		1.33	#1	420.14

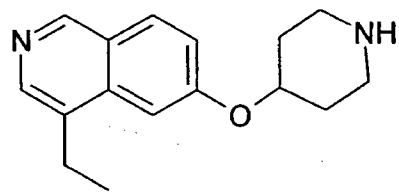
No.	Compound	RT	Method	Detected Mass [MH+]
252		1.12	#1	368.15
253		1.04	#1	354.14
254		1.07	#1	348.21
255		1.15	#1	456.23

No.	Compound	RT	Method	Detected Mass [MH^+]
256		1.11	#1	527.27
257		1.36	#1	540.21
258		1.15	#1	546.26
259		1.07	#1	486.24

No.	Compound	RT	Method	Detected Mass [MH+]
260		1.08	#1	527.27
261		0.95	#1	364.17
262		1.08	#1	450.24
263		1.14	#1	486.24

No.	Compound	RT	Method	Detected Mass [MH+]
264		1.03	#1	364.20
265		1.11	#1	390.22

4-Ethyl -6-(piperidin-4-yloxy) –isoquinoline (266)

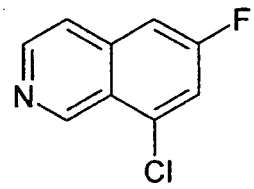


ClH

The compound 266 was synthesized in a similar fashion as described for compound 90, using ethyl iodide. LCMS Method # 1, retention time 0.98 min, detected mass 257.31 $[M+H]^+$

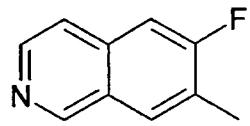
Also using the same reaction sequence as for the synthesis of 6-Fluoro-isoquinoline (23), the following two compounds were obtained:

8-Chloro-6-fluoro-isoquinoline (267)



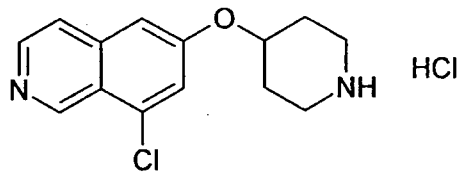
R_t = 0.83 min (Method #1). Detected mass: 182.12 ($M+H^+$).

6-Fluoro-7-Methylisoquinoline (268)



R_t = 0.70 min (Method #TOP). Detected mass: 162.3 ($M+H^+$).

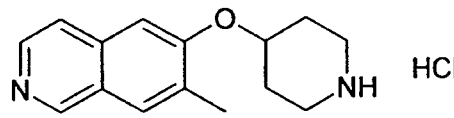
8-Chloro-6-(Piperidin-4-yloxy)- isoquinoline hydrochloride (269)



8-Chloro-6-(Piperidin-4-yloxy)- isoquinoline hydrochloride (269) was obtained in a similar fashion as described above for the synthesis of (124), starting from 267

R_t = 0.63 min (Method #1). Detected mass: 263.14 ($M+H^+$).

6-(Piperidin-4-yloxy)-7-Methyl isoquinoline hydrochloride (270)

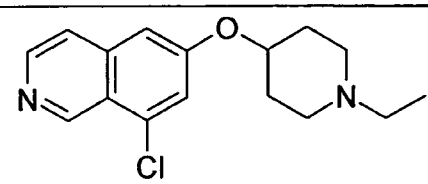
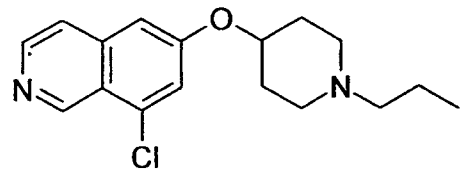
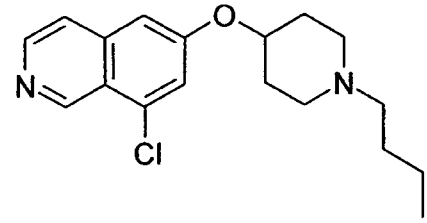
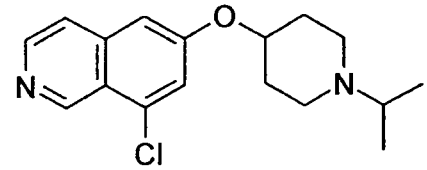
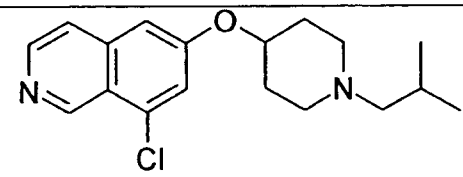


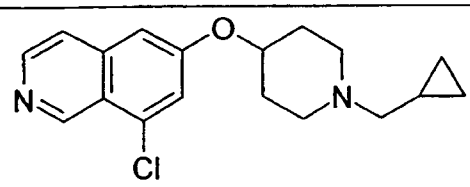
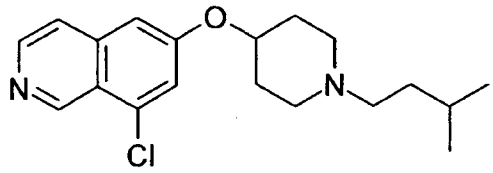
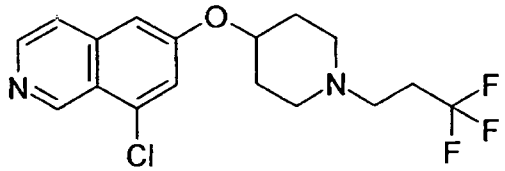
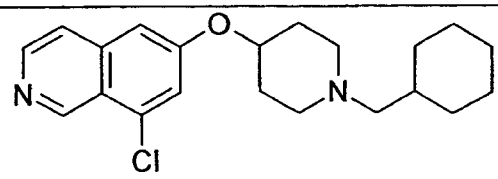
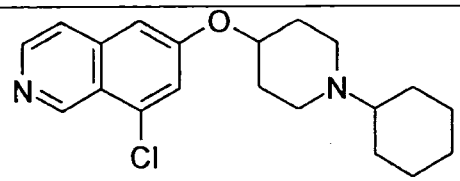
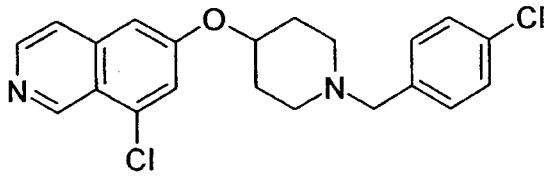
6-(Piperidin-4-yloxy)-7-methyl isoquinoline hydrochloride (270) was obtained in a similar fashion as described above for the synthesis of (124), starting from 268

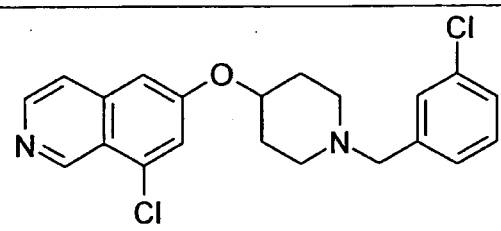
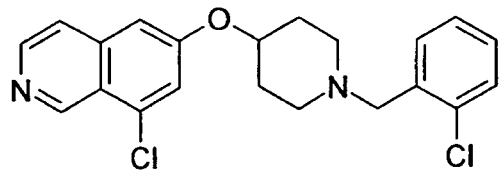
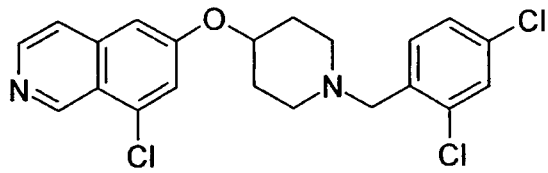
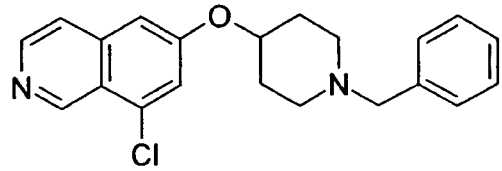
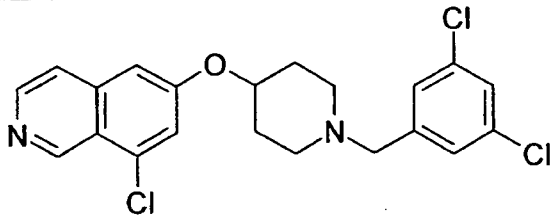
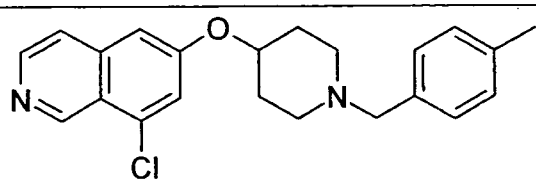
R_t = 0.64 min (Method #1). Detected mass: 243.18 ($M+H^+$).

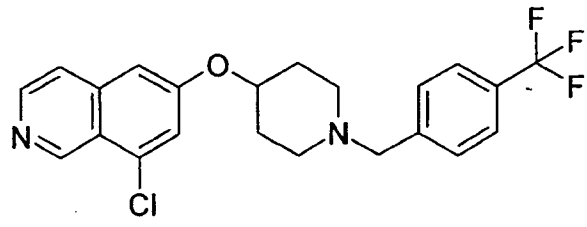
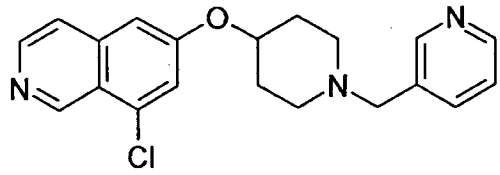
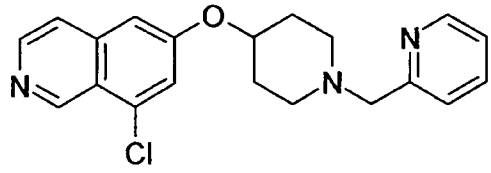
The following set of compounds was obtained the same way, following the reductive amination procedure used to obtain examples 93-123 using 269, 129 or 270,

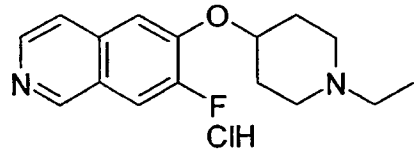
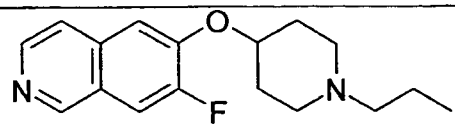
respectively and the corresponding aldehydes as starting material. All LCMS in the following tables were obtained using LCMS method #2.

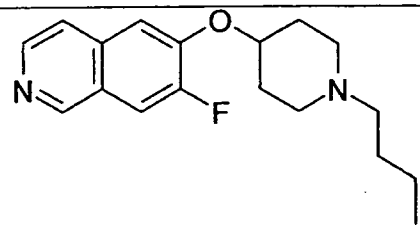
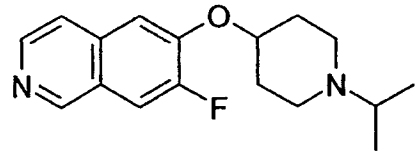
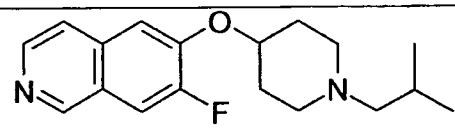
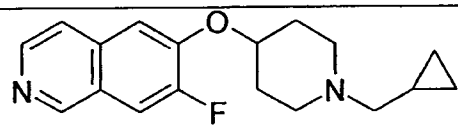
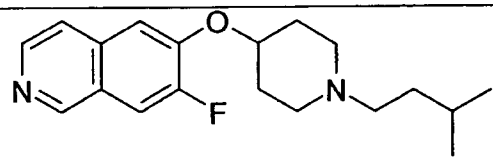
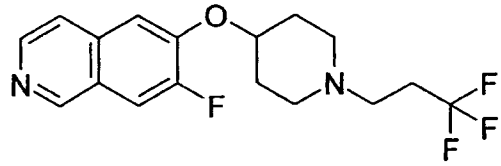
Example No	Formula	T_R	Mass [MH^+]
271	 ClH	0.71	291.09
272	 ClH	0.87	305.11
273	 ClH	0.85	319.11
274	 ClH	0.69	305.10
275	 ClH	0.85	319.20

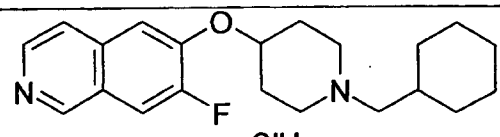
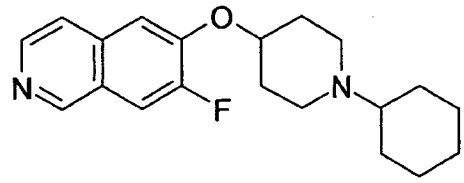
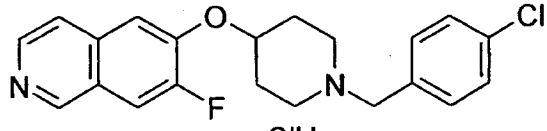
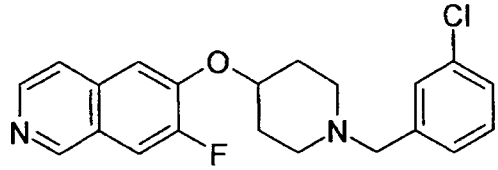
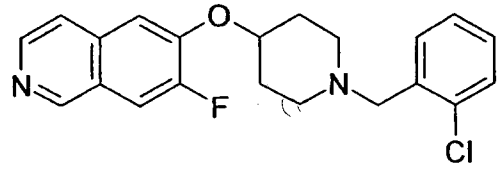
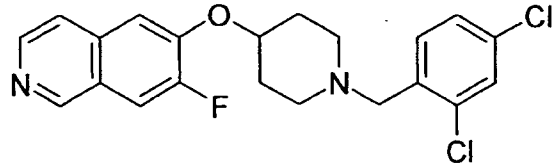
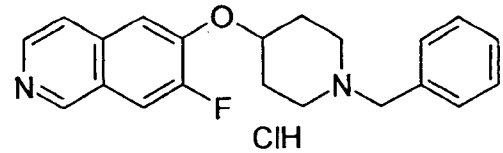
Example No	Formula	T_R	Mass [MH^+]
276	 ClH	0.79	317.10
277	 ClH	0.92	333.12
278	 ClH	0.87	359.06
279	 ClH	1.01	359.15
280	 ClH	0.90	345.13
281	 ClH	1.02	387.06

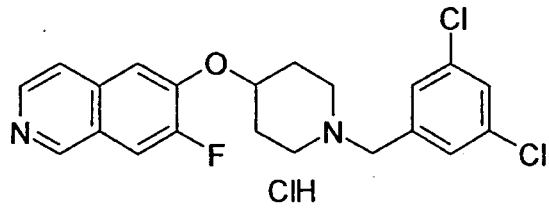
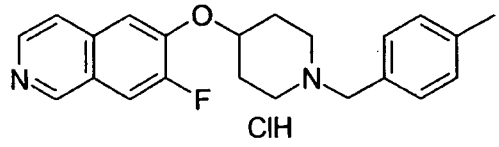
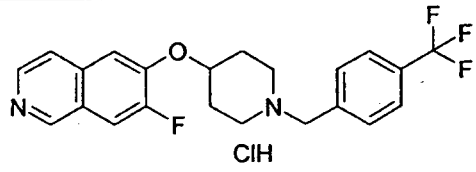
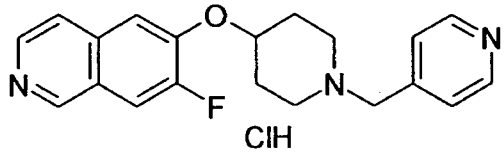
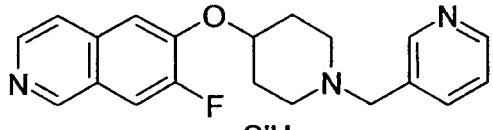
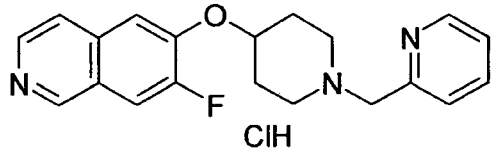
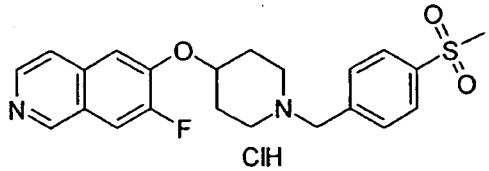
Example No	Formula	T_R	Mass [MH^+]
282	 ClH	1.09	387.05
283	 ClH	1.05	387.06
284	 ClH	1.10	421.02
285	 ClH	0.95	353.10
286	 ClH	1.14	421.02
287	 ClH	1.00	367.10

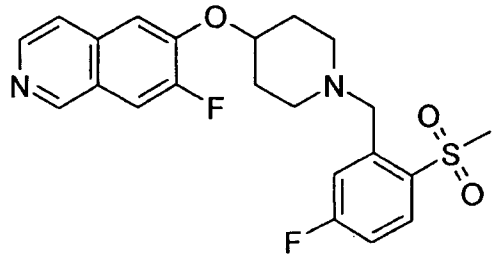
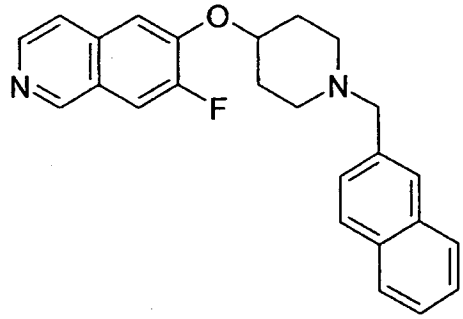
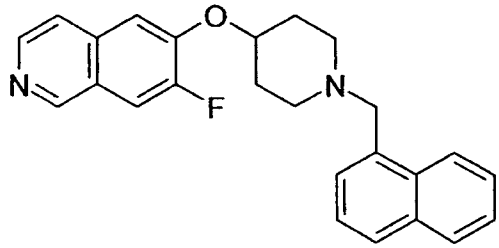
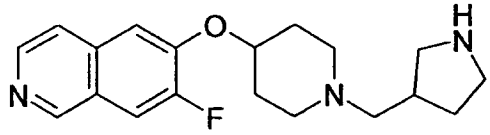
Example No	Formula	T_R	Mass [MH^+]
288	 ClH	1.13	421.06
289	 ClH	0.63	354.11
290	 ClH	0.90	354.11

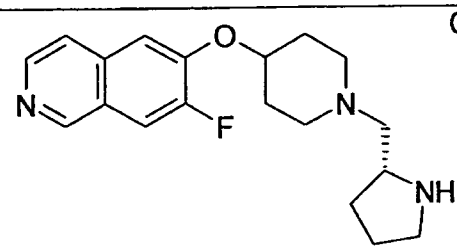
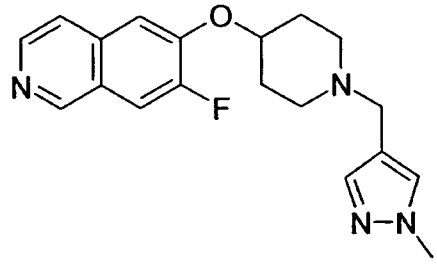
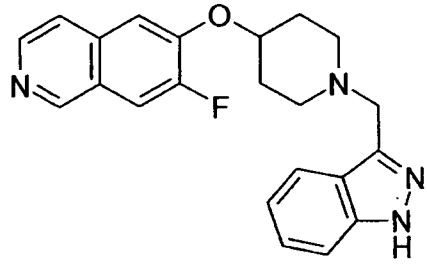
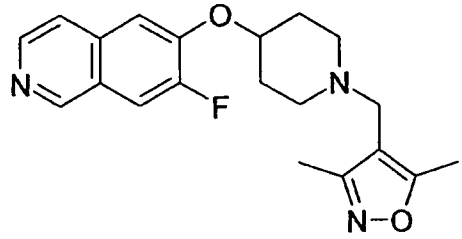
Example No	Formula	T_R	Mass [MH^+]
291	 ClH	0.46	275.33
292	 ClH	0.57	289.21

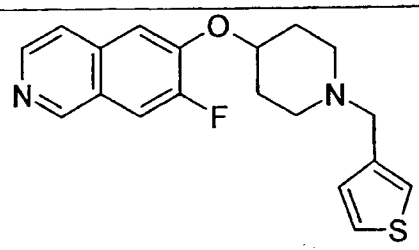
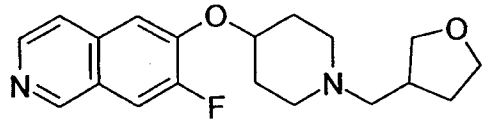
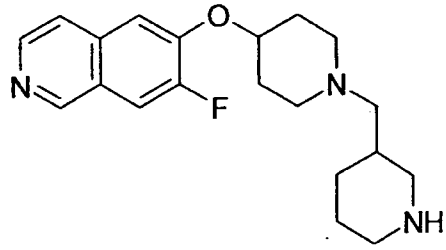
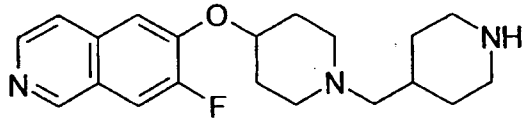
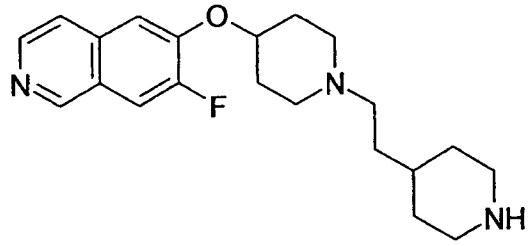
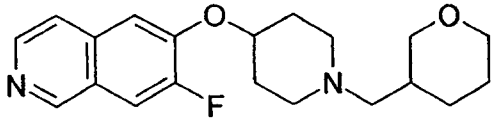
Example No	Formula	T_R	Mass [MH^+]
293	 ClH	0.73	303.22
294	 ClH	0.52	289.25
295	 ClH	0.65	303.23
296	 ClH	0.63	301.20
297	 ClH	0.90	317.26
298	 ClH	0.66	343.21

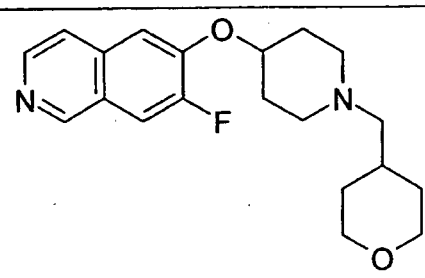
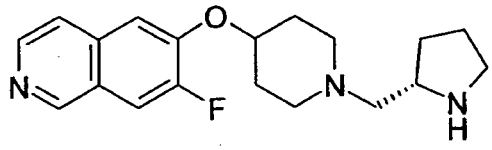
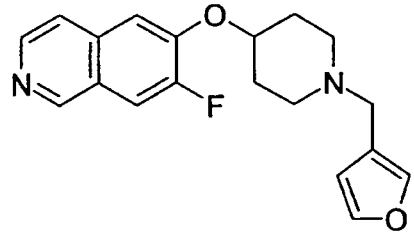
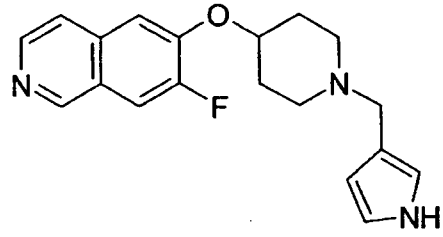
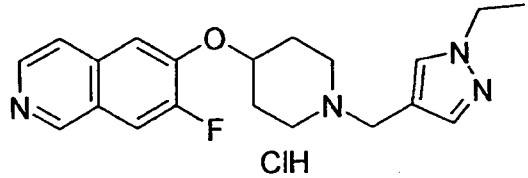
Example No	Formula	T_R	Mass [MH^+]
299	 ClH	0.96	343.27
300	 ClH	0.72	329.30
301	 ClH	0.97	371.19
302	 ClH	0.95	371.19
303	 ClH	0.88	371.19
304	 ClH	1.02	405.15 /407.15
305	 ClH	0.83	337.24

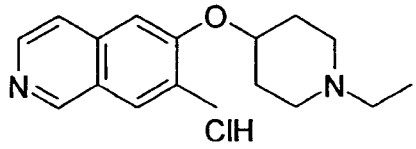
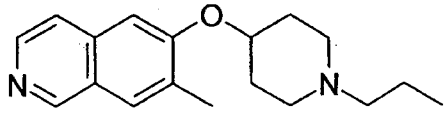
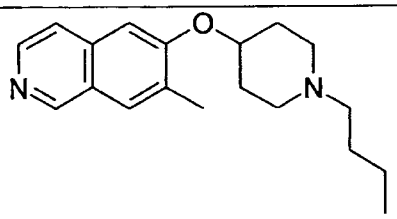
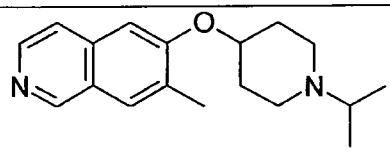
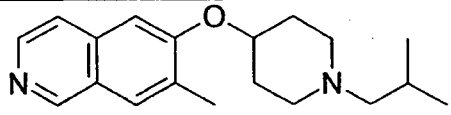
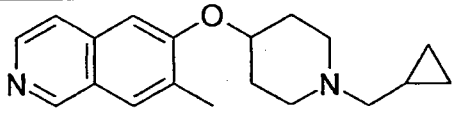
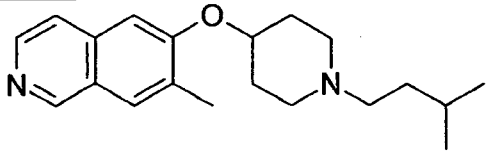
Example No	Formula	T_R	Mass [MH^+]
306	 ClH	1.07	405.19 /407.19
307	 ClH	0.94	351.28
308	 ClH	1.05	405.24
309	 ClH	0.23	338.23
310	 ClH	0.49	338.23
311	 ClH	0.67	338.23
312	 ClH	0.70	415.25

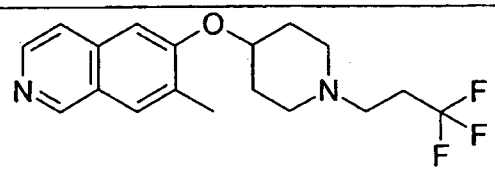
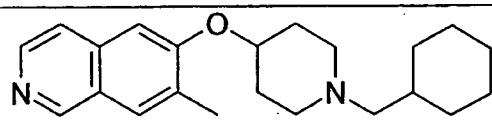
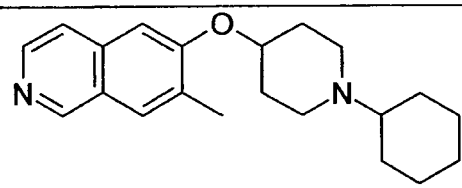
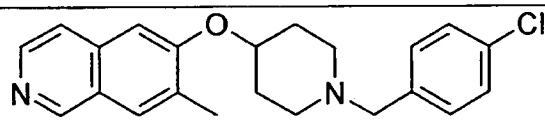
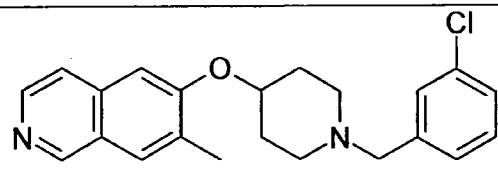
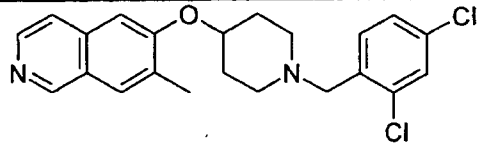
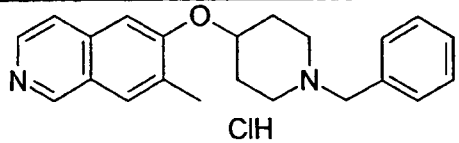
Example No	Formula	T_R	Mass [MH^+]
313	 ClH	0.74	433.24
314	 ClH	1.10	387.26
315	 ClH	1.05	387.26
316	 ClH	0.12	330.24

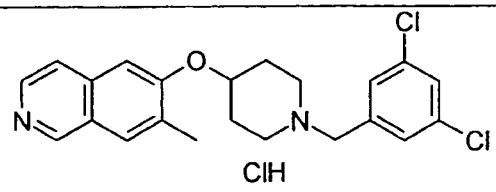
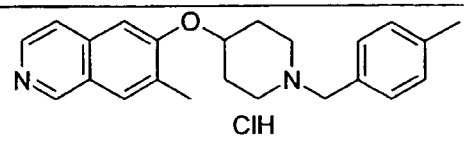
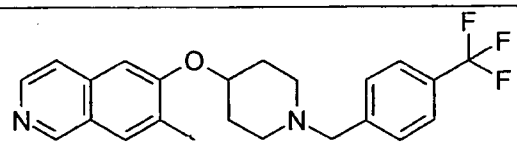
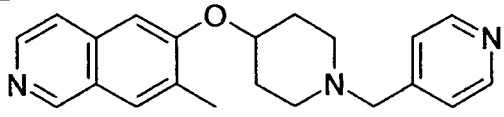
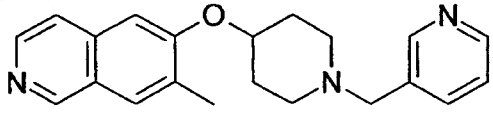
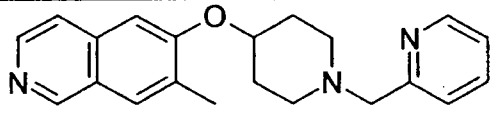
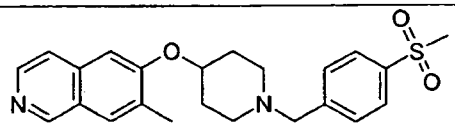
Example No	Formula	T_R	Mass [MH^+]
317	 Chiral ClH	0.28	330.27
318	 ClH	0.58	341.27
319	 ClH	0.87	377.25
320	 ClH	0.69	355.17

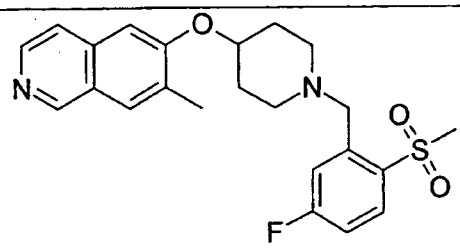
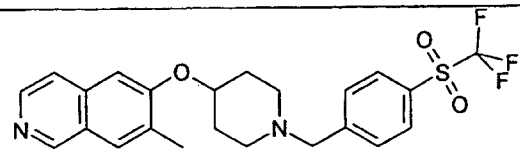
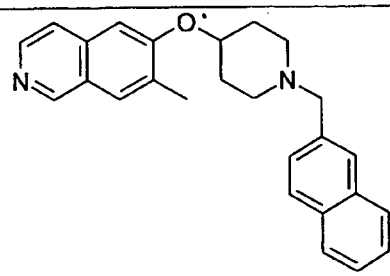
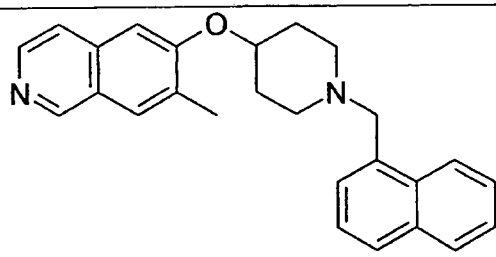
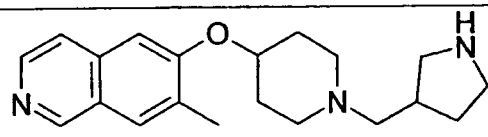
Example No	Formula	T_R	Mass [MH^+]
321	 ClH	0.80	343.19
322	 ClH	0.53	331.25
323	 ClH	0.18	344.30
324	 ClH	0.14	344.29
325	 ClH	0.14	358.29
326	 ClH	0.62	345.24

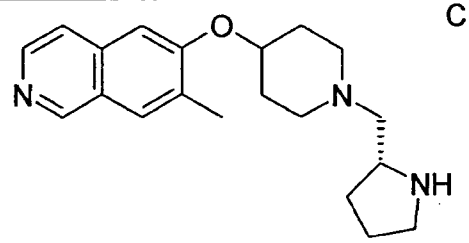
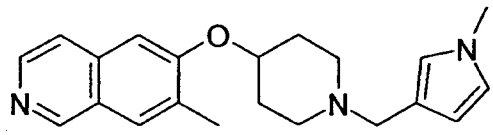
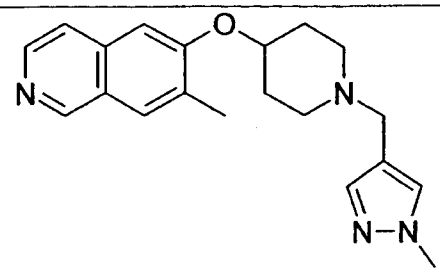
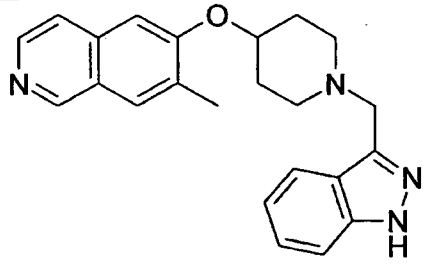
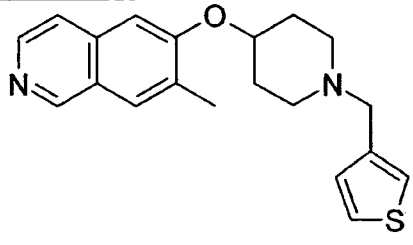
Example No	Formula	T_R	Mass [MH^+]
327	 ClH	0.60	345.27
328	Chiral  ClH	0.12	330.24
329	 ClH	0.67	327.24
330	 ClH	0.18	326.23
331	 ClH	0.23	335.26

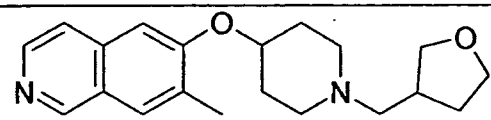
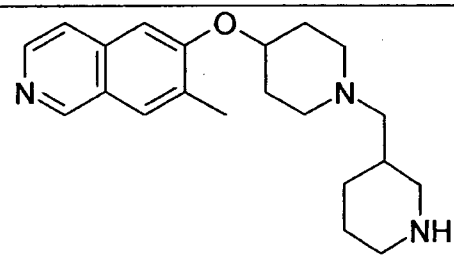
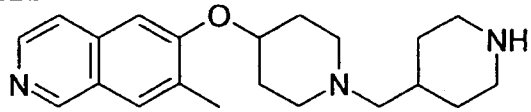
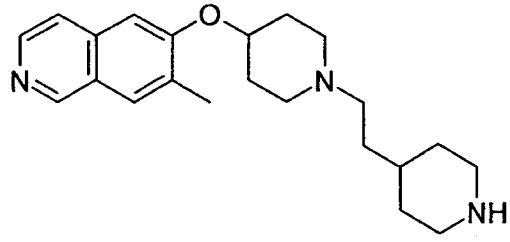
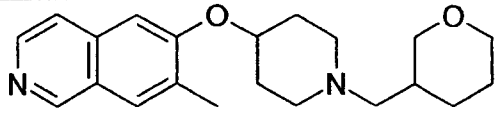
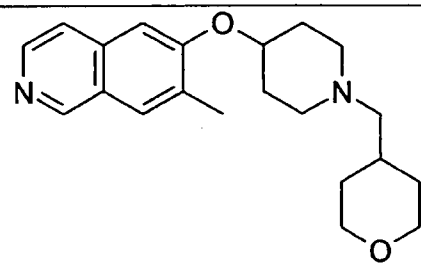
Example No	Formula	T_R	Mass [MH^+]
332	 ClH	0.70	271.17
333	 ClH	0.80	285.21
334	 ClH	0.87	299.19
335	 ClH	0.78	285.22
336	 ClH	0.92	299.20
337	 ClH	0.75	297.13
338		1.01	313.16

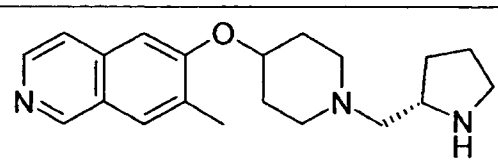
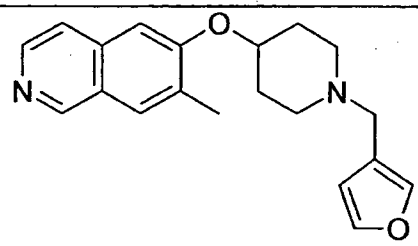
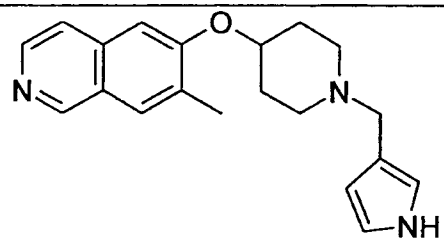
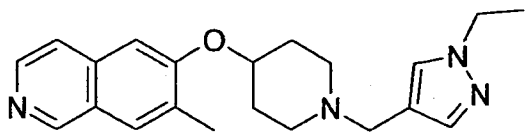
Example No	Formula	T_R	Mass [MH^+]
339	 ClH	0.77	339.10
340	 ClH	0.98	339.29
341	 ClH	0.91	325.23
342	 ClH	1.07	367.15
343	 ClH	1.01	367.15
344	 ClH	1.07	401.12/ 403.14
345	 ClH	0.99	333.19

Example No	Formula	T_R	Mass [MH^+]
346	 ClH	1.13	401.12/ 403.14
347	 ClH	1.00	347.24
348	 ClH	1.09	401.22
349	 ClH	0.63	334.23
350	 ClH	0.69	334.23
351	 ClH	0.90	334.24
352	 ClH	0.83	411.22

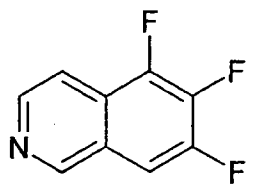
Example No	Formula	T_R	Mass [MH^+]
353	 ClH	0.88	429.20
354	 ClH	1.14	465.18
355	 ClH	1.17	383.25
356	 ClH	1.08	383.15
357	 ClH	0.60	326.26

Example No	Formula	T_R	Mass [MH^+]
358	 Chiral ClH	0.67	326.26
359	 ClH	0.89	336.25
360	 ClH	0.74	337.24
361	 ClH	0.91	373.23
362	 ClH	0.97	338.15

Example No	Formula	T_R	Mass [MH^+]
363	 ClH	0.73	327.24
364	 ClH	0.74	340.27
365	 ClH	0.62	340.28
366	 ClH	0.66	354.29
367	 ClH	0.79	341.26
368	 ClH	0.77	341.25

Example No	Formula	T_R	Mass [MH^+]
369	 Chiral ClH	0.76	326.26
370	 ClH	0.81	323.20
371	 ClH	0.84	322.22
372	 ClH	0.88	351.24

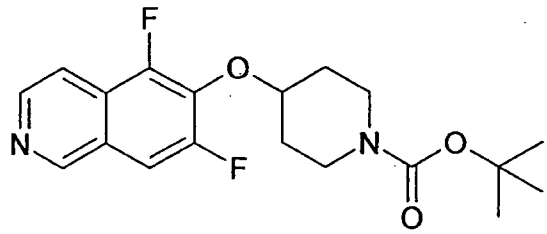
5,6,7-Trifluoro-isoquinoline (373)



5,6,7-Trifluoro-isoquinoline (373) is obtained by the same reaction sequence, used for the synthesis of 6-Fluoro-isoquinoline (23), starting from 3,4,5-Trifluorobenzaldehyde.

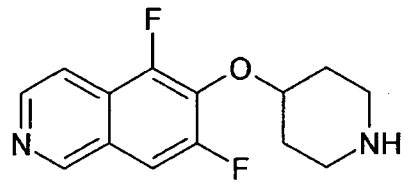
Final purification by preparative HPLC gave the desired isoquinoline as trifluoroacetat. R_t = 1.15 min (Method #2). Detected mass: 183.0.

4-(5,7-Difluoro-isoquinolin-6-yloxy)-piperidine-1-carboxylic acid tert-butyl ester (374)



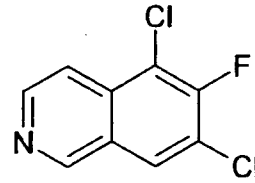
The title compound was synthesized following the protocol described for 4-(Isoquinolin-6-yloxy)-piperidine-1-carbocyclic acid-tert-butylester (154). R_t = 1.27 min (Method #TOP). Detected mass: 365.2 ($M+H^+$).

5,7-Difluoro-6-(piperidin-4-yloxy)-isoquinoline (375)



4-(5,7-Difluoro-isoquinolin-6-yloxy)-piperidine-1-carboxylic acid tert-butyl ester (374) is deprotected in Methanol/2 N HCl by the general procedure described in AAV2 to yield the title compound as HCl-salt. R_t = 0.43 min (Method #TOP). Detected mass: 265.1 ($M+H^+$).

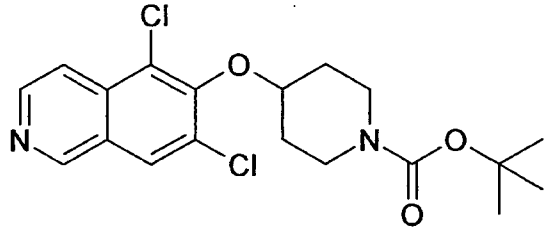
5,7-Dichloro-6-fluoro-isoquinoline (376)



5.0 g (27.5 mmol) 7-Chloro-6-fluoro-isoquinoline (150) were dissolved in 90 ml of conc. sulphuric acid. At room temperature 7.35 g (55.0 mmol) N-Chloro-succinimid were

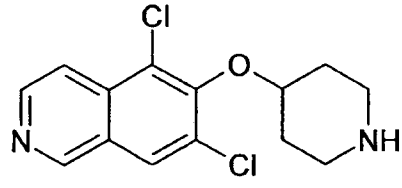
added and the mixture was stirred at 50 °C. After standing overnight at room temperature another 3 eq. N-Chloro-succinimid were added and at the following again 5 eq. N-Chloro-succinimid were added and the temperature was increased to 80 °C. After no further conversion could be detected, the mixture was cooled to room temperature and poured on ice. The aqueous solution was brought to basic pH by adding solid NaOH. The precipitate was filtered off and washed three times with dichloromethane. After drying the organic filtrates with MgSO4 and evaporation of the solvent 1.09 g of the desired isoquinoline could be isolated. R_t = 1.26 min (Method #TOP). Detected mass: 216.0/218.0 ($M+H^+$).

4-(5,7-Dichloro-isoquinolin-6-yloxy)-piperidine-1-carboxylic acid tert-butyl ester (377)



The title compound was synthesized following the protocol described for 4-(Isoquinolin-6-yloxy)-piperidine-1-carbocyclic acid-tert-butylester (154). After final purification by preparative HPLC and evaporation of the product fractions, the Boc-group is already partially cleaved. R_t = 1.71 min (Method #2). Detected mass: 397.2/399.2 ($M+H^+$).

5,7-Dichloro-6-(piperidin-4-yloxy)-isoquinoline (378)



150 mg 4-(5,7-Dichloro-isoquinolin-6-yloxy)-piperidine-1-carboxylic acid tert-butyl ester (377, already partially deprotected) were dissolved in 10 ml of dichloromethane and 1 ml of trifluoroacetic acid is added at 0 °C. The solution is stirred for 2 h at room temperature. For working up, 50 ml Dichloromethane were added and the solution was washed with saturated NaHCO3-solution. The layers were separated and the aqueous

phase was extracted once with Dichloromethane. The combined organic layers were again washed with saturated NaHCO3-solution , dried with MgSO4 and evaporated. The residue was purified by preparative HPLC. The product fractions were evaporated and the residue dissolved in 2 N HCl. After evaporation, the title compound was isolated as HCl-salt. R_t = 0.90 min (Method #2). Detected mass: 297.1/299.1 ($M+H^+$).

Determination of Rho kinase inhibition

To measure Rho-kinase inhibition, IC_{50} values were determined according to the following protocol:

Buffer: 25mM Tris pH7,5; 0,02% BSA; 5% Glycerol; 0,008% Triton X100; 2% DMSO, 1mM DTT; 1mM $MgCl_2$; 0,5µCi/well $\gamma^{33}P$ ATP
Enzyme: ROCKII or ROKα) (Upstate, Catalog # 14-451 Lot # 24880U) 0.1 ng/µl
Final concentration of ATP in reaction mixture 40µM
Biotinylated substrate, diluted to 0.25µM with buffer described above (without ATP)

1. 10µl Tris buffer (± Inhibitor)
2. Add 30 µL of enzyme solution
3. Start the reaction with 30µL of mix substrate/ATP/ATP33
4. Incubate for 20 min at room temperature
5. Stop reaction with 30µL of 50 mM EDTA
6. Transfer 50 µL of stopped solution to Streptavidin Flash Plate plus, Perkin Elmer, SMP 103A
7. Incubate for 30 min at RT
8. Wash 4 times with 300 µl of PBS/0.1% Tween 20
9. Radioactivity in the well was determined

No.	IC_{50}
29	+++
41	++++

44	++++
59	++++
67	+++
72	++++
81	++++
111	+++
100	+++
120	++++
133	++++
134	+++
138	++++
145	+++
156	++++
228	++++
261	++++
265	+++
266	+++
269	++++
378	++++

The given activity is denoted as the negative logarithm of the IC_{50} (pIC_{50}) as follows:

+: $3.0 \leq pIC_{50} < 4.0$

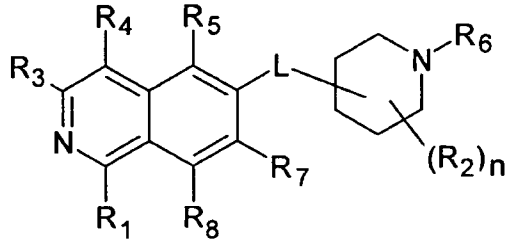
++ $4.0 \leq pIC_{50} < 5.0$

+++: $5.0 \leq pIC_{50} < 6.0$

++++: $6.0 \leq pIC_{50}$

Claims

1. A compound of the formula (I)



(I)

wherein

R_1 is

H,

$(C_1\text{-}C_6)$alkyl,

R',

NH-$(C_1\text{-}C_6)$alkyl,

NHR', or

N[$(C_1\text{-}C_6)$alkyl]$_2$;

R_2 is hydrogen, halogen or $(C_1\text{-}C_6)$alkyl;

R_3 is

H,

halogen,

$(C_1\text{-}C_6)$alkyl,

$(C_1\text{-}C_6)$alkylene-R',

OH,

O-R",

NH_2,

NHR",

NR"R" or

NH-C(O)-R",

R_4 is

H,

halogen,

hydroxy,

CN,

$(C_1$-$C_6)$alkyl,

R',

$(C_1$-$C_6)$alkylene-R';

R_5 is

H,

halogen,

CN,

NO_2,

$(C_1$-$C_6)$alkyl,

$(C_2$-$C_6)$alkenyl,

R',

$(C_1$-$C_6)$alkylene-$(C_6$-$C_{10})$aryl,

$(C_1$-$C_6)$alkenylene-$(C_6$-$C_{10})$aryl,

$(C_1$-$C_6)$alkylene-$(C_5$-$C_{10})$heterocyclyl,

CH(OH)-$(C_1$-$C_6)$alkyl,

NH_2,

NH-R',

NH-SO_2H,

NH-SO_2-$(C_1$-$C_6)$alkyl,

NH-SO_2-R',

NH-C(O)-$(C_1$-$C_6)$alkyl,

NH-C(O)-R',
C(O)N[(C_1-C_6)alkyl]$_2$,
C(O)OH, or
C(O)O-(C_1-C_6)alkyl;

R_6 is
H,
R',
(C_1-C_8)alkyl,
(C_1-C_6)alkylene-R',
(C_1-C_6)alkylene-O-(C_1-C_6)alkyl,
(C_1-C_6)alkylene-O-R',
(C_1-C_6)alkylene-CH[R']$_2$,
(C_1-C_6)alkylene-C(O)-R',
(C_1-C_6)alkylene-C(O)NH_2,
(C_1-C_6)alkylene-C(O)NH-R', or
(C_1-C_6)alkylene-C(O)N[R']$_2$;

R_7 is
H,
halogen,
CN,
NO_2,
(C_1-C_6)alkyl,
(C_2-C_6)alkenyl,
R',
(C_1-C_6)alkenylene-(C_6-C_{10})aryl,
(C_1-C_6)alkylene-R',
CH(OH)-(C_1-C_6)alkyl,

NH_2,

NH-R',

$NH-SO_2H$,

$NH-SO_2-(C_1-C_6)$alkyl,

$NH-SO_2-R'$,

SO_2-NH_2,

SO_2-NHR',

$NH-C(O)-(C_1-C_6)$alkyl,

NH-C(O)-R',

$C(O)N[(C_1-C_6)alkyl]_2$,

C(O)OH, or

$C(O)O-(C_1-C_6)$alkyl;

R_8 is H, halogen or (C_1-C_6)alkyl;

n is 1, 2, 3 or 4; and

L is O or $O-(C_1-C_6)$alkylene;

wherein

R' is

(C_3-C_8)cycloalkyl,

(C_5-C_{10})heterocyclyl,

(C_6-C_{10})aryl; and

R'' is

(C_3-C_8)cycloalkyl,

(C_5-C_{10})heterocyclyl,

(C_6-C_{10})aryl,

(C_1-C_6)alkyl,

(C_1-C_6)alkylene-R',

$(C_1$-$C_6)$alkylene-O-$(C_1$-$C_6)$alkyl,

$(C_1$-$C_6)$alkylene-O-R', or

$(C_1$-$C_6)$alkylene-NR_xR_y; and

wherein R_x and R_y are independently of each other

$(C_1$-$C_6)$alkyl,

$(C_5$-$C_{10})$heterocyclyl,

$(C_6$-$C_{10})$aryl,

$(C_1$-$C_4)$alkylene-$(C_5$-$C_{10})$heterocyclyl,

$(C_1$-$C_4)$alkylene-$(C_6$-$C_{10})$aryl,

$(C_1$-$C_4)$alkylene-NH$(C_1$-$C_6)$alkyl,

$(C_1$-$C_4)$alkylene-N$[(C_1$-$C_6)$alkyl$]_2$,

$(C_1$-$C_4)$alkylene-N$[(C_6$-$C_{10})$aryl$]_2$, or

$(C_1$-$C_4)$alkylene-N$[(C_5$-$C_{10})$heterocyclyl$]_2$; and

wherein in residues R_4, R_5, R_7 and R_8 one alkyl or alkylene hydrogen atom can optionally be substituted by OH, F, OCH_3, COOH, $COOCH_3$, NH_2, $NHCH_3$, $N(CH_3)_2$, $CONH_2$, $CONHCH_3$ or $CON(CH_3)_2$;

and their pharmaceutically acceptable salts and/or physiologically functional derivatives.

2. A compound according to claim 1, wherein R_1 is H, $(C_1$-$C_6)$alkyl, $(C_6$-$C_{10})$aryl, NH-$(C_1$-$C_6)$alkyl, NH-$(C_6$-$C_{10})$aryl or N$[(C_1$-$C_6)$alkyl$]_2$.

3. A compound according to one of claims 1 or 2, wherein R_1 is H, $(C_1$-$C_4)$alkyl, NH-$(C_1$-$C_4)$alkyl, N$[(C_1$-$C_4)$alkyl$]_2$ or NH-phenyl.

4. A compound according to one of claims 1 to 3, wherein R_1 is H, $(C_1$-$C_2)$alkyl or NH-$(C_1$-$C_2)$alkyl.

5. A compound according to one of claims 1 to 4, wherein R_1 is H.

6. A compound according to one of claims 1 to 5, wherein R_3 is H, halogen, $(C_1$-$C_4)$alkylene-R', O-R" or NHR", and wherein R' and R" are defined as in claim 1.

7. A compound according to one of claims 1 to 6, wherein R_3 is H or NHR".

8. A compound according to one of claims 1 to 7, wherein R_3 is H; NH-$(C_5$-$C_6)$heterocyclyl, preferably NH-$(C_5$-$C_6)$heteroaryl containing one or more N atoms; or NH-phenyl.

9. A compound according to one of claims 1 to 8, wherein R_8 is H, halogen or $(C_1$-$C_4)$alkyl.

10. A compound according to one of claims 1 to 9, wherein R_8 is H, Cl, F, methyl or ethyl.

11. A compound according to one of claims 1 to 10, wherein R_4 is H, halogen or $(C_1$-$C_6)$alkyl.

12. A compound according to one of claims 1 to 11, wherein R_4 is H, halogen or $(C_1$-$C_4)$alkyl.

13. A compound according to one of claims 1 to 12, wherein R_4 is H.

14. A compound according to one of claims 1 to 13, wherein R_5 is H, halogen, CN, $(C_1$-$C_6)$alkyl, R', NH-$(C_6$-$C_{10})$aryl or $(C_1$-$C_6)$alkylene-R'.

15. A compound according to one of claims 1 to 14, wherein R_5 is H, halogen, $(C_1$-$C_6)$alkyl, R', NH-$(C_6$-$C_{10})$aryl or $(C_1$-$C_6)$alkylene-R'.

16. A compound according to one of claims 1 to 15, wherein R_5 is H, halogen, $(C_1$-$C_6)$alkyl, $(C_6$-$C_{10})$aryl, NH-$(C_6$-$C_{10})$aryl, $(C_1$-$C_2)$alkyl-$(C_6$-$C_{10})$aryl or $(C_5$-$C_{10})$heteroaryl.

17. A compound according to one of claims 1 to 16, wherein R_7 is H, halogen, CN, $(C_1$-$C_6)$alkyl, $(C_2$-$C_6)$alkenyl, R' or $(C_1$-$C_6)$alkylene-$(C_3$-$C_8)$cycloalkyl.

18. A compound according to one of claims 1 to 17, wherein R_7 is H, halogen, CN, $(C_1$-$C_4)$alkyl, $(C_1$-$C_4)$alkenyl, phenyl, cyclopropyl or $(C_5$-$C_6)$heteroaryl.

19. A compound according to one of claims 1 to 18, wherein R_7 is H, fluoro, chloro, bromo, methyl, ethyl, phenyl, nitrile, cyclopropyl, thienyl or vinyl.

20. A compound according to one of claims 1 to 19, wherein n is 1, 2 or 3.

21. A compound according to one of claims 1 to 20, wherein n is 1.

22. A compound according to one of claims 1 to 21, wherein R_2 is H, halogen or $(C_1$-$C_4)$alkyl.

23. A compound according to one of claims 1 to 22, wherein R_2 is H or $(C_1$-$C_4)$alkyl.

24. A compound according to one of claims 1 to 23, wherein R_2 is H, $(C_1$-$C_2)$alkyl.

25. A compound according to one of claims 1 to 24, wherein R_6 is H, $(C_1$-$C_6)$alkyl, R', $(C_1$-$C_4)$alkylene-$(C_3$-$C_8)$cycloalkyl, $(C_1$-$C_4)$alkylene-$(C_5$-$C_{10})$heterocyclyl,

$(C_1$-$C_4)$alkylene-C(O)-$(C_5$-$C_{10})$heterocyclyl, $(C_1$-$C_4)$alkylene-C(O)-$(C_6$-$C_{10})$aryl or $(C_1$-$C_6)$alkylene-$(C_6$-$C_{10})$aryl.

26. A compound according to one of claims 1 to 25, wherein R_6 is H, $(C_1$-$C_6)$alkyl, $(C_5$-$C_{10})$heterocyclyl, $(C_1$-$C_4)$alkylene-$(C_5$-$C_{10})$heterocyclyl or $(C_1$-$C_6)$alkylene-$(C_6$-$C_{10})$aryl.

27. A compound according to one of claims 1 to 26, wherein L is attached to the 3-position or to the 4-position of the piperidine ring.

28. A compound according to one of claims 1 to 27, wherein L is attached to the 4-position of the piperidine ring.

29. A compound according to one of claims 1 to 28, wherein L is O-methylene, O-ethylene or preferably O.

30. A compound according to claim 1, wherein

R_1 is H, $(C_1$-$C_6)$alkyl, $(C_6$-$C_{10})$aryl, NH-$(C_1$-$C_6)$alkyl, NH-$(C_6$-$C_{10})$aryl, or $N[(C_1$-$C_6)alkyl]_2$;

R_2 is hydrogen, halogen, or $(C_1$-$C_6)$alkyl;

R_3 is H, halogen, $(C_1$-$C_4)$alkylene-R', O-R'' or NHR'', wherein R' and R'' are defined as in claim 1;

R_4 is H, halogen or $(C_1$-$C_6)$alkyl;

R_5 is H, $(C_1$-$C_6)$alkyl, halogen, CN, $(C_6$-$C_{10})$aryl, NH-$(C_6$-$C_{10})$aryl, $(C_1$-$C_6)$alkylene-$(C_6$-$C_{10})$aryl, $(C_5$-$C_{10})$heterocyclyl or $(C_1$-$C_6)$alkylene-$(C_5$-$C_{10})$heterocyclyl;

R_6 is H, $(C_1$-$C_6)$alkyl, R', $(C_1$-$C_4)$alkylene-$(C_5$-$C_{10})$heterocyclyl, $(C_1$-$C_6)$alkylene-C(O)-$(C_6$-$C_{10})$aryl, $(C_1$-$C_4)$alkylene-C(O)-$(C_5$-$C_{10})$heterocyclyl, or $(C_1$-$C_6)$alkylene-$(C_6$-$C_{10})$aryl;

R_7 is H, halogen, CN, $(C_1$-$C_6)$alkyl, $(C_2$-$C_6)$alkenyl or R';

R_8 is H, halogen or $(C_1$-$C_6)$alkyl;

n is 1, 2 or 3, and

L is O, O-methylene or O-ethylene.

31. A compound according to claim 1, wherein

R_1 is H, $(C_1$-$C_6)$alkyl, $(C_6$-$C_{10})$aryl, NH-$(C_1$-$C_6)$alkyl, NH-$(C_6$-$C_{10})$aryl, or N[$(C_1$-$C_6)$alkyl]$_2$;

R_2 is H or $(C_1$-$C_4)$alkyl;

R_3 is H, halogen or NHR", wherein R" is defined as above;

R_4 is H, halogen or $(C_1$-$C_4)$alkyl;

R_5 is H, $(C_1$-$C_6)$alkyl, halogen, $(C_6$-$C_{10})$aryl, NH-$(C_6$-$C_{10})$aryl, $(C_1$-$C_6)$alkylene-$(C_6$-$C_{10})$aryl or $(C_5$-$C_{10})$heterocyclyl;

R_6 is H, $(C_1\text{-}C_6)$alkyl, R', $(C_1\text{-}C_4)$alkylene-$(C_5\text{-}C_{10})$heterocyclyl or $(C_1\text{-}C_6)$alkylene-$(C_6\text{-}C_{10})$aryl;

R_7 is H, halogen, CN, $(C_1\text{-}C_6)$alkyl, $(C_2\text{-}C_6)$alkenyl or R';

R_8 is H, halogen or $(C_1\text{-}C_6)$alkyl;

n is 1, 2 or 3; and

L is O.

32. A compound according to claim 1, wherein

R_1 is H, $(C_1\text{-}C_4)$alkyl, NH-$(C_1\text{-}C_4)$alkyl, N[$(C_1\text{-}C_4)$alkyl]$_2$ or NH-phenyl;

R_2 is H, $(C_1\text{-}C_4)$alkyl;

R_3 is H, NH-$(C_5\text{-}C_6)$heteroaryl or NH-phenyl;

R_4 is H, halogen or $(C_1\text{-}C_4)$alkyl;

R_5 is H, $(C_1\text{-}C_4)$alkyl, halogen, $(C_6\text{-}C_{10})$aryl, NH-$(C_6\text{-}C_{10})$aryl, $(C_1\text{-}C_2)$alkyl-$(C_6\text{-}C_{10})$aryl or $(C_5\text{-}C_{10})$heteroaryl;

R_6 is H, $(C_1\text{-}C_6)$alkyl, $(C_5\text{-}C_{10})$heterocyclyl, $(C_1\text{-}C_4)$alkylene-$(C_5\text{-}C_{10})$heterocyclyl, $(C_6\text{-}C_{10})$aryl or $(C_1\text{-}C_6)$alkylene-$(C_6\text{-}C_{10})$aryl;

R_7 is H, halogen, CN, $(C_1\text{-}C_4)$alkyl, $(C_1\text{-}C_4)$alkenyl, phenyl, cyclopropyl, $(C_5\text{-}C_6)$heteroaryl;

R_8 is H, halogen or $(C_1\text{-}C_4)$alkyl;

n is 1; and

L is O.

33. Use of at least one compounds of the formula (I) and/or their physiologically acceptable salt as claimed in one of claims 1 to 32 for producing a medicament.

34. Use of at least one compounds of the formula (I) and/or their physiologically acceptable salt as claimed in one of claims 1 to 32 for producing a medicament for the treatment and/or prevention of hypertension, pulmonary hypertension, ocular hypertension, peripheral circulatory disorder, angina pectoris, cerebral vasospasm, asthma, premature birth, hyperaggregability of platelets, Peripheral Occlusive Arterial Disease (PAOD), Chronic Obstructive Pulmonary Disease (COPD), cancer development, erectile dysfunction, arteriosclerosis, ischemic organ failure (end organ damage), fibroid lung, fibroid liver, liver failure, fibroid kidney, renal glomerulosclerosis, kidney failure, organ hypertrophy, prostatic hypertrophy, complications of diabetes, blood vessel restenosis, atherosclerosis, cancer, cardiac hypertrophy, heart failure ischemic diseases; inflammation; autoimmune diseases; AIDS, osteopathy such as osteoporosis, brain functional disorder, infection of digestive tracts with bacteria, sepsis, adult respiratory distress syndrome, retinopathy, glaucoma or Alzheimer's disease.

35. A medicament comprising an effective amount of at least one compound as claimed in any of claims 1 to 32 and/or a pharmacologically acceptable salt thereof, physiologically tolerated excipients and carriers and, where appropriate, further additives and/or other active ingredients.

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2006/005648

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D401/12 C07D401/14 C07D405/14 C07D409/14 C07D413/14
C07D217/02 C07D217/22 A61K31/4725 A61P11/00 A61P27/00

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)
C07D A61K A61P

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

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, CHEM ABS Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 1 541 559 A (ASAHI KASEI PHARMA CORPORATION) 15 June 2005 (2005-06-15) the whole document	1-35
A	TAKAMI, ATSUYA ET AL: "Design and synthesis of Rho kinase inhibitors (I)" BIOORGANIC & MEDICINAL CHEMISTRY , 12(9), 2115-2137 CODEN: BMECEP; ISSN: 0968-0896, 2004, XP002309639 the whole document	1-35

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

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
25 September 2006	04/10/2006

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Gregoire, Ariane

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2006/005648

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 1541559 A	15-06-2005	AU 2003281623 A1	09-02-2004
		CA 2493230 A1	29-01-2004
		CN 1668600 A	14-09-2005
		WO 2004009555 A1	29-01-2004

La presente invención se refiere a derivados de isoquinolina novedosos, su preparación y su uso en el tratamiento y/o prevención de enfermedades relacionadas con la inhibición de Rho-cinasa y/o de la fosforilación mediada por Rho-cinasa de la fosfatasa de la cadena ligera de miosina.

La activación de la GTPasa pequeña RhoA tras la estimulación agonista da lugar a la conversión de RhoA desde su forma inactiva unida a GDP a la forma activa unida a GTP con una posterior unión a y activación de Rho-cinasa. Se conocen dos isoformas, Rho-cinasa 1 y Rho-cinasa 2. La Rho-cinasa 2 se expresa en células de músculo liso vascular y células endoteliales. La Activación de la Rho-cinasa 2 por la RhoA activa unida a GTP conduce a la sensibilización al calcio de las células del músculo liso a través de la inhibición mediada por fosforilación de la actividad de la fosfatasa de la cadena ligera de miosina y así la regulación por incremento de la actividad de la cadena ligera reguladora de la miosina (Uehata et al., Nature 1997, 389, 990-994).

Se sabe que la Rho-cinasa está implicada en la vasoconstricción, que incluye el desarrollo del tono miógeno (J. Appl. Physiol. 2005, 1940-8, 98), contracción del músculo liso bronquial (Am. J. Resp. Cell Mol. Biol. 20, 1190-1200), hipertensión, es decir hipertensión pulmonar (Heart, 91, 391-2, 2005) e hipertensión ocular (Invest. Ophthalmol. Visual Sci. 2001, 42, 137-144), disfunción endotelial (Eur. J. Pharmacol. 2005, 512, 247-249), arteriosclerosis, reestenosis (Arch. Mal. Coeur 2005, 98, 249-254), utilización de glucosa, hipertrofia cardiaca (Hypertension 2000, 35, 313-318), disfunción eréctil (Nature Medicina 2001, 7, 119-122), retinopatía, inflamación, enfermedades inmunitarias, SIDA, osteoporosis, trastorno funcional del cerebro, infección de los tubos digestivos con bacterias (WO 98/06433), desarrollo de cáncer, motilidad y proliferación del músculo liso vascular (Circ. Res. 1999, 84, 1186-1193; Atherosclerosis 2001, 155, 321-327), motilidad y proliferación endotelial (Biochem. Biophys. Res. Commun. 2000, 269, 633-640), formación de fibras de estrés (Science 1997, 275, 1308-1311; J. Cell Biol. 2000, 150, 797-806), agregación plaquetaria (FEBS Lett. 2000, 466, 70-74; Blood 1999, 94, 1665-1672), activación del sistema de transporte de intercambio Na/H (EMBO J. 1998, 17, 4712-4722), enfermedad de Alzheimer (Science 2003, 302, 1215-1217), activación de la aducina (J. Biol. Chem., 273, 5542-5548,

1998), y en la señalización del SREB (elemento de unión de respuesta del esterol) y sus efectos sobre el metabolismo lipídico (Circ. Res., 92,1296-304, 2003).

Por tanto, un compuesto que tiene efecto inhibitorio sobre la Rho-cinasa y/o sobre la fosforilación mediada por Rho-cinasa de la fosfatasa de la cadena ligera de miosina es útil para el tratamiento y/o prevención de enfermedades que implican a la Rho-cinasa como la causa principal de enfermedad, por ejemplo hipertensión, es decir hipertensión pulmonar e hipertensión ocular, trastorno circulatorio periférico, angina de pecho, vasoespasmo cerebral, asma, parto prematuro, hiperagregabilidad de plaquetas, Enfermedad Arterial Oclusiva Periférica (PAOD), Enfermedad Pulmonar Obstructiva Crónica (COPD), desarrollo de cáncer, y disfunción eréctil, o como la causa secundaria de enfermedad, por ejemplo, arteriosclerosis, insuficiencia orgánica isquémica (daño del órgano afectado), fibrosis pulmonar, fibrosis hepática, insuficiencia hepática, fibrosis renal, glomeruloesclerosis renal, insuficiencia renal, hipertrofia orgánica, hipertrofia prostática, complicaciones de diabetes, reestenosis de vasos sanguíneos, ateroesclerosis, cáncer, hipertrofia cardiaca, insuficiencia cardiaca; enfermedades isquémicas; inflamación; enfermedades autoinmunitarias; SIDA, osteopatía tal como osteoporosis, trastorno funcional del cerebro, infección de los tubos digestivos con bacterias, sepsis, síndrome de dificultad respiratoria aguda, retinopatía, glaucoma y enfermedad de Alzheimer.

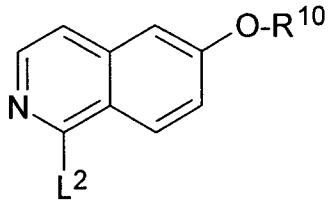
El documento WO 01/64238 describe derivados de isoquinolin-5-sulfonamida opcionalmente sustituidos por un grupo heterocíclico unido a $-(CH_2)_{1-6}-O-(CH_2)_{0-6}-$, a $-(CH_2)_{0-6}-S-(CH_2)_{0-6}-$ o a $-(CH_2)_{0-6}-$ útiles como agentes neuroprotectores.

El documento JP 10087629 A describe derivados de isoquinolina útiles para el tratamiento de infecciones causadas por Heliobacter pylori tales como por ejemplo gastritis o úlcera. Los derivados de isoquinolina están preferentemente sustituidos en posición 5 por X-[alquileno(C_1-C_6)]$_{0-1}$-Y en el que X puede ser oxígeno e Y puede ser un grupo arilo o un grupo heterocíclico.

Hagihara et al. (Bioorg. Med. Chem. 1999, 7, 2647-2666) describen la 6-benciloxi-isoquinolina para el tratamiento de infecciones causadas por Heliobacter pylori.

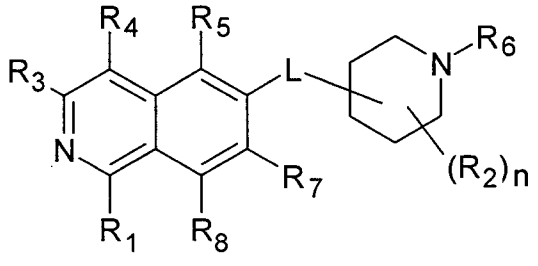
El documento US 5.480.883 describe genéricamente como inhibidores del receptor PDGF y/o EGF útiles para inhibir la proliferación celular a compuestos de la fórmula "Ar I – X – Ar II" en la que X puede ser $(CHR_1)_m$-Z-$(CHR_1)_n$, por ejemplo Z-CH_2, en el que Z puede ser O, R_1 es hidrógeno o alquilo, Ar I puede ser entre otros un sistema de anillo heteroarilo bicíclico C_{5-12} opcionalmente sustituido y Ar II puede ser entre otros un sistema heterocíclico saturado monocíclico C_{3-7} opcionalmente sustituido.

El documento WO 03/053330 describe derivados de isoquinolina de la fórmula



en la que L^2 es halógeno y R^{10} puede ser un grupo heterocíclicoC5-6-alquilenoC$_{1-5}$ como intermedios en la síntesis de inhibidores de GSK-3.

Una realización de la presente invención es un compuesto de la fórmula (I)



(I)

en la que

R_1 es

H,

alquilo(C_1-C_6),

R',

NH-alquil(C_1-C_6),

NH-R', o

N[alquil(C_1-C_6)]$_2$;

R_2 es hidrógeno, halógeno, o alquilo(C_1-C_6);

R_3 es
H,
halógeno,
alquilo(C_1-C_6),
alquileno(C_1-C_6)-R',
OH,
O-R",
NH_2,
NHR",
NR"R" o
NH-C(O)-R",

R_4 es
H,
halógeno,
hidroxi,
CN,
alquilo(C_1-C_6),
R',
alquileno(C_1-C_6)-R';

R_5 es
H,
halógeno,
CN,
NO_2,
alquilo(C_1-C_6),
alquenilo(C_2-C_6),
R',
alquileno(C_1-C_6)-aril(C_6-C_{10}),

alquenileno(C_1-C_6)-aril(C_6-C_{10}),

alquileno(C_1-C_6)-heterociclil(C_5-C_{10}),

CH(OH)-alquil(C_1-C_6),

NH_2,

NH-R',

NH-SO_2H,

NH-SO_2-alquil(C_1-C_6),

NH-SO_2-R',

NH-C(O)-alquil(C_1-C_6),

NH-C(O)-R',

C(O)N[alquil(C_1-C_6)]$_2$,

C(O)OH, o

C(O)O-alquil(C_1-C_6);

R_6 es

H,

R',

alquilo(C_1-C_8),

alquileno(C_1-C_6)-R',

alquileno(C_1-C_6)-O-alquil(C_1-C_6),

alquileno(C_1-C_6)-O-R',

alquileno(C_1-C_6)-CH[R']$_2$,

alquileno(C_1-C_6)-C(O)-R',

alquileno(C_1-C_6)-C(O)NH_2,

alquileno(C_1-C_6)-C(O)NH-R', o

alquileno(C_1-C_6)-C(O)N[R']$_2$;

R_7 es

H,

halógeno,

CN,

NO_2,

alquilo(C_1-C_6),
alquenilo(C_2-C_6),
R',
alquenileno(C_1-C_6)-aril(C_6-C_{10}),
alquileno(C_1-C_6)-R',
CH(OH)-alquil(C_1-C_6),
CH(OH)-aril(C_6-C_{10}),
CH(OH)-heterociclil(C_5-C_{10}),
NH_2,
NH-R',
NH-SO_2H,
NH-SO_2-alquil(C_1-C_6),
NH-SO_2-R',
SO_2-NH_2,
SO_2-NHR',
NH-C(O)-alquil(C_1-C_6),
NH-C(O)-R',
C(O)N[alquil(C_1-C_6)]$_2$,
C(O)OH, o
C(O)O-alquil(C_1-C_6);

R8 es H, halógeno o alquilo(C_1-C_6);

n es 1, 2, 3 o 4; y

L es O o O-alquileno(C_1-C_6);

en la que
R' es
cicloalquilo(C_3-C_8),
heterociclilo(C_5-C_{10}),
arilo(C_6-C_{10}); y

R" es

cicloalquilo(C_3-C_8),

heterociclilo(C_5-C_{10}),

arilo(C_6-C_{10}),

alquilo(C_1-C_6),

alquileno(C_1-C_6)-R',

alquileno(C_1-C_6)-O-alquil(C_1-C_6),

alquileno(C_1-C_6)-O-R', o

alquileno(C_1-C_6)-NR_xR_y; y

en el que R_x y R_y son independientemente uno del otro

alquilo(C_1-C_6),

heterociclilo(C_5-C_{10}),

arilo(C_6-C_{10}),

alquileno(C_1-C4)-heterociclil(C_5-C_{10}),

alquileno(C_1-C4)-aril(C_6-C_{10}),

alquileno(C_1-C4)-NHalquil(C_1-C_6),

alquileno(C_1-C4)-NH[alquil(C_1-C_6)]2,

alquileno(C_1-C_4)-N[aril(C_6-C_{10})]$_2$, o

alquileno(C_1-C4)-N[heterociclil(C_5-C_{10})]2;

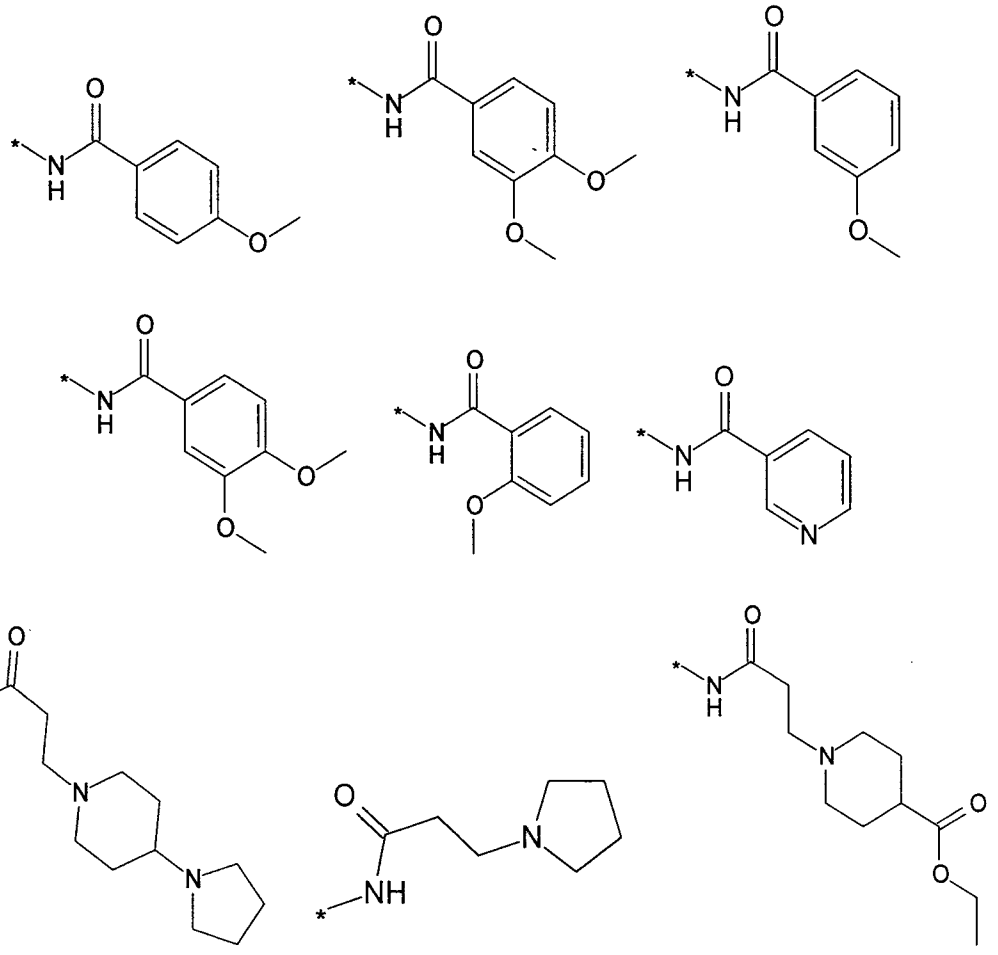
en la que en los residuos R_4, R_5, R_7 y R_8 un átomo de hidrógeno del alquilo o el alquileno opcionalmente puede estar sustituido por OH, F, OCH_3, COOH, $COOCH_3$, NH_2, $NHCH_3$, $N(CH_3)_2$, $CONH_2$, $CONHCH_3$ o $CON(CH_3)_2$;

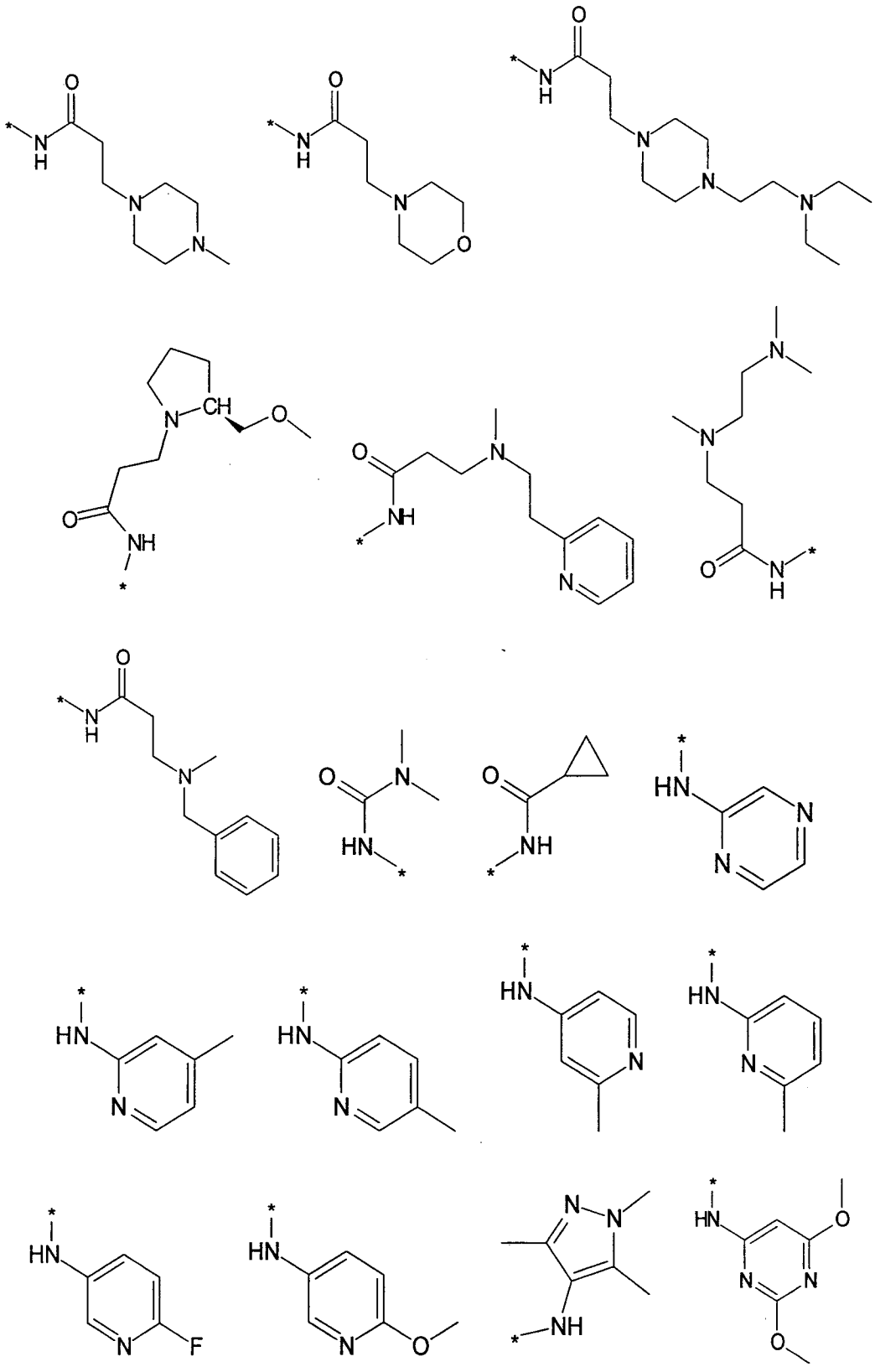
y sus sales farmacéuticamente aceptables y/o sus derivados fisiológicamente funcionales.

Preferentemente, R_1 es H, alquilo(C_1-C_6), arilo(C_6-C_{10}), NH-alquil(C_1-C_6), NH-aril(C_6-C_{10}) o N[alquil(C_1-C_6)]$_2$. Más preferentemente, R_1 es H, halógeno, alquilo(C_1-C_4), NH-alquil(C_1-C_4), N[alquil(C_1-C_4)]$_2$ o NH-fenil. Lo más preferentemente, R_1 es H, alquilo(C_1-C_2) o NH-alquil(C_1-C_2), preferido especialmente H.

Preferentemente, R_2 es H, halógeno o alquilo(C_1-C_4). Preferentemente, R_2 es H o alquilo(C_1-C_4). Más preferentemente, R_2 es H, alquilo(C_1-C_2). R_2 puede estar unido a cualquier átomo de carbono del anillo de piperidina incluyendo la posición en la que se enlaza el grupo de unión L.

R_3 es preferentemente H, halógeno, alquileno(C_1-C_4)-R', O-R'' o NHR''. Más preferido, R_3 es H o NHR''. Lo más preferido, R_3 es H, NH-heterociclil(C_5-C_6) o NH-fenil, especialmente preferidos son H, NH-heteroaril(C_5-C_6) que contiene uno o más átomos de N o NH-fenil. Los más preferido especialmente, R_3 es H. Ejemplos de sustituyentes R_3 son





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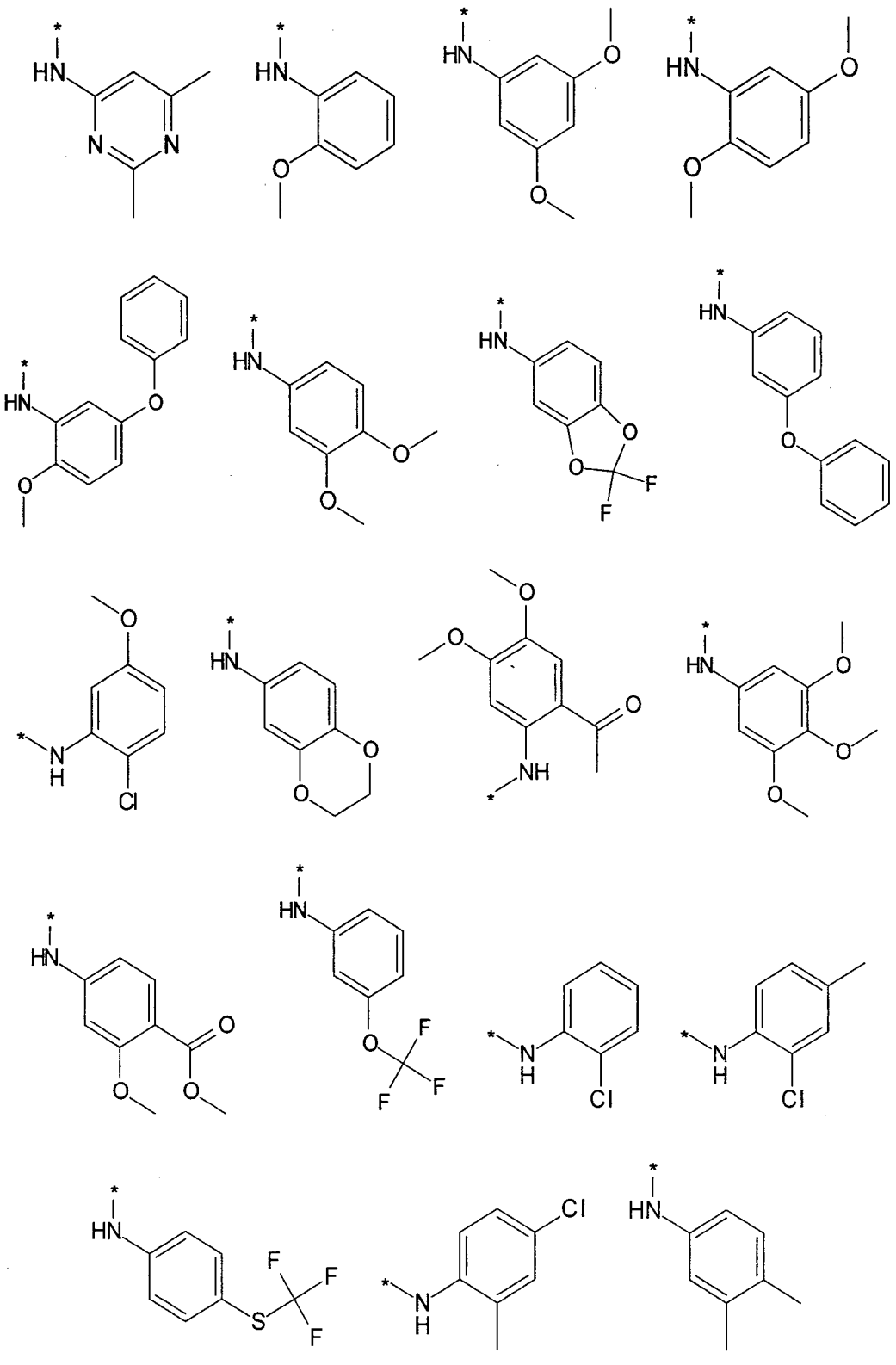

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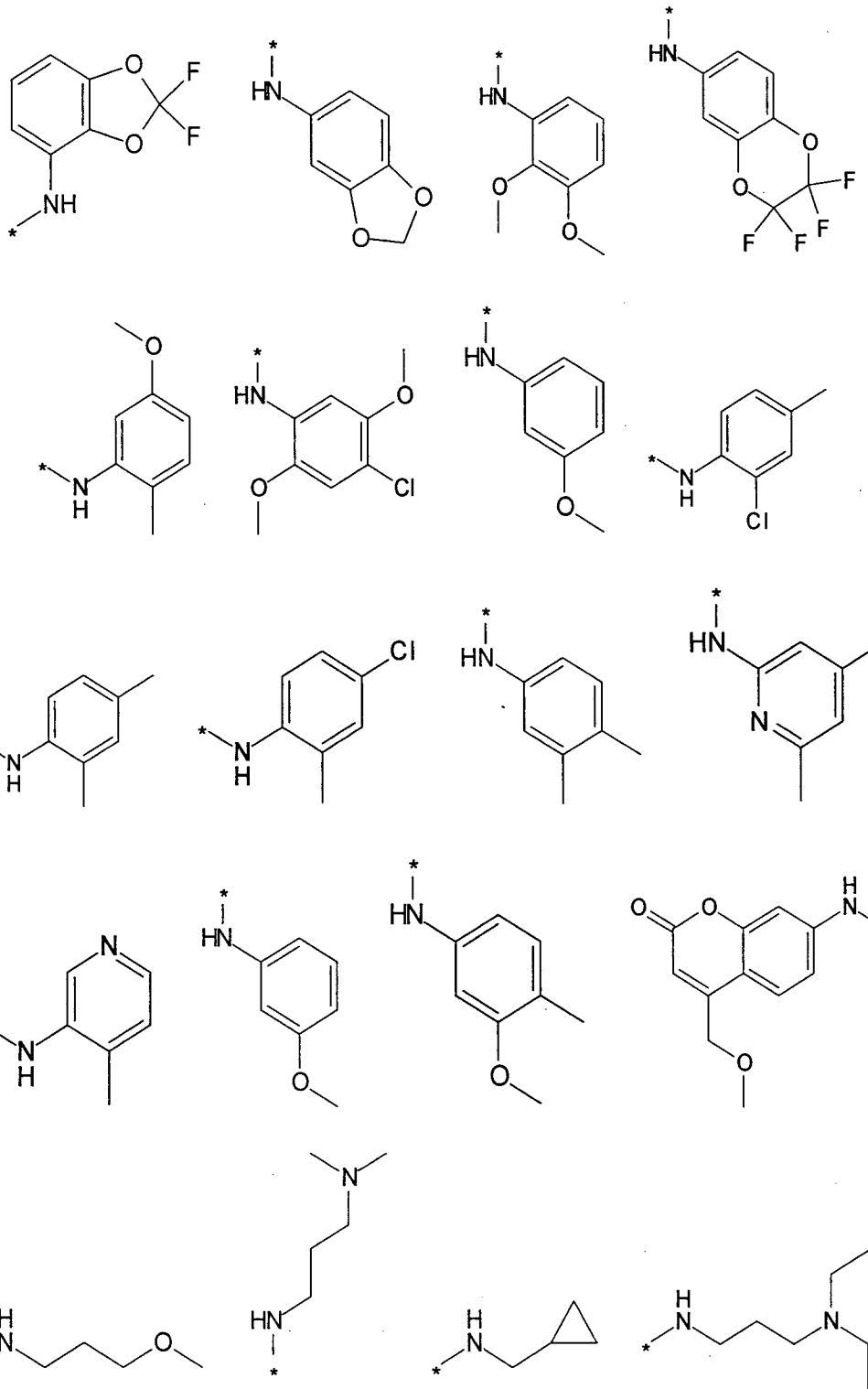

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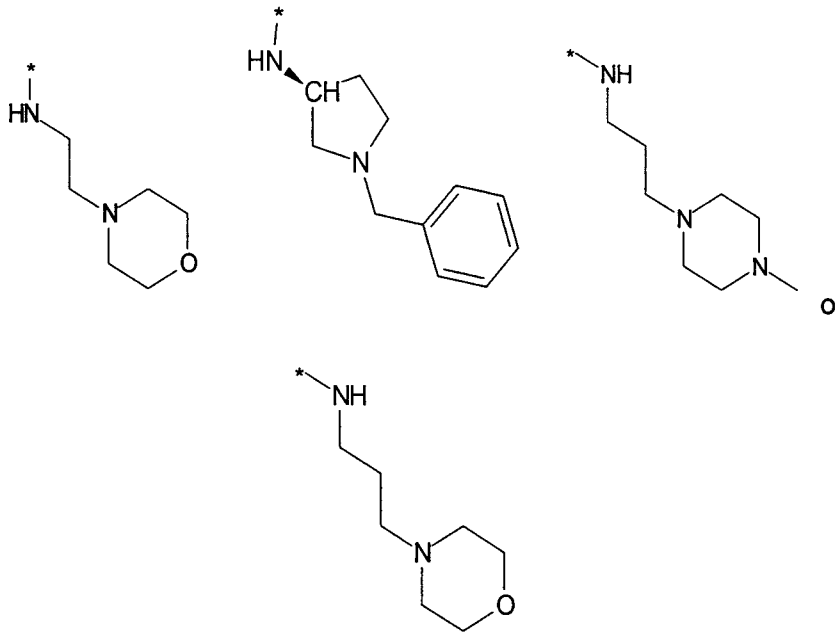
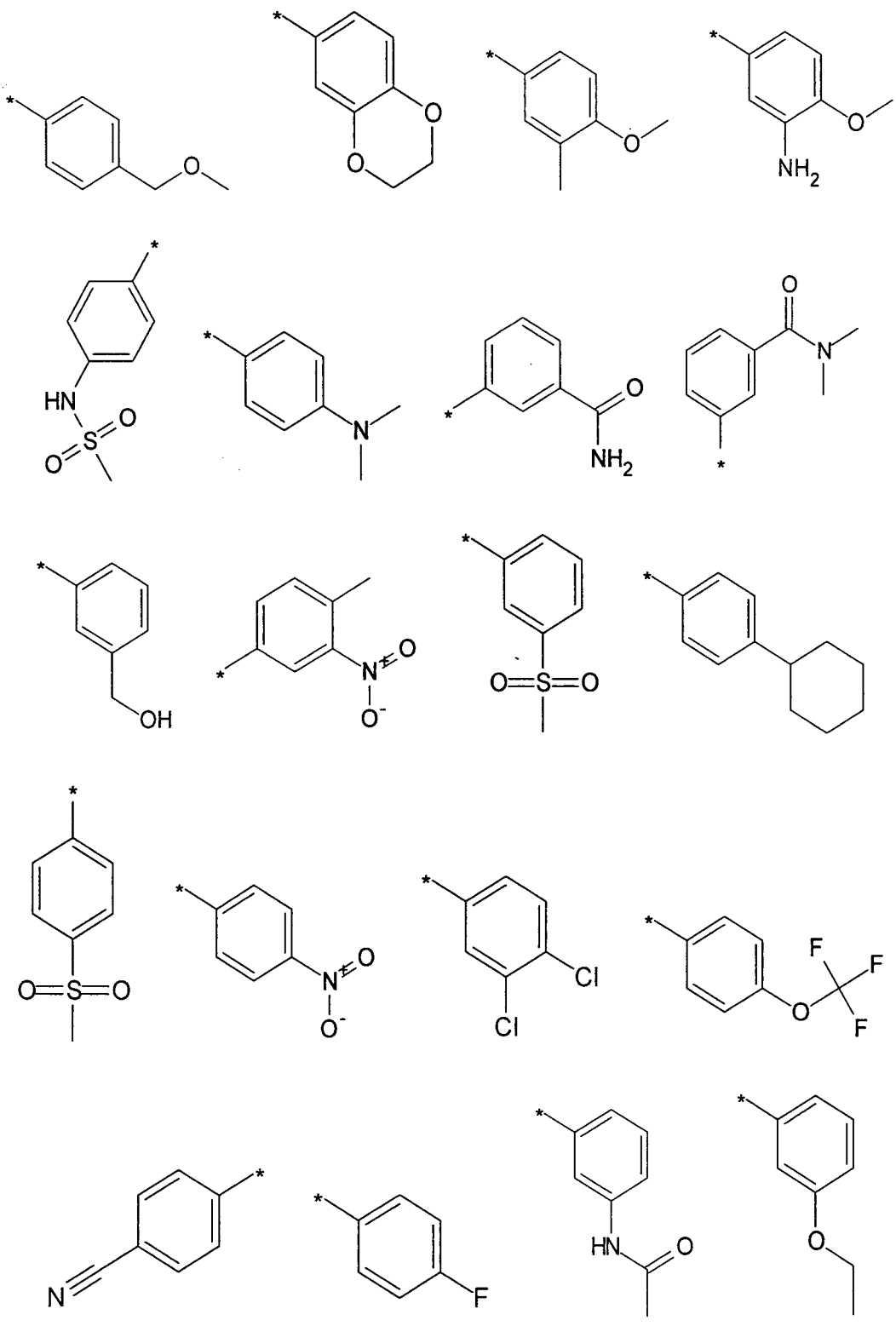


Preferentemente, R4 es H, halógeno o alquilo(C_1-C6). Más preferido, R_4 es H, halógeno o alquilo(C_1-C4). Lo más preferido, R_4 es H.

Preferentemente, R_5 es H, halógeno, CN, alquilo(C_1-C_6), R', NH-aril(C_6-C_{10}) o alquileno(C_1-C_6)-R'. Más preferentemente, R_5 es H, halógeno, alquilo(C_1-C_6), R', NH-aril(C_6-C_{10}) o alquileno(C_1-C_6)-R'. Lo más preferentemente, R_5 es H, halógeno, arilo(C_6-C_{10}), NH-aril(C_6-C_{10}), alquil(C_1-C_2)-aril(C_6-C_{10}), alquilo(C_1-C_6) o heteroarilo(C_5-C_{10}). Especialmente preferido, R_5 es H, halógeno, fenilo, alquilo(C_1-C_6) o heteroarilo(C_5-C_6). Ejemplos de R_5 son hidrógeno, fluoro, cloro, bromo, yodo, nitrilo, nitro, (p-metoxi)-fenilo, N-anilina, fenilo, bencilo, metilo, etilo, vinilo, 2-propenilo, s-butenilo, ciclopropilo, tienilo, tetrazol, amino, 4-metoxi-anilina, N-acetil o un sustituyente del grupo que consiste en



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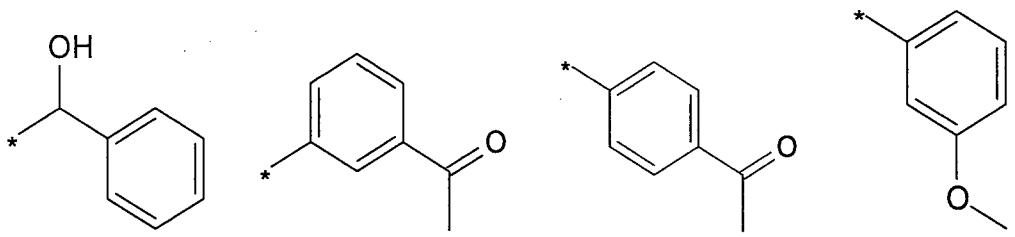
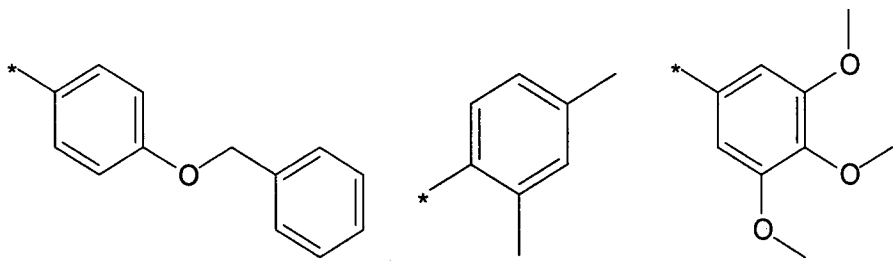
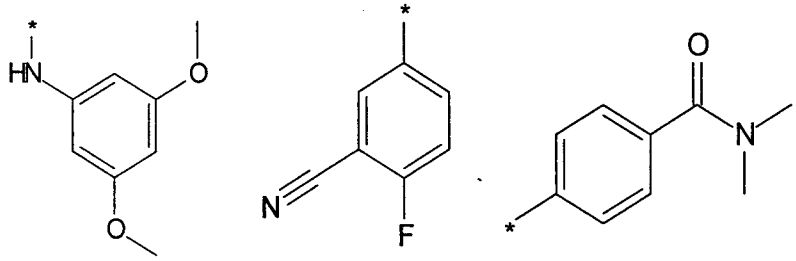
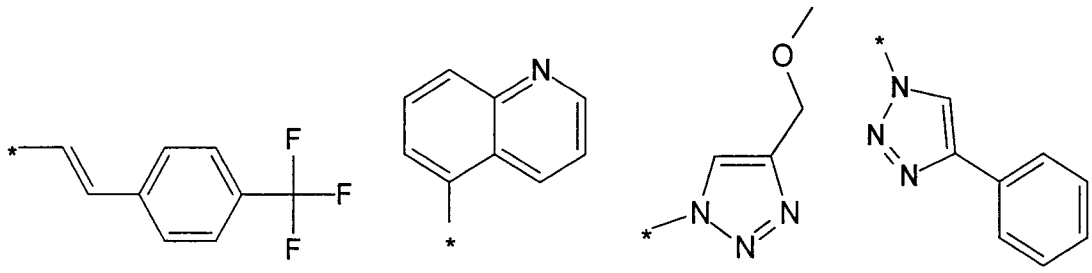
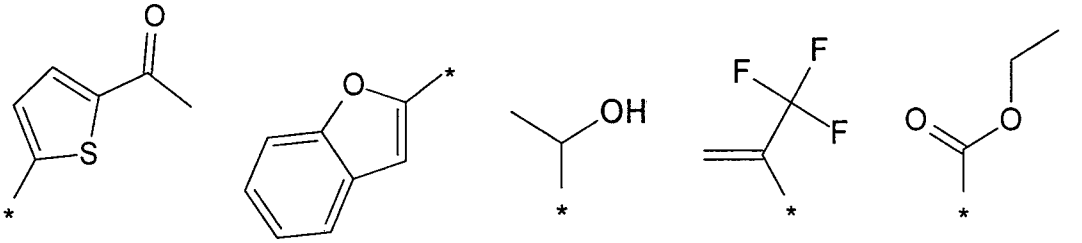
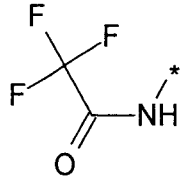




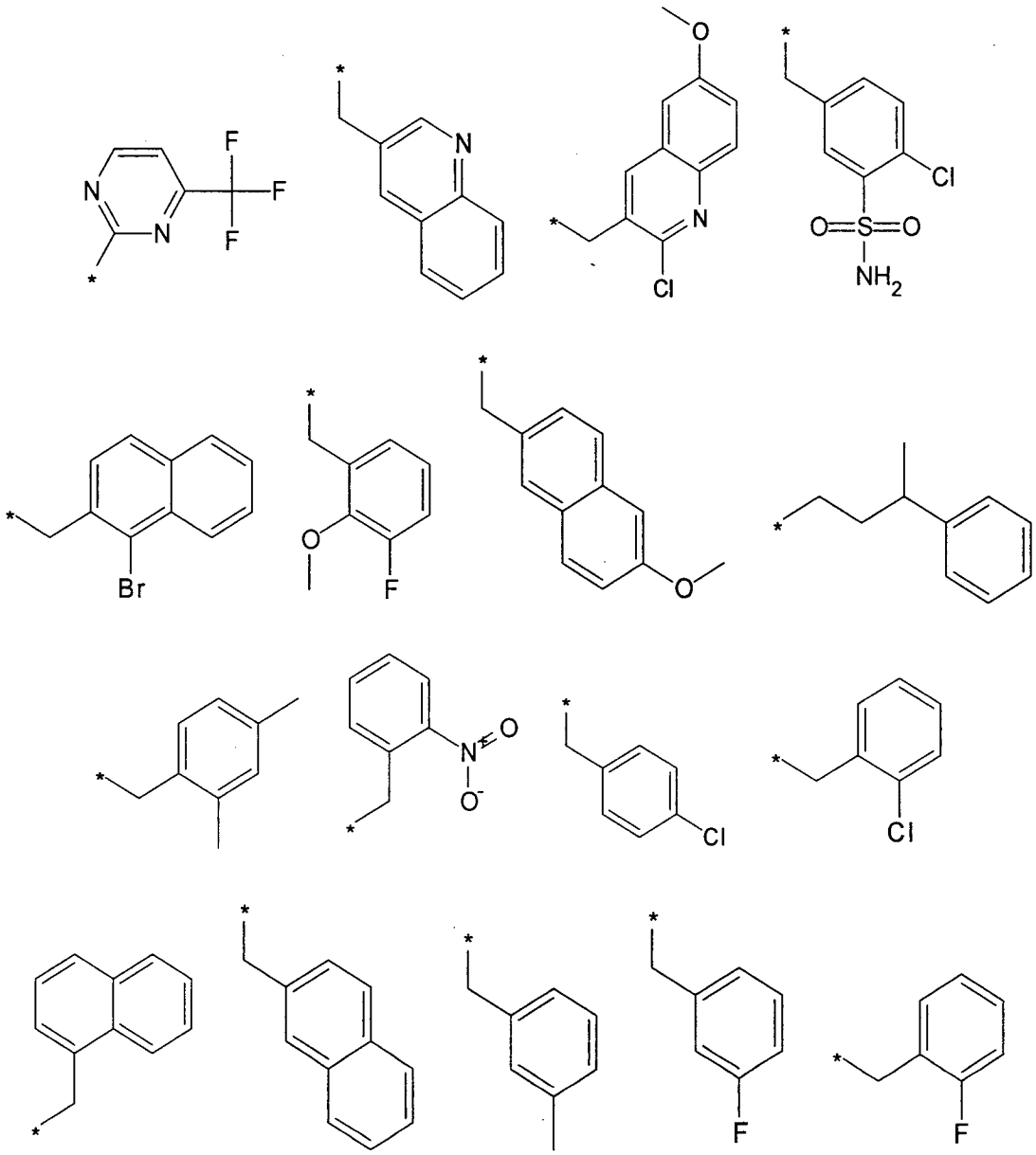


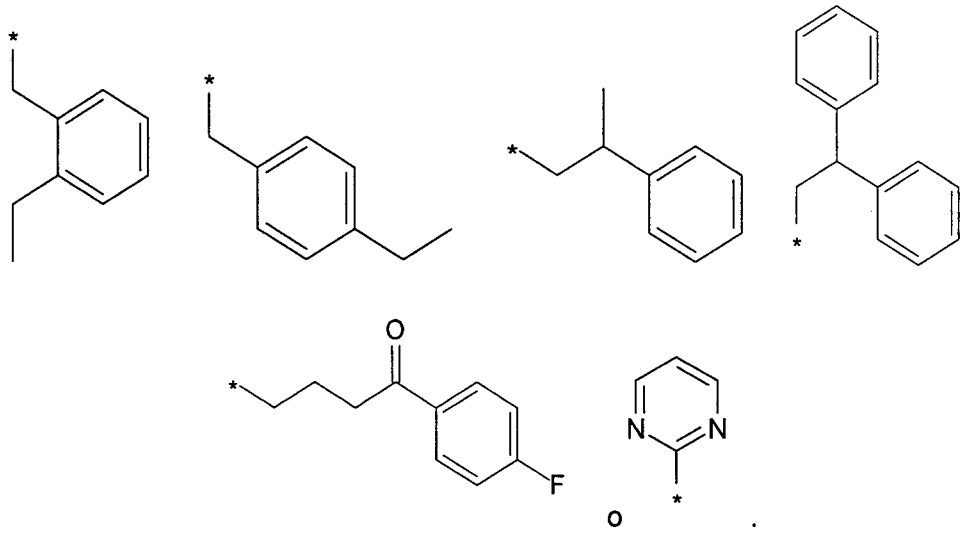






Preferentemente, R_6 es H, alquilo(C_1-C_6), R', alquileno(C_1-C_4)-cicloalquil(C_3-C_8), alquileno(C_1-C_4)-heterociclil(C_5-C_{10}), alquileno(C_1-C_4)-C(O)-heterociclil(C_5-C_{10}), alquileno(C_1-C_4)-C(O)-aril(C_6-C_{10}) o alquileno(C_1-C_6)-aril(C_6-C_{10}). Más preferido, R_6 es H, alquilo(C_1-C_6), heterociclilo(C_5-C_{10}), alquileno(C_1-C_4)- heterociclil(C_5-C_{10}) o alquileno(C_1-C_6)- aril(C_6-C_{10}). Ejemplos de R_6 son H, metilo, etilo, propilo, butilo, s-butilo, pentilo, 3-metil-butilo, isopropilo, trifluorometilo, 3,3,3-trifluorobutilo, ciclopropilo, metileno ciclopropil, 2-pyrimidinilo, bencilo o un sustituyente del grupo que consiste en



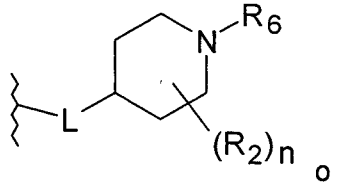


Preferentemente, R_7 es H, halógeno, CN, alquilo(C_1-C_6), alquenilo(C_2-C_6), R' o alquileno(C_1-C_6)-cicloalquil(C_3-C_8). Más preferido, R_7 es H, halógeno, CN, alquilo(C_1-C_4), alquenilo(C_1-C_4), fenilo, ciclopropilo o heteroarilo(C_5-C_6). Lo más preferentemente, R_7 es H, fluoro, cloro, bromo, metilo, etilo, fenilo, nitrilo, ciclopropilo, tienilo o vinilo.

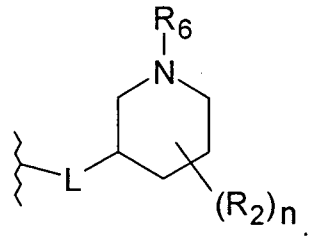
R_8 es preferentemente H, halógeno o alquil(C_1-C_4). Más preferido, R_8 es H, Cl, F, metilo o etilo.

Preferentemente, n es 1, 2 o 3. Más preferido, n es 1.

El grupo de unión L se puede enlazar al anillo de piperidina en cualquier posición vía un átomo de carbono del anillo de piperidina. En una realización preferida, L se une a la posición 4 del anillo de piperidina



L es une a la posición 3 del anillo de piperidina

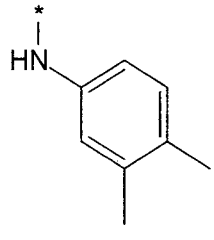


En una realización especialmente preferida, L se une a la posición 4 del anillo de piperidina.

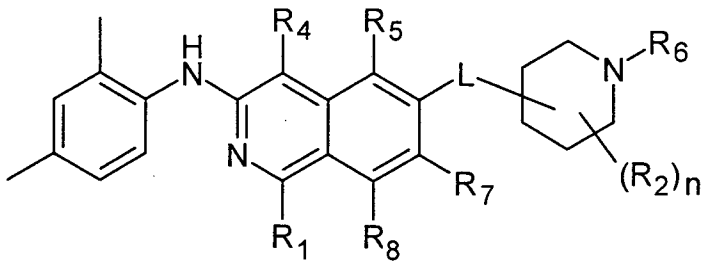
En una realización preferida adicional, L es O-metileno, O-etileno o preferentemente O. Más preferentemente, L es O-metileno, O-etileno u O unidos a la posición 4 del anillo de piperidina.

En las realizaciones preferidas de la presente invención uno o más o todos los grupos contenidos en los compuestos de fórmula (I) pueden, independientemente unos de otros, tener cualquiera de las definiciones preferidas, más preferidas o las más preferidas de los grupos especificados anteriormente o cualquiera o alguna de la denotaciones especificas que están comprendidas por las definiciones de los grupos y especificadas anteriormente, siendo todas las combinaciones de las definiciones preferidas, más preferidas o las más preferidas y/o denotaciones específicas un sujeto de la presente invención. También con respecto a todas las realizaciones preferidas la invención incluye los compuestos de la fórmula (I) en todas las formas estereoisómeras y mezclas de formas estereoisómeras y todas las proporciones, y sus sales fisiológicamente aceptables.

El término "*–" en los sustituyentes ejemplificados *vide supra* marca el punto en el que se une el sustituyente, lo que significa, por ejemplo, para un sustituyente R_3



un compuesto de la fórmula



Una realización preferida es un compuesto de la fórmula (I) en la que

R_1 es H, alquilo(C_1-C_6), arilo(C_6-C_{10}), NH-alquil(C_1-C_6), NH-aril(C_6-C_{10}), o N[alquil(C_1-C_6)]$_2$;

R_2 es hidrógeno, halógeno, o alquilo(C_1-C_6);

R_3 es H, halógeno, alquileno(C_1-C_4)-R', O-R'' o NHR'', en el que R' y R'' se definen como más arriba;

R4 es H, halógeno o alquilo(C_1-C_6);

R_5 es H, halógeno, alquilo(C_1-C_6), CN, arilo(C_6-C_{10}), NH-aril(C_6-C_{10}), alquileno(C_1-C_6)-aril(C_6-C_{10}), heterociclilo(C_5-C_{10}) o alquileno(C_1-C_6)-heterociclil(C_5-C_{10});

R_6 es H, R', alquileno(C_1-C_4)-heterociclil(C_5-C_{10}), alquileno(C_1-C_6)-C(O)-aril(C_6-C_{10}), alquileno(C_1-C_4)-C(O)-heterociclil(C_5-C_{10}), alquileno(C_1-C_6)-aril(C_6-C_{10}) o alquilo(C_1-C_6).

R_7 es H, halógeno, CN, alquilo(C_1-C_6), alquenilo(C_2-C_6) o R';

R8 es H, halógeno o alquilo(C_1-C_6);

n es 1, 2 o 3, y
L es O, O-metileno o O-etileno;

y sus sales farmacéuticamente aceptables y/o sus derivados fisiológicamente funcionales.

Una realización preferida adicional es un compuesto de la fórmula (I) en la que

R_1 es H, alquilo(C_1-C_6), arilo(C_6-C_{10}), NH-alquil(C_1-C_6), NH-aril(C_6-C_{10}), o N[alquil(C_1-C_6)]$_2$;

R_2 es H o alquilo(C_1-C_4);

R_3 es H, halógeno o NHR", en el que R" se define como más arriba;

R4 es H, halógeno o alquilo(C_1-C4);

R_5 es H, halógeno, alquilo(C_1-C_6), arilo(C_6-C_{10}), NH-aril(C_6-C_{10}), alquileno(C_1-C_6)-aril(C_6-C_{10}) o heterociclil(C_5-C_{10});

R_6 es H, alquilo(C_1-C_6), R', alquileno(C_1-C_4)-heterociclil(C_5-C_{10}) o alquileno(C_1-C_6)-aril(C_6-C_{10});

R_7 es H, halógeno, CN, alquilo(C_1-C_6), alquenilo(C_2-C_6) o R';

R8 es H, halógeno o alquilo(C_1-C_6);

n es 1, 2 ó 3; y

L es O;

y sus sales farmacéuticamente aceptables y/o sus derivados fisiológicamente funcionales.

Una realización especialmente preferida es un compuesto de la fórmula (I) en la que

R_1 es H, alquilo(C_1-C_4), NH-alquil(C_1-C_4), N[alquil(C_1-C_4)]$_2$ o NH-fenil;

R_2 es H, alquilo(C_1-C_4);

R_3 es H, NH-heteroaril(C_5-C_6) o NH-fenil;

R4 es H, halógeno o alquilo(C_1-C4);

R_5 es H, halógeno, alquilo(C_1-C_4), aril(C_6-C_{10}), NH-aril(C_6-C_{10}), alquilo(C_1-C_2)-aril(C_6-C_{10}) o heteroarilo(C_5-C_{10});

R_6 es H, alquilo(C_1-C_6), heterociclilo(C_5-C_{10}), alquileno(C_1-C_4)-heterociclil(C_5-C_{10}), arilo(C_6-C_{10}) o alquileno(C_1-C_6)-aril(C_6-C_{10});

R_7 es H, halógeno, CN, alquilo(C_1-C_4), alquenilo(C_1-C_4), fenilo, ciclopropilo, heteroarilo(C_5-C_6);

R8 es H, halógeno o alquilo(C_1-C4);

n es 1; y

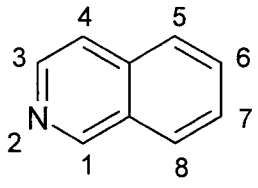
L es O;

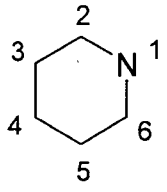
y sus sales fisiológicamente aceptables y/o sus derivados fisiológicamente funcionales.

Como en cualquier realización de la invención, en las realizaciones precedentes que contienen definiciones preferidas, más preferidas, las más preferidas o ejemplares de compuestos según la invención, uno o más o todos los grupos pueden tener cualquiera de sus definiciones preferidas, más preferidas, las más preferidas especifi-

cadas más arriba o cualquiera o alguna de la denotaciones específicas que están comprendidas por sus definiciones y se especifican más arriba.

Los patrones de sustitución de la isoquinolina y el piperidilo se numeran en el texto según las reglas de la IUPAC:





Las sales fisiológicamente aceptables de los compuestos de la fórmula (I) se refieren tanto a sus sales orgánicas como a sus sales inorgánicas según se describe en Remington's Pharmaceutical Sciences (17ª edición, página 1418 (1985)). Debido a la estabilidad física y química y a la solubilidad, se da preferencia a grupos de carácter ácido entre otros a sales de sodio, potasio, calcio y amonio; se da preferencia a grupos de carácter básico, entre otros a sales de ácido maleico, ácido fumárico, ácido succínico, ácido málico, ácido tartárico, ácido metilsulfónico, ácido clorhídrico, ácido sulfúrico, ácido fosfórico, o de ácidos carboxílicos o ácidos sulfónicos, por ejemplo en forma de hidrocloruros, hidrobromuros, fosfatos, sulfatos, metanosulfonatos, acetatos, lactatos, maleatos, fumaratos, malatos, gluconatos, y sales de aminoácidos, de bases naturales o ácidos carboxílicos. La preparación de sales fisiológicamente aceptables a partir de compuestos de la fórmula (I) y (II) que son capaces de formación de sales, incluyendo sus formas estereoisómeras, tiene lugar de una forma conocida per se. Los compuestos de fórmula (I) forman sales estables de metal alcalino, de metal alcalinotérreo o sales de amonio opcionalmente sustituido, con reactivos básicos tales como hidróxidos, carbonatos, bicarbonatos, alcoholatos y amoníaco o bases orgánicas, por ejemplo trimetilamina o trietilamina, etanolamina, dietanolamina o trietanolamina, trometamol o aminoácidos básicos, por ejemplo lisina, ornitina o arginina. Cuando los compuestos de fórmula (I) tienen grupos básicos, también se pueden preparar, con ácidos fuertes, sales estables por adición de ácidos. Las sales de adición de ácido farmacéuticamente aceptables adecuadas de los compuestos de la invención son sales de ácidos inorgánicos tales como ácido clorhídrico, bromhídrico, fosfórico, metafosfórico, nítrico y ácido sulfúrico, y de ácidos orgánicos tales como, por ejemplo, ácido acético, bencenosulfónico, benzoico, cítrico, etanosulfónico, fumárico, glucónico, glicólico, isetiónico, láctico, lactobiónico, maleico, málico, metanosulfónico, succínico, p-toluensulfónico y ácido

tartárico.

Las sales con un anión fisiológicamente inaceptable tal como, por ejemplo, el trifluoroacetato también están dentro del marco de la invención como intermedios útiles para la preparación o purificación de sales farmacéuticamente aceptables y/o para el uso en aplicaciones no terapéuticas, por ejemplo in vitro.

La terminología "derivado fisiológicamente funcional" utilizada en la presente memoria se refiere a cualquier derivado fisiológicamente tolerado de un compuesto de la fórmula (I) de la invención, por ejemplo un N-óxido, que tras administración a un mamífero tal como, por ejemplo, un ser humano es capaz de formar (directa o indirectamente) un compuesto de fórmula (I) o un metabolito activo del mismo.

Los derivados fisiológicamente funcionales incluyen profármacos de los compuestos de la invención, tal como se describen, por ejemplo, en H. Okada et al., Chem. Pharm. Bull. 1994, 42, 57-61. Tales profármacos se pueden metabolizar in vivo a un compuesto de la invención. Estos profármacos pueden ellos mismos ser activos o no serlo.

La invención se refiere a compuestos de la fórmula (I) en la forma de sus racematos, mezclas racémicas y enantiómeros puros y a sus diastereómeros y sus mezclas.

Si los radicales o sustituyentes pueden darse más de una vez en el compuesto de la fórmula (I), todos pueden, independientemente unos de otros, tener el significado establecido y ser idénticos o diferentes.

Los compuestos de la invención también pueden existir en diversas formas polimorfas, por ejemplo como formas polimorfas amorfas o cristalinas. Todas las formas polimorfas de los compuestos de la invención están dentro del marco de la invención y son un aspecto adicional de la invención.

Todas las referencias a "compuesto(s) de fórmula (I)" en adelante en la presente memoria se refieren a compuesto(s) de la fórmula (I) como se describe más arriba, y

a sus sales fisiológicamente aceptables, solvatos y derivados fisiológicamente funcionales como se describen en la presente memoria.

Los términos alquilo(C_1-C_2), alquilo(C_1-C_4), alquilo(C_1-C_6), alquilo(C_1-C_8) y los correspondientes sustituyentes alquileno se entienden como un residuo hidrocarbonado que puede ser lineal, es decir de cadena lineal, o ramificado y que tiene 1, 2, 3, 4, 5, 6, 7, u 8 átomos de carbono, respectivamente. Esto también aplica si un grupo alquilo se da como un sustituyente sobre otro grupo, por ejemplo en un grupo alcoxi (O-alquil), S-alquil o un -O-alquileno(C_1-C_6)-O-, un grupo alcoxicarbonilo o un grupo arilalquilo. Ejemplos de grupos alquilo son metilo, etilo, propilo, butilo, pentilo o hexilo, los n-isómeros de todos estos grupos, isopropilo, isobutilo, 1-metilbutilo, isopentilo, neopentilo, 2,2-dimetilbutilo, 2-metilpentilo, 3-metilpentilo, isohexilo, sec-butilo, terc-butilo o terc-pentilo. Las grupos alquilo - si no se indica lo contrario - pueden estar halogenados una vez o más, es decir los grupos alquilo pueden estar fluorados, es decir perfluorados. Ejemplos de grupos alquilo halogenados son CF_3 y CH_2CF_3, OCF_3, SCF_3, o -O-$(CF_2)_2$-O-.

Alquenilo son, por ejemplo, vinilo, 1-propenilo, 2-propenilo (= alilo), 2-butenilo, 3-butenilo, 2-metil-2-butenilo, 3-metil-2-butenilo, 5-hexenilo o 1,3-pentadienilo.

Alquinilo son, por ejemplo, etinilo, 1-propinilo, 2-propinilo (= propargilo) o 2-butinilo.

Halógeno significa flúor, cloro, bromo o yodo.

Los grupos cicloalquilo(C_3-C_8) son grupos alquilo cíclicos que contienen anillos de 3, 4, 5, 6, 7 u 8 átomos de carbono como ciclopropilo, ciclobutilo, ciclopentilo, ciclohexilo o ciclooctilo, que también pueden estar sustituidos y/o contener 1 o 2 doble s enlaces (grupos cicloalquilo insaturados) como, por ejemplo, ciclopentenilo o ciclohexenilo se pueden enlazar vía cualquier átomo de carbono.

Un grupo arilo(C_6-C_{10}) significa un anillo aromático o un sistema anular que comprende dos anillos aromáticos que están fusionados o si no unidos, por ejemplo un

grupo fenilo, naftilo, bifenilo, tetrahidronaftilo, alfa- o beta-tetralon-, indanil- o indan-1-on-ilo. Un grupo arilo(C_6-C_{10}) preferido es fenilo.

Un grupo heterociclilo(C_5-C_{10}) significa un sistema anular mono- o bicíclico que comprende, aparte de carbono, uno o más heteroátomos tales como, por ejemplo, 1, 2 o 3 átomos de nitrógeno, 1 o 2 átomos de oxígeno, 1 o 2 átomos de azufre o combinaciones de diferentes heteroátomos. Los residuos heterociclilo pueden estar enlazados en cualquier posición, por ejemplo en la posición 1, posición 2, posición 3, posición 4, posición 5, posición 6, posición 7 o posición 8. Los grupos heterociclilo(C_5-C_{10}) pueden ser (1) aromáticos [= grupos heteroarilo] o (2) saturados o (3) mixtos aromáticos/saturados.

Los grupos heterociclilo(C_5-C_{10}) adecuados incluyen acridinilo, azocinilo, benzimidazolilo, benzofurilo, benzomorfolinilo, benzotienilo, benzotiofenilo, benzoxazolilo, benzotiazolilo, benzotriazolilo, benzotetrazolilo, benzisoxazolilo, benzisotiazolilo, carbazolilo, 4aH-carbazolilo, carbolinilo, furanilo, quinazolinilo, quinolinilo, 4H-quinolizinilo, quinoxalinilo, quinuclidinilo, cromanilo, cromenilo, cromen-2-onilo, cinnolinilo, decahidroquinolinilo, 2H,6H-1,5,2-ditiazinilo, dihidrofuro[2,3-b]-tetrahidrofuran, furilo, furazanilo, homomorfolinilo, homopiperazinilo, imidazolidinilo, imidazolinilo, imidazolilo, 1H-indazolilo, indolinilo, indolizinilo, indolilo, 3H-indolilo, isobenzofuranilo, isocromanilo, isoindazolilo, isoindolinilo, isoindolilo, isoquinolinilo (benzimidazolilo), isotiazolilo, isoxazolilo, morfolinilo, naftiridinilo, octahidroisoquinolinilo, oxadiazolilo, 1,2,3-oxadiazolilo, 1,2,4-oxadiazolilo, 1,2,5-oxadiazolilo, 1,3,4-oxadiazolilo, oxazolidinilo, oxazolilo, oxazolidinilo, pirimidinilo, fenantridinilo, fenantrolinilo, fenazinilo, fenotiazinilo, fenoxatiinilo, fenoxazinilo, ftalazinilo, piperazinilo, piperidinilo, prolinilo, pteridinilo, purinilo, piranilo, pirazinilo, piroazolidinilo, pirazolinilo, pirazolilo, piridazinilo, piridonilo, piridooxazoles, piridoimidazoles, piridotiazoles, piridinilo, piridilo, pirimidinilo, pirrolidinilo, pirrolinilo, 2H-pirrolilo, pirrolilo, tetrahidrofuranilo, tetrahidroisoquinolinilo, tetrahidroquinolinilo, 6H-1,2,5-tiadazinilo, tiazolilo, 1,2,3-tiadiazolilo, 1,2,4-tiadiazolilo, 1,2,5-tiadiazolilo, 1,3,4-tiadiazolilo, tienilo, triazolilo, tetrazolilo y xantenilo. Piridilo representa 2-, 3- y 4-piridilo. Tienilo representa 2- y 3-tienilo. Furilo representa 2- y 3-furilo. También están incluidos los correspondientes N-óxidos de estos compuestos, por ejemplo, 1-oxi-2-, 3- o 4-piridilo.

Las sustituciones en residuos heterociclilo(C_5-C_{10}) pueden darse sobre átomos de carbono libres o sobre átomos de nitrógeno.

Ejemplos preferidos de residuos heterociclilo(C_5-C_{10}) son pirazinilo, piridilo, pirimidinilo, pirazolilo, morfolinilo, pirrolidinilo, piperazinilo, piperidinilo, tienilo, benzofurilo, quinolinilo, tetrazolilo y triazolilo.

Los grupos arilo(C_6-C_{10}) y heterociclilo(C_5-C_{10}) están sin sustituir o sustituidos uno o más veces por grupos adecuados independientemente seleccionados de halógeno, CF_3, NO_2, N_3, CN, C(O)-alquil(C_1-C_6), C(O)-aril(C_1-C_6), COOH, COOalquil(C_1-C_6), $CONH_2$, CONHalquil(C_1-C_6), CON[alquil(C_1-C_6)]$_2$, cicloalquilo(C_3-C_8), alquilo(C_1-C_6), alquileno(C_1-C_6)-OH, alquileno(C_1-C_6)-NH_2, alquileno(C_1-C_6)-NHalquil(C_1-C_6), alquileno(C_1-C_6)-N[alquil(C_1-C_6)]$_2$, alquenilo(C_2-C_6), alquinilo(C_2-C_6), O-alquil(C_1-C_6), O-C(O)-alquil(C_1-C_6), O-C(O)-aril(C_6-C_{10}), O-C(O)-heterociclil(C_5-C_{10}), PO_3H_2, SO_3H, SO_2-NH_2, SO_2NHalquil(C_1-C_6), SO_2N[alquil(C_1-C_6)]$_2$, S-alquil(C_1-C_6); S-alquileno(C_1-C_6)-aril(C_6-C_{10}), S-alquileno(C_1-C_6)-heterociclil(C_5-C_{10}), SO-alquil(C_1-C_6), SO-alquileno(C_1-C_6)-aril(C_6-C_{10}), SO-alquileno(C_1-C_6)-heterociclil(C_5-C_{10}), SO_2-alquil(C_1-C_6), SO_2-alquileno(C_1-C_6)-aril(C_6-C_{10}), SO_2-alquileno(C_1-C_6)-heterociclil(C_5-C_{10}), SO_2-NHalquileno(C_1-C_6)-aril(C_6-C_{10}), SO_2-NHalquileno(C_1-C_6)-heterociclil(C_5-C_{10}), SO_2-N[alquil(C_1-C_6)][alquileno(C_1-C_6)-aril(C_6-C_{10})], SO_2-N[alquil(C_1-C_6)][alquileno(C_1-C_6)-heterociclil(C_5-C_{10})], SO_2-N[alquileno(C_1-C_6)-aril(C_6-C_{10})]$_2$, SO_2-N[alquileno(C_1-C_6)-heterociclil(C_5-C_{10})]$_2$,

C(NH)(NH_2), NH_2, NH-alquil(C_1-C_6), N[alquil(C_1-C_6)]$_2$, NH-C(O)-alquil(C_1-C_6), NH-C(O)O-alquil(C_1-C_6), NH-C(O)-aril(C_6-C_{10}), NH-C(O)-heterociclil(C_5-C_{10}), NH-C(O)O-aril(C_6-C_{10}), NH-C(O)O-heterociclil(C_5-C_{10}), NH-C(O)-NH-alquil(C_1-C_6), NH-C(O)-NH-aril(C_6-C_{10}), NH-C(O)-NH-heterociclil(C_5-C_{10}), NH-SO_2-alquil(C_1-C_6), NH-SO_2-aril(C_6-C_{10}), NH-SO_2-heterociclil(C_5-C_{10}), Nalquil(C_1-C_6)-C(O)-alquil(C_1-C_6), Nalquil(C_1-C_6)-C(O)O-alquil(C_1-C_6), Nalquil(C_1-C_6)-C(O)-aril(C_6-C_{10}), Nalquil(C_1-C_6)-C(O)-heterociclil, Nalquil(C_1-C_6)-C(O)O-aril(C_6-C_{10}), Nalquil(C_1-C_6)-C(O)O-heterociclil(C_5-C_{10}), Nalquil(C_1-C_6)-C(O)-NH-alquil(C_1-C_6)], Nalquil(C_1-C_6)-C(O)-NH-

aril(C_6-C_{10}), Nalquil(C_1-C_6)-C(O)-NH-heterociclil(C_5-C_{10}), N[alquil(C_1-C_6)]-C(O)-N[alquil(C_1-C_6)]$_2$, N[alquil(C_1-C_6)]-C(O)-N[alquil(C_1-C_6)]-aril(C_6-C_{10}), N[alquil(C_1-C_6)]-C(O)-N[alquil(C_1-C_6)]-heterociclil(C_5-C_{10}), N[alquil(C_1-C_6)]-C(O)-N[aril(C_6-C_{10})]$_2$, N[alquil(C_1-C_6)]-C(O)-N[heterociclil(C_5-C_{10})]$_2$, N[aril(C_6-C_{10})]-C(O)-alquil(C_1-C_6), N[heterociclil(C_5-C_{10})]-C(O)-alquil(C_1-C_6), N[aril(C_6-C_{10})]-C(O)O-alquil(C_1-C_6), N[heterociclil(C_5-C_{10})]-C(O)O-alquil(C_1-C_6), N(aril)-C(O)-aril(C_6-C_{10}), N[heterociclil(C_5-C_{10})]-C(O)-aril(C_6-C_{10}), N[aril(C_6-C_{10})]-C(O)O-aril(C_6-C_{10}), N[heterociclil(C_5-C_{10})]-C(O)O-aril(C_6-C_{10}), N[aril(C_6-C_{10})]-C(O)-NH-alquil(C_1-C_6), N[heterociclil(C_5-C_{10})]-C(O)-NH-alquil(C_1-C_6), N(aril)-C(O)-NH-aril(C_6-C_{10}), N[heterociclil(C_5-C_{10})]-C(O)-NH-aril(C_6-C_{10}), N[aril(C_6-C_{10})]-C(O)-N[alquil(C_1-C_6)]$_2$, N[heterociclil(C_5-C_{10})]-C(O)-N[alquil(C_1-C_6)]$_2$, N[aril(C_6-C_{10})]-C(O)-N[alquil(C_1-C_6)]-aril(C_6-C_{10}), N[heterociclil(C_5-C_{10})]-C(O)-N[alquil(C_1-C_6)]-aril(C_6-C_{10}), N[aril(C_6-C_{10})]-C(O)-N[aril(C_6-C_{10})]$_2$, N[heterociclil(C_5-C_{10})]-C(O)-N[aril(C_6-C_{10})]$_2$, arilo(C_6-C_{10}), alquileno(C_1-C_6)- aril(C_6-C_{10}), O-alquileno(C_1-C_6)-aril(C_6-C_{10}), heterociclilo(C_5-C_{10}), alquileno(C_1-C_6)- heterociclil(C_5-C_{10}), O-alquileno(C_1-C_6)-heterociclil(C_5-C_{10}), en los que arilo(C_6-C_{10}) o heterociclilo(C_5-C_{10}) pueden estar sustituidos de una a 3 veces por halógeno, OH, NO_2, CN, O-alquilo(C_1-C_6), alquilo(C_1-C_6), NH_2, NHalquil(C_1-C_6), N[alquil(C_1-C_6)]$_2$, SO_2CH_3, COOH, C(O)O-alquil(C_1-C_6), $CONH_2$, alquileno(C_1-C_6)-O-alquil(C_1-C_6), alquileno(C_1-C_6)-O-aril(C_6-C_{10}), O-alquileno(C_1-C_6)-aril(C_6-C_{10}); o en los que arilo(C_6-C_{10}) está sustituido vecinalmente por un grupo O-alquileno(C_1-C_4)-O por lo que se forma junto con los átomos de carbono a los que están unidos los átomos de oxígeno un anillo de 5-8 miembros. Los sustituyentes arilo o heterociclilo de los grupos arilo(C_6-C_{10}) y heterociclilo(C_5-C_{10}) no pueden estar sustituidos adicionalmente por un grupo que contiene arilo o heterociclilo.

Los sustituyentes preferidos para los grupos arilo(C_6-C_{10}) son alquilo(C_1-C_4), O-alquil(C_1-C_4), O-fenil, C(O)O-alquil(C_1-C_6), C(O)OH, C(O)-alquil(C_1-C_4), halógeno, NO_2, SO_2NH_2, CN, SO_2-alquil(C_1-C_4), NH-SO_2-alquil(C_1-C_4), NH_2, NH-C(O)-al-

quil(C_1-C_4), cicloalquilo(C_3-C_8), alquilo(C_1-C_4)-OH, C(O)N[alquil(C_1-C_4)]$_2$, C(O)NH_2, N[alquil(C_1-C_4)]$_2$, alquenileno(C_1-C_4)-aril(C_6-C_{10}), en los que el arilo(C_6-C_{10}) puede estar sustituidos adicionalmente por alquilo(C_1-C_4), alquileno(C_1-C_4)-O-alquil(C_1-C_6), O-alquil(C_1-C_6)-aril(C_6-C_{10}), o pueden estar sustituidos vecinalmente por un grupo O-alquileno(C_1-C_4)-O por lo que se forma junto con los átomos de carbono a los que están unidos los átomos de oxígenos un anillo de 5-8 miembros.

En los grupos fenilo monosustituidos el sustituyente puede estar situado en la posición 2, la posición 3 o la posición 4, siendo la posición 3 y la posición 4 las preferidas. Si un grupo fenilo porta dos sustituyentes, éstos pueden estar ubicados en la posición 2,3, en la posición 2,4, en la posición 2,5, en la posición 2,6, en la posición 3,4 o en la posición 3,5. En los grupos fenilo que portan tres sustituyentes los sustituyentes se pueden situar en posición 2,3,4, posición 2,3,5, posición 2,3,6, posición 2,4,5, posición 2,4,6, o posición 3,4,5.

Las declaraciones de más arriba relativas a grupos fenilo aplican correspondientemente a grupos divalentes derivados de grupos fenilo, es decir fenileno que puede ser no sustituido o 1,2-fenileno, 1,3-fenileno o 1,4-fenileno sustituidos. Las declaraciones de más arriba también aplican correspondientemente al subgrupo arilo en grupos arilalquileno. Ejemplos de grupos arilalquileno, que también pueden ser no sustituidos o sustituidos en el subgrupo arilo así como en el subgrupo alquileno, son bencilo, 1-feniletileno, 2-feniletileno, 3-fenilpropileno, 4-fenilbutileno, 1-metil-3-fenil-propileno.

Sustituyentes preferidos para los grupos heterociclilo(C_5-C_{10}) son alquilo(C_1-C_4), O-alquil(C_1-C_4), alquileno(C_1-C_4)-fenil, halógeno, alquileno(C_1-C_4)-O-alquil(C_1-C_4), heterociclilo(C_5-C_{10}), alquileno(C_1-C_4)-N[alquil(C_1-C_4)]$_2$, o arilo(C_6-C_{10}), en los que el arilo(C_6-C_{10}) puede estar adicionalmente sustituido por alquilo(C_1-C_4), alquileno(C_1-C_4)-O-alquil(C_1-C_6), O-alquil(C_1-C_6)-aril(C_6-C_{10}), o puede estar vecinalmente sustituido por un grupo O-alquileno(C_1-C_4)-O por lo que se forma junto con los átomos de carbono a los que están unidos los átomos de oxígenos un anillo de 5-8 miembros.

Los sustituyentes generales y preferidos de los grupos arilo(C_6-C_{10}) y heterociclilo(C_5-C_{10}) se pueden combinar con las definiciones generales y preferidas de R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8, n y L según se describe más arriba.

Por lo tanto la presente invención también se refiere a los compuestos de la fórmula (I) y/o sus sales fisiológicamente aceptables y/o sus profármacos para el uso como productos farmacéuticos (o medicamentos), al uso de los compuestos de la fórmula (I) y/o sus sales fisiológicamente aceptables y/o sus profármacos para la producción de productos farmacéuticos para el tratamiento y/o prevención de enfermedades asociadas con Rho-cinasa y/o la fosforilación mediada por Rho-cinasa de la fosfatasa de la cadena ligera de miosina, es decir para el tratamiento y/o prevención de hipertensión, es decir hipertensión pulmonar e hipertensión ocular, trastorno circulatorio periférico, angina de pecho, vasoespasmo cerebral, asma, parto prematuro, hiperagregabilidad de las plaquetas, Enfermedad Arterial Oclusiva Periférica (PAOD), Enfermedad Pulmonar Obstructiva Crónica (COPD), desarrollo de cáncer, disfunción eréctil, arteriosclerosis, insuficiencia orgánica isquémica (daño del órgano afectado), fibrosis pulmonar, fibrosis hepática, insuficiencia hepática, fibrosis renal, glomeruloesclerosis renal, insuficiencia renal, hipertrofia orgánica, hipertrofia prostática, complicaciones de diabetes, reestenosis de vasos sanguíneos, ateroesclerosis, cáncer, hipertrofia cardiaca, insuficiencia cardiaca; enfermedades isquémicas; inflamación; enfermedades autoinmunitarias; SIDA, osteopatía tal como osteoporosis, trastorno funcional del cerebro, infección de los tubos digestivos con bacterias, sepsis, síndrome de dificultad respiratoria aguda, retinopatía, glaucoma y enfermedad de Alzheimer.

La presente invención se refiere además a preparaciones farmacéuticas (o composiciones farmacéuticas) que contienen una cantidad eficaz de por lo menos un compuesto de la fórmula (I) y/o sus sales fisiológicamente aceptables y/o sus profármacos y un vehículo farmacéuticamente aceptable, es decir uno o más sustancias portadoras (o vehículos) farmacéuticamente aceptables y/o aditivos (o excipientes). Los productos farmacéuticos se pueden administrar por vía oral, por ejemplo en forma de píldoras, comprimidos, comprimidos laqueados, comprimidos recubiertos, gránulos, cápsulas de gelatina dura y blanda, disoluciones, jarabes, emulsiones, suspensiones o mezclas en aerosol. Sin embargo, la administración también se puede llevar a cabo por vía rectal, por ejemplo, en forma de supositorios, o por vía parenteral, por ejemplo por vía intravenosa, intramuscular o subcutánea, en forma de soluciones para inyec-

ción o soluciones para infusión, microcápsulas, implantes o barras, o por vía percutánea o tópica, por ejemplo, en forma de pomadas, soluciones o tinturas, o en otras formas, por ejemplo en forma de aerosoles o pulverizadores nasales.

Las preparaciones farmacéuticas según la invención se preparan de una manera conocida per se y familiar para el experto en la técnica, usándose vehículos inorgánicos y/u orgánicos y/o aditivos inertes farmacéuticamente aceptables además del compuesto(s) de la fórmula (I) y/o sus sales fisiológicamente aceptables y/o sus profármacos. Para la producción de píldoras, comprimidos, comprimidos recubiertos, cápsulas de gelatina dura es posible utilizar, por ejemplo, lactosa, almidón de maíz o sus derivados, talco, ácido esteárico o sus sales, etc. Vehículos para cápsulas de gelatina blanda y supositorios son, por ejemplo, grasas, ceras, polioles semisólidos y líquidos, aceites naturales o hidrogenados, etc. Vehículos adecuados para la producción de disoluciones, por ejemplo disoluciones inyectables, o de emulsiones o jarabes son, por ejemplo, agua, solución salina, alcoholes, glicerol, polioles, sacarosa, azúcar invertido, glucosa, aceites vegetales, etc. Vehículos adecuados para microcápsulas, implantes o barras son, por ejemplo, copolímeros de ácido glicólico y ácido láctico. Las preparaciones farmacéuticas contienen normalmente de aproximadamente 0,5 a aproximadamente 90% en peso de los compuestos de la fórmula (I) y/o sus sales fisiológicamente aceptables y/o sus profármacos. La cantidad del principio activo de la fórmula (I) y/o sus sales fisiológicamente aceptables y/o sus profármacos en las preparaciones farmacéuticas es normalmente de aproximadamente 0,5 a aproximadamente 1000 mg, preferentemente de aproximadamente 1 a aproximadamente 500 mg. Además de los principios activos de la fórmula (I) y/o sus sales fisiológicamente aceptables y/o profármacos y de los vehículos, las preparaciones farmacéuticas pueden contener uno o más aditivos tales como, por ejemplo, materiales de carga, disgregantes, aglutinantes, lubricantes, agentes humectantes, estabilizadores, emulsionantes, conservantes, edulcorantes, colorantes, saborizantes, aromatizantes, espesantes, diluyentes, sustancias tampón, disolventes, solubilizantes, agentes para conseguir un efecto de depósito, sales para alterar la presión osmótica, agentes de recubrimiento o antioxidantes. También pueden contener dos o más compuestos de la fórmula (I) y/o sus sales fisiológicamente aceptables y/o sus profármacos. En caso de que una preparación farmacéutica contenga dos o más compuestos de la fórmula (I) la selección de los compuestos individuales puede tener como objetivo un perfil farmacológico global específico de la preparación farmacéutica. Por ejemplo, un compuesto altamente potente con una du-

ración de acción más corta se puede combinar con un compuesto de acción prolongada de potencia más baja. La flexibilidad permitida con respecto a la elección de sustituyentes en los compuestos de la fórmula (I) permite mucho control sobre las propiedades biológicas y fisico-químicas de los compuestos y de este modo permite la selección de tales compuestos deseados. Además, aparte de por lo menos un compuesto de la fórmula (I) y/o sus sales fisiológicamente aceptables y/o sus profármacos, las preparaciones farmacéuticas también pueden contener uno o más de otros principios terapéutica o profilácticamente activos.

Cuando se utilizan los compuestos de la fórmula (I) la dosis puede variar dentro de límites amplios y, como es habitual y es conocido por el médico, debe ser apropiada para las dolencias del individuo en cada caso particular. Depende, por ejemplo, del compuesto específico empleado, de la naturaleza y gravedad de la enfermedad que se va a tratar, del modo y el programa de administración, o de si una dolencia aguada o crónica se trata o si se lleva a cabo profilaxis. Se puede establecer una dosificación apropiada usando aproximaciones clínicas bien conocidas en la técnica médica. En general, la dosis diaria para alcanzar los resultados deseados en un adulto que pese aproximadamente 75 kg es de aproximadamente 0,01 a aproximadamente 100 mg/kg, preferentemente de aproximadamente 0,1 a aproximadamente 50 mg/kg, en particular de aproximadamente 0,1 a aproximadamente 10 mg/kg, (en cada caso en mg por kg de peso corporal). La dosis diaria se puede dividir, en particular en el caso de la administración de cantidades relativamente grandes, en varias, por ejemplo 2, 3 ó 4, administraciones separadas. Como es habitual, dependiendo del comportamiento individual puede ser necesario desviarse hacia arriba o hacia abajo de la dosis diaria indicada.

Además, los compuestos de la fórmula (I) se pueden utilizar como intermedios de síntesis para la preparación de otros compuestos, en particular de otros principios activos farmacéuticos, que son obtenibles a partir de los compuesto de la fórmula I, por ejemplo por introducción de sustituyentes o modificación de grupos funcionales.

Los compuestos de la fórmula (I) se pueden preparar según los compuestos de ejemplo siguientes sin limitar el alcance de las reivindicaciones.

En general, los grupos protectores que aún pueden estar presentes en los productos obtenidos en la reacción de acoplamiento se quitan después por procedimientos estándar. Por ejemplo, el grupo protector terc-butilo, en particular un grupo terc-

butoxicarbonilo que es una forma protegida de un grupo amidino, se puede desproteger, es decir convertir en el grupo amidino, por tratamiento con ácido trifluoroacético. Como ya se ha explicado, después de la reacción de acoplamiento también se pueden generar grupos funcionales a partir de grupos precursores adecuados. Además, después se puede llevar a cabo una conversión en una sal fisiológicamente aceptable o un profármaco de un compuesto de la fórmula (I) por procedimientos conocidos. En general, una mezcla de reacción que contiene un compuesto final de la fórmula (I) o un intermedio se elabora y, si se desea, a continuación el producto se purifica por procedimientos habituales conocidos por los expertos en la técnica. Por ejemplo, un compuesto sintetizado se puede purificar utilizando métodos bien conocidos tales como cristalización, cromatografía o cromatografía líquida de alta eficacia en fase reversa (RP-HPLC) u otros métodos de separación basados, por ejemplo, en el tamaño, carga o hidrofobicidad del compuesto. Igualmente, se pueden utilizar métodos bien conocidos tales como análisis de secuencia de aminoácidos, RMN, IR y espectrometría de masas (MS) para caracterizar un compuesto de la invención. Se entiende que las modificaciones que no afecten sustancialmente la actividad de las diversas realizaciones de esta invención están incluidas dentro de la invención descrita en la presente memoria. Por consiguiente, los ejemplos siguientes tienen la finalidad de ilustrar pero no de limitar la presente invención.

Métodos LCMS

Método #1

Columna: YMC J'shere 33x2 4µm

gradiente (AcN+0,05% de TFA) : H2O+0,05% de TFA; 5:95 (0min) a 95:5 (2,5 min) a 95:5 (3 min)

Método #2

Columna: YMC J'shere 33x2 4µm

gradiente (AcN+0,05% de TFA) : H2O+0,05% de TFA, 5:95 (0min) a 95:5 (3,4min) a 95:5 (4,4min)

Método #3

Columna: YMC J'shere 33x2 4µm

gradiente AcN+0,08% de FA : H2O+0,1% de FA; 5:95 (0min) a 95:5 (2,5 min) a 95:5 (3 min)

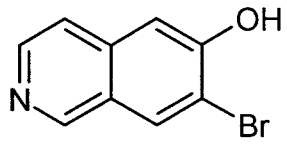
Método #Superior

Columna: YMC YMC J`sfere ODS H80 20X2 1 4µ

gradiente 0 min 96% de H2O(0,05% de TFA) 2,0min - 95% de ACN; 95% de ACN bis 2,4min; 4% de ACN 2,45min

Síntesis de unidades estructurales

7-Bromo-isoquinolin-6-ol (1)



25 g (116,3 mmol) de 3-bromo-4-metoxibenzaldehído, 19,0 mL (18,3 g, 174,5 mmol) de dimetil acetal del aminoacetaldehído y 250 mL de tolueno se calentaron a reflujo durante 6 horas utilizando un aparato Dean-Stark. El disolvente y el exceso de reactivo se destilaron y el producto bruto (aprox. 37 g) se utilizó para la siguiente etapa sin ninguna purificación adicional.

La imina se disolvió en 240 mL de THF. Se añadieron gota a gota a 0ºC 11,1 mL (12,6 g, 116,3 mmol) de cloroformiato de etilo. Después de agitar durante 5 minutos, se añadieron gota a gota 24,3 mL (23,2 g, 139,2 mmol) de trietilfosfito. La mezcla se agitó durante 18 h a temperatura ambiente. A continuación se destilaron los disolventes. El exceso de reactivo se eliminó por adición repetida de 100 ml de tolueno y evaporación de los disolventes. El P,N–acetal (aprox. 62 g) se utilizó para la siguiente etapa sin ninguna purificación adicional.

El P,N–acetal, 51,3 mL (88,2 g, 465,2 mmol) de tetracloruro de titanio y 300 mL de cloroformo se calentaron a reflujo durante 48 h. La mezcla se vertió sobre hielo y el pH se ajustó a 9 utilizando amoniaco acuoso. La extracción repetida con acetato de etilo seguida por eliminación de los disolventes dio 14,8 g (53%.) de 7-bromo-6-metoxiisoquinolina.

RMN de ^{1}H (d_6-DMSO): δ = 9,16 (1H, s), 8,46 (1H, d, J = 5,9 Hz), 8,46 (1H, s), 7,76 (1H, d, J = 5,9 Hz), 7,51 (1H, s), 4,01 (3H, s).

MS: m/z = 238 (MH^+).

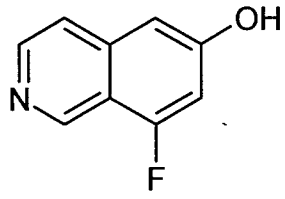
Se añadieron a 0ºC 3,6 mL (9,5 g, 37,8 mmol) de BBr_3 a una disolución de 4,5 g (18,9 mmol) de 7-bromo-6-metoxi-isoquinolina en 30 mL de diclorometano y se agitó durante 18 h a temperatura ambiente. Se añadió disolución acuosa de $NaHCO_3$ para ajustar el pH a 8. La extracción con cloroformo/isopropanol (3/1) seguido por secado sobre sulfato sódico y eliminación de los disolventes dio 2,7 g (64%) del compuesto 1.

RMN de ^1H (d_6-DMSO): δ = 9,19 (1H, s), 8,49 (1H, s), 8,38 (1H, d, J = 6,1 Hz), 7,78 (1H, d, J = 6,1 Hz), 7,34 (1H, s).

MS: m/z = 224 (MH^+).

Los intermedios siguientes se sintetizaron utilizando este procedimiento:

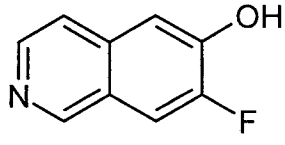
8-Fluoro-isoquinolin-6-ol (2)



RMN de ^1H (d_6-DMSO): δ = 10,84 (1H, s), 9,21 (1H, s), 8,40 (1H, d, J = 5,8 Hz), 7,67 (1H, d, J = 5,8 Hz), 7,01 (2H, m).

MS: m/z = 164 (MH^+).

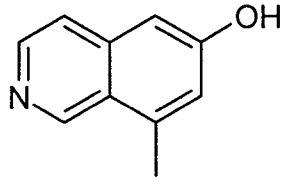
7-Fluoro-isoquinolin-6-ol (3)



RMN de ^1H (d_6-DMSO): δ = 11,06 (1H, s), 9,07 (1H, s), 8,33 (1H, d, J = 5,6 Hz), 7,88 (1H, d, J = 11,4 Hz), 7,64 (1H, d, J = 5,6 Hz), 7,31 (1H, d, J = 8,6 Hz).

MS: m/z = 164 (MH^+).

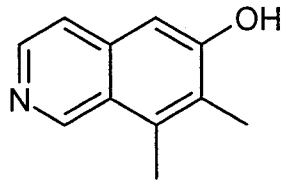
8-Metil-isoquinolin-6-ol (4)



RMN de ^1H (d_6-DMSO): δ = 11,55 (1H, s), 9,47 (1H, s), 8,42 (1H, d, J = 6,5 Hz), 8,11 (1H, d, J = 6,5 Hz), 7,31 (1H, s), 7,25 (1H, s), 2,76 (3H, s).

MS: m/z = 160 (MH^+).

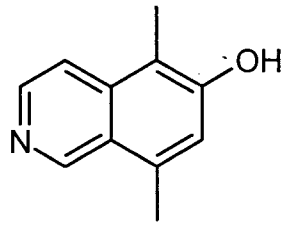
7,8-Dimetil-isoquinolin-6-ol (5)



RMN de ^1H (d_6-DMSO): δ = 11,87 (1H, s), 9,58 (1H, s), 8,41 (1H, d, J = 6,5 Hz), 8,18 (1H, d, J = 6,5 Hz), 7,35 (1H, s), 7,25 (1H, s), 2,71 (3H, s), 2,35 (3H, s).

MS: m/z = 174 (MH^+).

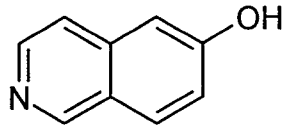
5,8-Dimetil-isoquinolin-6-ol (6)



RMN de ^1H (d_6-DMSO): δ = 11,55 (1H, s), 9,52 (1H, s), 8,47 (1H, d, J = 6,8 Hz), 8,26 (1H, d, J = 6,8Hz), 7,42 (1H, s), 2,76 (3H, s), 2,42 (3H, s).

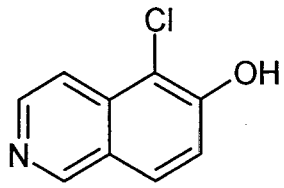
MS: m/z = 174 (MH^+).

6-Hidroxi-isoquinolina (7)



Método de LCMS # 1, tiempo de retención 0,14 min, masa detectada 146,08 $[M+H]^+$

5-Cloroisoquinolin-6-ol (8)

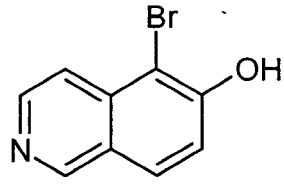


Se añadieron 0,61 mL (1,02 g, 7,6 mmol) de cloruro de sulfurilo a una disolución de 1,0 g (6,9 mmol) del compuesto 7 en 30 mL de diclorometano. Se añadieron tres gotas de dietil éter y la reacción se agitó a temperatura ambiente durante 5 h. Los disolventes se eliminaron por destilación y el resto se trató con disolución acuosa de $NaHCO_3$. El precipitado se filtró, se lavó con agua y se secó para dar 1,1 g (89%) del compuesto 8 como un sólido verde-amarillo.

RMN de ^1H (d_6-DMSO): δ = 11,37 (1H, s), 9,18 (1H, s), 8,50 (1H, d, J = 6 Hz), 8,00 (1H, d, J= 8,8 Hz), 7,83 (1H, J = 6 Hz), 7,44 (1H, d, J = 8,7 Hz).

MS: m/z = 180 (MH^+).

5-Bromoisoquinolin-6-ol (9)

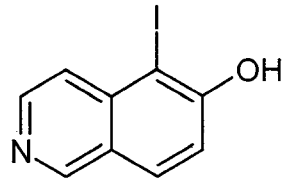


Se añadieron gota a gota 7,9 mL (19,18 g, 120 mmol) de bromo a una suspensión de 17,42 g (120 mmol) del compuesto 7 en 250 mL de cloroformo a temperatura ambiente. Después de agitar durante 2 h se añadió acetato de etilo. El precipitado se filtró, se lavó con acetato de etilo y se secó. Se añadió cuidadosamente disolución acuosa de $NaHCO_3$. El precipitado se filtró y se lavó con disolución de $NaHCO_3$ hasta que el filtrado tuvo un pH de 8. El secado dio 23,78 g (88%) del compuesto 9 como un sólido blanquecino.

RMN de ^1H (d_6-DMSO): δ = 11,30 (1H, s), 9,13 (1H, s), 8,48 (1H, d, J = 5,9 Hz), 8,02 (1H, d, J= 8,8 Hz), 7,78 (1H, J = 5,9 Hz), 7,40 (1H, d, J = 8,8 Hz).

MS: m/z = 224 (MH^+).

5-Yodoisoquinolin-6-ol (10)

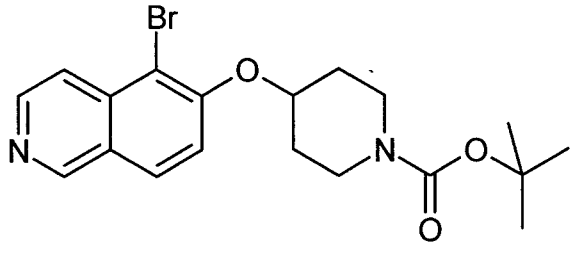


En atmósfera de argón se añadieron 1,77 g (12,2 mmol) del compuesto 7 a una disolución de 5,0 g (13,5 mmol) de tetrafluoroborato de bis(piridin)yodonio en 100 mL de diclorometano seco. Se añadió gota a gota a 0ºC una disolución de 2,4 mL (4 g, 26,8 mmol) de ácido trifluorometanosulfónico en 20 mL de diclorometano seco y la mezcla se agitó durante 3 horas a temperatura ambiente. Los disolventes se eliminaron por destilación y el resto se trató con disolución acuosa de $NaHCO_3$. El precipitado se filtró, se lavó con agua y se secó para rendir 3,2 g (97%) del compuesto 10 como un sólido beige.

RMN de ^1H (d_6-DMSO): δ = 9,09 (1H, s), 8,47 (1H, d, J = 6,1 Hz), 8,04 (1H, d, J= 8,8 Hz), 7,76 (1H, J = 6,1 Hz), 7,37 (1H, d, J = 8,8 Hz).

MS: m/z = 272 (MH^+).

Éster terc-butílico del ácido 4-(5-Bromo-isoquinolin-6-iloxi)-piperidin-1-carboxílico (11)



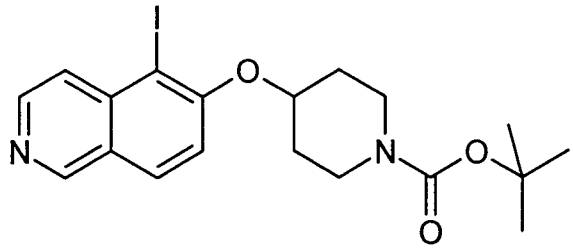
Se añadieron 3,75 mL (4,15 g, 23,8 mmol) de azo dicarboxilato de dietilo a 12,7 g (19,9 mmol) de trifenilfosfina unida a polímero (PS-PPh_3, aprox. 1,6 mmol/g, Argonaut) en 250 mL de diclorometano a 0°C y se agitaron durante 15 min. Se añadieron 4,45 g (19,9 mmol) de 5-bromo-isoquinolin-6-ol (9), 4,0 g (19,9 mmol) de Boc-(4-hidroxi)piperidina y 4,1 mL (3,0 g, 29,8 mmol) de trietilamina. La mezcla se agitó durante 16 h. El polímero se eliminó por filtración a través de Celite y los disolventes se destilaron. Se añadieron 20 mL de diclorometano y el precipitado se aisló por filtración. El producto bruto (8 g) se purificó por cromatografía instantánea ("flash") utilizando acetato de etilo/n-heptano como eluyente para dar 4,78 g (60%) del compuesto 11.

RMN de ^1H (d_6-DMSO): δ = 9,24 (1H, s), 8,97 (1H, s), 8,56 (1H, d, J = 6 Hz), 8,20 (1H, d, J = 9 Hz), 7,85 (1H, d, J= 6 Hz), 7,75 (1H, d, J = 9 Hz), 5,02 (1H, m), 3,58 (2H, m), 3,40 (2H, m), 1,91 (2H, m), 1,70 (2H, m), 1,41 (9H, s).

MS: m/z = 407 (MH^+).

Las unidades estructurales siguientes se sintetizaron según este método:

Éster terc-butílico del ácido 4-(5-yodo-isoquinolin-6-iloxi)-piperidin-1-carboxílico (12)

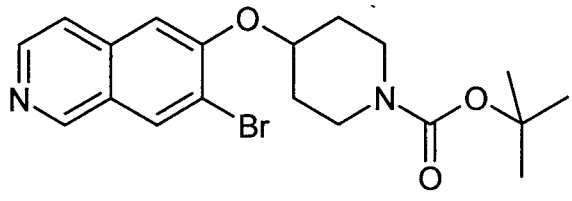


utilizando el compuesto 10 como producto de partida

^{1}H-RMN ($CDCl_3$): δ = 9,04 (1H, s), 8,55 (1H, d, J = 6 Hz), 7,93 (1H, d, J = 9 Hz), 7,86 (1H, d, J = 6 Hz), 7,27 (1H, d, J= 9 Hz), 4,87 (1H, m), 3,66 (4H, m), 1,93 (4H, m), 1,48 (9H, s).

MS: m/z = 455 (MH^+).

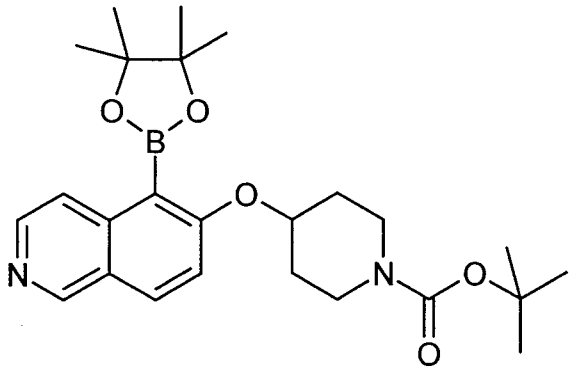
Éster terc-butílico del ácido 4-(7-bromo-isoquinolin-6-iloxi)-piperidin-1-carboxílico (13)



utilizando el compuesto 1 como producto de partida

Método de LCMS # 4, tiempo de retención 1,13 min, masa detectada 407,4 $[M+H]^+$

Éster terc-butílico del ácido 4-[5-(4,4,5,5-tetrametil-[1,3,2]dioxaborolan-2-il)-isoquinolin-6-iloxi]-piperidin-1-carboxílico (14)

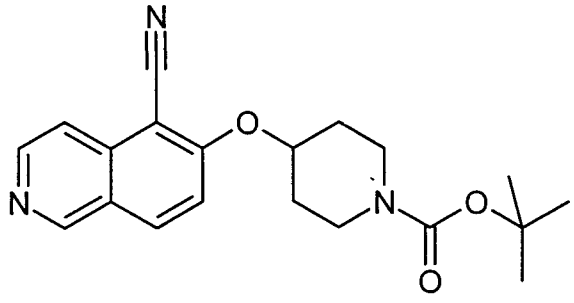


Una disolución de 0,55 g (1,34 mmol) de éster terc-butílico del ácido 4-(5-bromo-isoquinolin-6-iloxi)-piperidin-1-carboxílico (11) en 14 mL de DMSO se añadió a

una mezcla de 1,0 g (4,0 mmol) de bis(pinacolato)diboro, 0,78 g (8,0 mmol) de K_2CO_3 y 29 mg (0,03 eq.) de $Pd(dppf)Cl_2$. Se burbujeó argón a través de la mezcla durante 30 min y a continuación se calentó la mezcla de reacción en un reactor de microondas (CEM Discovery) a 100ºC durante 60 min. Después de enfriar a temperatura ambiente se añadió agua. La mezcla se extrajo con acetato de etilo. Después de eliminar el disolvente el producto se aisló por cromatografía instantánea (acetato de etilo/n-heptano) para rendir: 269 mg (44%) del compuesto 14 como un sólido blanco.

Método de LCMS # 4, tiempo de retención 1,30 min, masa detectada 433,3 $[M+H]^+$

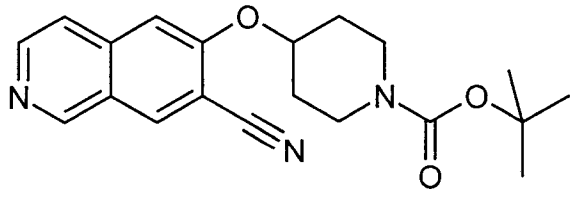
Éster terc-butílico del ácido 4-(5-ciano-isoquinolin-6-iloxi)-piperidin-1-carboxílico (15)



En atmósfera de argón se añadieron 47 mg (0,4 mmol) de $Zn(CN)_2$ y 23 mg de $Pd(PPh_3)_4$ (0,02 eq) a una disolución de 62 mg (0,4 mmol) de éster terc-butílico del ácido 4-(5-bromo-isoquinolin-6-iloxi)-piperidin-1-carboxílico (11) en DMF. La reacción se calentó durante 5 minutos a 150ºC en un reactor de microondas (CEM Discovery). Después de enfriar a temperatura ambiente se añadieron agua y acetato de etilo. La mezcla se filtró a través de celita, se lavó con acetato de etilo y se concentró para rendir 176 mg del compuesto 15.

MS: m/z = 354 (MH^+).

Éster terc-butílico del ácido 4-(7-ciano-isoquinolin-6-iloxi)-piperidin-1-carboxílico (16)

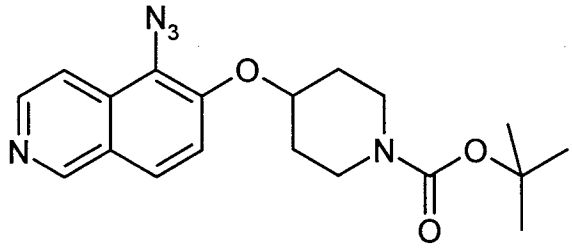


En atmósfera de argón se añadieron 35 mg (0,3 mmol) de $Zn(CN)_2$ y 17 mg (0,05 eq) de $Pd(PPh_3)_4$ a una disolución de 122 mg (0,3 mmol) de éster terc-butílico

del ácido 4-(7-bromo-isoquinolin-6-iloxi)-piperidin-1-carboxílico (13) en DMF. La reacción se calentó durante 5 minutos a 150ºC en un reactor de microondas (CEM Discovery). Después de enfriar a temperatura ambiente se añadieron agua y acetato de etilo. La mezcla se filtró a través de Celite, se lavó con acetato de etilo y se concentró. El producto crudo se purificó por HPLC preparativa para rendir 77 mg del compuesto 16.

Método de LCMS # 4, tiempo de retención 1,06 min, masa detectada 354,5 $[M+H]^+$

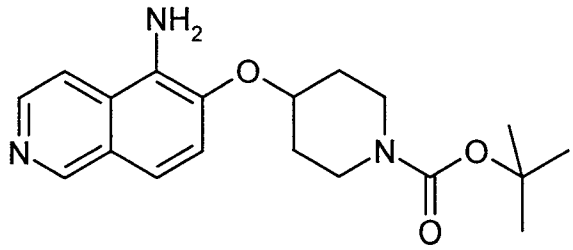
Éster terc-butílico del ácido 4-(5-azido-isoquinolin-6-iloxi)-piperidin-1-carboxílico (17)



En atmósfera de argón se añadieron 40 µL (0,04 mmol) de NaOH 1N, 4,6 mg (0,04 mmol) de L-prolina, 3,8 mg (0,02 mmol) de CuI y 15,6 mg (0,24 mmol) de NaN_3 a una disolución de 91 mg (0,2 mmol) de éster terc-butílico del ácido 4-(5-yodo-isoquinolin-6-iloxi)-piperidin-1-carboxílico (12) en 2 mL de DMSO. La mezcla se calentó a 60ºC durante 18 h. Se añadieron de nuevo, en las mismas cantidades, NaOH y L-prolina y la reacción se calentó a 60ºC durante 5 h. Después de enfriar a temperatura ambiente se añadió agua. El precipitado se filtró, se lavó con agua y se secó a vacío para dar 74 mg del compuesto 17, que se utilizó sin ninguna purificación adicional.

MS: m/z = 370 (MH^+).

Éster terc-butílico del ácido 4-(5-amino-isoquinolin-6-iloxi)-piperidin-1-carboxílico (18)

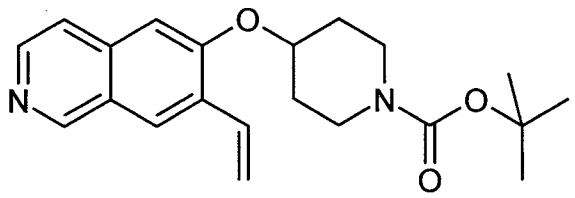


En atmósfera de argón se añadieron 600 µL (0,6 mmol) de NaOH 1N, 13,8 mg (0,12 mmol) de L-prolina, 7,6 mg (0,04 mmol) de CuI y 52 mg (0,8 mmol) de NaN_3 a una disolución de 163 mg (0,4 mmol) de éster terc-butílico del ácido 4-(5-bromo-

isoquinolin-6-iloxi)-piperidin-1-carboxílico (11) en 0.6 mL de agua. La mezcla se calentó a 95ºC durante 3 h en un reactor de microondas (CEM Discovery). Después de enfriar a temperatura ambiente se añadieron agua y acetato de etilo. La mezcla se filtró a través de Celite, se lavó con acetato de etilo y se concentró. El producto bruto se purificó por HPLC preparativa para rendir 42 mg del compuesto 18 (que contenía algo de 11 como impureza).

Método de LCMS # 4, tiempo de retención 0,97 min, masa detectada 344,5 $[M+H]^+$

Éster terc-butílico del ácido 4-(7-vinil-isoquinolin-6-iloxi)-piperidin-1-carboxílico (19)



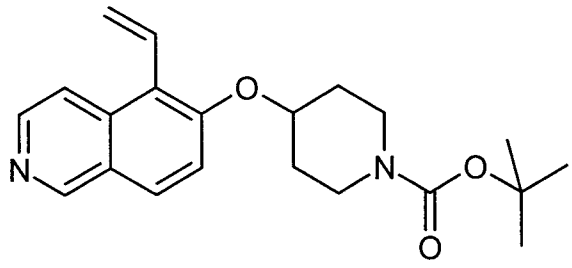
En atmósfera de argón se añadieron 340 mg de tributil-vinil-estannano (1,07 mmol, 1,2 eq.) y 103 mg de $Pd(PPh_3)_4$ (0,1 eq.) a una disolución de 364 mg de éster terc-butílico del ácido 4-(7-Bromo-isoquinolin-6-iloxi)-piperidin-1-carboxílico (13) (0,98 mmol) en 4 ml de tolueno. La reacción se calentó a 100ºC en un reactor de microondas (CEM Discovery) durante 1 h.

Después de enfriar a temperatura ambiente se añadieron agua y acetato de etilo. La mezcla se filtró a través de un cartucho de Celite, se lavó con acetato de etilo y se concentró. El producto crudo se purificó por HPLC preparativa para rendir 256 mg (81%) del compuesto 19.

Método de LCMS # 4, tiempo de retención 1,19 min, masa detectada 355,5 $[M+H]^+$

Las unidades estructurales siguientes se sintetizaron según este método:

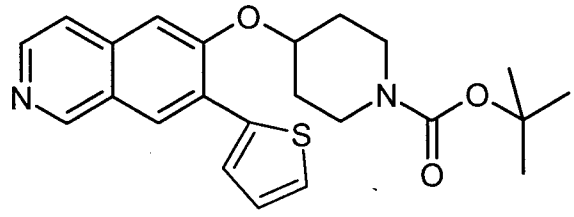
Éster terc-butílico del ácido 4-(5-vinil-isoquinolin-6-iloxi)-piperidin-1-carboxílico (19A)



utilizando el compuesto 11 como producto de partida

Método de LCMS # 4, tiempo de retención 1,11 min, masa detectada 355,4 $[M+H]^+$

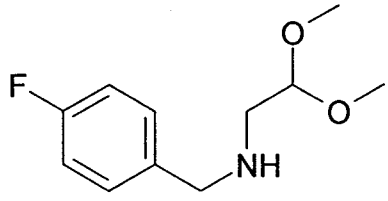
Éster terc-butílico del ácido 4-(7-tiofen-2-il-isoquinolin-6-iloxi)-piperidin-1-carboxílico (20)



utilizando el compuesto 13 y tributil-tiofen-2-il-estannano como productos de partida.

Método de LCMS # 4, tiempo de retención 1,26 min, masa detectada 411,5 $[M+H]^+$

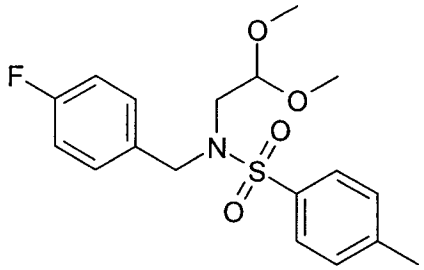
(2,2-Dimetoxi-etil)-(4-fluoro-bencil)-amina (21)



Se disolvieron 12,4 g de 4-fluorobenzaldehído en 100 mL de tolueno y se hicieron reaccionar con 10,5 g del dimetilacetal del 2-aminoacetaldehído y 1,90 g (10 mmol) de ácido p-toluensulfónico monohidratado durante dos horas en un aparato Dean Stark. La disolución se dejó enfriar, se extrajo con bicarbonato sódico saturado, agua y salmuera, se secó sobre sulfato magnésico y se evaporó a sequedad. El producto bruto se disolvió en 100 mL de etanol. Se añadieron en porciones 1,89 g de borohidruro sódico. Se continuó agitando durante toda la noche. Para la elaboración, se añadió

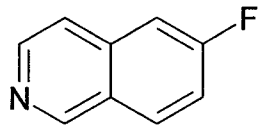
ácido acético hasta que no se pudo observar ninguna evolución de gas. A continuación la disolución se evaporó a sequedad, se recogió en diclorometano y se lavó dos veces con agua. La capa orgánica se extrajo con salmuera, se secó sobre sulfato magnésico y se evaporó a sequedad. El producto bruto obtenido (20 g) se utilizó para reacciones adicionales sin purificación. R_t = 0,86 min (Método #1). Masa detectada: 182,1 ($M-OMe^-$), 214,2 ($M+H^+$).

N-(2,2-Dimetoxi-etil)-N-(4-fluoro-bencil)-4-metil-bencenosulfonamida (22)



Se disolvieron 20 g de (2,2-dimetoxi-etil)-(4-fluoro-bencil)-amina (21) en 120 ml de diclorometano. Se añadieron 20 mL de piridina. Se añadió gota a gota a 0 °C una disolución de 23,8 g de cloruro del ácido p-toluensulfónico en diclorometano. La reacción se dejó calentar a temperatura ambiente y se continuó agitando hasta que se completó la conversión. Para la elaboración, la mezcla de reacción se extrajo dos veces con ácido clorhídrico 2M, dos veces con bicarbonato sódico y una vez con salmuera. La capa orgánica se secó sobre sulfato magnésico, se evaporó a sequedad y el producto bruto obtenido se purificó por cromatografía en gel de sílice para rendir 22,95 g del compuesto 22 como un aceite naranja. R_t = 1,71 min (Método #4). Masa detectada: 336,1 ($M-OMe^-$).

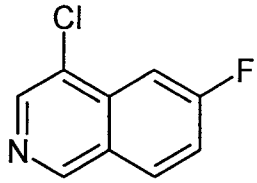
6-Fluoro-isoquinolina (23)



Se suspendieron 41,6 g de $AlCl_3$ en 400 mL de diclorometano. A temperatura ambiente, se añadió una disolución de 22,95 g de N-(2,2-Dimetoxi-etil)-N-(4-fluoro-bencil)-4-metil-bencenosulfonamida (22) en 150 ml de diclorometano. Se continuó agitando a temperatura ambiente durante toda la noche, la disolución se vertió sobre hielo, la capa orgánica se separó, la fase acuosa se extrajo dos veces con diclorometano y a continuación las capas orgánicas combinadas se extrajeron dos veces con bicar-

bonato sódico. La capa orgánica se secó sobre sulfato magnésico, se evaporó a sequedad y el producto bruto obtenido (8,75 g) se purifica por cromatografía en gel de sílice para rendir 2,74 g del compuesto 23. R_t = 0,30 min (Método #4). Masa detectada: 148,1 ($M+H^+$).

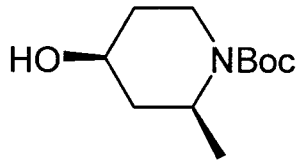
4-Cloro-6-fluoro-isoquinolina (24)



Una disolución de 1,5 g de 6-fluoro-isoquinolina (23) en 4,5 ml de cloruro de sulfurilo se calentó a 60°C en un reactor de microondas (CEM Discovery) durante 8 h. Después de enfriar a temperatura ambiente la mezcla se vertió sobre hielo y se extrajo tres veces con $CHCl_3$. Después de secar sobre Na_2SO_4 el disolvente se eliminó por destilación y el producto crudo se purificó por cromatografía instantánea para rendir 930 mg del compuesto 24.

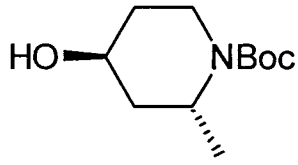
Método de LCMS # 1, tiempo de retención 1,37 min, masa detectada 182,01 $[M+H]^+$

Cis y trans N-Boc-2-metil-piperidin-4-ol (25 y 26)



racémico - cis

25



racémico - trans

26

Se añadieron en porciones 213 mg (5,6 mmol) de $NaBH_4$ a 0°C a una disolución de 1,0 g (4,7 mmol) de 1-Boc-2-metil-piperidin-4-on en 10 mL de EtOH. La mezcla se agitó a temperatura ambiente durante otras 2 h. El disolvente se eliminó por destilación y el resto se disolvió en agua y acetato de etilo. La capa acuosa se extrajo dos veces con acetato de etilo y las capas orgánicas combinadas se secaron sobre Na_2SO_4. Después de la filtración el disolvente se eliminó por destilación y el producto

bruto se purificó por cromatografía en columna con n-heptano/acetato de etilo (1/1) para rendir 367 mg (36%) del isómero cis 25 y 205 mg (20%) del isómero trans 26 además de 97 mg (10%) de la mezcla de ambos isómeros.

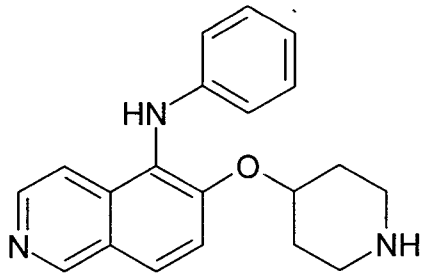
Isómero Cis (25):

^{1}H-RMN ($CDCl_3$): δ= 4,28 (1H, m), 4,17 (1H, m), 3,82 (1H, m), 3,26 (1H, m), 1,85 (1H, ddd, J= 14,7, 6,6, y 3,4 Hz), 1,77 (1H, m), 1,66 (2H, m), 1,33 (3H, d, J = 7,1 Hz).

Isómero Trans (26):

^{1}H-RMN ($CDCl_3$): δ = 4,50 (1H, m), 4,04 (1H, m), 3,95 (1H, m), 2,87 (1H, dt, J = 2,9 y 13,6 Hz), 1,93 (1H, m), 1,83 (1H, m), 1,53 (1H, m), 1,32 (1H, m), 1,14 (3H, d, J = 7,1 Hz).

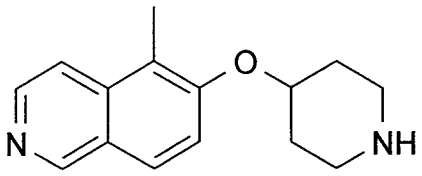
Fenil-[6-(piperidin-4-iloxi)-isoquinolin-5-il]-amina (27)



En una atmósfera de argón se añadieron 81 mg (0,2 mmol) de éster terc-butílico del ácido 4-(5-bromo-isoquinolin-6-iloxi)-piperidin-1-carboxílico (11) y 24 mg (0,26 mmol) de anilina a una disolución de 27 mg (0,28 mmol) de NaO*t*Bu en 3 mL de tolueno. Después de agitar a temperatura ambiente durante 10 min., se añadieron 9 mg (0,05 eq) de Pd_2dba_3 y la mezcla se calentó a 100ºC en un reactor de microondas (CEM Discovery) durante 1 h. Después de enfriar a temperatura ambiente se añadieron agua y acetato de etilo. La capa orgánica se separó, se secó sobre Na_2SO_4 y se concentró. La purificación por HPLC dio el intermedio protegido con Boc que se trató con 2 mL de HCl 5-6 N en isopropanol durante 2 h. Se filtró el hidrocloruro y se sometió a otra cromatografía de HPLC para rendir el compuesto 27 como trifluoroacetato (31,3 mg).

Método de LCMS # 2, tiempo de retención 0,78 min, masa detectada 320,26 $[M+H]^+$

Hidrocloruro de 5-metil-6-(piperidin-4-iloxi)-isoquinolina (28)

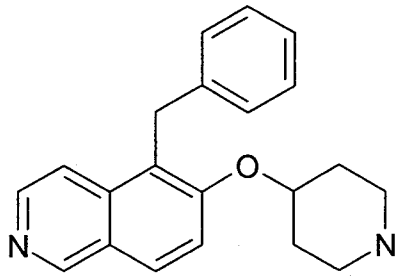


ClH

En una atmósfera de argón se añade una disolución 2 M de dimetil zinc (0,5 mL, 93,7 mg, 4 eq.) en tolueno a una disolución de 100 mg (0,24 mmol) de éster terc-butílico del ácido 4-(5-bromo-isoquinolin-6-iloxi)-piperidin-1-carboxílico (11) y 10 mg de cloruro de (1,1'-bis(difenilfosfino)ferrocen)paladio(II) (0,056 eq. $Pd(dppf)Cl_2$) en 3 mL de dioxano. La mezcla se calentó a 100°C durante 5 h. Después de enfriar los disolventes se eliminaron por destilación y el resto se sometió a HPLC preparativa para dar el intermedio protegido con Boc que se trató con HCl 5-6 N en isopropanol durante 2 h a temperatura ambiente. La eliminación de los disolventes dio 13,7 mg (18%) del compuesto 28.

Método de LCMS # 1, tiempo de retención 0,67 min, masa detectada 243,24 $[M+H]^+$

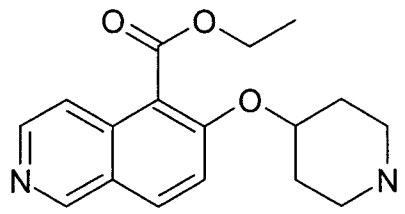
5-Bencil-6-(piperidin-4-iloxi)-isoquinolina (29)



Se añadieron 0,3 mL de agua a una disolución de 81 mg (0,2 mmol) de éster terc-butílico del ácido 4-(5-bromo-isoquinolin-6-iloxi)-piperidin-1-carboxílico (11), 195 mg (0,6 mmol) de Cs_2CO_3, 14,6 mg (0,02 mmol) de $Pd(dppf)Cl_2$ y 51 mg (0,26 mmol) de benciltrifluoroborato potásico en 3 mL de THF. Se burbujeó argón a través de la mezcla durante 10 minutos y a continuación la reacción se calentó a reflujo durante 16 h (conversión incompleta). Después de enfriar a temperatura ambiente se añadieron agua y acetato de etilo. La capa orgánica se separó, se secó sobre Na_2SO_4. Después de la eliminación de los disolventes se añadieron 2 mL de HCl 5-6 N en isopropanol. Después de 2 h los disolventes se separaron por destilación y el resto se sometió dos veces a HPLC preparativa para dar 3,5 mg del compuesto 29 como trifluoroacetato.

Método de LCMS # 3, tiempo de retención 0,56 min, masa detectada 319,23 $[M+H]^+$

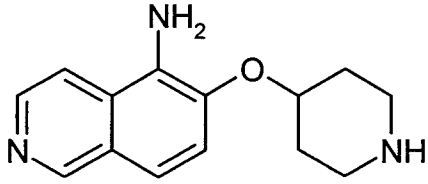
Éster etílico del ácido 6-(Piperidin-4-iloxi)-isoquinolin-5-carboxílico (30)



Una disolución de 200 mg (0,44 mmol) de éster terc-butílico del ácido 4-(5-yodo-isoquinolin-6-iloxi)-piperidin-1-carboxílico (12), 107 mg (0,88 mmol) de DMAP, 4,7 mg (0,1 eq) de Pd sobre carbón (10%), 150 µL (0,88 mmol) de trietilamina y 58 mg (0,22 mmol) de $Mo(CO)_6$ en 3 mL de etanol se calentó a 135°C durante 1 h en un reactor de microondas (CEM Discovery). A continuación se añadieron agua y acetato de etilo y la mezcla se filtró a través de un cartucho de Celite. Después de la eliminación de los disolventes el resto se sometió a HPLC preparativa para dar 7,4 mg de intermedio protegido con Boc. Para eliminar el grupo Boc el intermedio se trató con 2 mL de HCl 5-6 N en isopropanol a temperatura ambiente durante 2 h. La purificación por HPLC preparativa dio 2,5 mg del compuesto 30 como sal de TFA.

Método de LCMS # 3, tiempo de retención 0,14 min, masa detectada 301,29 $[M+H]^+$

6-(Piperidin-4-iloxi)-isoquinolin-5-ilamina (31)



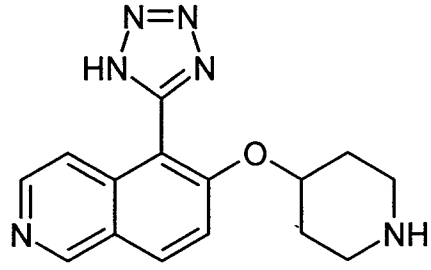
Se añadieron 60 µL de disolución de NaOH 1N, 6,9 mg (0,3 eq) de L-prolina, 3,8 mg (0,1 eq) de CuI y 26 mg (0,4 mmol) de NaN_3 a una disolución de 82 mg (0,2 mmol) de éster terc-butílico del ácido 4-(5-Bromo-isoquinolin-6-iloxi)-piperidin-1-carboxílico (11) en 2 mL de etanol/agua (7/3). La mezcla se calentó a 95°C durante 3 h en un reactor de microondas (CEM Discovery). Después de enfriar se añadieron agua y acetato de etilo y la mezcla se filtró a través de un cartucho de Celite. Después de eliminar los disolventes por destilación el resto se sometió a HPLC preparativa. El intermedio protegido en el N con Boc se desprotegió por tratamiento con 2 mL de HCl 5-

6 N en isopropanol durante 2 h a temperatura ambiente. Después se añadió agua y todos los disolventes se eliminaron por liofilización para dar 18 mg del compuesto 31 como hidrocloruro.

RMN de ^1H (d_6-DMSO): δ = 9,60 (1H, s), 8,95 (2H, s ancho), 8,56 (1H, d, J = 7,1 Hz), 8,41 (1H, d, J = 7,1 Hz), 7,85 (1H, d, J = 9,0 Hz), 7,81(1H, d, J = 9,0 Hz), 5,03 (1H, m), 3,13 (1H, m), 2,92 (1H, m), 2,15 (2H, m), 1,99 (2H, m), 1,84 (1H, m), 1,55 (1H, m).

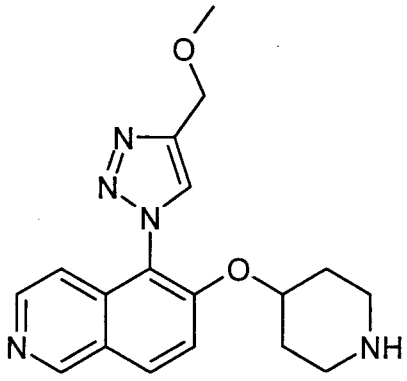
Método de LCMS # 1, tiempo de retención 0,35 min, masa detectada 244,25 $[M+H]^+$

6-(Piperidin-4-iloxi)-5-(1H-tetrazol-5-il)-isoquinolina (32)



En atmósfera de argón se añadieron 78 mg (1,2 mmol) de NaN_3 y 64 mg (1,2 mmol) de NH_4Cl a una disolución de 35 mg (0,1 mmol) de éster terc-butílico del ácido 4-(5-Ciano-isoquinolin-6-iloxi)-piperidin-1-carboxílico (15) en 1 mL de DMF. La mezcla se calentó a aproximadamente 160ºC y 7 bares de presión durante 3 h en un reactor de microondas (CEM Discovery). Después de enfriar a temperatura ambiente se añadió disolución acuosa de NH_4Cl y diclorometano. La mezcla se filtró a través de un cartucho de separación de fases y la capa acuosa se lavó dos veces con diclorometano. Las capas orgánicas se combinaron y los disolventes se separaron por destilación. El resto se sometió a HPLC preparativa para rendir 4 mg (8%) del compuesto 32 como trifluoroacetato. Método de LCMS # 3, tiempo de retención 0,90 min, masa detectada 297,04 $[M+H]^+$

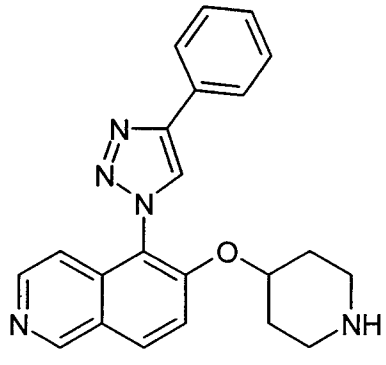
5-(4-Metoximetil-[1,2,3]triazol-1-il)-6-(piperidin-4-iloxi)-isoquinolina (33)



Se añadieron 4 mg (0,1 eq.) de ascorbato sódico y 0,5 mg (0,01 eq.) de sulfato de Cobre(II) hidratado a una disolución de 73 mg (0,2 mmol) de éster terc-butílico del ácido 4-(5-Azido-isoquinolin-6-iloxi)- piperidin-1-carboxílico (17) y 14 mg (0,2 mmol) de metil propargil éter en 4 ml de agua/terc-butanol (1/1). La mezcla se agitó durante 18 h a temperatura ambiente. A continuación se añadió acetato de etilo y la mezcla se filtró a través de un cartucho de Celita. Después de eliminar los disolventes el resto se sometió a HPLC preparativa. El intermedio protegido en el N con Boc se desprotegió por tratamiento con 2 mL de HCl 5-6 N en isopropanol durante 2 h a temperatura ambiente. A continuación el disolvente se evaporó y el producto se aisló por HPLC preparativa para rendir 2,8 mg del compuesto 33 como trifluoroacetato.

Método de LCMS # 3, tiempo de retención 0,08 min, masa detectada 340,17 $[M+H]^+$

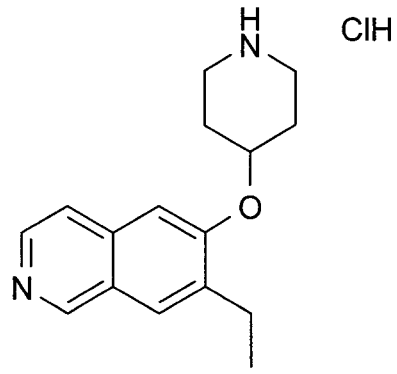
5-(4-Fenil-[1,2,3]triazol-1-il)-6-(piperidin-4-iloxi)-isoquinolina (34)



El compuesto del título se obtuvo utilizando 20 mg (0,2 mmol) de fenilacetileno según el procedimiento descrito para el compuesto 33. Rendimiento 2,5 mg del compuesto 34 como trifluoroacetato.

Método de LCMS # 3, tiempo de retención 0,14 min, masa detectada 372,2 $[M+H]^+$

Hidrocloruro de 7-etil-6-(piperidin-4-iloxi)-isoquinolina (35)



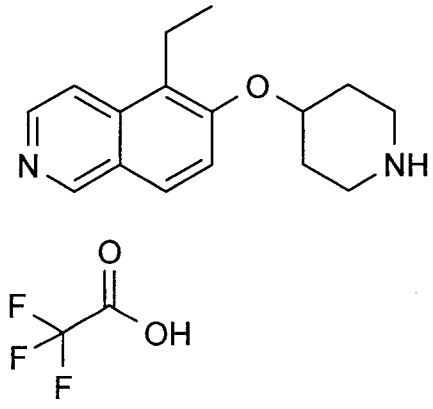
Se añadió 1 mg de Paladio al 5% sobre carbón (0,02 eq.) a una disolución de 174 mg de éster terc-butílico del ácido 4-(7-vinil-isoquinolin-6-iloxi)-piperidin-1-carboxílico (19) (0,49 mmol, 1 eq.) en 15 mL de metanol. La olefina se hidrogenó a 5 bares de H_2 a temperatura ambiente durante toda la noche. Solo se observó conversión parcial, así que se eliminó el catalizador por filtración y se añadió catalizador nuevo. Otro tratamiento bajo las mismas condiciones de hidrogenación completó la reacción. A continuación el catalizador se eliminó por filtración y el producto crudo se purificó por HPLC preparativa para dar 97 mg del intermedio protegido con Boc.

El grupo protector se eliminó por tratamiento con HCl 5-6 N en isopropanol durante 2 h a temperatura ambiente. El disolvente se destiló y se añadieron agua y acetonitrilo. La liofilización de la mezcla dio 53 mg del compuesto 35.

Método de LCMS # 1, tiempo de retención 0,71 min, masa detectada 257,18 $[M+H]^+$

El compuesto de ejemplo siguiente se sintetizó según este método:

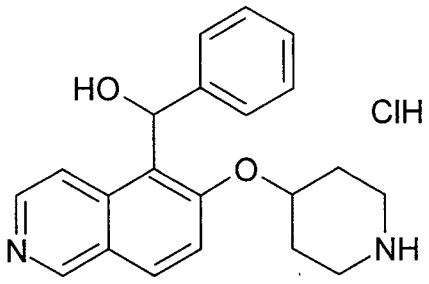
Trifluoroacetato de 5-etil-6-(piperidin-4-iloxi)-isoquinolina (36)



utilizando el compuesto 19A como el producto de partida

Método de LCMS # 2, tiempo de retención 0,17 min, masa detectada 257,21 $[M+H]^+$

Hidrocloruro de fenil-[6-(piperidin-4-iloxi)-isoquinolin-5-il]-metanol (37)



A –78°C se añadieron 0,6 mL (0,98 mmol, 1,6 M en hexano) de n-butil litio a una disolución de 200 mg (0,49 mmol, 1 eq.) de éster terc-butílico del ácido 4-(5-bromo-isoquinolin-6-iloxi)-piperidin-1-carboxílico (11) en 3 mL de THF. Después de 30 min se añadieron 110 µL (115 mg, 1,08 mmol) de benzaldehído y la mezcla se dejó calentar a temperatura ambientes. Después de 2 h de agitación a temperatura ambiente se añadieron agua y acetato de etilo. Las capas se separaron y la capa orgánica se lavó con agua y salmuera. Después de secado sobre Na_2SO_4 y evaporación del disolvente el resto se sometió a HPLC preparativa para rendir el intermedio protegido con Boc.

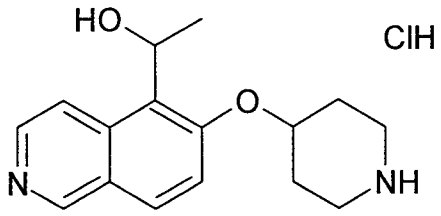
El grupo Boc se eliminó por disolución del intermedio en isopropanol y adición de HCl 5-6 N en isopropanol. El hidrocloruro precipitado se aisló por filtración para rendir 5,2 mg del compuesto 37 (3 %).

RMN de ^1H (d_6-DMSO): δ = 9,43 (1H, s), 8,50 (1H, s ancho), 8,40 (1H, s ancho), 8,30 (3H, m), 7,87 (1H, d, J = 9,2 Hz), 7,33 (2H, d, J = 7,4 Hz), 7,28 (2H, t, J= 7,4 Hz), 7,19 (1H, t, J = 7,4 Hz), 6,74 (1H, s), 6,34 (1H, s), 5,10 (1H, m), 3,25 (2H, m), 3,15 (2H, m), 2,19 (2H, m), 1,93 (2H, m).

Método de LCMS # 1, tiempo de retención 0,80 min, masa detectada 335,22 $[M+H]^+$

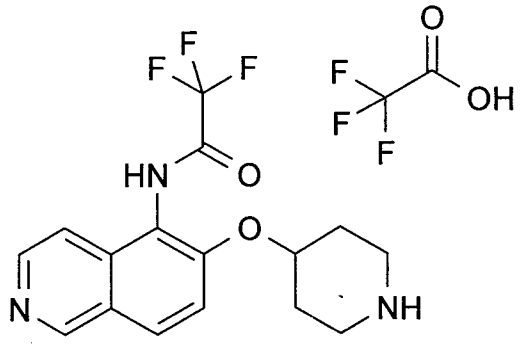
El compuesto de ejemplo siguiente también se sintetizó según este método:

Hidrocloruro de 1-[6-(piperidin-4-iloxi)-isoquinolin-5-il]-etanol (38)



Método de LCMS # 1, tiempo de retención 0,55 min, masa detectada 273,2 $[M+H]^+$

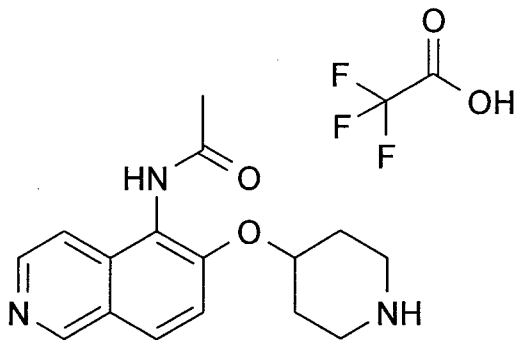
Trifluoroacetato de 2,2,2-trifluoro-N-[6-(piperidin-4-iloxi)-isoquinolin-5-il]-acetamida (39)



Se añadieron 62,8 mg de carbonato potásico (0,46 mmol, 4 eq.) y 10,7 µL de cloruro de metanosulfonilo (0,13 mmol, 1,2 eq.) a una disolución de 39 mg (0,11 mmol) de éster terc-butílico del ácido 4-(5-Amino-isoquinolin-6-iloxi)-piperidin-1-carboxílico (18) (que contiene algo de compuesto 11) en 3 mL de DMF. La reacción se agitó durante 4 h a temperatura ambiente. A continuación se añadieron agua y acetato de etilo. La mezcla se filtró a través de Celite, se lavó con acetato de etilo y se concentró para rendir un único producto. El intermedio protegido en el N con Boc se desprotegió por tratamiento con 2 mL de HCl 5-6 N en isopropanol durante 2 h a temperatura ambiente. A continuación el disolvente se evaporó y el producto se aisló por HPLC preparativa para rendir 18,5 mg del compuesto 39.

Método de LCMS # 1, tiempo de retención 0,39 min, masa detectada 340,15 $[M+H]^+$

Trifluoroacetato de N-[6-(piperidin-4-iloxi)-isoquinolin-5-il]-acetamida (40)

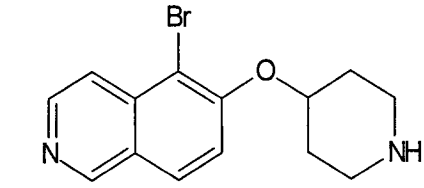
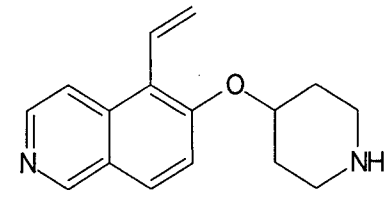
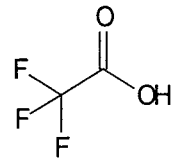
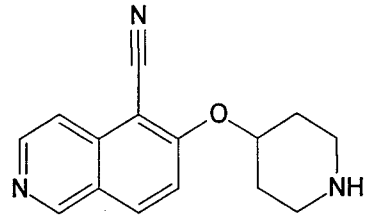
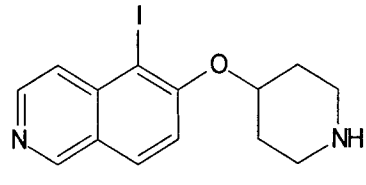


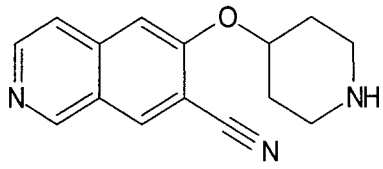
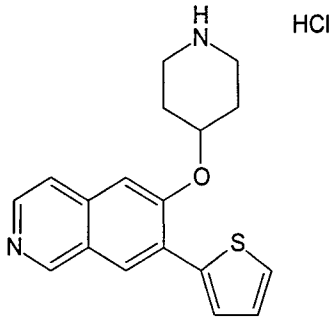
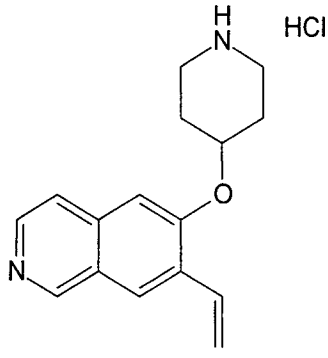
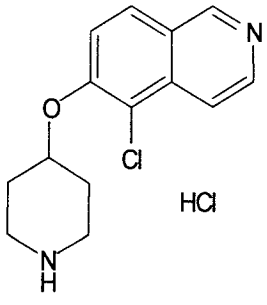
En atmósfera de argón se añadieron 81,5 mg (0,2 mmol) de éster terc-butílico del ácido 4-(5-bromo-isoquinolin-6-iloxi)-piperidin-1-carboxílico (11) y 14,2 mg de acetamida (0,24 mmol, 1,2 eq.) a una disolución de 27 mg (0,28 mmol, 1,4 eq) de NaOtBu en 3 mL de tolueno. Después de agitar durante 10 minutos a temperatura ambiente se añadieron 9,1 mg (0,01 mmol, 0,05 eq) de $Pd_2(dba)_3$ y 11,9 mg (0,04 mmol, 0,2 eq) de 2-(dt-butilfosfino)bifenilo. La reacción se calentó a 120°C durante 2 h en un reactor de microondas (CEM Discovery). A continuación se añadieron agua y acetato de etilo. La mezcla se filtró a través de Celite, se lavó con acetato de etilo y se concentró. El resto se sometió dos veces a HPLC preparativa para rendir el intermedio protegido en el N con Boc. El intermedio protegido en el N con Boc se desprotegió por tratamiento con 2 mL de HCl 5-6 N en isopropanol durante 2 h a temperatura ambiente. A continuación el disolvente se evaporó y el producto se aisló por HPLC preparativa para rendir 2,5 mg del compuesto 40.

Método de LCMS # 3, tiempo de retención 0,15 min, masa detectada 286,15 $[M+H]^+$

Procedimiento general para la desprotección del Boc de unidades estructurales:

Los correspondientes compuestos protegidos en N con Boc se trataron con HCl 5-6 N en isopropanol durante 2 h a temperatura ambiente. Los hidrocloruros precipitados se aislaron por filtración y se secaron. Cuando fue necesario, se llevó a cabo una purificación adicional por HPLC preparativa.

Nº	Compuesto	Producto de partida	Método de LCMS #	Tiempo de retención	Masa detectada $[M+H]^+$
41	 HCl	11	2	0,57	307,13
42	 	19 A	2	0,64	255,19
43	 HCl	15	2	0,46	254,15
44	 HCl	12	1	0,67	355,04

Nº	Compuesto	Producto de partida	Método de LCMS #	Tiempo de retención	Masa detectada $[M+H]^+$
45	 HCl	16	1	0,64	254,13
46	 HCl	20	1	0,87	311,12
47	 HCl	19	1	0,72	255,19
48	 HCl	8	1	0,52	263,10

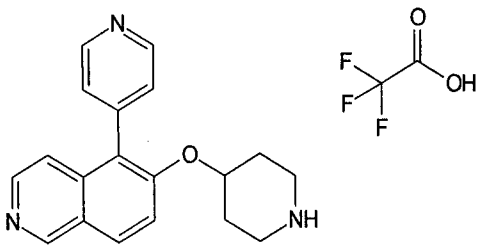
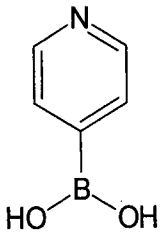
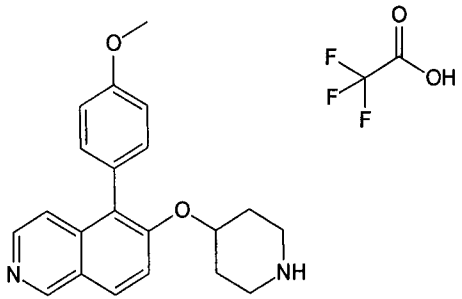
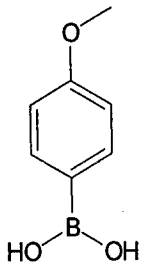
Procedimiento general para acoplamiento de Suzuki con éster terc-butílico del ácido 4-(5-Bromo-isoquinolin-6-iloxi)-piperidin-1-carboxílico (11)

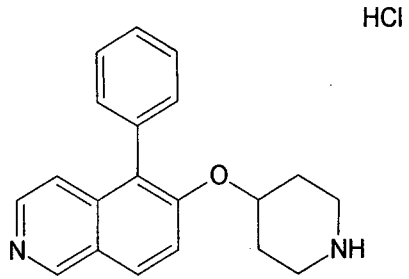
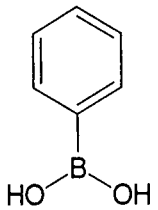
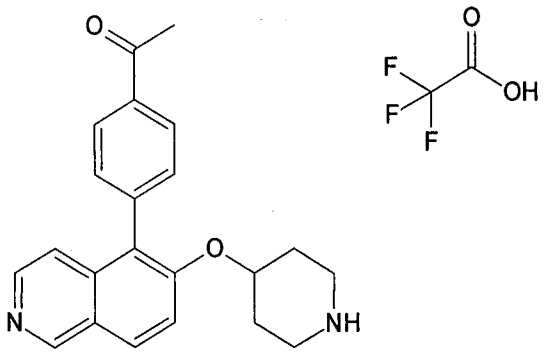
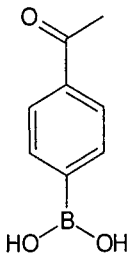
Se añadió disolución acuosa de Na_2CO_3 (0,2 ml, 0,4 mmol, 2 eq. 2M) a una disolución de 81 mg (0,2 mmol, 1 eq.) de éster terc-butílico del ácido 4-(5-Bromo-isoquinolin-6-iloxi)-piperidin-1-carboxílico (11) y 1,5 eq. (0,3 mmol) del correspondiente ácido borónico (reactivo 2) en 3 mL de DME. Se burbujeó argón a través de la mezcla de reacción durante 10 min. A continuación se añadieron 23 mg (0,1 eq.) de $Pd(PPh_3)_4$ y la reacción se agitó a 95°C durante toda la noche bajo atmósfera de argón. Después de enfriar se añadieron 2 mL de agua y 10 mL de acetato de etilo. La capa orgánica se separó, se secó y el disolvente se separó por destilación. El resto se sometió a HPLC preparativa.

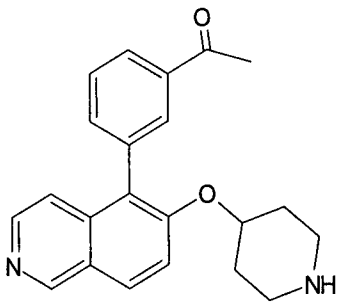
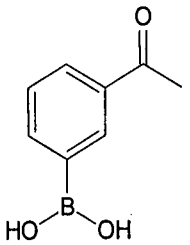
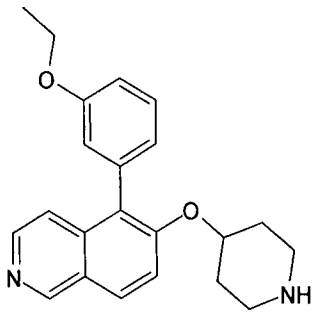
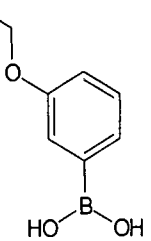
El grupo Boc se eliminó por disolución del intermedio en isopropanol y adición de HCl 5-6 N en isopropanol. El precipitado se aisló por filtración.

En algunas reacciones no precipitó el hidrocloruro o la pureza del precipitado fue insatisfactoria. En estos casos el disolvente se destiló y el resto se purificó por HPLC preparativa.

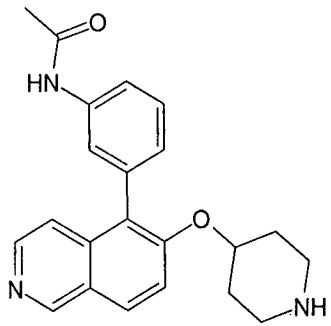
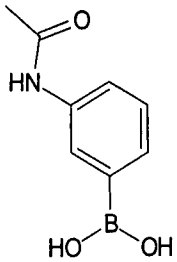
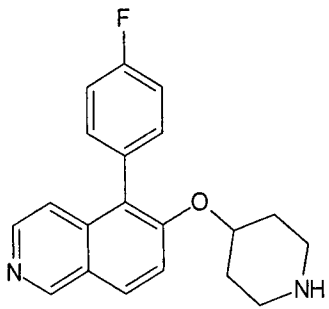
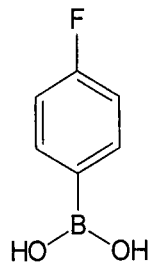
Los ejemplos siguientes se sintetizaron utilizando este método:

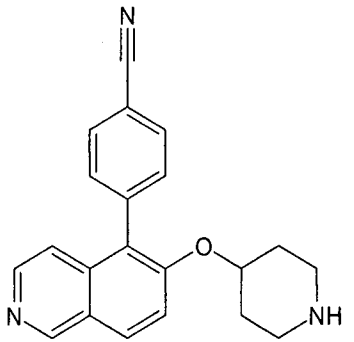
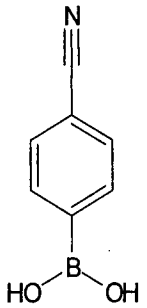
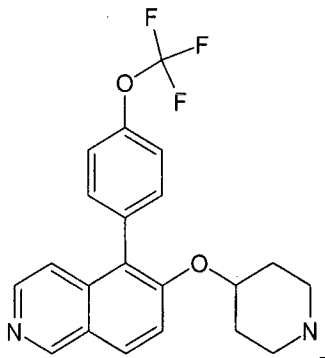
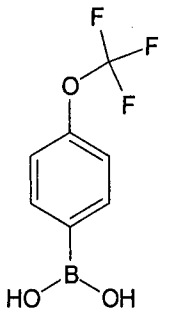
Nº	Compuesto	Reactivo 1	Reactivo 2	Método #	Tiempo de retención	Masa detectada $[M+H]^+$
49		11		2	0,15	306,22
50		11		4	0,75	335,20

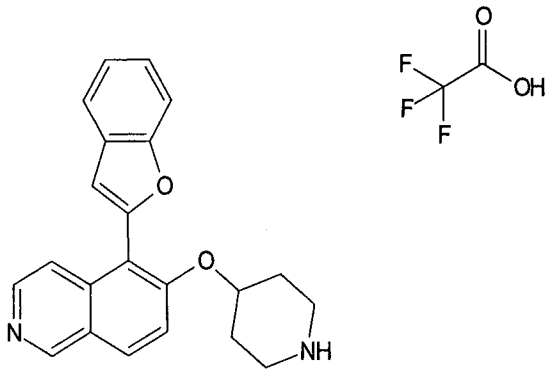
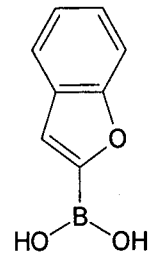
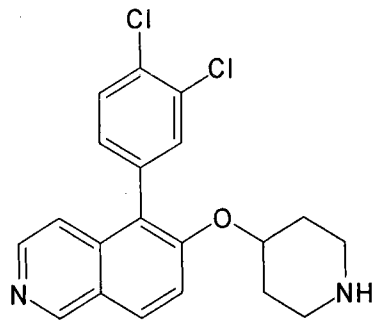
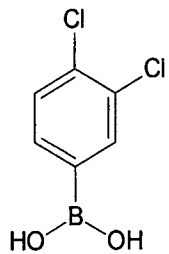
Nº	Compuesto	Reactivo 1	Reactivo 2	Método #	Tiempo de retención	Masa detectada $[M+H]^+$
51		11		4	0,76	305,15
52		11		1	0,81	347,18

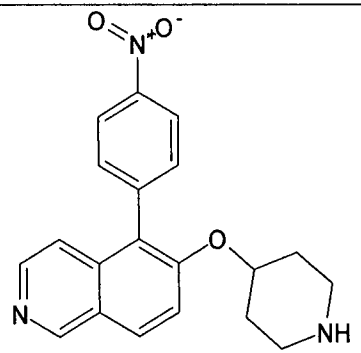
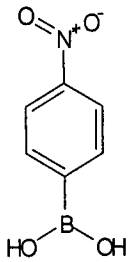
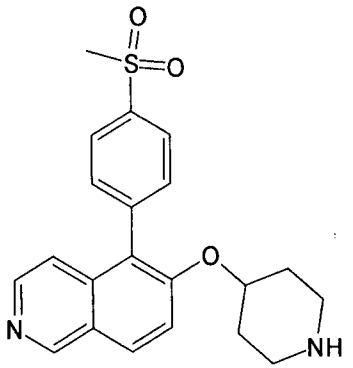
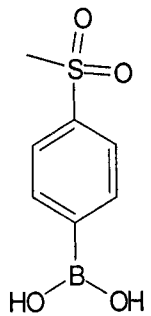
Nº	Compuesto	Reactivo 1	Reactivo 2	Método #	Tiempo de retención	Masa detectada $[M+H]^+$
53	 HCl	11		1	0,84	347,17
54	 HCl	11		1	0,90	349,24

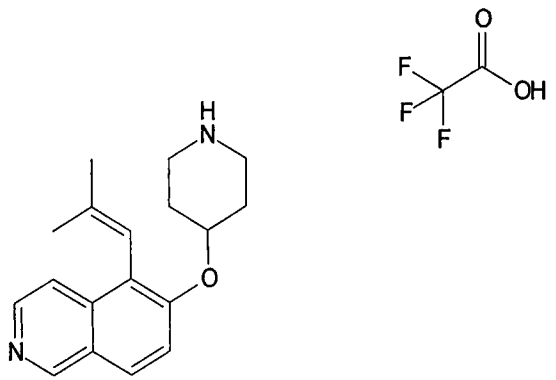
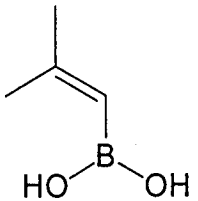
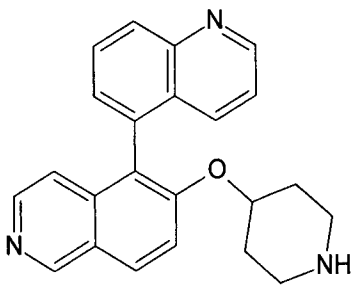
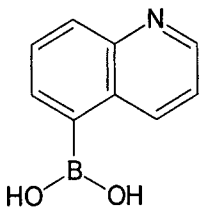
151

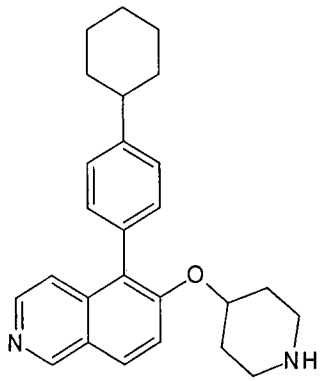
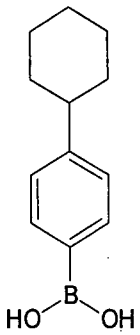
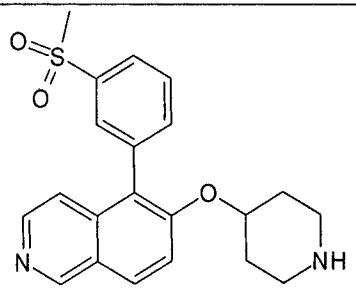
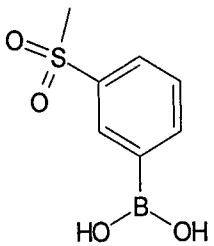
Nº	Compuesto	Reactivo 1	Reactivo 2	Método #	Tiempo de retención	Masa detectada $[M+H]^+$
55	 HCl	11		1	0,75	362,22
56	 HCl	11		1	0,88	323,20

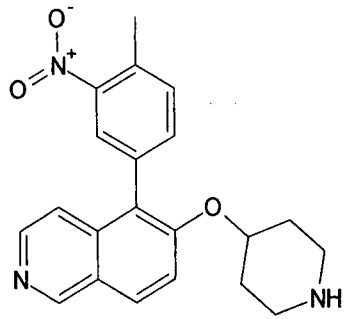
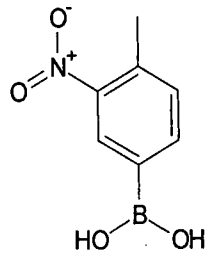
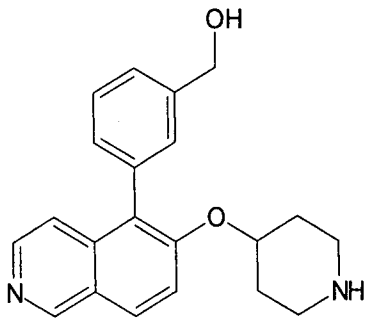
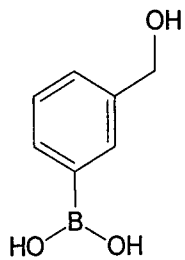
Nº	Compuesto	Reactivo 1	Reactivo 2	Método #	Tiempo de retención	Masa detectada $[M+H]^+$
57	 TFA	11		3	0,44	371,24 $[M+MeCN+H]^+$
58	 TFA	11		3	1,09	389,13

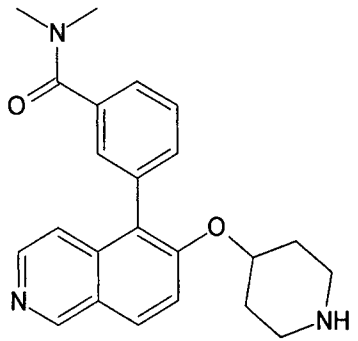
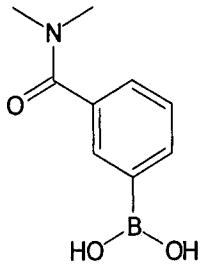
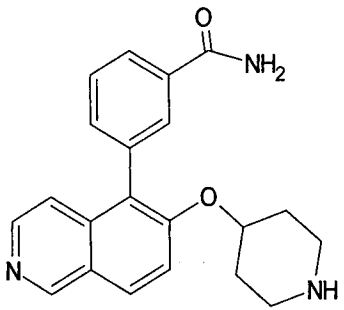
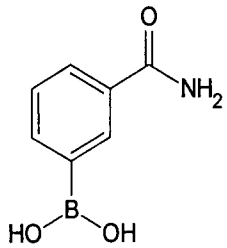
Nº	Compuesto	Reactivo 1	Reactivo 2	Método #	Tiempo de retención	Masa detectada $[M+H]^+$
59		11		3	1,02	345,14
60	 TFA	11		3	1,06	373,03

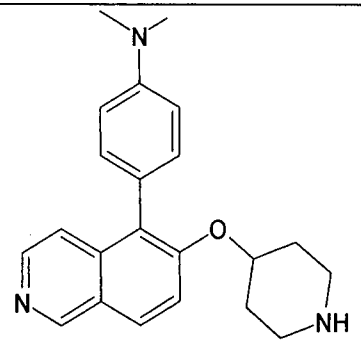
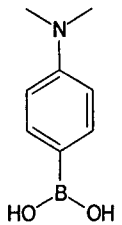
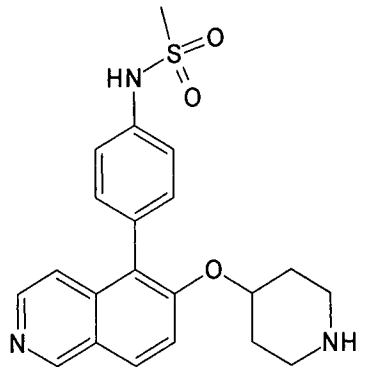
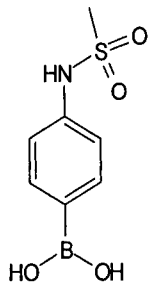
Nº	Compuesto	Reactivo 1	Reactivo 2	Método #	Tiempo de retención	Masa detectada $[M+H]^+$
61	 TFA	11		1	0,87	350,16
62	 HCl	11		1	0,72	383,14

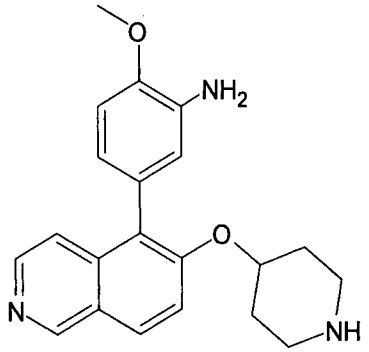
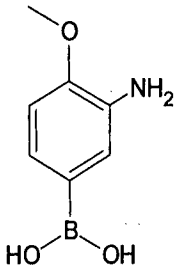
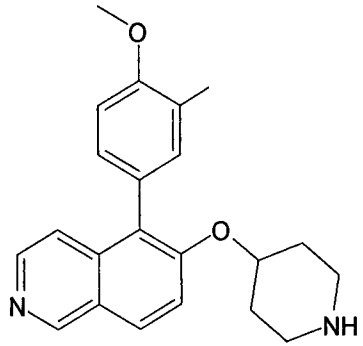
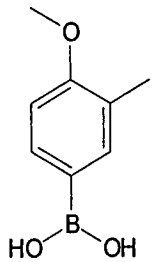
Nº	Compuesto	Reactivo 1	Reactivo 2	Método #	Tiempo de retención	Masa detectada $[M+H]^+$
62 A		11		1	0,79	283,18
63	 TFA	11		2	0,18 0,47	356,21 356,23

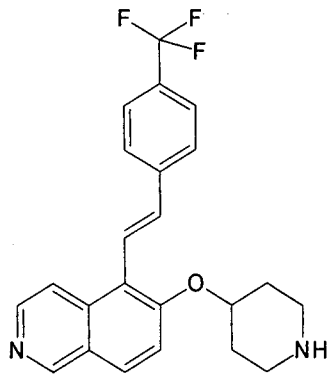
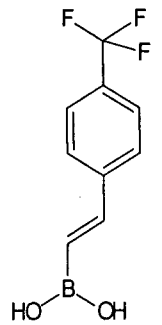
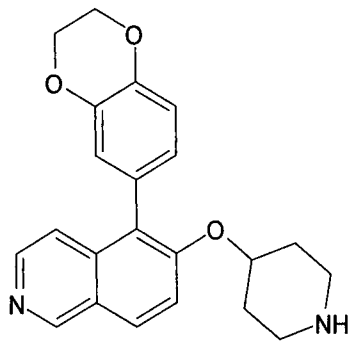
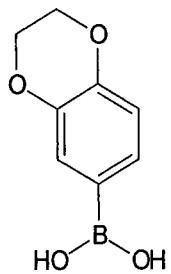
Nº	Compuesto	Reactivo 1	Reactivo 2	Método #	Tiempo de retención	Masa detectada $[M+H]^+$
64	 TFA	11		2	1,31	387,30
65	 HCl	11		2	0,73	383,21

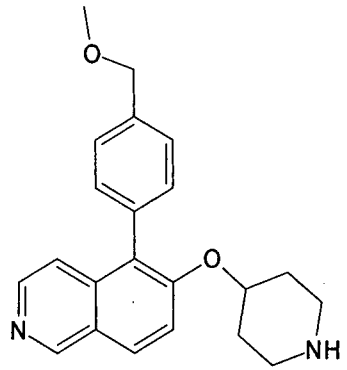
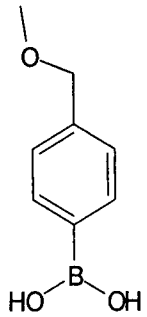
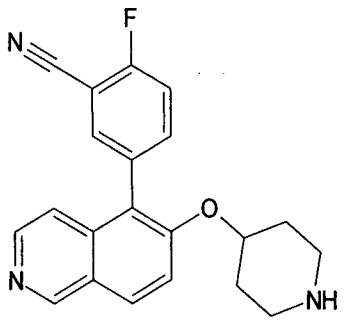
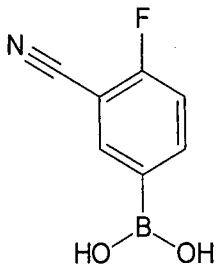
Nº	Compuesto	Reactivo 1	Reactivo 2	Método #	Tiempo de retención	Masa detectada $[M+H]^+$
66	 TFA	11		1	0,90	364,15
67	 TFA	11		1	0,76	335,17

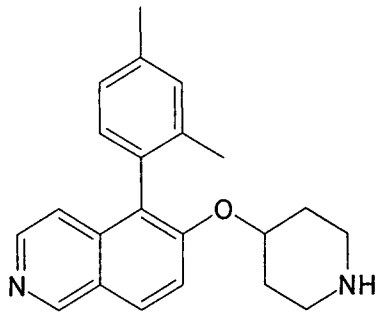
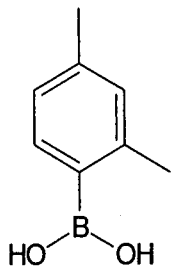
Nº	Compuesto	Reactivo 1	Reactivo 2	Método #	Tiempo de retención	Masa detectada $[M+H]^+$
68	 TFA	11		3	0,42	376,18
69	 HCl	11		2	0,61	348,23

Nº	Compuesto	Reactivo 1	Reactivo 2	Método #	Tiempo de retención	Masa detectada $[M+H]^+$
70	 HCl	11		1	0,61	348,21
71	 HCl	11		4	0,75	398,15

Nº	Compuesto	Reactivo 1	Reactivo 2	Método #	Tiempo de retención	Masa detectada $[M+H]^+$
72	 TFA	11		2	0,64	350,24
73	 TFA	11		2	0,93	349,24

Nº	Compuesto	Reactivo 1	Reactivo 2	Método #	Tiempo de retención	Masa detectada $[M+H]^+$
74	 TFA	11		2	1,22	399,23
75	 TFA	11		2	0,75	363,23

Nº	Compuesto	Reactivo 1	Reactivo 2	Método #	Tiempo de retención	Masa detectada $[M+H]^+$
76	 TFA	11		2	0,87	349,25
77	 TFA	11		2	0,81	348,20

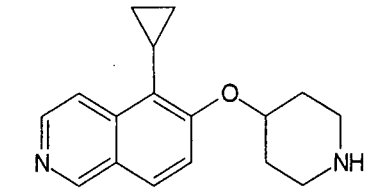
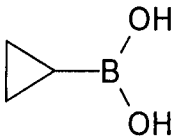
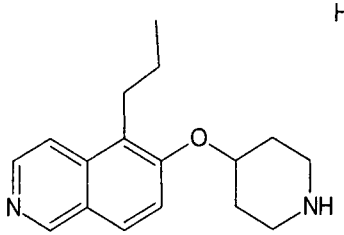
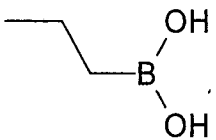
Nº	Compuesto	Reactivo 1	Reactivo 2	Método #	Tiempo de retención	Masa detectada $[M+H]^+$
78	 TFA	11		2	1,00	333,25

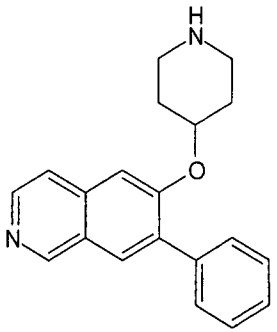
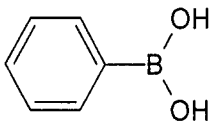
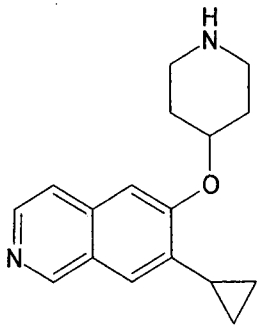
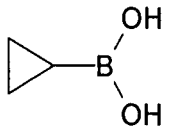
Procedimiento de acoplamiento de Suzuki para la variación en la posición 5 y 7

Se añadió la base a una disolución del reactivo 1 (típicamente 0,2 mmol) y el reactivo 2 en DME. Se burbujeó argón a través de la mezcla de reacción durante 10 min. A continuación se añadió el catalizador y la reacción se agitó a temperatura de reflujo durante toda la noche bajo atmósfera de argón. Después de enfriar se añadieron 2 mL de agua y 10 mL de acetato de etilo. La mezcla se filtró a través de un cartucho de celita. Los disolventes se eliminaron por destilación y el resto se sometió a HPLC preparativa.

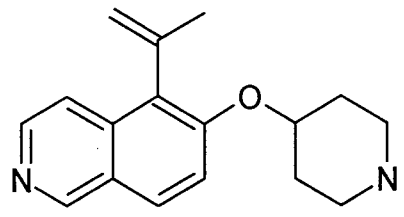
El intermedio aislado se desprotegió por tratamiento con 2 mL de HCl 5-6 N en isopropanol durante 2 h a temperatura ambiente. El disolvente se destiló y el precipitado se aisló por filtración. En algunas reacciones no precipitó el hidrocloruro o la pureza del precipitado fue insatisfactoria. En estos casos el disolvente se destiló y el resto se purificó por HPLC preparativa.

Los ejemplos siguientes se prepararon utilizando este método:

Nº	Compuesto	Reactivo 1	Reactivo 2	Catalizador	Base	Método de LCMS #	Tiempo de retención	Masa detectada $[M+H]^+$
79	 HCl	12		0,05 eq. $PdOAc_2$ 0,1 eq. $P(Cy)_3$	3,5 eq. K_3PO_4	2	0,66	269,17
80	HCl 	12		0,05 eq. $PdOAc_2$ 0,1 eq. $P(Cy)_3$	3,5 eq. K_3PO_4	1	0,81	271,19

Nº	Compuesto	Reactivo 1	Reactivo 2	Catalizador	Base	Método de LCMS #	Tiempo de retención	Masa detectada $[M+H]^+$
81	 TFA	13		0,15 eq. $Pd(PPh_3)_4$	2 eq. K_2CO_3	1	0,87	305,16
82	 TFA	13		0,15 eq. $Pd(PPh_3)_4$	2 eq. K_2CO_3	1	0,85	269,2

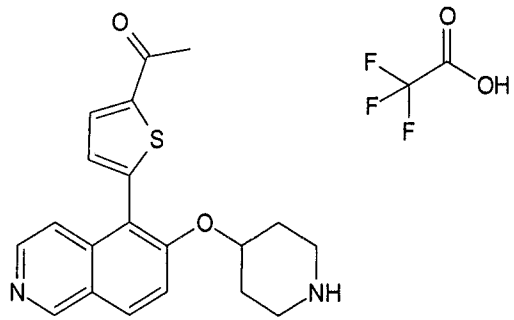
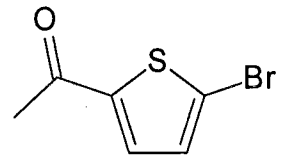
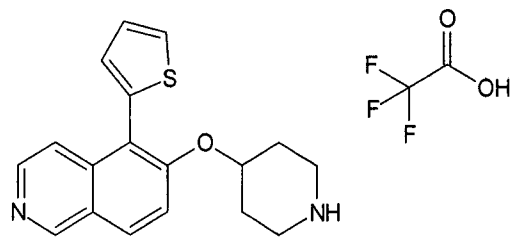
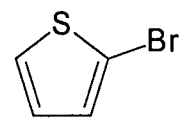
5-Isopropenil-6-(piperidin-4-iloxi)-isoquinolina (83)

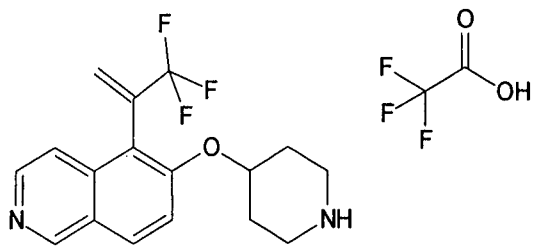
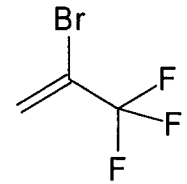


Se añadieron 85 mg (0,62 mmol) de K_2CO_3 y 70 mg (0,15 mmol) de éster terc-butílico del ácido 4-[5-(4,4,5,5-tetrametil-[1,3,2]dioxaborolan-2-il)-isoquinolin-6-iloxi]-piperidin-1-carboxílico (14) a una disolución de 22 mg (0,18 mmol) 2-bromo-propeno en 2 mL de DMF. En atmósfera de argón se añadieron 5,6 mg (0,05 eq) de $Pd(dppf)Cl_2$ y la mezcla se calentó a 100ºC durante 16 h. Después de enfriar a temperatura ambiente se añadieron agua y diclorometano. La mezcla se filtró a través de un cartucho de celita. Los disolventes se eliminaron por destilación y el resto se sometió a HPLC preparativa. El intermedio aislado se desprotegió por tratamiento con 2 mL de HCl 5-6 N en isopropanol durante 2 h a temperatura ambiente. El disolvente se destiló y se aisló el compuesto 83 por HPLC preparativa para dar 3,2 mg como trifluoroacetato.

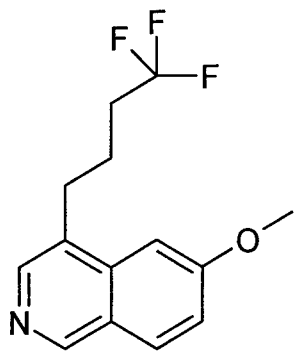
Método de LCMS # 3, tiempo de retención 0,15 min, masa detectada 269,15 $[M+H]^+$

Los ejemplos siguientes se prepararon utilizando este método:

Nº	Compuesto	Reactivo	Método de LCMS #	Tiempo de retención	Masa detectada $[M+H]^+$
84			3	0,14	353,16
85			3	0,41	311,22

Nº	Compuesto	Reactivo	Método de LCMS #	Tiempo de retención	Masa detectada $[M+H]^+$
86			3	0,56	323,15

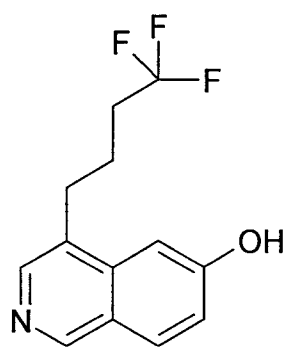
6-Metoxi-4-(4,4,4-trifluoro-butil)-isoquinolina (87)



Se disolvieron 2 g de 6-metoxi-isoquinolina en 25 mL de tetrahidrofurano seco. Se añadieron gota a gota 12,56 mL de una disolución 1 M de trietil borohidrato de potasio. La disolución se dejó agitar a temperatura ambiente durante 2 h, a continuación se añadieron gota a gota 3,29 g de 4,4,4-trifluoro-1-yodobutano. La disolución se dejó agitar durante toda la noche, después se añadieron 32 mL de hidróxido sódico 1M y 12 mL de disolución de peróxido sódico (35%). Se continuó agitando durante otras 3 horas, después la disolución se diluyó con diclorometano, se extrajo con agua y salmuera y la capa orgánica se secó sobre sulfato sódico y se evaporó a sequedad. La cromatografía en gel de sílice rinde 1,03 g del producto deseado.

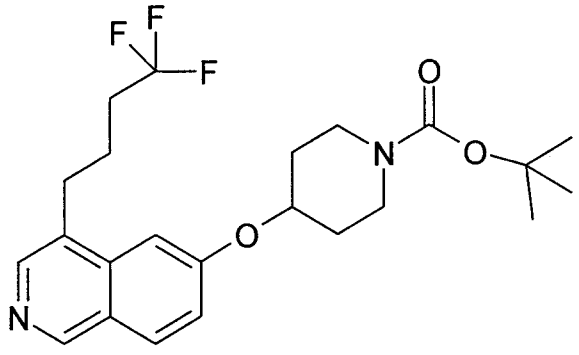
Método de LCMS # 1, tiempo de retención 1,20 min, masa detectada 270,06 $[M+H]^+$

6-Hidroxi-4-(4,4,4-trifluoro-butil)-isoquinolina (88)



Se trataron 1,02 g de 6-metoxi-4-(4,4,4-trifluoro-butil)-isoquinolina (87) con tribromuro de boro como se ha descrito para la síntesis del compuesto 1 para dar 410 mg del producto deseado 88. Método de LCMS # 1, tiempo de retención 1,04 min, masa detectada 256,00 $[M+H]^+$

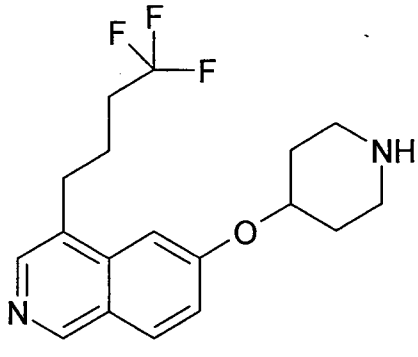
Éster terc-butílico del ácido 4-[4-(4,4,4-trifluoro-butil)-isoquinolin-6-iloxi]-piperidin-1-carboxílico (89)



Se disolvieron 100 mg del compuesto 88, 118 mg de Boc-(4-hidroxi)piperidina y 416 mg de Difenil-[4-[1H,1H,2H,2H-perfluorodecil]fenil]fosfina en 5 mL de tetrahidrofurano seco. Se añadieron 208 mg de Bis(1H,2H,2H,3H,3H-perflourononil)-azodicarboxilato y la reacción se dejó agitar durante toda la noche. La mezcla se evaporó a sequedad y se filtró sobre un cartucho de Fluoro-Flash de 5 g. El producto crudo obtenido se purificó por HPLC preparativa para rendir 46 mg del producto deseado.

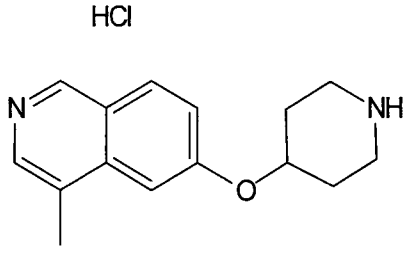
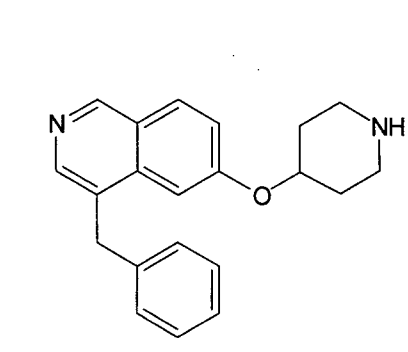
Método de LCMS # 1, tiempo de retención 1,51 min, masa detectada 439,13 $[M+H]^+$

6-(Piperidin-4-iloxi)-4-(4,4,4-trifluoro-butil)-isoquinolina (90)



Se disolvieron 42 mg del compuesto 89 en ácido clorhídrico 5M en isopropanol. La disolución se agitó a temperatura ambiente durante 2 horas y otras 2 horas a 40°C, se evaporó a sequedad y se recogió en agua y se liofilizó tres veces para dar 32 mg del producto deseado como la sal de hidrocloruro. Método de LCMS # 1, tiempo de retención 0,98 min, masa detectada 338,16 $[M+H]^+$

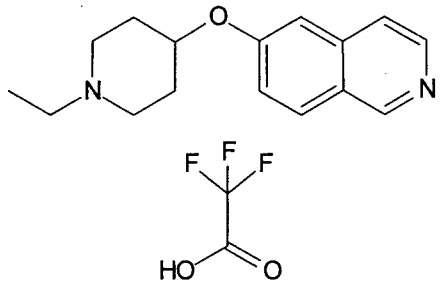
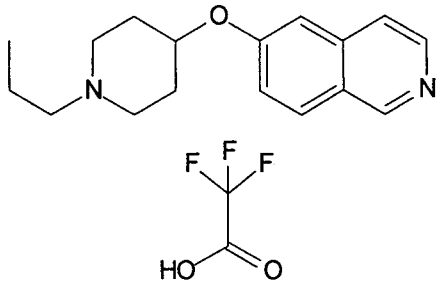
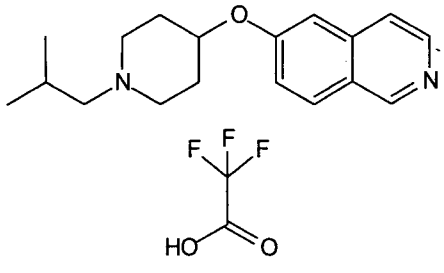
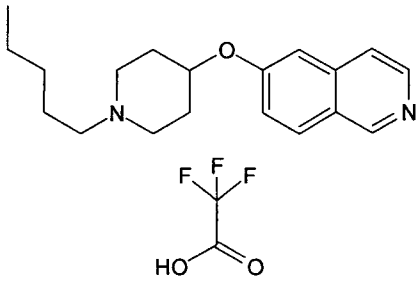
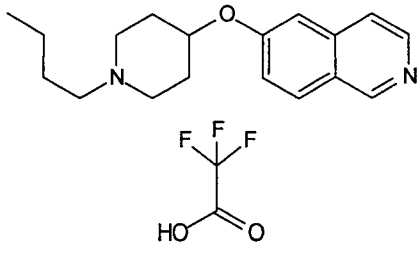
Las isoquinolinas siguientes se sintetizaron de una manera similar según se ha descrito para el compuesto 90, utilizando los haluros de alquilo apropiados:

Nº	Compuesto	Cambio de	Método	RT [min]	Masa Detectada [MH^+]
91		242,14	1	0,56	243,13
92		318,17	1	0,84	319,17

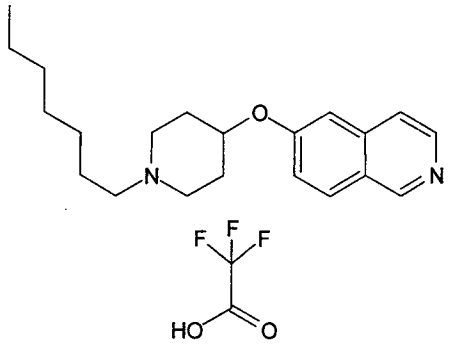
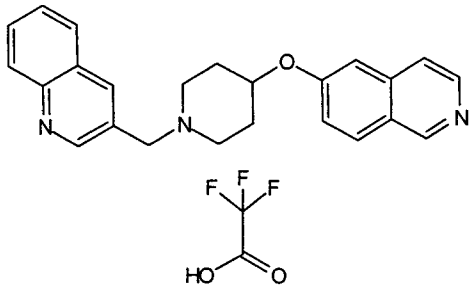
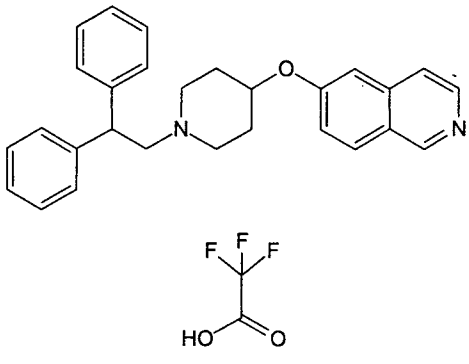
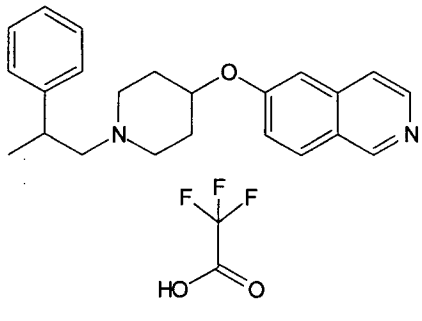
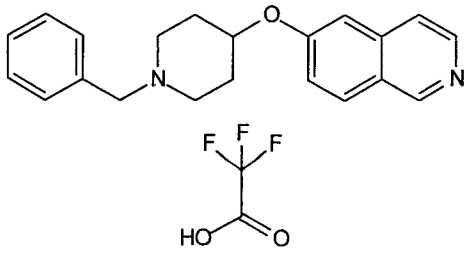
Procedimiento general para la aminación reductora:

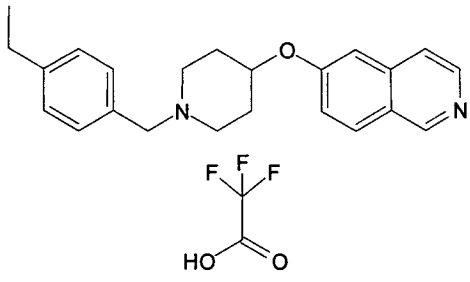
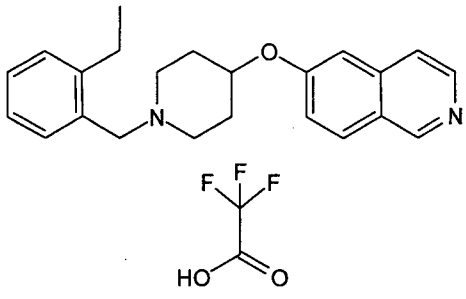
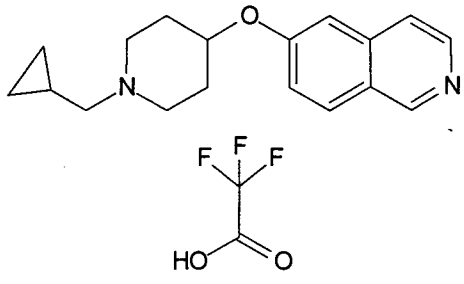
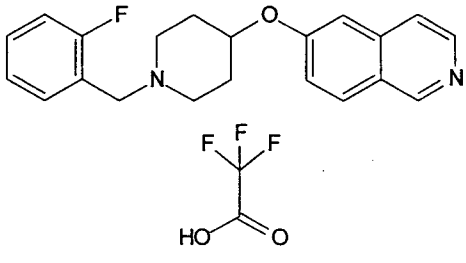
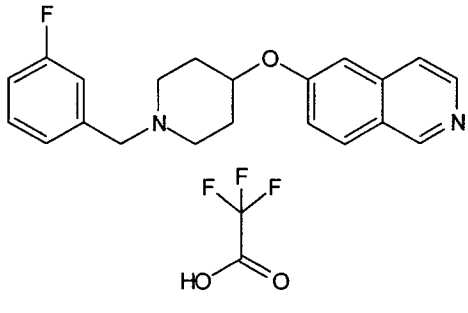
Se disolvieron 1,5 eq de aldehído en 1 mL de metanol y se añadieron, disueltos en metanol, 50 mg del compuesto 124 y 27 mg de acetato sódico anhidro. Se añadieron 0,250 mL de una disolución 1M de cianoborohidruro sódico en THF. La reacción se dejó en marcha durante toda la noche, a continuación la disolución se filtró, se evaporó a sequedad y el residuo se recogió en acetato de etilo. La capa orgánica se extrajo con una disolución de carbonato sódico al 5% en agua, y después con cloruro sódico al 5% en agua. La capa orgánica se secó, se evaporó a sequedad y se purificó por cromatografía en RP.

Este procedimiento se utilizó para obtener los compuestos 93 a 123:

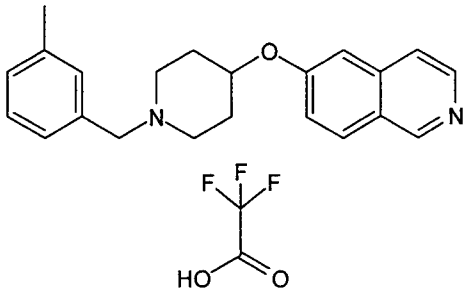
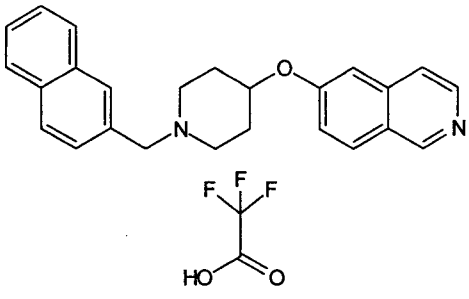
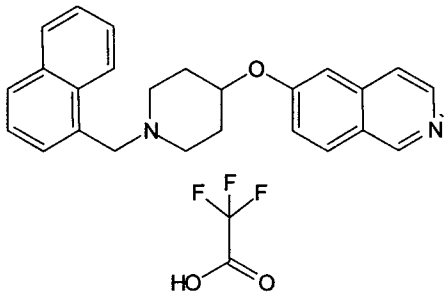
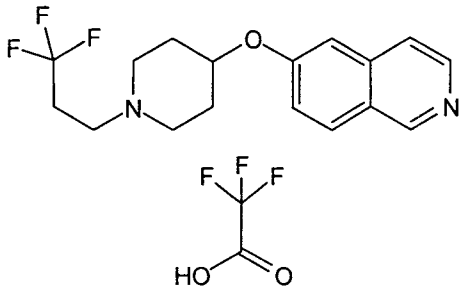
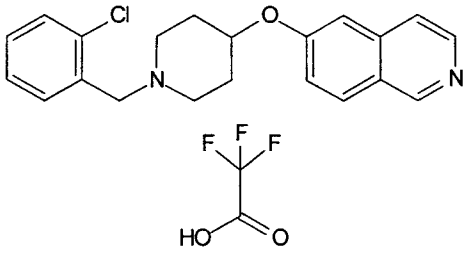
Nº	Compuesto	RT	Masa $[MH]^+$
93		0,13	257,23
94		0,53	271,26
95		0,79	285,27
96		0,92	299,29
97		0,74	285,27

175

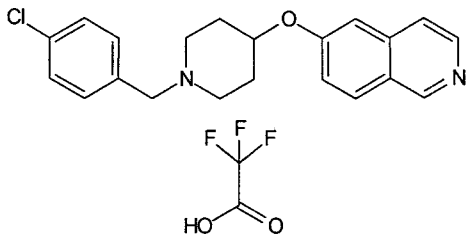
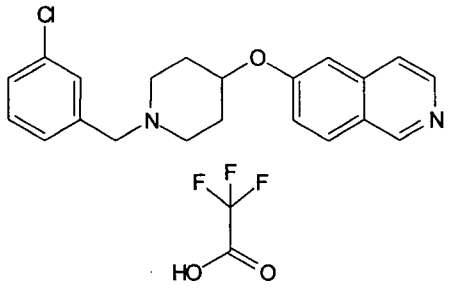
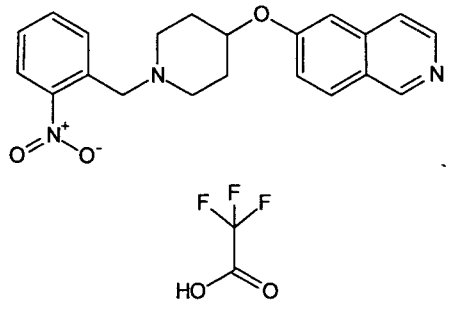
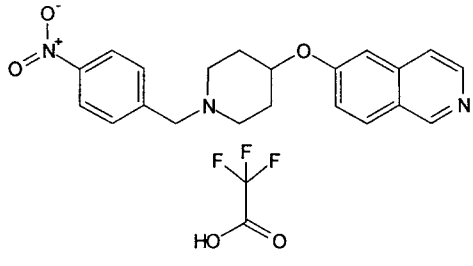
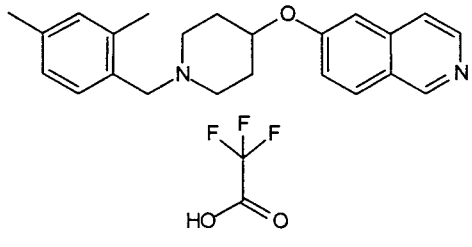
Nº	Compuesto	RT	Masa $[MH]^+$
98		1,22	327,30
99		0,89	370,29
100		1,25	409,34
101		1,06	347,29
102		0,89	319,26

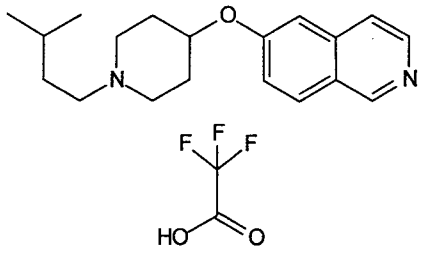
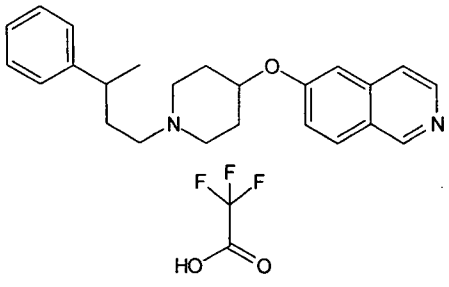
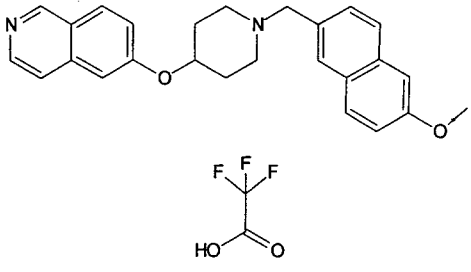
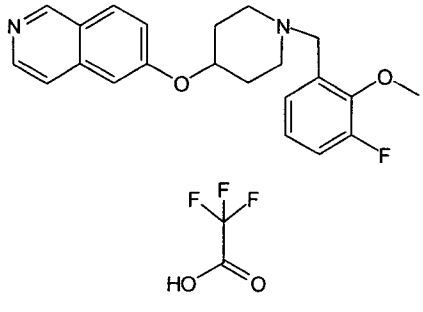
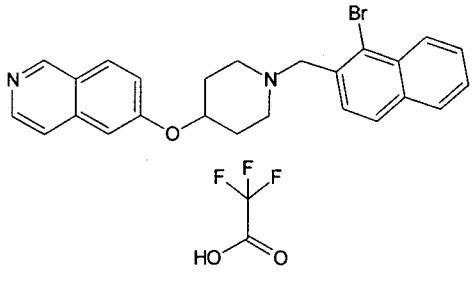
Nº	Compuesto	RT	Masa $[MH]^+$
103		0,99	347,32
104		0,96	347,29
105		0,60	283,15
106		0,74	337,26
107		0,95	337,24

177

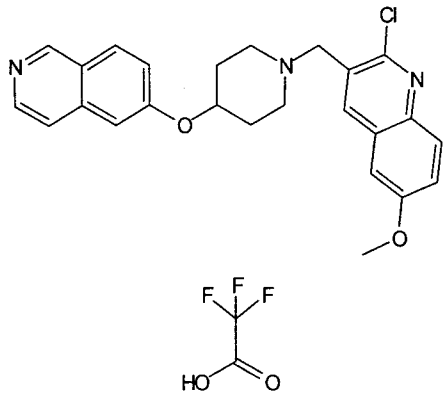
Nº	Compuesto	RT	Masa $[MH]^+$
108		1,01	333,28
109		1,04	369,29
110		1,14	369,30
111		0,58/0,74	325,23
112		1,00	353,22/355,23

178

Nº	Compuesto	RT	Masa $[MH]^+$
113		0,91	353,23/355,23
114		0,88	353,24/355,24
115		0,87	364,20
116		0,92	364,26
117		1,10	347,31

Nº	Compuesto	RT	Masa $[MH]^+$
118		0,77	299,28
119		1,13	361,31
120		1,07	399,30
121		0,86	367,27
122		1,15	447,22/449,68

180

Nº	Compuesto	RT	Masa $[MH]^+$
123		1,13	434,16

Todas las LCMS en esta tabla se obtuvieron utilizando el método de LCMS #2.

Procedimiento general para la reacción de aminoalcoholes protegidos con boc con 6-hidroxi isoquinolinas (reacción de Mitsunobu):

AAV1:

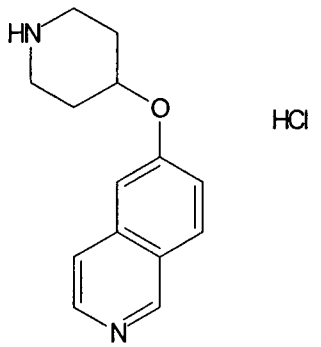
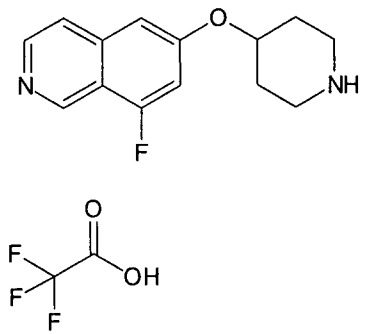
A 500 mg (1,5 mmol) de trifenilfosfina (enlazada a poliestireno, 3mmol/g) y 10 ml de diclorometano se añadieron 0,195 mL (1,2 mmol) de azodicarboxilato de dietilo (o alternativamente azodicarboxilato de diisopropilo). La mezcla de reacción se dejó agitar durante 10 min. y a continuación se añadieron 0,14 mL de trietilamina, 145 mg de 6-hidroxiisoquinolina (7) (o una cantidad equivalente de un isoquinol adecuado diferente) (reactivo 1) y 1 mmol del aminoalcohol protegido con boc deseado (reactivo 2). La reacción se agitó a temperatura ambiente hasta que no se pudo observar por LCMS ninguna conversión adicional. Para la elaboración, la disolución se filtró, el residuo se lavó con diclorometano y la capa orgánica se lavó dos veces con hidróxido sódico 1N, dos veces con agua y una vez con salmuera, se secó sobre sulfato magnésico y se evaporó. El producto crudo se purificó por HPLC preparativa para rendir del producto acoplado protegido con boc.

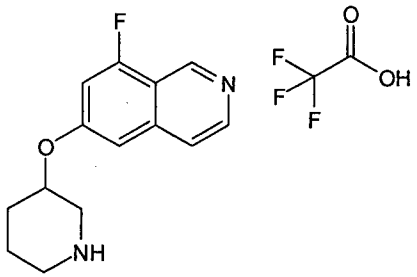
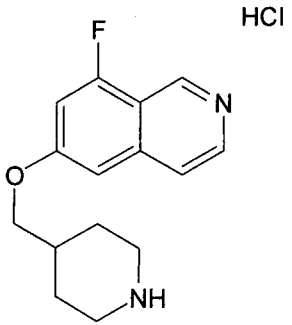
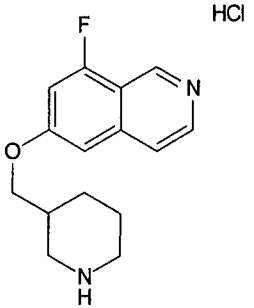
Procedimiento general para eliminar el grupo boc (AAV2):

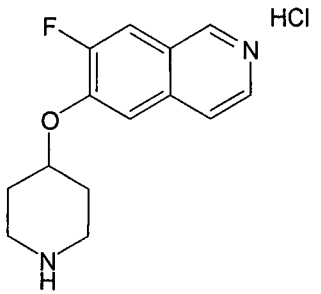
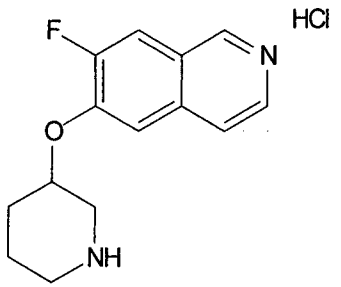
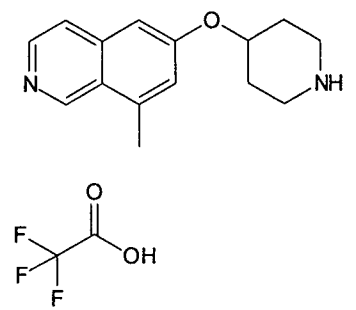
El producto de partida se disolvió en ácido clorhídrico 2M y se hizo reaccionar durante toda la noche. A los compuestos con solubilidad acuosa deficiente, se les añadió metanol o dioxano hasta que se obtuvo una disolución homogénea. Alternativamente, se utilizó ácido clorhídrico 4M en isopropanol para hacer reaccionar el compuesto. La mezcla de reacción

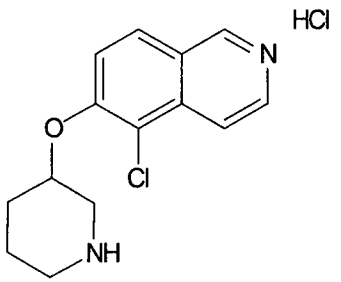
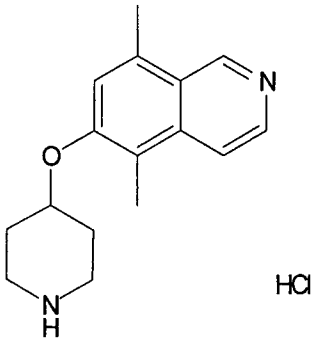
se liofilizó y se obtuvo el producto desprotegido como el correspondiente hidrocloruro de la amina libre.

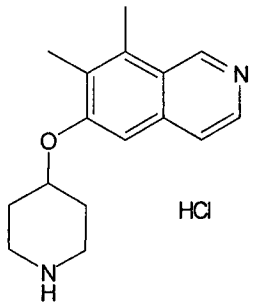
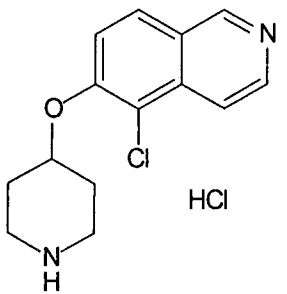
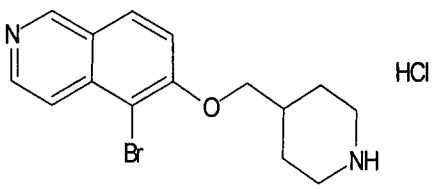
5

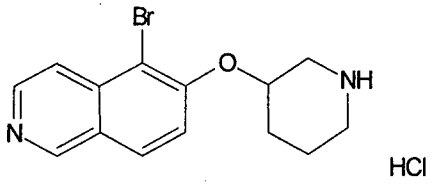
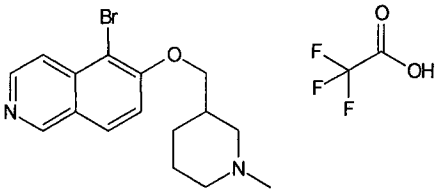
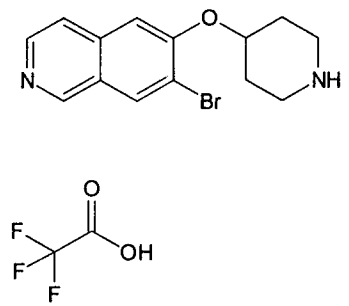
Nº	Compuesto	Reactivo 1	Reactivo 2	Método de LCMS #	Tiempo de retención	Masa detectada [M+H]+
124		7	Éster terc-butílico del ácido 4-hidroxipiperidin-1-carboxílico	1	0,47	229,21
125		2	Éster terc-butílico del ácido 4-hidroxipiperidin-1-carboxílico	4	0,37	247,4

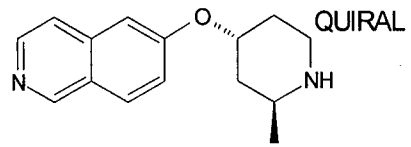
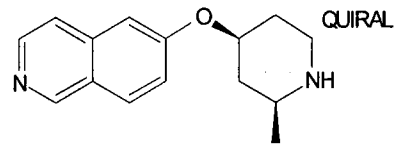
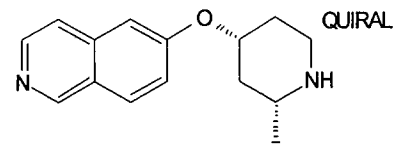
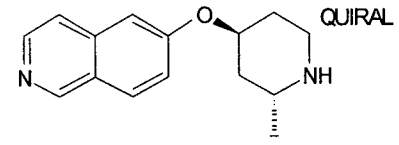
Nº	Compuesto	Reactivo 1	Reactivo 2	Método de LCMS #	Tiempo de retención	Masa detectada [M+H]+
126		2	Éster terc-butílico del ácido 3-hidroxipiperidin-1-carboxílico	4	0,34	247,35
127		2	Éster terc-butílico del ácido 4-piperidilmetanol-1-carboxílico	4	0,53	261,20
128		2	Éster terc-butílico del ácido 3-piperidilmetanol-1-carboxílico	4	0,57	261,20

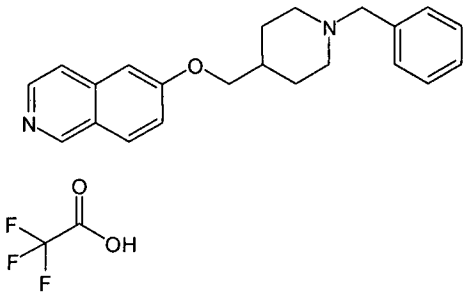
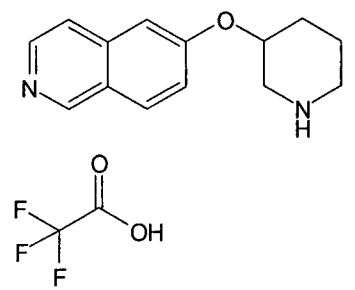
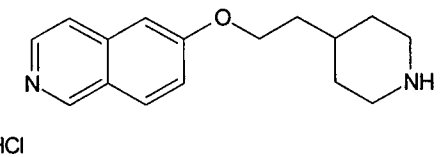
Nº	Compuesto	Reactivo 1	Reactivo 2	Método de LCMS #	Tiempo de retención	Masa detectada [M+H]+
129		3	Éster terc-butílico del ácido 4-hidroxipiperidin-1-carboxílico	4	0,35	247,10
130		3	Éster terc-butílico del ácido 3-hidroxipiperidin-1-carboxílico	4	0,35	247,10
131		4	Éster terc-butílico del ácido 4-hidroxipiperidin-1-carboxílico	3	0,14	243,12

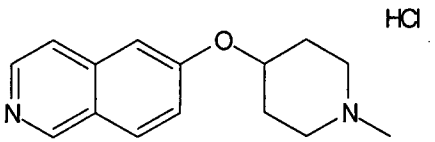
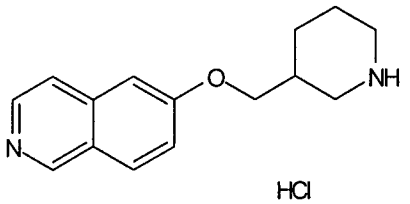
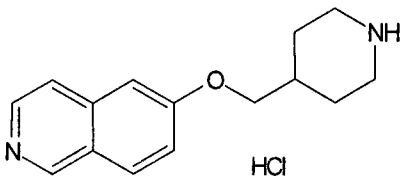
Nº	Compuesto	Reactivo 1	Reactivo 2	Método de LCMS #	Tiempo de retención	Masa detectada [M+H]+
132		8	Éster terc-butílico del ácido 3-hidroxipiperidin-1-carboxílico	4	0,60	263,15
133		6	Éster terc-butílico del ácido 4-hidroxipiperidin-1-carboxílico	4	0,67	257,15

Nº	Compuesto	Reactivo 1	Reactivo 2	Método de LCMS #	Tiempo de retención	Masa detectada [M+H]+
134		5	Éster terc-butílico del ácido 4-hidroxipiperidin-1-carboxílico	1	0,68	257,20
135		8	Éster terc-butílico del ácido 4-hidroxipiperidin-1-carboxílico	1	0,52	263,10
136		9	Éster terc-butílico del ácido 4-hidroximetil-piperidin-1-carboxílico	2	0,33	321,14/323,15

Nº	Compuesto	Reactivo 1	Reactivo 2	Método de LCMS #	Tiempo de retención	Masa detectada [M+H]+
137		9	Éster terc-butílico del ácido 3-hidroxi-piperidin-1-carboxílico	2	0,31	307,12/309,12
138		9	N-Metil-3-piperidilmetanol	1	0,75	335,12
139		1	Éster terc-butílico del ácido 4-hidroxipiperidin-1-carboxílico	2	0,62	307,06

Nº	Compuesto	Reactivo 1	Reactivo 2	Método de LCMS #	Tiempo de retención	Masa detectada [M+H]+
140	 HCl	7	26	1	0,60	243,22
141	 HCl	7	25	1	0,60	243,19
142	 HCl	7	25	1	0,60	243,29
143	 HCl	7	26	3	0,12	243,13

Nº	Compuesto	Reactivo 1	Reactivo 2	Método de LCMS #	Tiempo de retención	Masa detectada [M+H]+
144		7	(1-Bencil-piperidin-4-il)-metanol	2	0,17	333,2
145		7	Éster terc-butílico del ácido 3-hidroxi-piperidin-1-carboxílico	2	0,2	229,2
146		7	Éster terc-butílico del ácido 4-(2-hidroxi-etil)-piperidin-1-carboxílico	2	0,18	257,2

Nº	Compuesto	Reactivo 1	Reactivo 2	Método de LCMS #	Tiempo de retención	Masa detectada [M+H]+
147		7	1-Metil-piperidin-4-ol	1	0,45	243,2
148		7	Éster terc-butílico del ácido 3-hidroximetil-piperidin-1-carboxílico	2	0,17	243,2
149		7	Éster terc-butílico del ácido 4-hidroximetil-piperidin-1-carboxílico	2	0,17	243,2

Resolución cromatográfica de los compuestos 140 y 143:

El intermedio protegido en el N con Boc, obtenido como una mezcla enantiomérica de compuesto 140 y compuesto 143, se separó en los enantiómeros en una columna quiral (Chiralcel OD-H/56 250 x 4,6 mm). La eliminación del grupo protector como la etapa final se llevó a cabo como se ha descrito en el procedimiento general.

No se ha determinado la configuración absoluta de los estereocentros.

Compuesto 140: intermedio protegido con Boc que eluye más pronto;

Compuesto 143: intermedio protegido con Boc que eluye más tarde

Resolución cromatográfica de los compuestos 141 y 142:

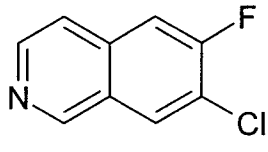
El intermedio protegido en el N con Boc, obtenido como una mezcla enantiomérica de compuesto 141 y compuesto 142, se separó en los enantiómeros en una columna quiral (Chiralpak AD-H/40 250 x 4,6 mm). La eliminación del grupo protector como la etapa final se llevó a cabo como se ha descrito en el procedimiento general.

No se ha determinado la configuración absoluta de los estereocentros.

Compuesto 141: intermedio protegido con Boc que eluye más pronto;

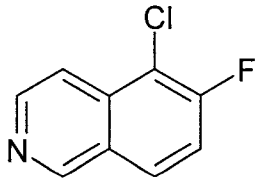
Compuesto 142: intermedio protegido con Boc que eluye más tarde.

7-Cloro-6-fluoro-isoquinolina (150)



La 7-cloro-6-fluoro-isoquinolina se obtiene por la misma secuencia de reacción, utilizada para la síntesis de la 6-Fluoro-isoquinolina (23), partiendo de 3-Cloro-4-fluoro-benzaldehído. R_t = 0,77 min (Método #2). Masa detectada: 182,1/184,1 ($M+H^+$).

Trifluoroacetato de 5-cloro-6-fluoro-isoquinolina (151)

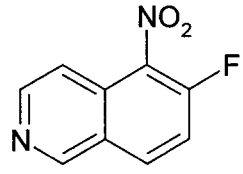


TFA

Se disuelven 7,0 g (38,1 mmol) de 6-fluoroisoquinolina (23) en 60 mL de ácido sulfúrico concentrado. A 0°C se añaden 10,18 g de N-clorosuccinimida. Después de 1 h se aña-

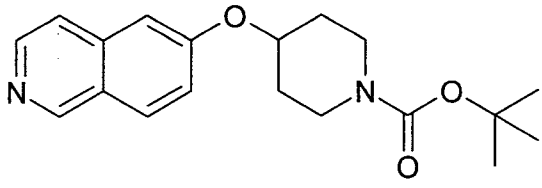
den otros 5,2 g de N-clorosucciminida y la disolución se calienta a 50°C. Se añaden dos porciones más de 5,2 g de N-clorosuccinimida sucesivamente y se continúa agitando a 50°C hasta que la reacción se completa. La mezcla de reacción se enfría a temperatura ambiente, se vierte sobre hielo y se ajusta a pH 10 por adición de hidróxido sódico. El precipitado se filtra, se recoge en diclorometano y se lava con hidróxido sódico acuoso. La capa orgánica se seca sobre sulfato magnésico, se evapora y el producto bruto se purifica por HPLC preparativa para rendir 4,04 g de 5-cloro-6-fluoro-isoquinolina (151) como trifluoroacetato. R_t = 0,97 min (Método #2). Masa detectada: 182,0/184,0 ($M+H^+$).

6-Fluoro-5-nitro-isoquinolina (152)



Bajo enfriamiento se añaden 2,0 mL de ácido nítrico concentrado a 2,8 mL de ácido sulfúrico. Posteriormente se añaden 350 mg de 6-fluoroisoquinolina (23), la reacción se calienta a temperatura ambiente y se deja agitar durante toda la noche. La mezcla de reacción se vierte sobre hielo, se extrae con diclorometano y se ajusta a pH alcalino por adición de hidróxido sódico. La capa acuosa se extrae de nuevo con diclorometano. La capa de diclorometano se seca sobre sulfato magnésico y se evapora para dar 90 mg de 6-Fluoro-5-nitro-isoquinolina, que se puede utilizar sin purificación adicional. R_t = 1,03 min (Método #1). Masa detectada: 193,0 ($M+H^+$).

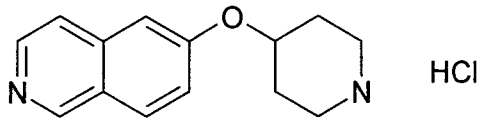
Éster terc-butílico del ácido 4-(isoquinolin-6-iloxi)-piperidin-1-carboxílico (154)



Se disuelven 7,49 g de éster terc-butílico del ácido 4-hidroxi-piperidin-1-carboxílico en 20 mL de dimetilacetamida seca. Se añaden 1,49 g de hidruro sódico (60%). A continuación se añade gota a gota una disolución de 3,65 g de 6-fluoroisoquinolina (23). La disolución se calienta a 80°C durante 2 horas, después se elimina el disolvente y el residuo se recoge en diclorometano. La capa orgánica se extrae dos veces con agua y luego con salmuera, se seca sobre sulfato magnésico y se evapora a sequedad. El producto bruto se purifica por cromatografía en gel de sílice para rendir 6,22g de éster terc-butílico del ácido 4-

(isoquinolin-6-iloxi)-piperidin-1-carboxílico. R_t = 1,32 min (Método #1). Masa detectada: 329,1 ($M+H^+$).

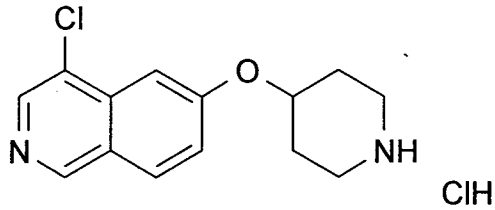
Hidrocloruro de 6-(piperidin-4-iloxi)-isoquinolina (124)



El éster terc-butílico del ácido 4-(isoquinolin-6-iloxi)-piperidin-1-carboxílico (154) se desprotege por el procedimiento general descrito en AAV2 para rendir el compuesto del título como sal de HCL. R_t = 0,20 min (Método #2). Masa detectada: 229,1 ($M+H^+$).

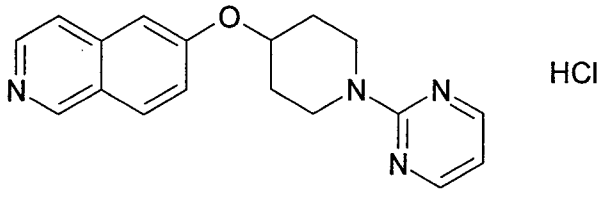
El ejemplo siguiente se sintetizó según este método:

Hidrocloruro de 4-cloro-6-(piperidin-4-iloxi)-isoquinolina (156)



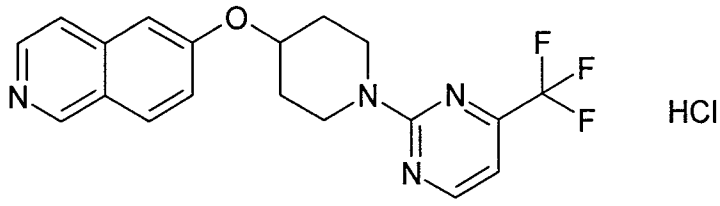
Utilizando como producto de partida la 4-cloro-6-fluoro-isoquinolina (24)
Método de LCMS # 2, tiempo de retención 0,56 min, masa detectada 263,12 $[M+H]^+$

Hidrocloruro de 6-(1-pirimidin-2-il-piperidin-4-iloxi)-isoquinolina (157)



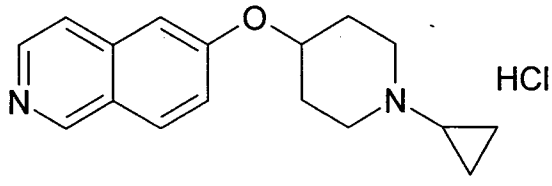
Se disuelven 150 mg de hidrocloruro de 6-(piperidin-4-iloxi)-isoquinolina (124) en 10 mL de piridina seca. Se añaden 177 mg de trietilamina y 69 mg de 4-cloropirimidina y la disolución se agita a 65ºC durante 6 horas. La mezcla de reacción se vierte sobre salmuera y se extrae tres veces con acetato de etilo. Las capas orgánicas combinadas se secan sobre sulfato magnésico, se evaporan a sequedad y el producto bruto se purifica por HPLC preparativa. El producto se convierte en la correspondiente sal de HCl recogiendo el producto en mL de ácido clorhídrico 1 N seguido por liofilización. Rendimiento: 47 mg. R_t = 1,05 min (Método #2). Masa detectada: 307,1 ($M+H^+$).

Hidrocloruro de 6-[1-(4-trifluorometil-pirimidin-2-il)-piperidin-4-iloxi]-isoquinolina (158)



Se disuelven 75 mg de hidrocloruro de 6-(piperidin-4-iloxi)-isoquinolina (124) en 5 mL de piridina seca y 5 mL de DMF. Se añaden 55 mg de 2-cloro-4-trifluorometil-pirimidina y la disolución se agita a 60°C durante 3 horas. Los disolventes se eliminan a vacío y el residuo se recoge en salmuera y se extrae tres veces con acetato de etilo. Las capas orgánicas combinadas se secan sobre sulfato magnésico, se evaporan a sequedad y el producto bruto se purifica por HPLC preparativa. El producto se convierte en la correspondiente sal de HCl recogiendo el producto en mL de ácido clorhídrico 1 N seguido por liofilización. Rendimiento: 29 mg. R_t = 1,69 min (Método #2). Masa detectada: 375,1 ($M+H^+$).

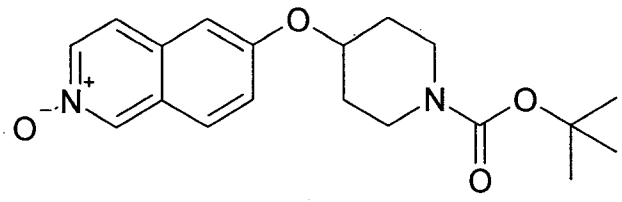
Hidrocloruro de 6-(1-ciclopropil-piperidin-4-iloxi)-isoquinolina (159)



Se disuelven 300 mg (1,13 mmol) de hidrocloruro de 6-(piperidin-4-iloxi)-isoquinolina (124) en 10 mL de metanol. Se añaden sucesivamente 202 mg de trietilamina, tamices moleculares 4A, 600 mg de ácido acético glacial, 871 mg de (1-etoxi-ciclopropiloxi)-trimetil-silano y 101 mg de cianoborohidrato de sodio y la mezcla de reacción se calienta a reflujo durante 6 horas. La mezcla de reacción se enfría a temperatura ambiente, se añaden 6 mL de hidróxido sódico 2N y la mezcla de reacción se filtra. El filtrado se evapora, el residuo se recoge en diclorometano, se extrae con hidróxido sódico 2 N y salmuera, se seca sobre sulfato sódico, se evapora a sequedad y el producto bruto se purifica por HPLC preparativa. Las fracciones del producto se evaporan, el producto se recoge en ácido clorhídrico 2 N y se liofiliza.

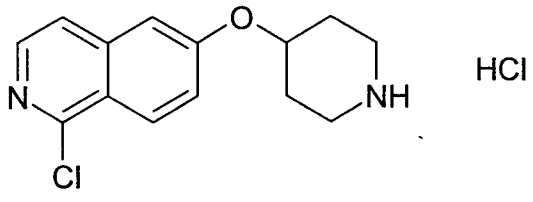
Rendimiento: 60 mg. R_t = 0,50 min (Método #1). Masa detectada: 269,2 ($M+H^+$).

Éster terc-butílico del ácido 4-(2-oxi-isoquinolin-6-iloxi)-piperidin-1-carboxílico (160)



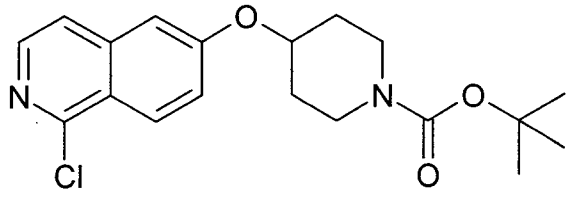
Se disuelven 3,97 g (12,1 mmol) de éster terc-butílico del ácido 4-(isoquinolin-6-iloxi)-piperidin-1-carboxílico (154) en 100 ml de diclorometano y se añaden 4,47 g (18,1 mmol) de ácido 3-cloro-perbenzoico (70 %) a temperatura ambiente. La mezcla de reacción se agita durante 1 h y a continuación se lava con disolución saturada de bicarbonato sódico. La fase acuosa se separa y extrae con diclorometano. Las capas orgánicas combinadas se secan sobre sulfato magnésico y se evaporan, para rendir 4,19 g de producto bruto, que se puede utilizar para conversión adicional sin purificación. R_t = 1,46 min (Método #1). Masa detectada: 345,2 ($M+H^+$).

Hidrocloruro de 1-cloro-6-(piperidin-4-iloxi)-isoquinolina (161)



Se disuelven 3,5 g (10,16 mmol) de éster terc-butílico del ácido 4-(2-oxi-isoquinolin-6-iloxi)-piperidin-1-carboxílico (160) en 250 ml de etanol saturado con HCl a 50°C. La disolución transparente se concentró a vacío y el residuo se refluyó en 50 ml $POCl_3$. Después de 3 h el $POCl_3$ se eliminó a vacío y el residuo se recogió en H_2O. El pH se ajustó a 11, añadiendo hidróxido sódico y la disolución acuosa se extrajo dos veces con diclorometano. Las capas orgánicas combinadas se secaron sobre sulfato magnésico y se evaporaron a sequedad. El residuo se purificó por HPLC preparativa, mediante la cual se obtuvo el compuesto del título como trifluoroacetato. Éste se convirtió en la correspondiente sal de HCl disolviendo el producto en HCl 2 N seguido de liofilización. Rendimiento: 950 mg. R_t = 1,03 min (Método #1). Masa detectada: 263,1/265,1 ($M+H^+$).

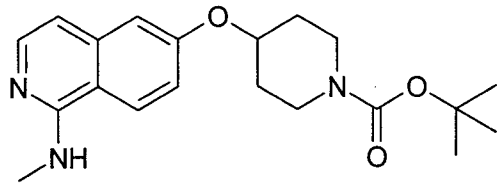
Éster terc-butílico 4-(1-cloro-isoquinolin-6-iloxi)-piperidin-1-carboxílico (162)



Se disuelven 1,23 g (4,11 mmol) de hidrocloruro de 1-cloro-6-(piperidin-4-iloxi)-isoquinolina (161) en 50 ml de diclorometano y se añaden 0,85 ml (6,15 mmol) de trietilami-

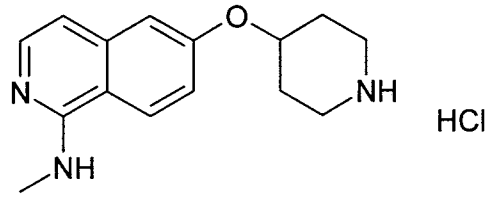
na. A 0 °C se añade gota a gota una disolución de 1,09 g (5,0 mmol) de carbonato de terc-butilo en 10 ml de diclorometano y la mezcla se deja estar a temperatura ambiente durante toda la noche. Para la elaboración, la mezcla se lavó dos veces con H_2O, se secó sobre sulfato magnésico y se evaporó, para rendir 1,1 g del producto deseado, que se pudo utilizar sin purificación adicional. R_t = 1,86 min (Método #4). Masa detectada: 363,1/365,2 ($M+H^+$).

Éster terc-butílico del ácido 4-(1-metilamino-isoquinolin-6-iloxi)-piperidin-1-carboxílico (163)



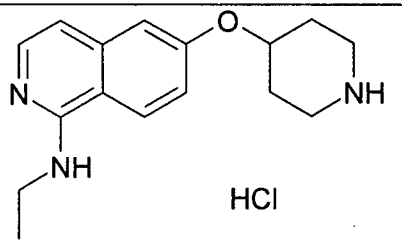
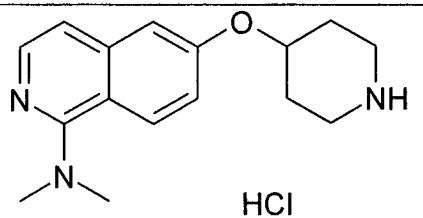
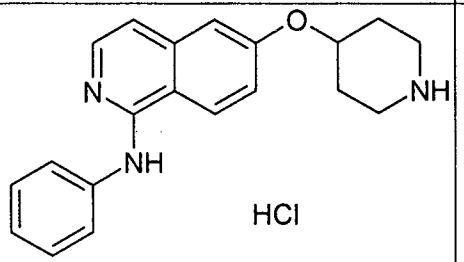
Se calentaron 154 mg (0,42 mmol) de éster terc-butílico del ácido 4-(1-cloro-isoquinolin-6-iloxi)-piperidin-1-carboxílico (162) en 15 ml de una disolución acuosa de metilamina (40%) a 110°C en un tubo sellado. Después de 7 h la mezcla de reacción se evaporó y el residuo se recogió en disolución saturada de bicarbonato sódico y se extrajo con acetato de etilo. La capa orgánica se separó, se secó sobre sulfato magnésico y el disolvente se eliminó a vacío. El residuo se purificó por cromatografía en gel de sílice (acetato de etilo/metanol 5:1). Rendimiento: 45 mg. R_t = 1,14 min (Método #4). Masa detectada: 358,3 ($M+H^+$).

Hidrocloruro de metil-[6-(piperidin-4-iloxi)-isoquinolin-1-il]-amina (164)

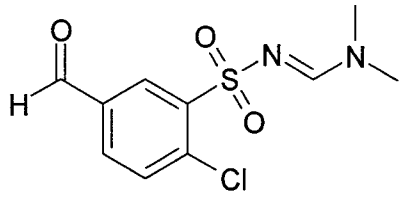


El éster terc-butílico del ácido 4-(1-metilamino-isoquinolin-6-iloxi)-piperidin-1-carboxílico (163) se convirtió en el compuesto del título desprotegido por el procedimiento general, descrito en AAV2, por el que se pudieron obtener 34 mg de la correspondiente sal de HCl. R_t = 0,69 min (Método #1). Masa detectada: 258,3 ($M+H^+$).

Siguiendo la ruta sintética, descrita para el compuesto 164, se prepararon los compuestos siguientes partiendo del éster terc-butílico del ácido 4-(1-cloro-isoquinolin-6-iloxi)-piperidin-1-carboxílico (162) y de las correspondientes aminas:

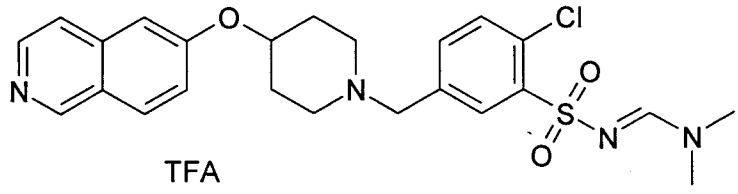
Nº	Compuesto	Amina	T [°C]	Masa [MH^+]	Tiempo de retención [min]	Método
165	 HCl	Etilamina; 70 % en H_2O	110ºC.	272,28	0,72	1
166	 HCl	Dimetilamina; 2 M en THF	110ºC.	272,29	0,68	1
167	 HCl	Anilina; 1:1 en dioxano (v/v)	120ºC.	320,20	0,88	1

2-Cloro-N-dimetilaminometilen-5-formil-bencenosulfonamida (168)



Se disuelven 5,0 g (22,8 mmol) de 2-cloro-5-formil-bencenosulfonamida en 50 ml de diclorometano. Se añaden 4,08 g (34,3 mmol) de dimetilformamida dimetilacetal y la mezcla se refluyó durante 2 h. Después de enfriar a temperatura ambiente, la disolución se lavó dos veces con H_2O, se secó sobre sulfato magnésico y se evaporó. Se obtuvieron 5,16 g del producto bruto y se utilizaron en la siguiente etapa sin purificación adicional. R_t = 1,14 min (Método #1). Masa detectada: 275,1/277,1 ($M+H^+$).

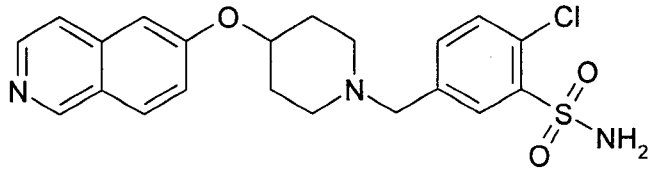
Trifluoroacetato de 2-cloro-N-dimetilaminometilen-5-[4-(isoquinolin-6-iloxi)-piperidin-1-ilmetil]-bencenosulfonamida (169)



TFA

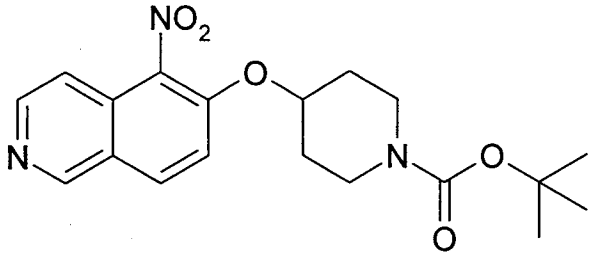
Se disuelven 200 mg (0,88 mmol) de hidrocloruro de 6-(piperidin-4-iloxi)-isoquinolina (124) en 20 ml de metanol y se añaden 158 mg (1,56 mmol) de trietilamina. Después de agitar durante 15 minutos a temperatura ambiente se añadieron 467 mg (7,78 mmol) de ácido acético glacial, 482 mg (1,76 mmol) de 2-cloro-N-dimetilaminometilen-5-formil-bencenosulfonamida (168), 166 mg (2,64 mmol) de cianoborohidruro sódico y tamices moleculares recientemente secados y la mezcla se refluyó durante 3 h. Después de agitar toda la noche a temperatura ambiente, la mezcla se filtró y el filtrado se evaporó. El residuo se disolvió en diclorometano y se lavó dos veces con disolución saturada de bicarbonato sódico y salmuera. Después de secado sobre sulfato magnésico y evaporación del disolvente, el producto bruto se purificó por HPLC preparativa, por la cual se pudieron aislar 133 mg del producto deseado como trifluoroacetato. R_t = 0,87 min (Método #2), Masa detectada: 487,2/489,2 ($M+H^+$).

2-Cloro-5-[4-(isoquinolin-6-iloxi)-piperidin-1-ilmetil]-bencenosulfonamida (170)



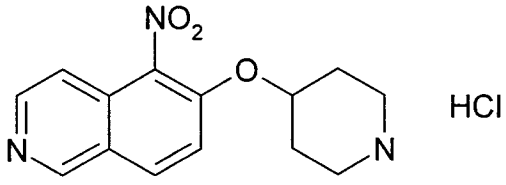
Se disuelven 133 mg (0,27 mmol) de 2-cloro-N-dimetilaminometilen-5-[4-(isoquinolin-6-iloxi)-piperidin-1-ilmetil]-bencenosulfonamida (169) en etanol. Después de añadir 50 ml de NaOH 2N, la disolución se calentó a 60°C durante 6 h. Después de enfriar a temperatura ambiente, la mezcla se neutralizó por adición de HCl acuoso y el disolvente se eliminó a vacío. El residuo se agitó con etanol, se filtraron las sales inorgánicas y el filtrado se evaporó. R_t = 0,78 min (Método #2), Masa detectada: 432,1 ($M+H^+$).

Éster terc-butílico del ácido 4-(5-Nitro-isoquinolin-6-iloxi)-piperidin-1-carboxílico (171)



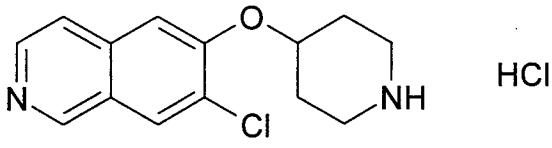
Se trataron 90 mg (0,47 mmol) de 6-Fluoro-5-nitro-isoquinolina (152) con éster terc-butílico del ácido 4-hidroxi-piperidin-1-carboxílico siguiendo el método descrito para la preparación del compuesto 154.

Hidrocloruro de 5-nitro-6-(piperidin-4-iloxi)-isoquinolina (172)



Se desprotegieron 18,5 mg (0,05 mmol) de éster terc-butílico del ácido 4-(5-nitro-isoquinolin-6-iloxi)-piperidin-1-carboxílico (171) siguiendo el procedimiento, descrito en AAV2, por el que se pudieron aislar 12,5 mg del compuesto del título como sal de HCl. R_t = 0,57 min (Método #1). Masa detectada: 274,2 ($M+H^+$).

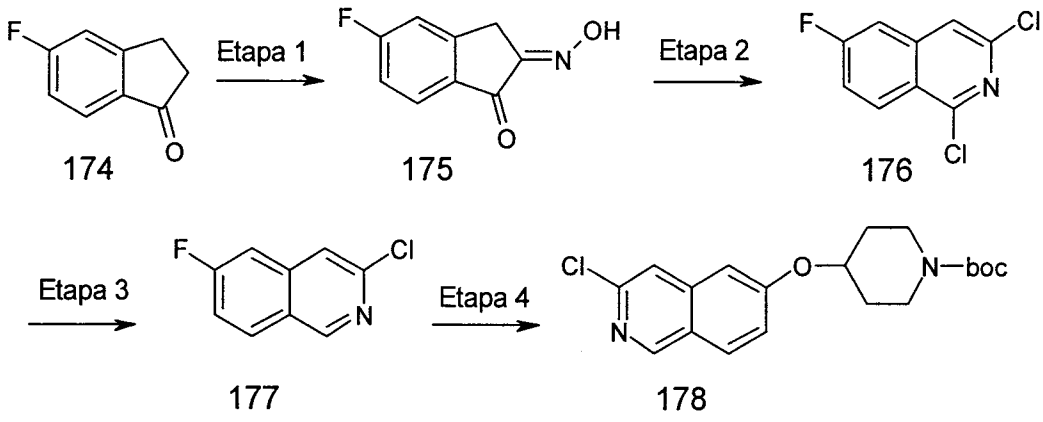
Hidrocloruro de 7-cloro-6-(piperidin-4-iloxi)-isoquinolina (173)



Partiendo de 7-cloro-6-fluoro-isoquinolina (150), se preparó el compuesto del título por la misma ruta sintética que para el compuesto 124. R_t = 0,66 min (Método #1), Masa detectada: 263,1/265,1 ($M+H^+$).

Procedimiento sintético para la generación de isoquinolinas disustituidas en 3 y 6

Esquema general de reacción:



Etapa 1:

Se disolvieron 188 g de 5-fluoro-indanona-1 (174) en 1,8 l de éter dietílico, se añaden 50 ml de EtOH saturado con HCl a 0°C y se añaden durante un periodo de 1 hora 1,1 l de una disolución de nitrito de etilo al 15% en éter.

Se deja agitar la disolución durante 3 horas más para alcanzar la temperatura ambiente, a continuación el disolvente se elimina parcialmente y el producto precipitado se recoge por filtración.

Etapa 2

Se añadieron los 129 g del producto de la Etapa 1 a una mezcla de 170 g de PCl_5 en 2 l de $POCl_3$. A continuación se añadió HCl gaseoso a 0°C hasta que se alcanzó la saturación de la disolución. La mezcla que quedaba se calentó a 60°C durante 6 h, el disolvente se eliminó parcialmente a vacío y el residuo se hidrolizó sobre una mezcla de hielo picado/agua. El producto precipitado se aisló por filtración.

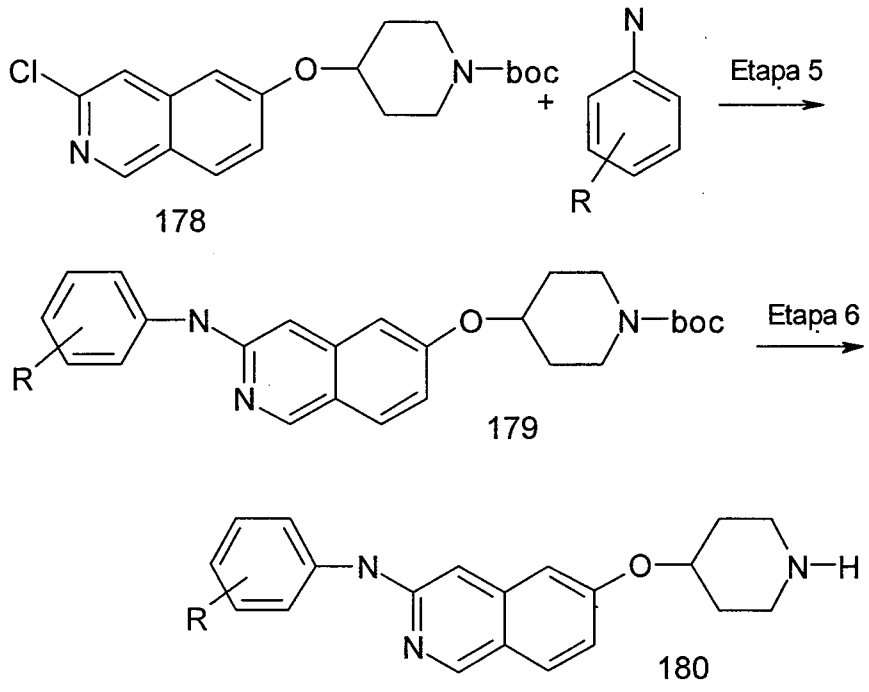
Etapa 3

Se añadieron 155g del producto de la Etapa 2 a una mezcla de 740 ml de HOAc y 330 ml de HI (57%) que contenía 53 g de fósforo rojo. Después de calentar a reflujo durante 4 horas, la disolución se trató con NaOH concentrado (hasta pH = 8) y el producto precipitado se aisló por filtración.

Etapa 4:

Se disolvieron 16,5 g de N-Boc-4-hidroxipiperidina en 210 ml de diglime y se trataron con 4,1 g de NaH al 50% bajo nitrógeno. La mezcla resultante se agitó durante 1 h a tempe-

ratura ambiente, a continuación se añadieron 14,8 g del producto de la Etapa 4. La mezcla se dejó agitar durante 1 día a temperatura ambiente, luego se añadieron 100 ml de tolueno y la mezcla resultante se lavó con agua tres veces. Se recogieron las fases orgánicas y el disolvente se eliminó a vacío.



Etapa 5:

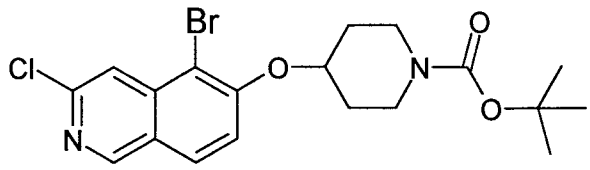
Se disuelven 100 mg del compuesto 178 y 1,1 equivalentes de la correspondiente anilina en 5 ml de dioxano, se añaden 350 mg de Cs_2CO_3, 20mg de $Pd(OAc)_2$ y 60 mg de XANTHPHOS y la mezcla resultante se calienta a reflujo bajo nitrógeno hasta que se consume el producto de partida (la reacción se sigue por LCMS). El disolvente se elimina a vacío y el residuo se somete a cromatografía en un sistema de HPLC.

Etapa 6:

Los productos de la Etapa 5 se disuelven en 5 ml de etanol saturado con HCl gaseoso. Después de agitar durante 5 h se aísla el producto deseado por eliminación del disolvente a vacío.

Todos los derivados trisustituidos en 3, 5 y 6 se sintetizaron según el procedimiento ilustrado por la síntesis del compuesto 184. Para la síntesis del compuesto 185, se utilizó acetamida como componente amina en la etapa de acoplamiento de Pd.

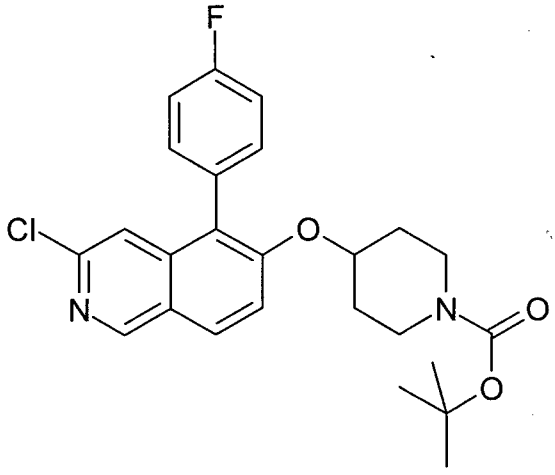
Síntesis del éster terc-butílico del ácido 4-(5-bromo-3-cloro-isoquinolin-6-iloxi)-piperidin-1-carboxílico (181)



Se disolvieron 200 mg de éster terc-butílico del ácido 4-(3-cloro-isoquinolin-6-iloxi)-piperidin-1-carboxílico (178) en 5 ml de CH_3CN y se calentaron a 85°C. A continuación se añadió como sólido una mezcla de 148 mg de N-bromosuccinimida y 9 mg de AIBN y la mezcla resultante se calentó a reflujo durante 1 h. El disolvente se eliminó a vacío y el residuo se sometió a cromatografía instantánea en columna. El rendimiento del producto aislado fue 41%

LCMS: masa detectada: 441,03, R_t= 2,41 min (Método #1)

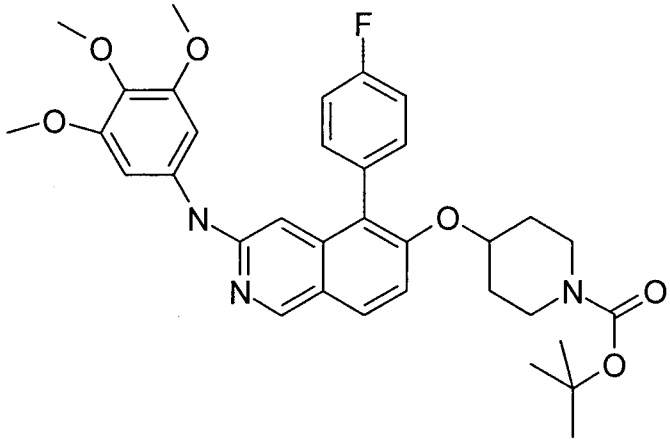
Síntesis del éster terc-butílico del ácido 4-[3-cloro-5-(4-fluoro-fenil)-isoquinolin-6-iloxi]-piperidin-1-carboxílico (182)



Se disolvieron 150 mg de éster terc-butílico del ácido 4-(5-bromo-3-cloro-isoquinolin-6-iloxi)-piperidin-1-carboxílico (181) en una mezcla de 9 ml de dioxano y 3 ml de agua, se añadieron 47 mg de ácido 4-fluoro-benceno-borónico, 47 mg de Na_2CO_3 y 40 mg de $Pd(PPh_3)_4$ y la mezcla resultante se calentó a 100ºC durante 6 h. El disolvente se eliminó a vacío y el residuo se sometió a cromatografía en un sistema de HPLC. Rendimiento: 44%

LCMS: masa detectada: 457,22, R_t= 2,45 min (Método #1)

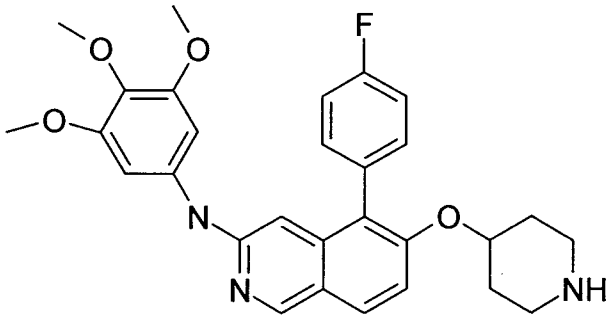
Síntesis del éster terc-butílico del ácido 4-[5-(4-fluoro-fenil)-3-(3,4,5-trimetoxi-fenilamino)-isoquinolin-6-iloxi]-piperidin-1-carboxílico (183)



Se disolvieron 70 mg de éster terc-butílico del ácido 4-[3-cloro-5-(4-fluoro-fenil)-isoquinolin-6-iloxi]-piperidin-1-carboxílico (182) en 7ml de tolueno, se añadieron 20 mg de $Pd(OAc)_2$, 60 mg de XANTHPHOS, 400 mg de Cs_2CO_3 y 30 mg de 3,4,5-trimetoxianilina y la mezcla resultante se calentó a 100°C durante 6 h. A continuación el disolvente se eliminó a vacío y el residuo se sometió a cromatografía en un sistema de HPLC. El rendimiento de producto aislado fue 24%

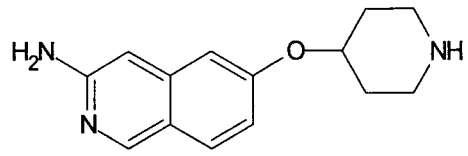
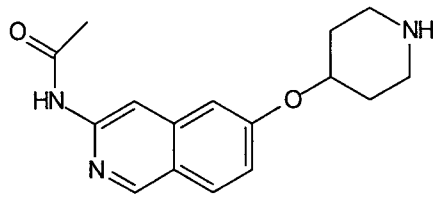
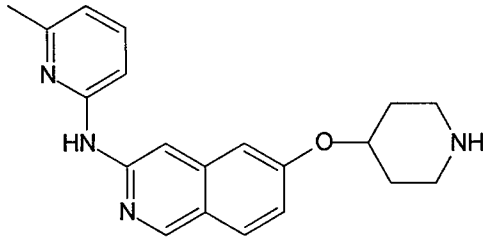
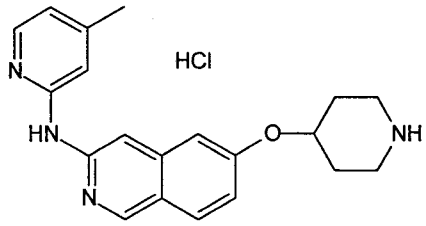
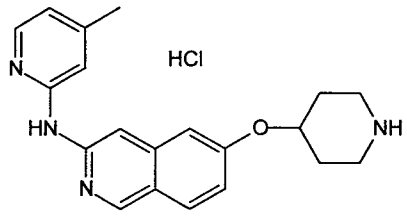
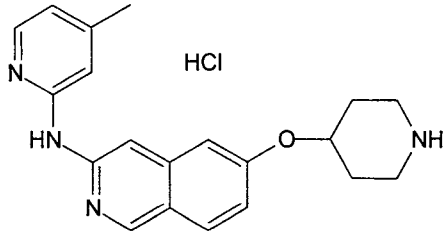
LCMS: masa detectada: 604,17, RT = 1,81 min (Método #1)

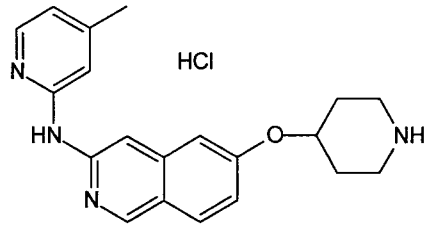
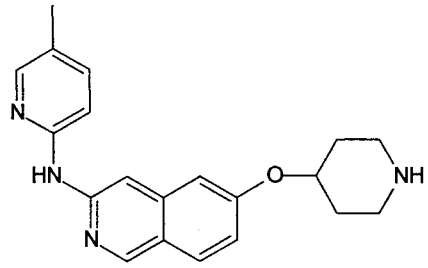
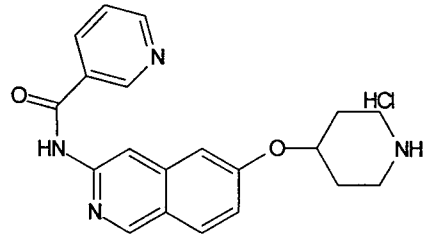
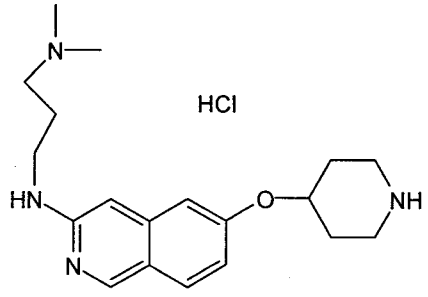
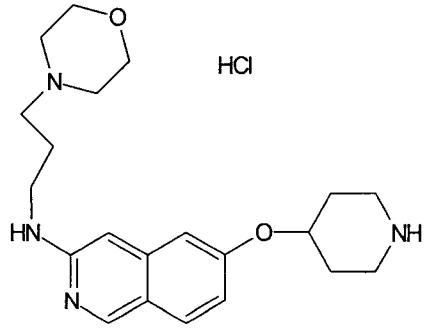
Síntesis de [5-(4-fluoro-fenil)-6-(piperidin-4-iloxi)-isoquinolin-3-il]-(3,4,5-trimetoxi-fenil)-amina (184)

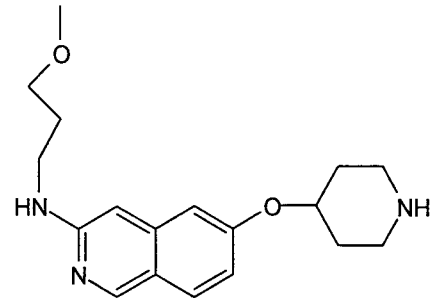
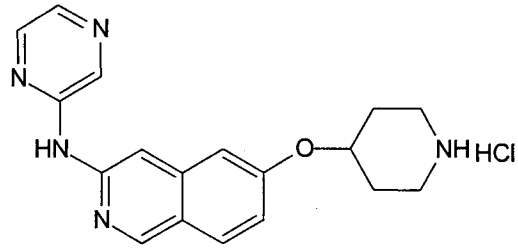
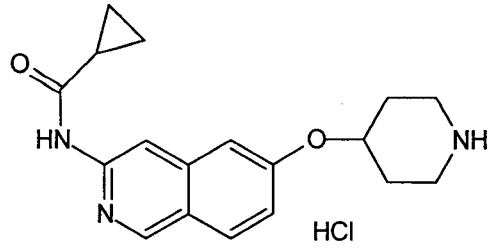
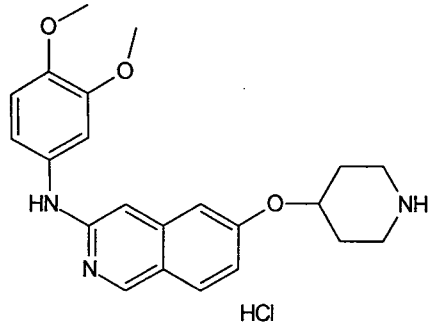
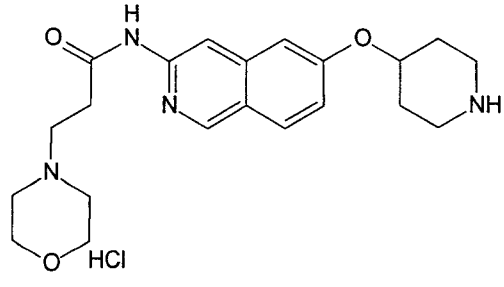


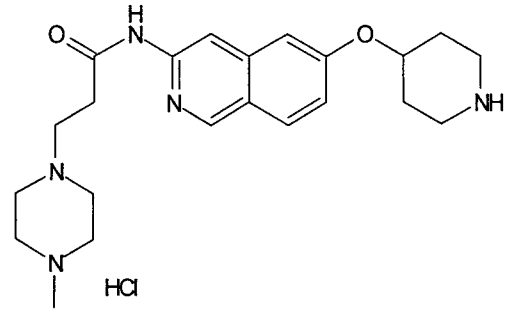
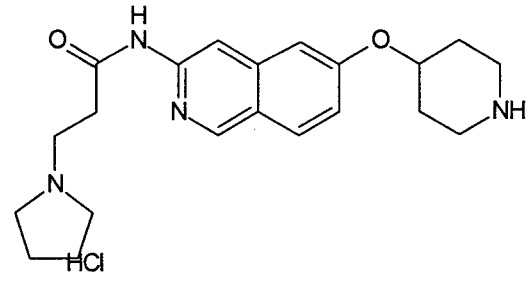
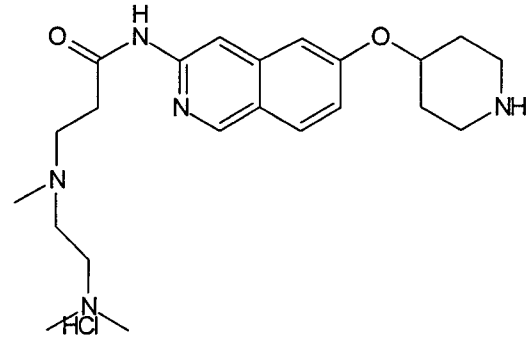
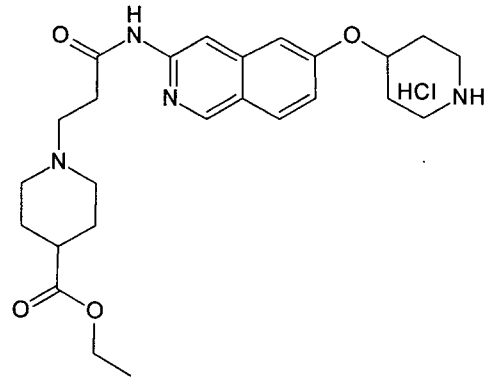
Se disolvieron 20 mg de éster terc-butílico del ácido 4-[5-(4-fluoro-fenil)-3-(3,4,5-trimetoxi-fenilamino)-isoquinolin-6-iloxi]-piperidin-1-carboxílico (183) en 5 ml de etanol saturado con HCl (gaseoso). La mezcla resultante se agitó durante 1, a continuación se evaporó el disolvente y el producto se recogió. Rendimiento: 85%

LCMS: masa detectada: 503,22, R_t= 1,22 min (Método #1)

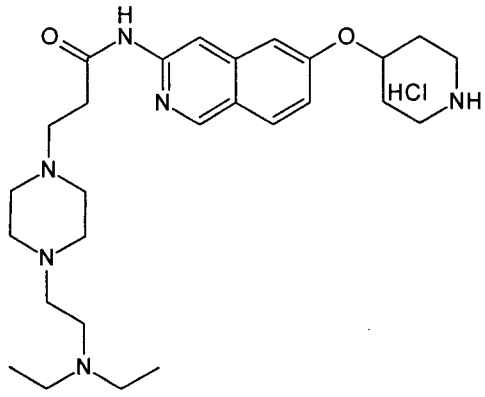
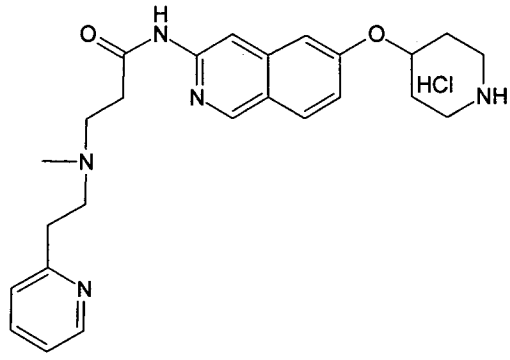
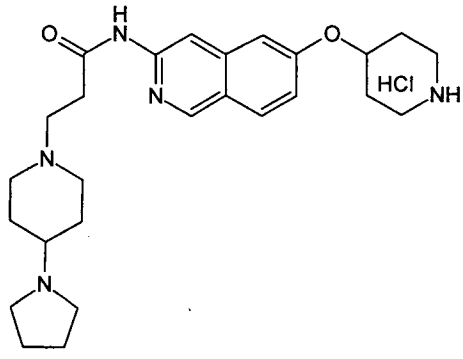
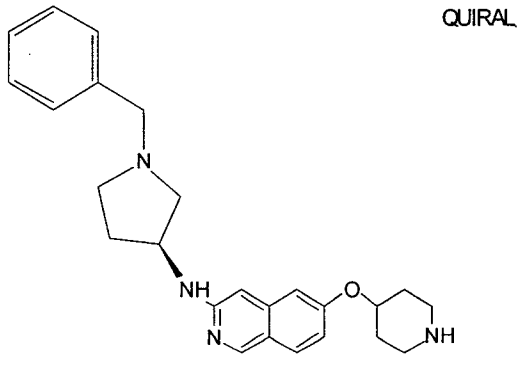
Nº	Compuesto	RT	Método	Masa Detecta-da [MH^+]
185		0,12	Nº 2	244,14
186	HCl 	0,19	Nº 2	286,18
187		0,17	Nº 2	335,21
188	HCl 	1,02	Nº 2	335,21
189	HCl 	1,02	Nº 2	335,21
190	HCl 	1,02	Nº 2	335,21

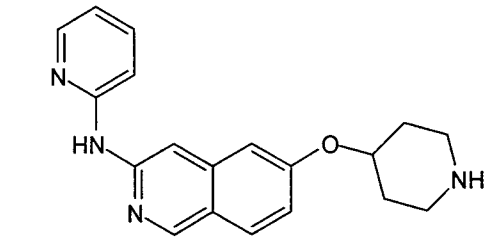
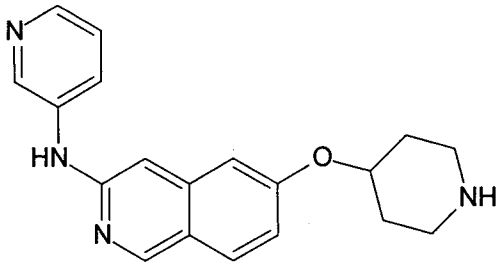
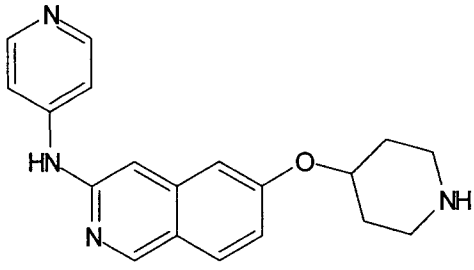
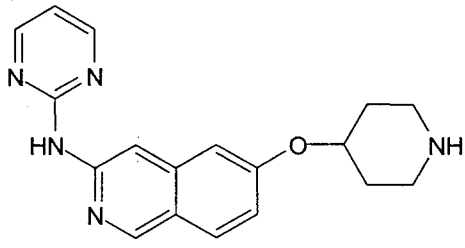
Nº	Compuesto	RT	Método	Masa Detecta-da [MH^+]
191		1,02	Nº 2	335,21
192		1,32	Nº 2	335,20
193		1,21	Nº 2	349,21
194		0,11	Nº 2	329,34
195		0,17	Nº 2	371,32

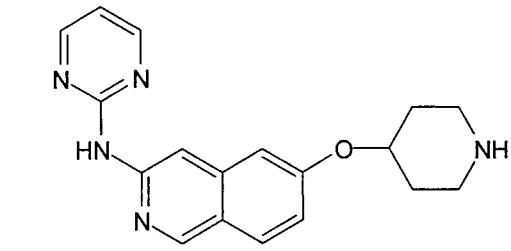
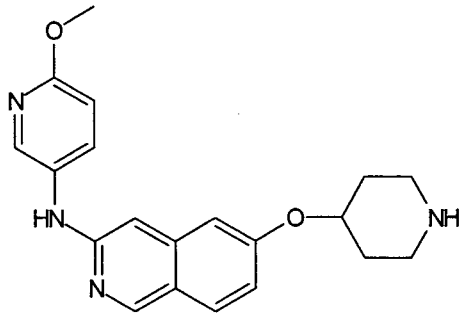
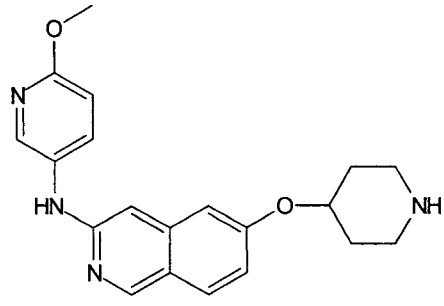
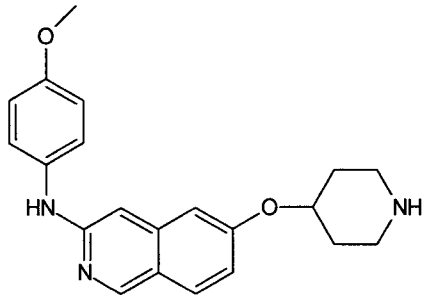
Nº	Compuesto	RT	Método	Masa Detecta-da [MH^+]
196		0,15	Nº 2	316,21
197		1,18	Nº 2	322,25
198		1,18	Nº 2	312,18
199		1,29	Nº 2	380,30
200		0,63	Nº 2	385,29

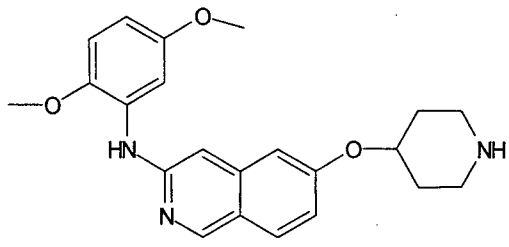
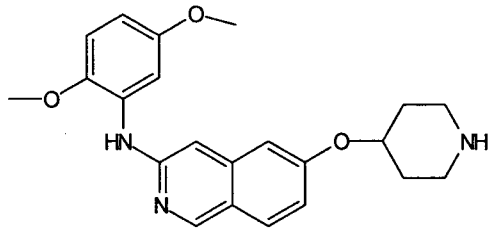
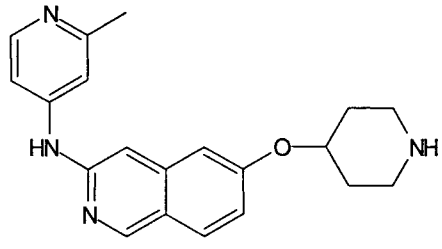
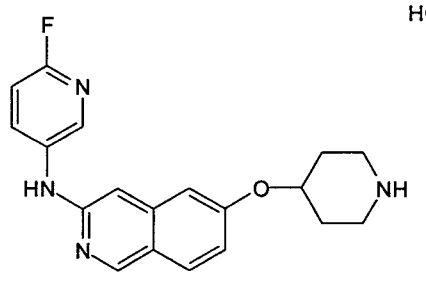
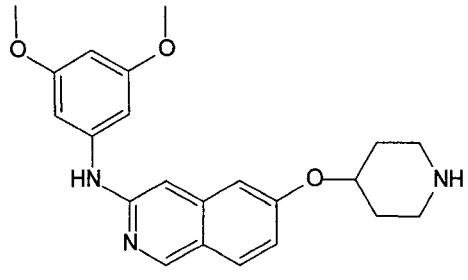
Nº	Compuesto	RT	Método	Masa Detecta-da [MH^+]
201		0,2	Nº 2	398,34
202		0,18	Nº 2	369,30
203		0,2	Nº 2	400,27
204		0,16	Nº 2	455,27

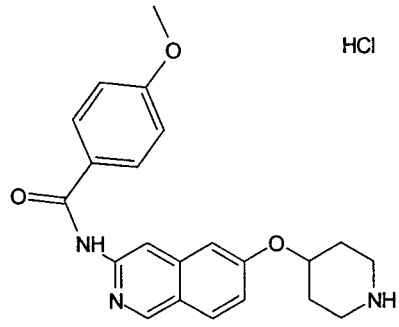
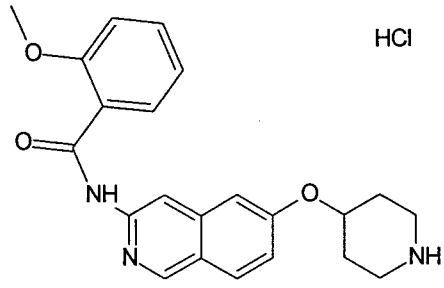
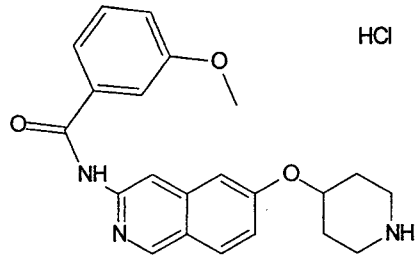
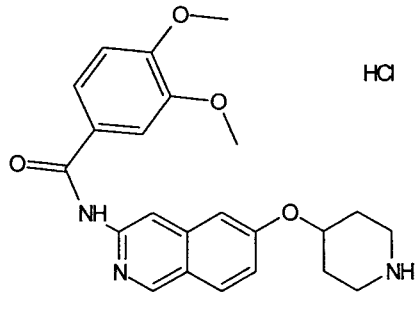
208

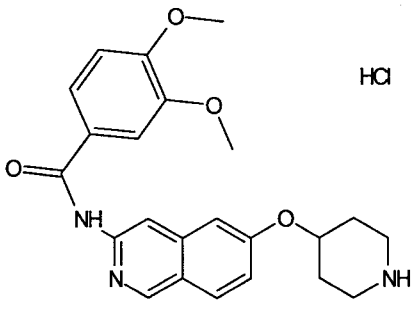
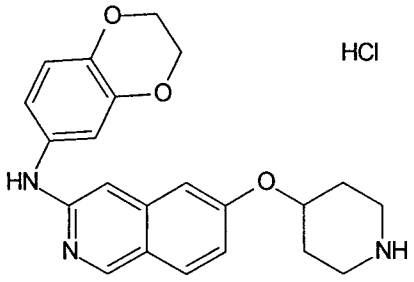
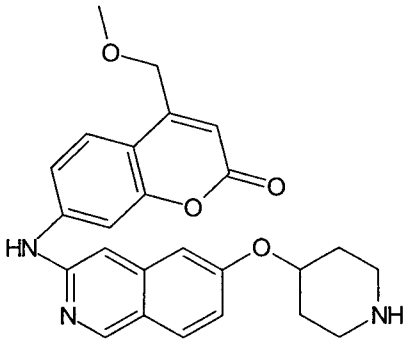
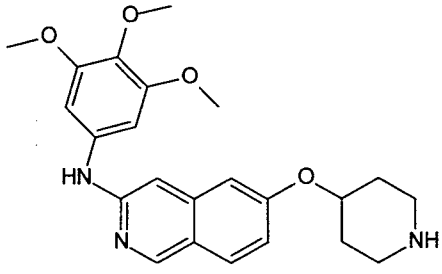
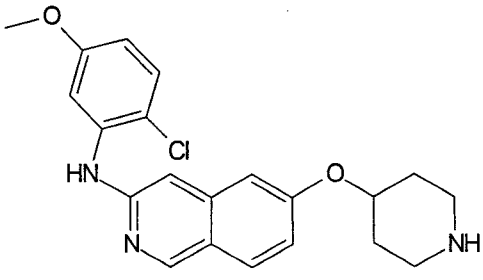
Nº	Compuesto	RT	Método	Masa Detecta-da [MH^+]
205		0,16	Nº 2	483,34
206		0,16	Nº 2	434,26
206 A		0,15	Nº 2	452,30
207	 QUIRAL	0,15	Nº 2	403,25

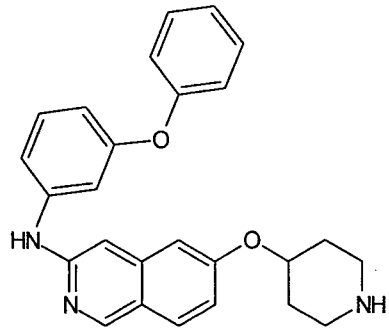
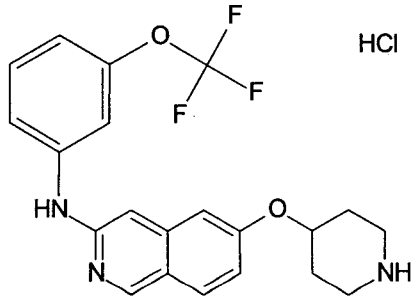
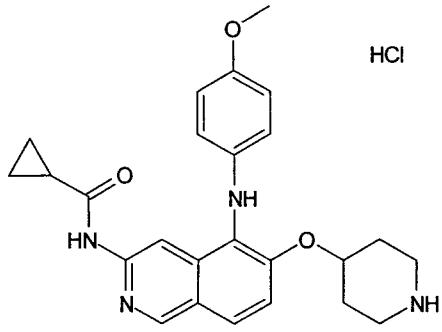
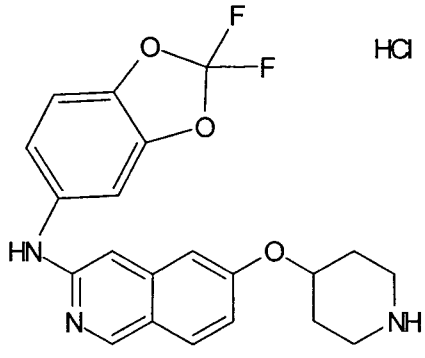
Nº	Compuesto	RT	Método	Masa Detectada [MH^+]
208	 HCl	1,02	Nº 2	321,17
209		1,02	Nº 2	321,17
210	 HCl	1,06	Nº 2	321,17
211	 HCl	0,85	Nº 2	322,17

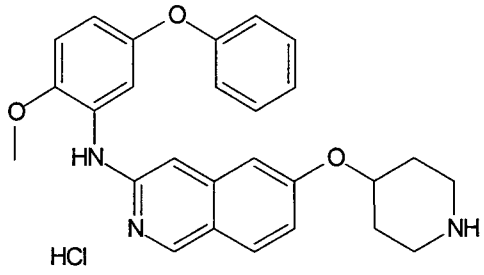
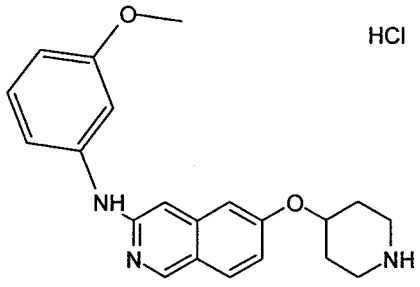
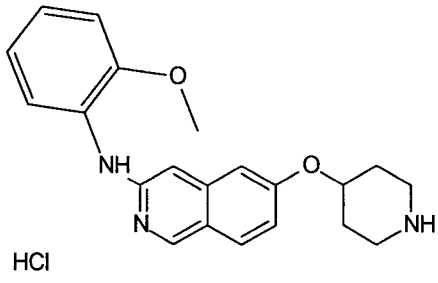
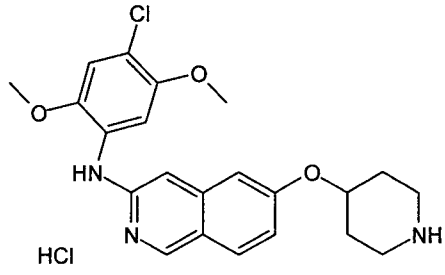
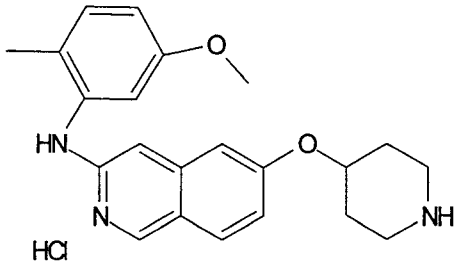
Nº	Compuesto	RT	Método	Masa Detecta-da [MH^+]
212	 HCl	0,85	Nº 2	322,17
213	HCl 	0,89	Nº 2	351,18
214	HCl 	0,89	Nº 2	351,18
215	HCl 	1,03	Nº 2	350,19

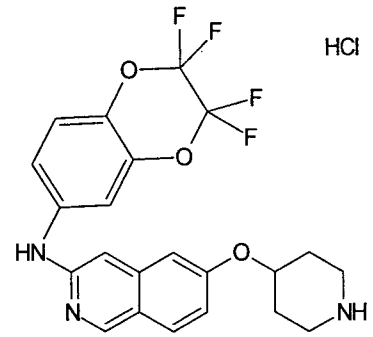
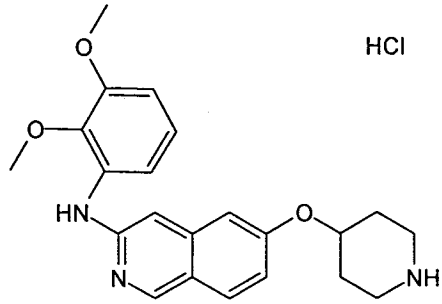
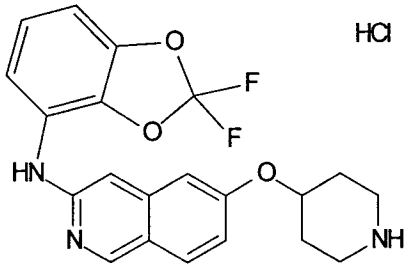
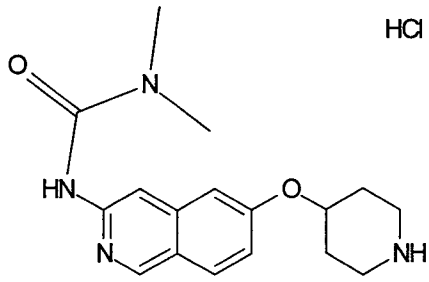
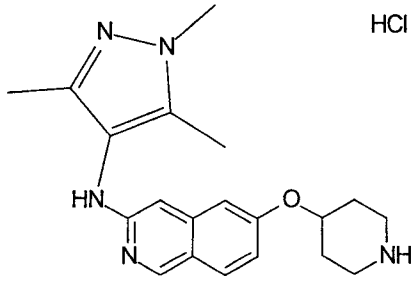
Nº	Compuesto	RT	Método	Masa Detectada [MH^+]
216	 HCl	1	Nº 2	380,20
217	 HCl	1	Nº 2	380,20
218	 HCl	0,95	Nº 2	335,19
219	 HCl	1	Nº 2	339,16
220		1,05	Nº 1	380,20

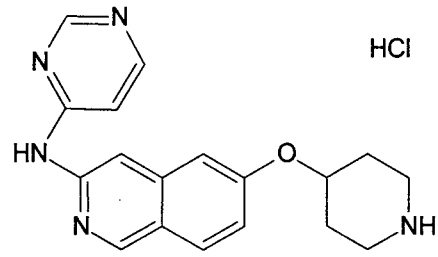
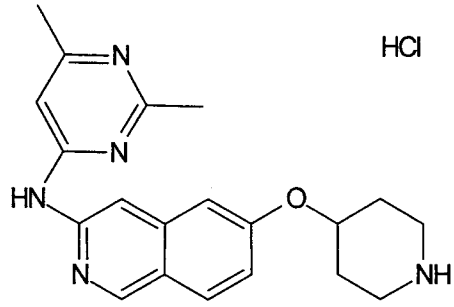
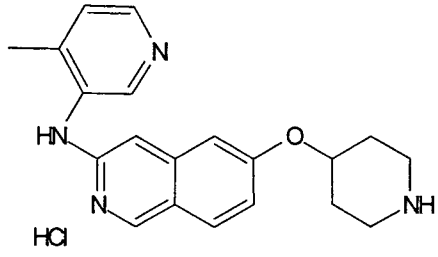
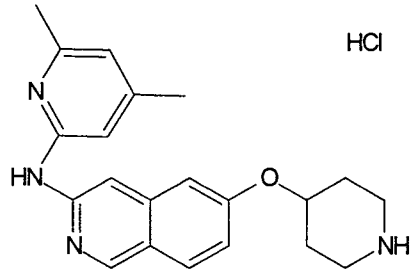
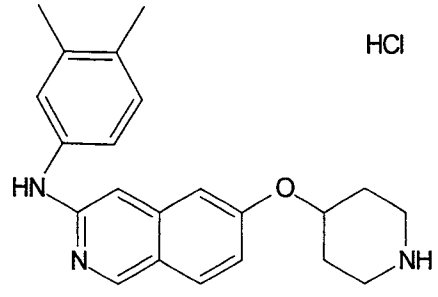
Nº	Compuesto	RT	Método	Masa Detecta-da [MH^+]
221	 HCl	1,06	Nº 1	378,18
222	 HCl	1,17	Nº 1	378,18
223	 HCl	1,12	Nº 1	378,18
224	 HCl	1,04	Nº 1	408,19

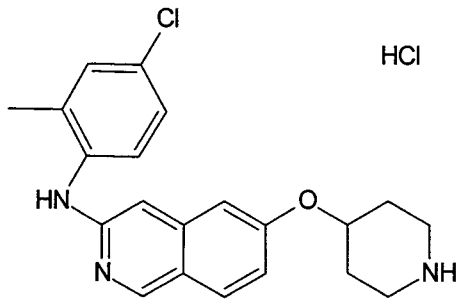
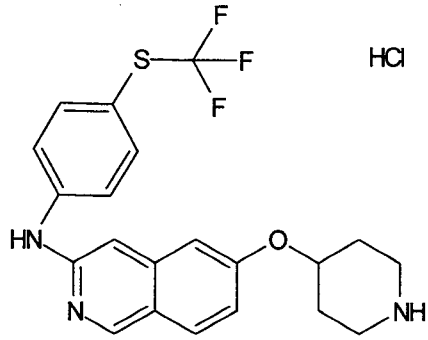
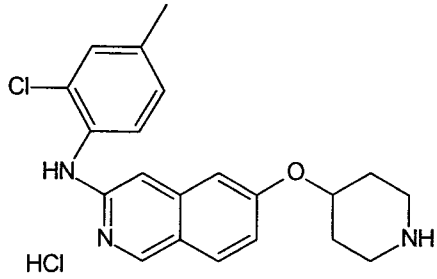
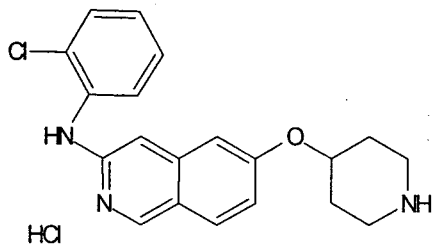
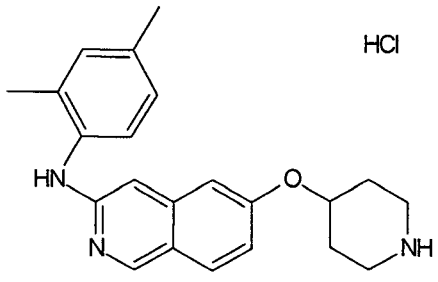
Nº	Compuesto	RT	Método	Masa Detecta-da [MH^+]
225		1,04	Nº 1	408,19
226		0,95	Nº 1	378,18
227		1,1	Nº 1	432,19
228		1,02	Nº 1	410,21
230		1,12	Nº 1	384,15

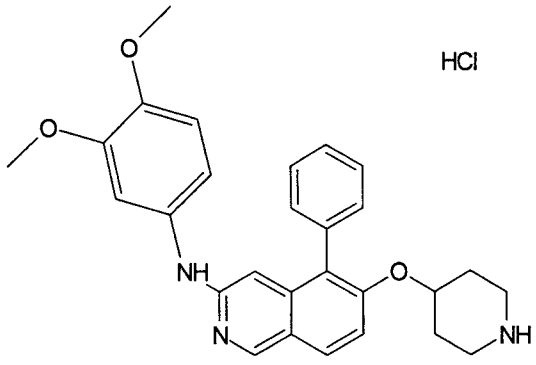
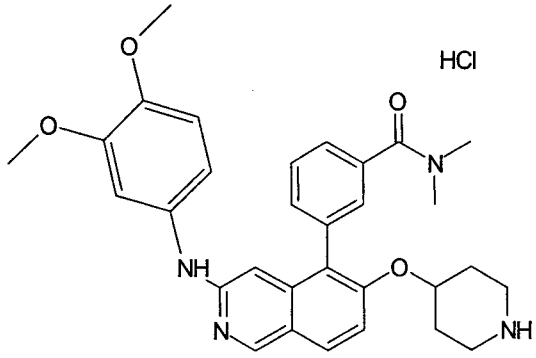
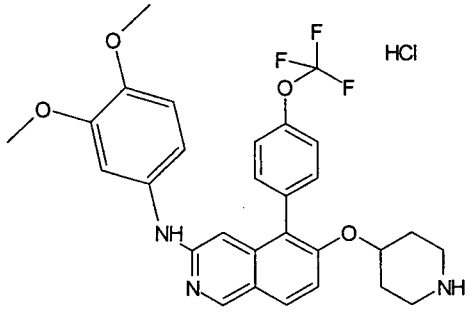
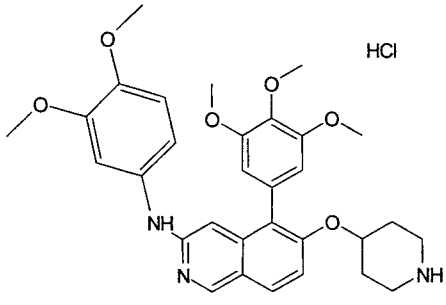
Nº	Compuesto	RT	Método	Masa Detecta-da [MH^+]
231		1,28	Nº 1	412,20
232		1,31	Nº 1	404,16
233		1,15	Nº 1	433,22
234		1,25	Nº 1	400,15

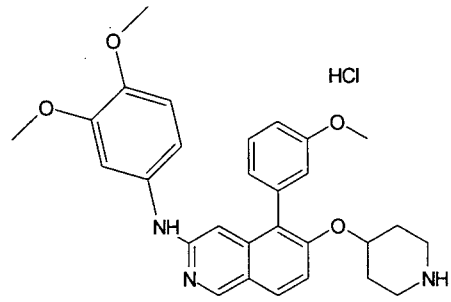
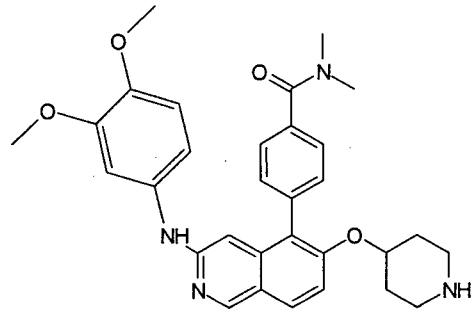
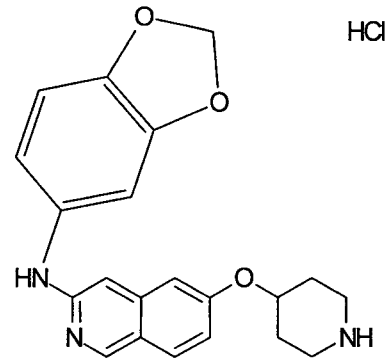
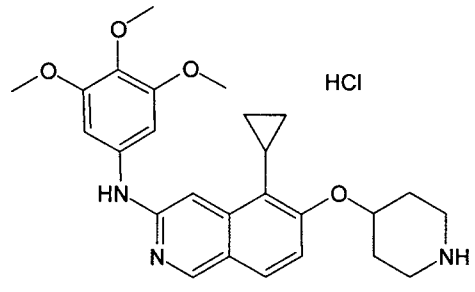
Nº	Compuesto	RT	Método	Masa Detectada [MH^+]
235		1,39	Nº 1	442,21
236		1	Nº 1	350,19
237		0,99	Nº 1	350,19
238		1,13	Nº 1	414,16
239		1,03	Nº 1	364,20

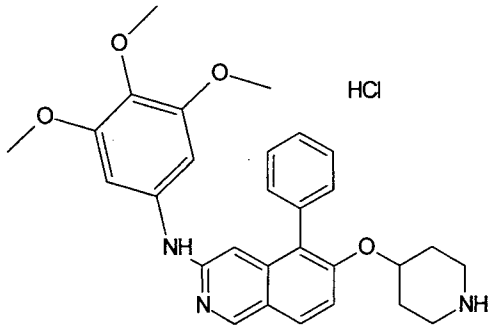
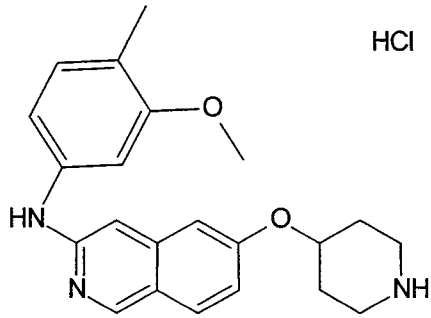
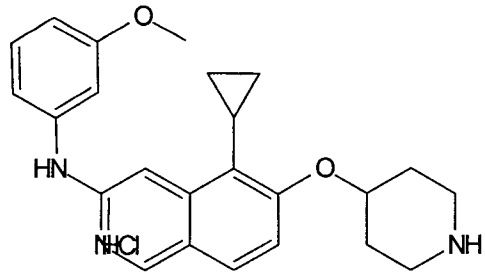
Nº	Compuesto	RT	Método	Masa Detecta-da [MH^+]
240		1,5	Nº 1	450,14
241		0,99	Nº 1	380,20
242		1,25	Nº 1	400,15
243		0,75	Nº 1	315,18
244		0,83	Nº 1	352,21

Nº	Compuesto	RT	Método	Masa Detectada [MH^+]
245		0,73	Nº 1	322,17
246		0,84	Nº 1	350,20
247		0,85	Nº 1	335,19
248		1,05	Nº 1	349,20
249		1,1	Nº 1	348,21

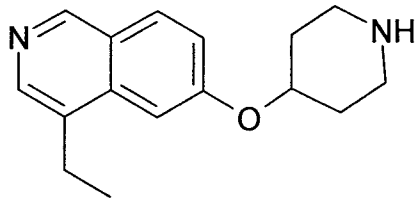
Nº	Compuesto	RT	Método	Masa Detecta-da [MH^+]
250		1,1	Nº 1	368,15
251		1,33	Nº 1	420,14
252		1,12	Nº 1	368,15
253		1,04	Nº 1	354,14
254		1,07	Nº 1	348,21

Nº	Compuesto	RT	Método	Masa Detecta-da [MH^+]
255		1,15	Nº 1	456,23
256		1,11	Nº 1	527,27
257		1,36	Nº 1	540,21
258		1,15	Nº 1	546,26

Nº	Compuesto	RT	Método	Masa Detecta-da [MH^+]
259		1,07	Nº 1	486,24
260		1,08	Nº 1	527,27
261		0,95	Nº 1	364,17
262		1,08	Nº 1	450,24

Nº	Compuesto	RT	Método	Masa Detectada [MH^+]
263		1,14	Nº 1	486,24
264		1,03	Nº 1	364,20
265		1,11	Nº 1	390,22

4-Etil-6-(piperidin-4-iloxi)-isoquinolina (266)

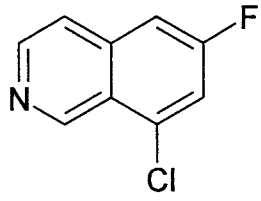


ClH

El compuesto 266 se sintetizó de una forma similar a la descrita para el compuesto 90, utilizando yoduro de etilo. Método de LCMS # 1, tiempo de retención 0,98 min, masa detectada 257,31 $[M+H]^+$

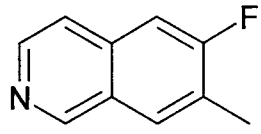
También utilizando la misma secuencia de reacción que para la síntesis de la 6-Fluoro-isoquinolina (23), se obtuvieron los dos compuestos siguientes:

8-Cloro-6-fluoro-isoquinolina (267)



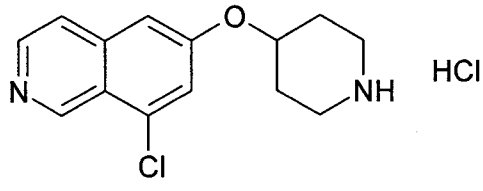
R_t = 0,83 min (Método #1). Masa detectada: 182,12 ($M+H^+$).

6-Fluoro-7-Metilisoquinolina (268)



R_t = 0,70 min (Método #Superior). Masa detectada: 162,3 ($M+H^+$).

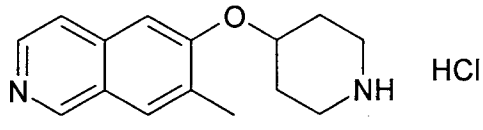
Hidrocloruro de 8-cloro-6-(piperidin-4-iloxi)-isoquinolina (269)



El hidrocloruro de 8-cloro-6-(piperidin-4-iloxi)-isoquinolina (269) se obtuvo de un modo similar al descrito más arriba para la síntesis de (124), partiendo de 267.

R_t = 0,63 min (Método #1). Masa detectada: 263,14 ($M+H^+$).

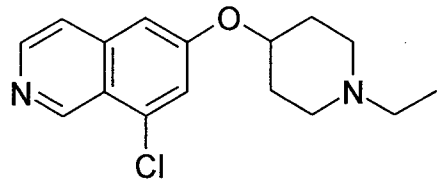
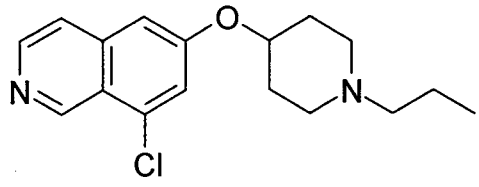
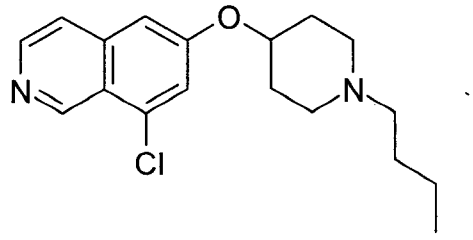
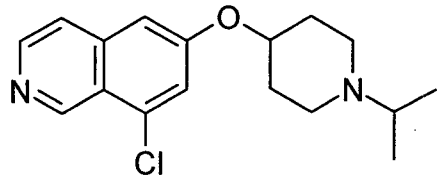
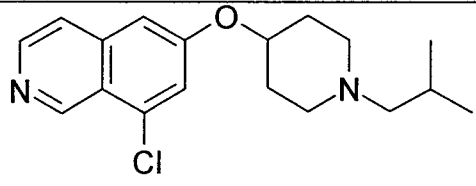
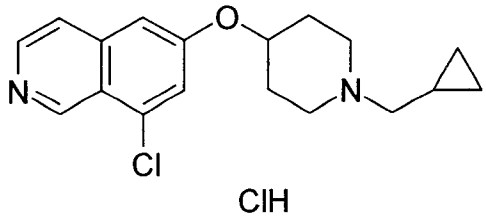
Hidrocloruro de 6-(piperidin-4-iloxi)-7-metil isoquinolina (270)

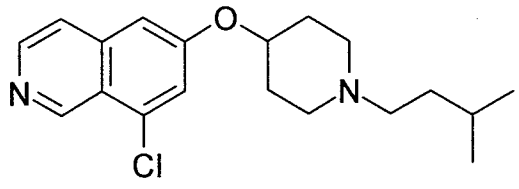
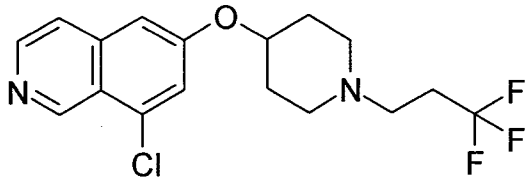
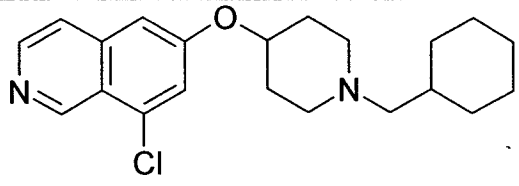
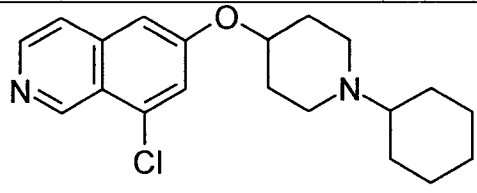
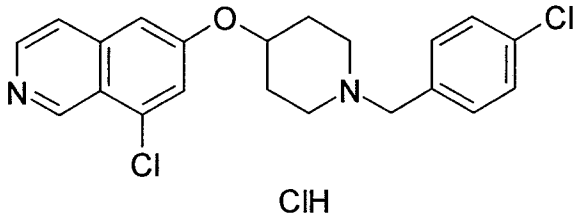
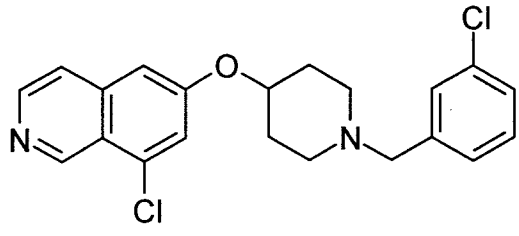


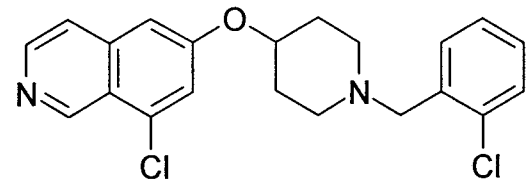
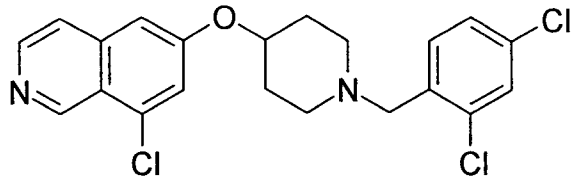
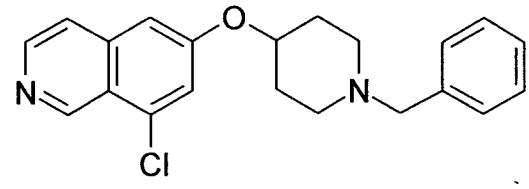
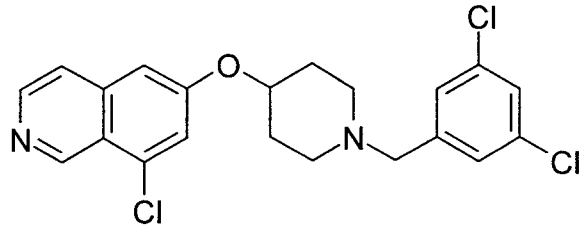
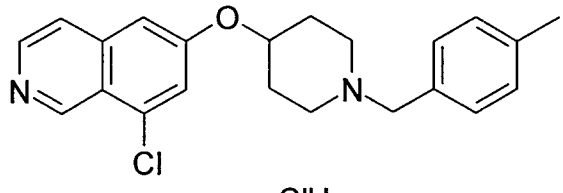
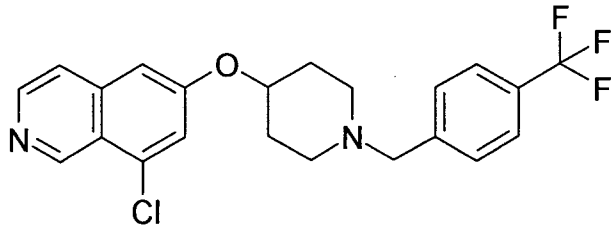
El hidrocloruro de 6-(piperidin-4-iloxi)-7-metil isoquinolina (270) se obtuvo de un modo similar al descrito más arriba para la síntesis de (124), partiendo de 268.

R_t = 0,64 min (Método #1). Masa detectada: 243,18 ($M+H^+$).

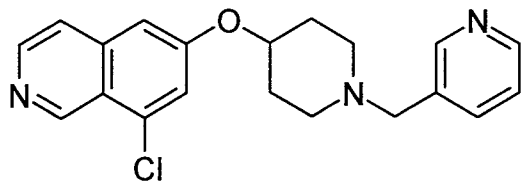
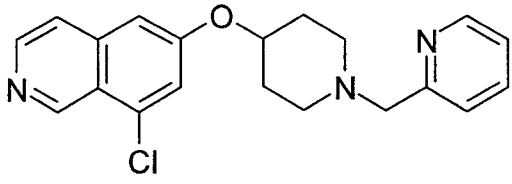
El siguiente conjunto de compuestos se obtuvo de la misma manera, siguiendo el procedimiento de aminación reductora utilizado para obtener los ejemplos 93-123 utilizando 269, 129 o 270, respectivamente y los aldehídos correspondientes como producto de partida. Todas las LCMS en las tablas siguientes se obtuvieron utilizando el método de LCMS #2.

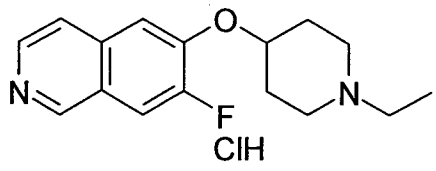
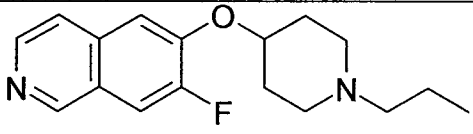
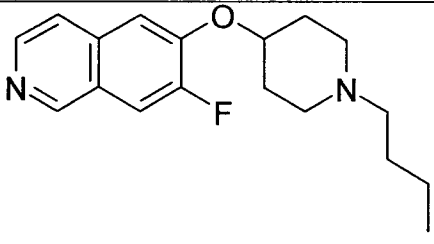
Ejemplo Nº	Fórmula	T_R	Masa [MH^+]
271	 ClH	0,71	291,09
272	 ClH	0,87	305,11
273	 ClH	0,85	319,11
274	 ClH	0,69	305,10
275	 ClH	0,85	319,20
276	 ClH	0,79	317,10

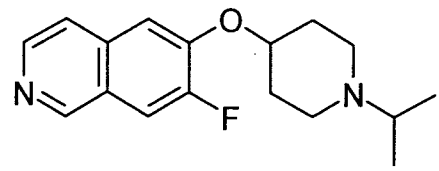
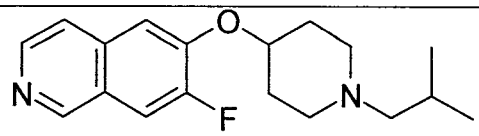
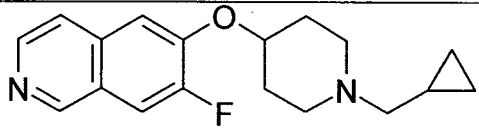
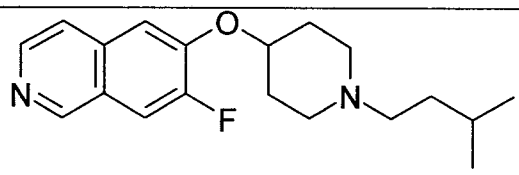
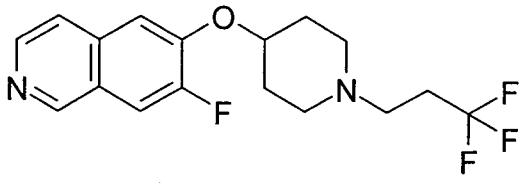
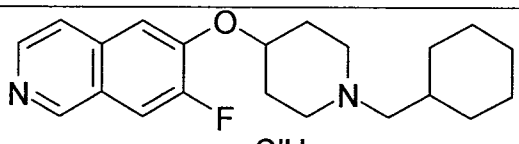
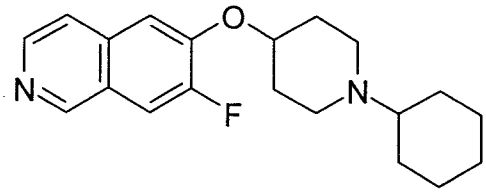
Ejemplo Nº	Fórmula	T_R	Masa [MH^+]
277	 ClH	0,92	333,12
278	 ClH	0,87	359,06
279	 ClH	1,01	359,15
280	 ClH	0,90	345,13
281	 ClH	1,02	387,06
282	 ClH	1,09	387,05

Ejemplo Nº	Fórmula	T_R	Masa [MH^+]
283	 ClH	1,05	387,06
284	 ClH	1,10	421,02
285	 ClH	0,95	353,10
286	 ClH	1,14	421,02
287	 ClH	1,00	367,10
288	 ClH	1,13	421,06

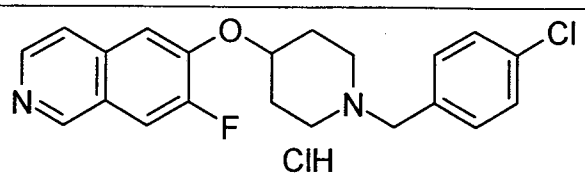
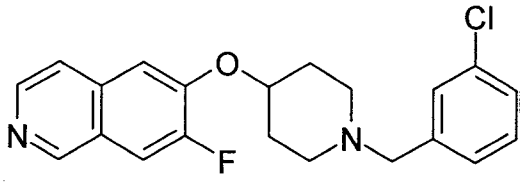
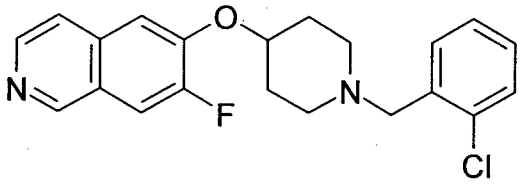
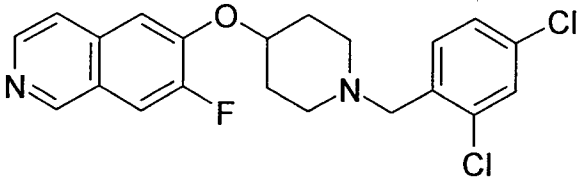
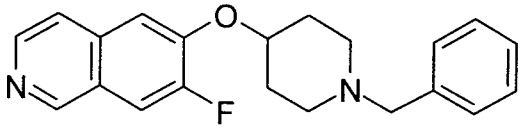
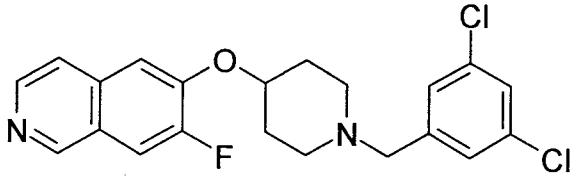
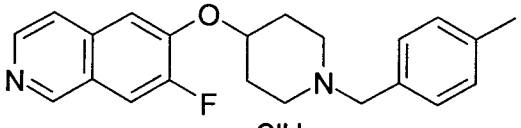
227

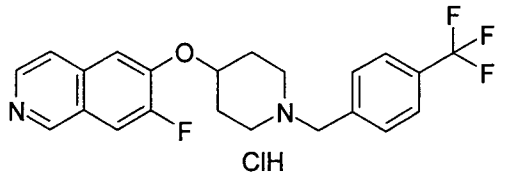
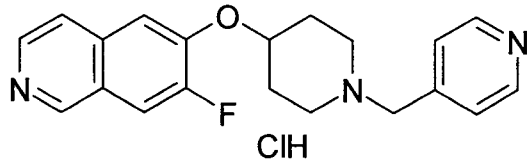
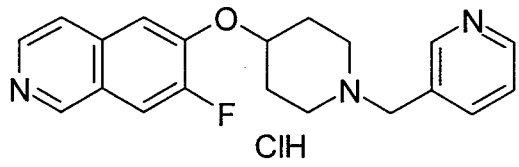
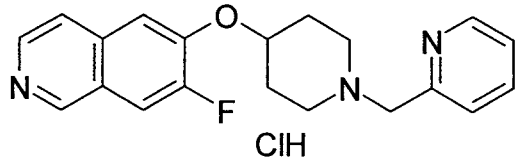
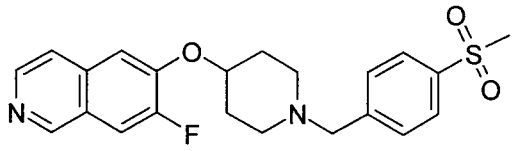
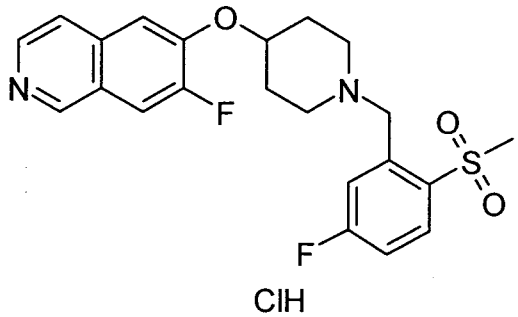
Ejemplo Nº	Fórmula	T_R	Masa [MH^+]
289	 ClH	0,63	354,11
290	 ClH	0,90	354,11

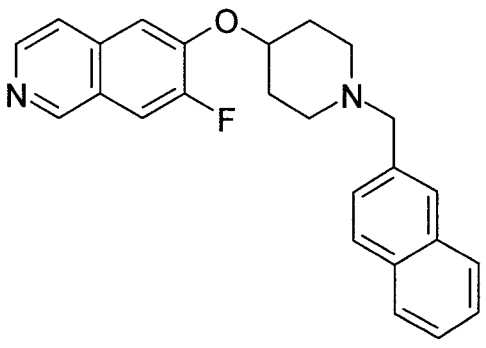
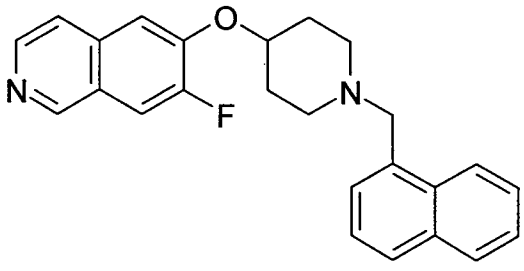
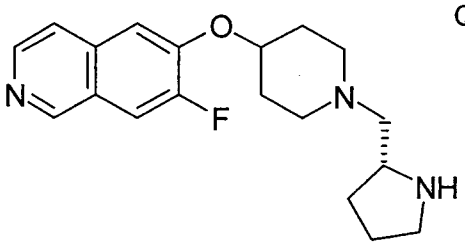
Ejemplo Nº	Fórmula	T_R	Masa [MH^+]
291	 ClH	0,46	275,33
292	 ClH	0,57	289,21
293	 ClH	0,73	303,22

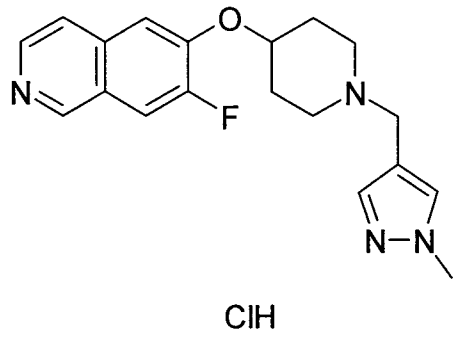
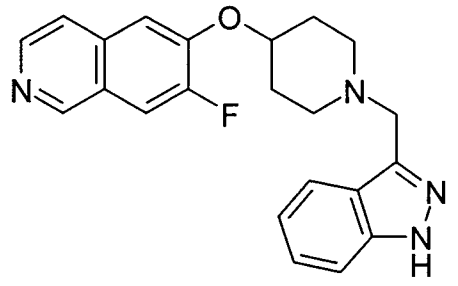
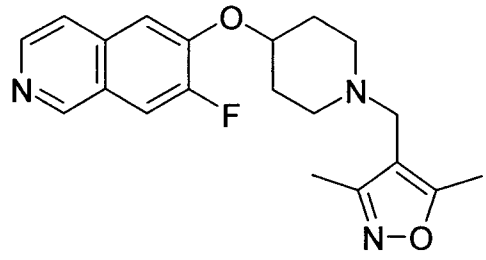
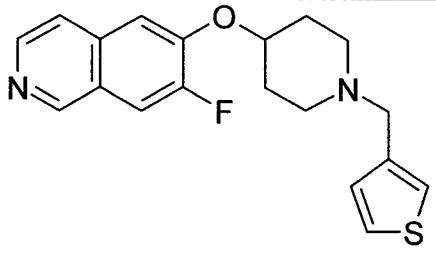
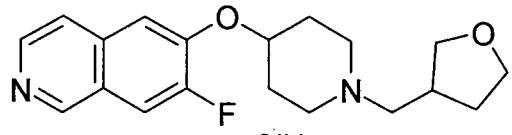
Ejemplo Nº	Fórmula	T_R	Masa [MH^+]
294	 ClH	0,52	289,25
295	 ClH	0,65	303,23
296	 ClH	0,63	301,20
297	 ClH	0,90	317,26
298	 ClH	0,66	343,21
299	 ClH	0,96	343,27
300	 ClH	0,72	329,30

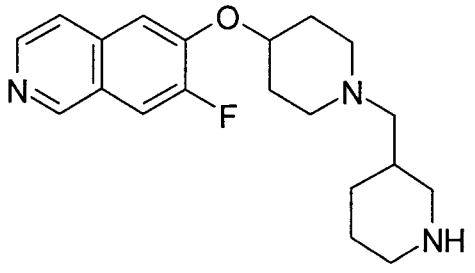
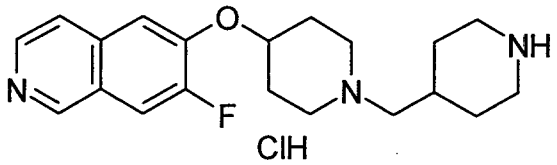
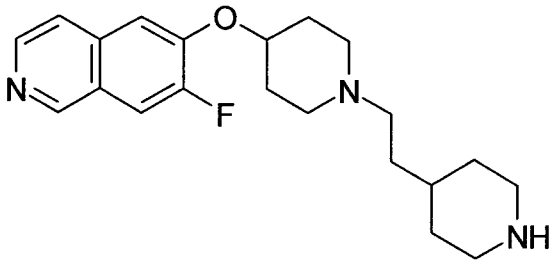
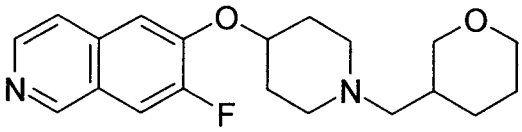
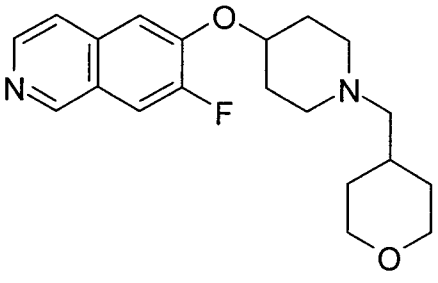
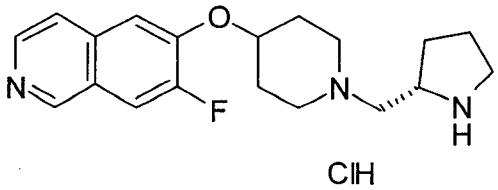
229

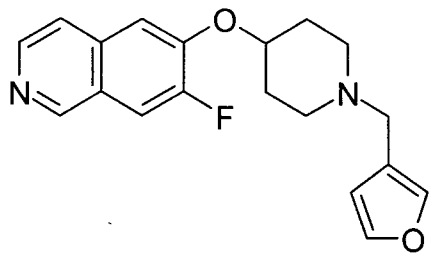
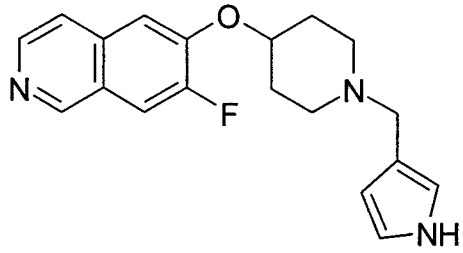
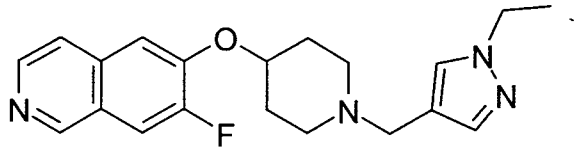
Ejemplo Nº	Fórmula	T_R	Masa [MH^+]
301	 ClH	0,97	371,19
302	 ClH	0,95	371,19
303	 ClH	0,88	371,19
304	 ClH	1,02	405,15 /407,15
305	 ClH	0,83	337,24
306	 ClH	1,07	405,19 /407,19
307	 ClH	0,94	351,28

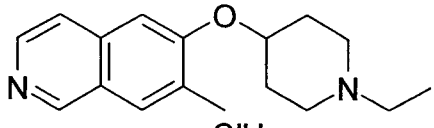
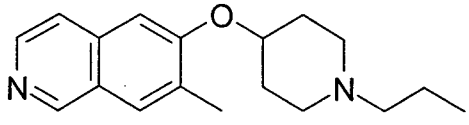
Ejemplo Nº	Fórmula	T_R	Masa [MH^+]
308	 ClH	1,05	405,24
309	 ClH	0,23	338,23
310	 ClH	0,49	338,23
311	 ClH	0,67	338,23
312	 ClH	0,70	415,25
313	 ClH	0,74	433,24

Ejemplo Nº	Fórmula	T_R	Masa [MH^+]
314	 ClH	1,10	387,26
315	 ClH	1,05	387,26
316	 ClH	0,12	330,24
317	Quiral  ClH	0,28	330,27

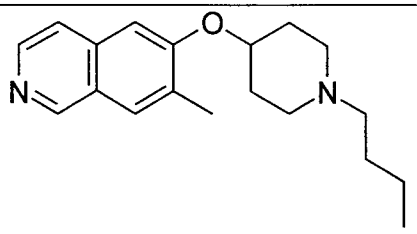
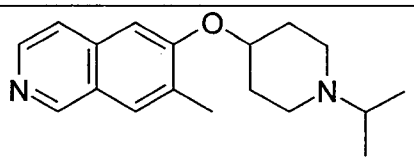
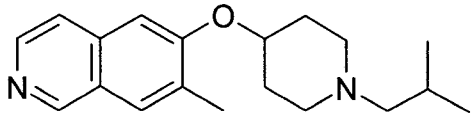
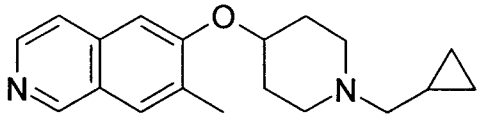
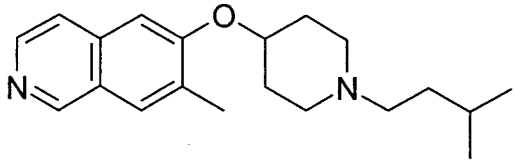
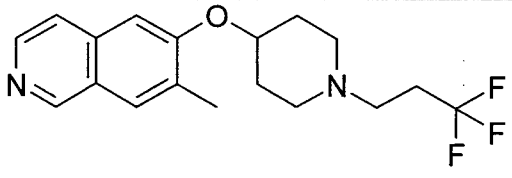
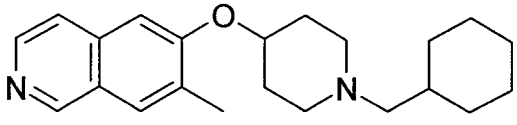
Ejemplo Nº	Fórmula	T_R	Masa [MH^+]
318	 ClH	0,58	341,27
319	 ClH	0,87	377,25
320	 ClH	0,69	355,17
321	 ClH	0,80	343,19
322	 ClH	0,53	331,25

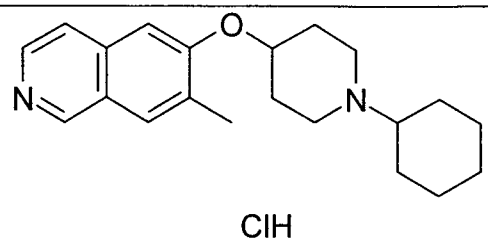
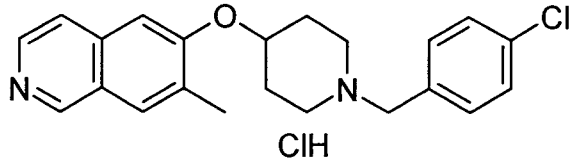
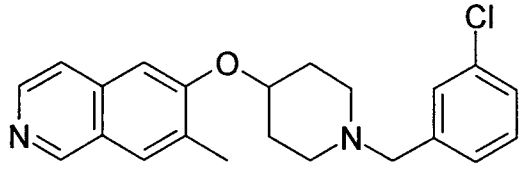
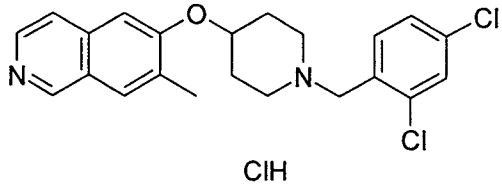
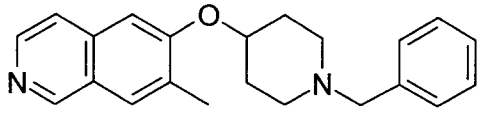
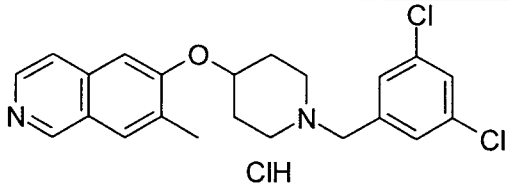
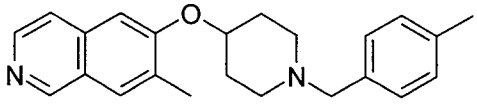
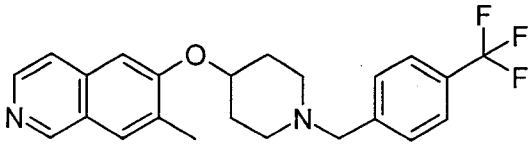
Ejemplo Nº	Fórmula	T_R	Masa [MH^+]
323	 ClH	0,18	344,30
324	 ClH	0,14	344,29
325	 ClH	0,14	358,29
326	 ClH	0,62	345,24
327	 ClH	0,60	345,27
328	 Quiral ClH	0,12	330,24

Ejemplo Nº	Fórmula	T_R	Masa [MH^+]
329	 ClH	0,67	327,24
330	 ClH	0,18	326,23
331	 ClH	0,23	335,26

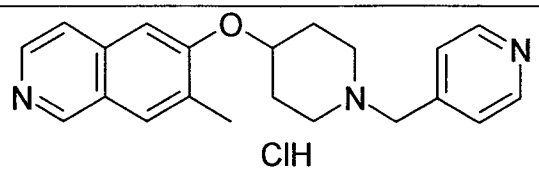
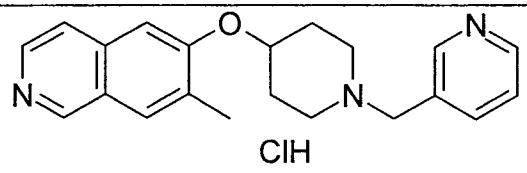
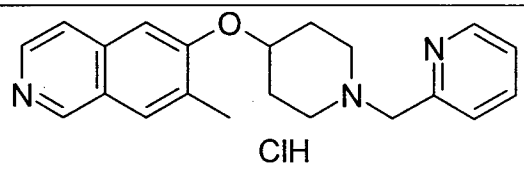
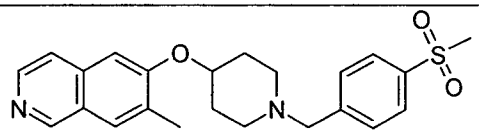
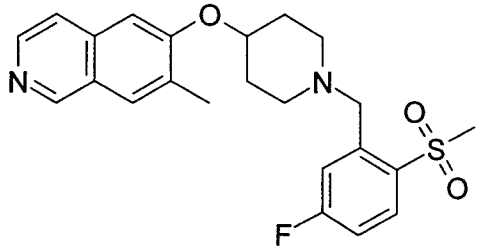
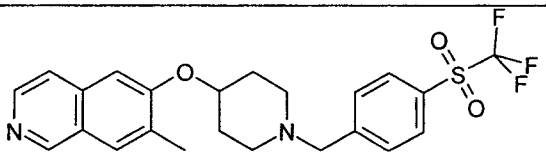
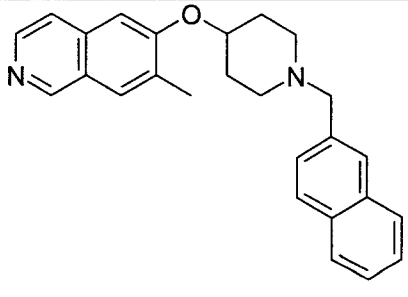
Ejemplo Nº	Fórmula	T_R	Masa [MH^+]
332	 ClH	0,70	271,17
333	 ClH	0,80	285,21

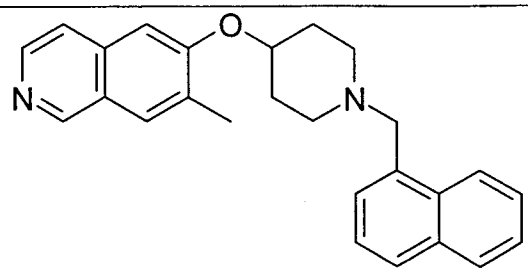
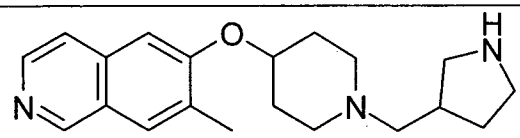
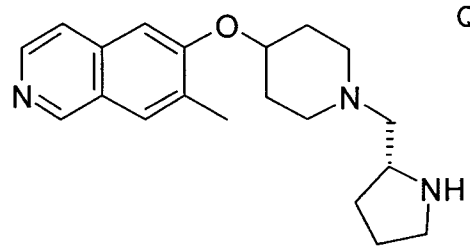
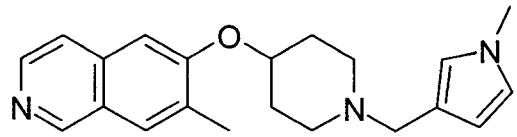
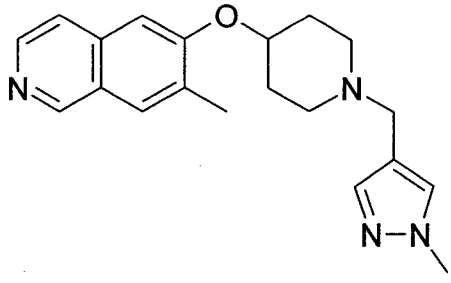
235

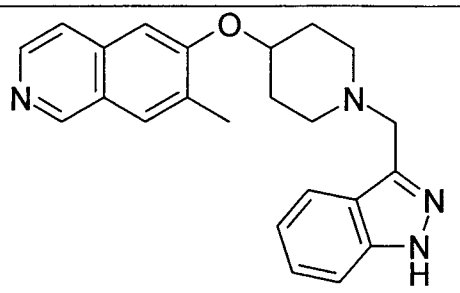
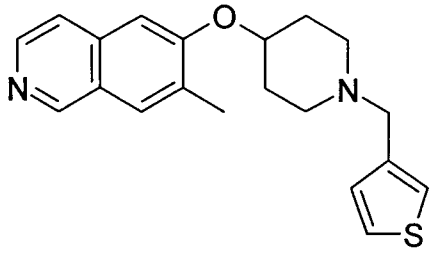
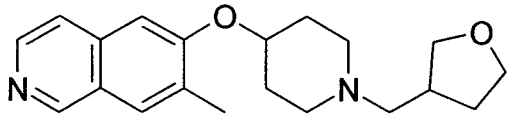
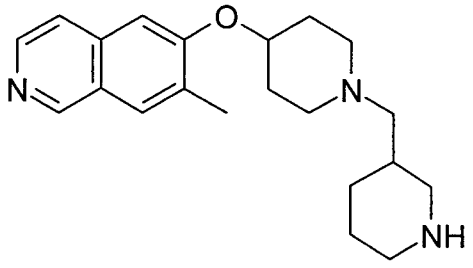
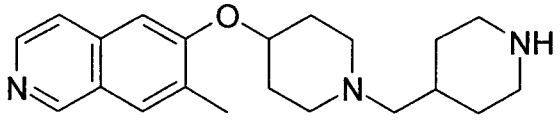
Ejemplo Nº	Fórmula	T_R	Masa [MH^+]
334	 ClH	0,87	299,19
335	 ClH	0,78	285,22
336	 ClH	0,92	299,20
337	 ClH	0,75	297,13
338		1,01	313,16
339	 ClH	0,77	339,10
340	 ClH	0,98	339,29

Ejemplo Nº	Fórmula	T_R	Masa [MH^+]
341	 ClH	0,91	325,23
342	 ClH	1,07	367,15
343	 ClH	1,01	367,15
344	 ClH	1,07	401,12/403,14
345	 ClH	0,99	333,19
346	 ClH	1,13	401,12/403,14
347	 ClH	1,00	347,24
348	 ClH	1,09	401,22

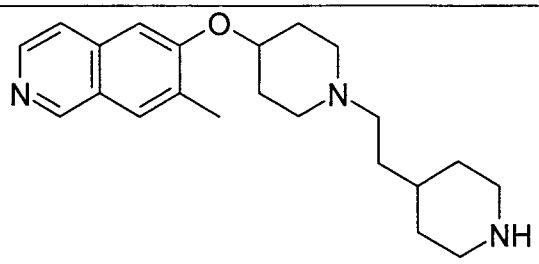
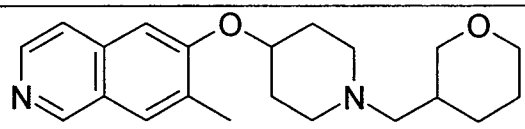
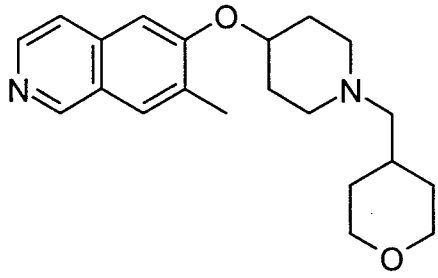
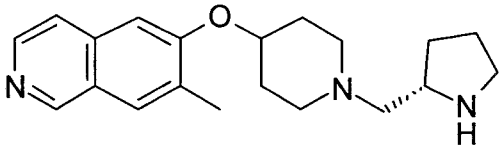
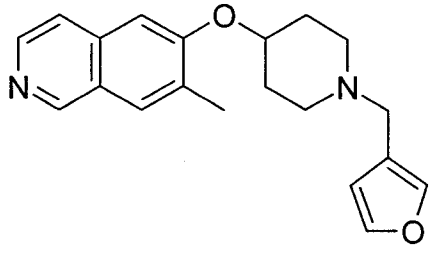
237

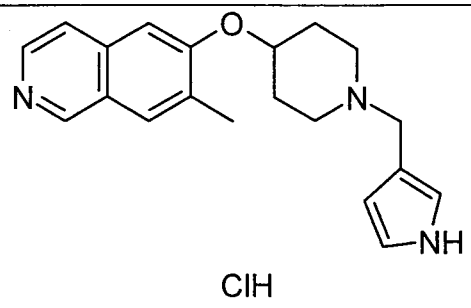
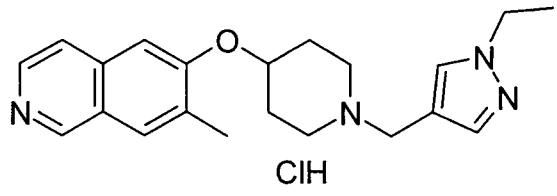
Ejemplo Nº	Fórmula	T_R	Masa [MH^+]
349	 ClH	0,63	334,23
350	 ClH	0,69	334,23
351	 ClH	0,90	334,24
352	 ClH	0,83	411,22
353	 ClH	0,88	429,20
354	 ClH	1,14	465,18
355	 ClH	1,17	383,25

Ejemplo Nº	Fórmula	T_R	Masa [MH^+]
356	 ClH	1,08	383,15
357	 ClH	0,60	326,26
358	Quiral  ClH	0,67	326,26
359	 ClH	0,89	336,25
360	 ClH	0,74	337,24

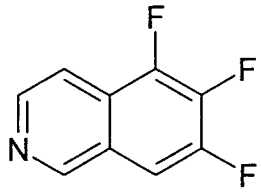
Ejemplo Nº	Fórmula	T_R	Masa [MH^+]
361	 ClH	0,91	373,23
362	 ClH	0,97	338,15
363	 ClH	0,73	327,24
364	 ClH	0,74	340,27
365	 ClH	0,62	340,28

240

Ejemplo Nº	Fórmula	T_R	Masa [MH^+]
366	 ClH	0,66	354,29
367	 ClH	0,79	341,26
368	 ClH	0,77	341,25
369	 ClH Quiral	0,76	326,26
370	 ClH	0,81	323,20

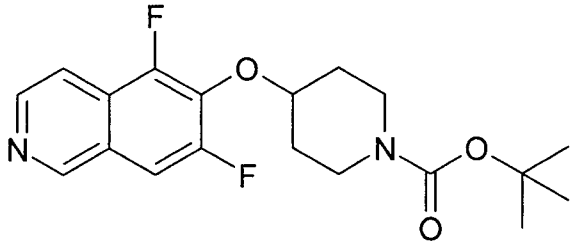
Ejemplo Nº	Fórmula	T_R	Masa [MH^+]
371	 ClH	0,84	322,22
372	 ClH	0,88	351,24

5,6,7-Trifluoro-isoquinolina (373)



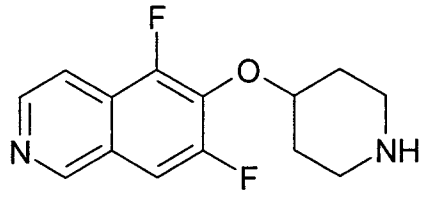
La 5,6,7-trifluoro-isoquinolina (373) se obtiene por la misma secuencia de reacción, utilizada para la síntesis de la 6-fluoro-isoquinolina (23), partiendo de 3,4,5-trifluorobenzaldehído. La purificación final por HPLC preparativa dio la isoquinolina deseada como trifluoroacetato. R_t = 1,15 min (Método #2). Masa detectada: 183,0.

Éster terc-butílico del ácido 4-(5,7-Difluoro-isoquinolin-6-iloxi)-piperidin-1-carboxílico (374)



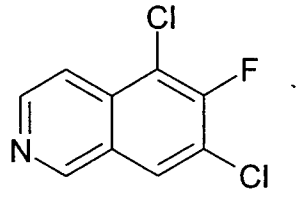
El compuesto del título se sintetizó siguiendo el protocolo descrito para el éster terc-butílico del ácido 4-(isoquinolin-6-iloxi)-piperidin-1-carboxílico (154). R_t = 1,27 min (Método #Superior). Masa detectada: 365,2 ($M+H^+$).

5,7-Difluoro-6-(piperidin-4-iloxi)-isoquinolina (375)



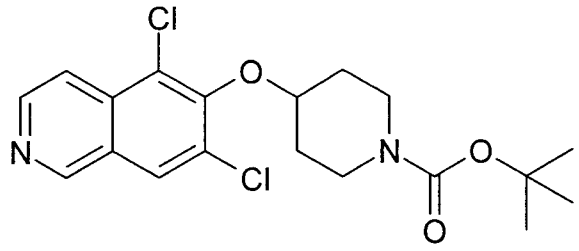
Se desprotege el éster terc-butílico del ácido 4-(5,7-difluoro-isoquinolin-6-iloxi)-piperidin-1-carboxílico (374) en Metanol/HCl 2 N por el procedimiento general descrito en AAV2 para rendir el compuesto del título como sal de HCl. R_t = 0,43 min (Método #Superior). Masa detectada: 265,1 ($M+H^+$).

5,7-Dicloro-6-fluoro-isoquinolina (376)



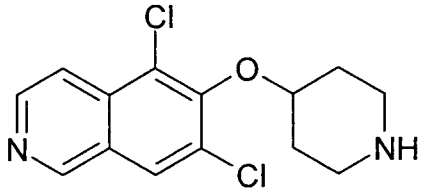
Se disolvieron 5,0 g (27,5 mmol) de 7-cloro-6-fluoro-isoquinolina (150) en 90 ml de ácido sulfúrico conc. A temperatura ambiente se añadieron 7,35 g (55,0 mmol) de N-cloro-succinimida y la mezcla se agitó a 50°C. Después de dejar estar durante toda la noche a temperatura ambiente se añadieron otros 3 eq. de N-cloro-succinimida y en la siguiente se añadieron de nuevo 5 eq. de N-cloro-succinimida y se aumentó la temperatura a 80°C. Después de que no se pudiera detectar ninguna conversión adicional, la mezcla se enfrió a temperatura ambiente y se vertió sobre hielo. La disolución acuosa se llevó a pH básico añadiendo NaOH sólido. El precipitado se filtró y se lavó tres veces con diclorometano. Después del secado de los filtrados orgánicos con MgSO4 y la evaporación del disolvente se pudieron aislar 1,09 g de la isoquinolina deseada. R_t = 1,26 min (Método #Superior). Masa detectada: 216,0/218,0 ($M+H^+$).

Éster terc-butílico del ácido 4-(5,7-dicloro-isoquinolin-6-iloxi)-piperidin-1-carboxílico (377)



El compuesto del título se sintetizó siguiendo el protocolo descrito para el éster terc-butílico del ácido 4-(isoquinolin-6-iloxi)-piperidin-1-carboxílico (154). Después de la purificación final por HPLC preparativa y evaporación de las fracciones del producto, el grupo Boc ya está parcialmente desprendido. R_t = 1,71 min (Método #2). Masa detectada: 397,2/399,2 ($M+H^+$).

5,7-Dicloro-6-(piperidin-4-iloxi)-isoquinolina (378)



Se disolvieron 150 mg de éster terc-butílico del ácido 4-(5,7-dicloro-isoquinolin-6-iloxi)-piperidin-1-carboxílico (377, ya parcialmente desprotegido) en 10 ml de diclorometano y se añade 1 ml de ácido trifluoroacético a 0°C. La disolución se agita durante 2 h a temperatura ambiente. Para la elaboración, se añadieron 50 ml de diclorometano y la disolución se lavó con disolución saturada de NaHCO3. Se separaron las capas y la fase acuosa se extrajo una vez con diclorometano. Las capas orgánicas combinadas se lavaron de nuevo con disolución saturada de NaHCO3, se secaron con MgSO4 y se evaporaron. El residuo se purificó por HPLC preparativa. Las fracciones del producto se evaporaron y el residuo se disolvió en HCl 2 n. Después de la evaporación, se aisló el compuesto del título como sal de HCl. R_t = 0,90 min (Método #2). Masa detectada: 297,1/299,1 ($M+H^+$).

Determinación de la inhibición de Rho cinasa

Para medir la inhibición de Rho-cinasa, se determinaron los valores de IC_{50} según el protocolo siguiente:

Tampón: Tris 25 mM pH 7,5; BSA al 0,02%; Glicerol al 5%; Triton X100 0,008%; DMSO al 2%, DTT 1 mM; $MgCl_2$ 1 mM; $\gamma^{33}P$ ATP 0,5 µCi/pocillo

Enzima: ROCKII o ROKα) (Upstate, Catálogo # 14-451 Lot # 24880U) 0,1 ng/µl

Concentración final de ATP en al mezcla de reacción 40 µM

Sustrato biotinilado, diluido a 0,25 µM con tampón descrito más arriba (sin ATP)

1. 10 µl de tampón Tris (± Inhibidor)
2. Añadir 30 µL de disolución de enzima
3. Comenzar la reacción con 30 µL de mezcla sustrato/ATP/ATP33
4. Incubar durante 20 min a temperatura ambiente
5. Parar la reacción con 30 µL de EDTA 50 mM
6. Transferir 50 µL de la disolución parada a la Streptavidin Flash Plate plus (placa con estreptavidina), Perkin Elmer, SMP 103A
7. Incubar durante 30 min a temperatura ambiente
8. Lavar 4 veces con 300 µl de PBS/Tween 20 al 0,1%
9. Se determinó la radioactividad en el pocillo

Nº	IC50
29	+++
41	++++
44	++++
59	++++
67	+++
72	++++
81	++++
111	+++
100	+++
120	++++
133	++++
134	+++
138	++++
145	+++
156	++++
228	++++
261	++++
265	+++
266	+++
269	++++
378	++++

La actividad dada se denota como el logaritmo negativo de la IC_{50} (pIC_{50}) como sigue:

+: $3,0 \leq pIC_{50} < 4,0$

++: $4,0 \leq pIC_{50} < 5,0$

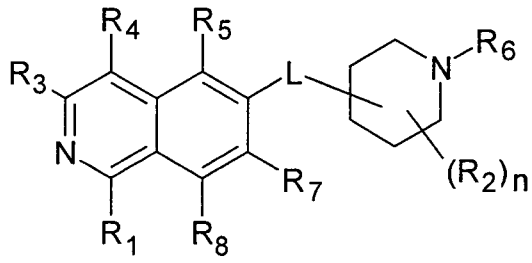
+++: $5,0 \leq pIC_{50} < 6,0$

++++: $6,0 \leq pIC_{50}$

246

REIVINDICACIONES

1. Un compuesto de la fórmula (I)



(I)

en la que

R_1 es

H,

alquilo(C_1-C_6),

R',

NH-alquil(C_1-C_6),

NHR', o

N[alquil(C_1-C_6)]$_2$;

R_2 es hidrógeno, halógeno o alquilo(C_1-C_6);

R_3 es

H,

halógeno,

alquilo(C_1-C_6),

alquileno(C_1-C_6)-R',

OH,

O-R",

NH_2,

NHR",

NR"R" o

NH-C(O)-R",

R_4 es

H,

halógeno,

hidroxi,

CN,

alquilo(C_1-C_6),

R',

alquileno(C_1-C_6)-R';

R_5 es

H,

halógeno,

CN,

NO_2,

alquilo(C_1-C_6),

alquenilo(C_2-C_6),

R',

alquileno(C_1-C_6)-aril(C_6-C_{10}),

alquenileno(C_1-C_6)-aril(C_6-C_{10}),

alquileno(C_1-C_6)-heterociclil(C_5-C_{10}),

CH(OH)-alquil(C_1-C_6),

NH_2,

NH-R',

$NH-SO_2H$,

$NH-SO_2$-alquil(C_1-C_6),

$NH-SO_2$-R',

NH-C(O)-alquil(C_1-C_6),

NH-C(O)-R',

C(O)N[alquil(C_1-C_6)]$_2$,

C(O)OH, o

C(O)O-alquil(C_1-C_6);

R_6 es

H,

R',

alquilo(C_1-C_8),

alquileno(C_1-C_6)-R',

alquileno(C_1-C_6)-O-alquil(C_1-C_6),

alquileno(C_1-C_6)-O-R',

alquileno(C_1-C_6)-CH[R']$_2$,

alquileno(C_1-C_6)-C(O)-R',

alquileno(C_1-C_6)-C(O)NH_2,

alquileno(C_1-C_6)-C(O)NH-R', o

alquileno(C_1-C_6)-C(O)N[R']$_2$;

R_7 es

H,

halógeno,

CN,

NO_2,

alquilo(C_1-C_6),

alquenilo(C_2-C_6),

R',

alquenileno(C_1-C_6)-aril(C_6-C_{10}),

alquileno(C_1-C_6)-R',

CH(OH)-alquil(C_1-C_6),

NH_2,

NH-R',

NH-SO_2H,

NH-SO_2-alquil(C_1-C_6),

NH-SO_2-R',

SO_2-NH_2,

SO_2-NHR',

NH-C(O)-alquil(C_1-C_6),

NH-C(O)-R',

C(O)N[alquil(C_1-C_6)]$_2$,

C(O)OH, o

C(O)O-alquil(C_1-C_6);

R8 es H, halógeno o alquilo(C_1-C_6);

n es 1, 2, 3 o 4; y

L es O o O-alquileno(C_1-C_6);

en la que

R' es

cicloalquilo(C_3-C_8),

heterociclilo(C_5-C_{10}),

arilo(C_6-C_{10}); y

R" es

cicloalquilo(C_3-C_8),

heterociclilo(C_5-C_{10}),

arilo(C_6-C_{10}),

alquilo(C_1-C_6),

alquileno(C_1-C_6)-R',

alquileno(C_1-C_6)-O-alquil(C_1-C_6),

alquileno(C_1-C_6)-O-R', o

alquileno(C_1-C_6)-NR_xR_y; y

en el que R_x y R_y son independientemente uno del otro

alquilo(C_1-C_6),

heterociclilo(C_5-C_{10}),

arilo(C_6-C_{10}),

alquileno(C_1-C4)-heterociclil(C_5-C_{10}),

alquileno(C_1-C4)-aril(C_6-C_{10}),

alquileno(C_1-C4)-NHalquil(C_1-C_6),

alquileno(C_1-C4)-NH[alquil(C_1-C_6)]2,

alquileno(C_1-C_4)-N[aril(C_6-C_{10})]$_2$, o

alquileno(C_1-C4)-N[heterociclil(C_5-C_{10})]2; y

en la que en los residuos R_4, R_5, R_7 y R_8 un átomo de hidrógeno del alquilo o el alquileno opcionalmente puede estar sustituido por OH, F, OCH_3, COOH, $COOCH_3$, NH_2, $NHCH_3$, $N(CH_3)_2$, $CONH_2$, $CONHCH_3$ o $CON(CH_3)_2$;

y sus sales farmacéuticamente aceptables y/o sus derivados fisiológicamente funcionales.

2. Un compuesto según la reivindicación 1, en el que R_1 es H, alquilo(C_1-C_6), arilo(C_6-C_{10}), NH-alquil(C_1-C_6), NH-aril(C_6-C_{10}) o N[alquil(C_1-C_6)]$_2$.

3. Un compuesto según una de las reivindicaciones 1 o 2, en el que R_1 es H, alquilo(C_1-C_4), NH-alquil(C_1-C_4), N[alquil(C_1-C_4)]$_2$ o NH-fenil.

4. Un compuesto según una de las reivindicaciones 1 a 3, en el que R_1 es H, alquilo(C_1-C_2) o NH-alquil(C_1-C_2).

5. Un compuesto según una de las reivindicaciones 1 a 4, en el que R_1 es H.

6. Un compuesto según una de las reivindicaciones 1 a 5, en el que R_3 es H, halógeno, (C_1-C_4)alquileno-R', O-R'' o NHR'', y en el que R' y R'' se definen como en la reivindicación 1.

7. Un compuesto según una de las reivindicaciones 1 a 6, en el que R_3 es H o NHR''.

8. Un compuesto según una de las reivindicaciones 1 a 7, en el que R_3 es H; NH-heterociclil(C_5-C_6), preferentemente NH-heteroaril(C_5-C_6) que contiene uno o más átomos de N; o NH-fenil.

9. Un compuesto según una de las reivindicaciones 1 a 8, en el que R_8 es H, halógeno o alquilo(C_1-C_4).

10. Un compuesto según una de las reivindicaciones 1 a 9, en el que R_8 es H, Cl, F, metilo o etilo.

11. Un compuesto según una de las reivindicaciones 1 a 10, en el que R_4 es H, halógeno o alquilo(C_1-C6).

12. Un compuesto según una de las reivindicaciones 1 a 11, en el que R_4 es H, halógeno o alquilo(C_1-C_4).

13. Un compuesto según una de las reivindicaciones 1 a 12, en el que R_4 es H.

14. Un compuesto según una de las reivindicaciones 1 a 13, en el que R_5 es H, halógeno, CN, alquilo(C_1-C_6), R', NH-aril(C_6-C_{10}) o alquileno(C_1-C_6)-R'.

15. Un compuesto según una de las reivindicaciones 1 a 14, en el que R_5 es H, halógeno, alquilo(C_1-C_6), R', NH-aril(C_6-C_{10}) o alquileno(C_1-C_6)-R'.

16. Un compuesto según una de las reivindicaciones 1 a 15, en el que R_5 es H, halógeno, alquilo(C_1-C_6), aril(C_6-C_{10}), NH-aril(C_6-C_{10}), alquilo(C_1-C_2)-aril(C_6-C_{10}) o heteroarilo(C_5-C_{10}).

17. Un compuesto según una de las reivindicaciones 1 a 16, en el que R_7 es H, halógeno, CN, alquilo(C_1-C_6), alquenilo(C_2-C_6), R' o alquileno(C_1-C_6)-cicloalquil(C_3-C_8).

18. Un compuesto según una de las reivindicaciones 1 a 17, en el que R_7 es H, halógeno, CN, alquilo(C_1-C4), alquenilo(C_2-C4), fenilo, ciclopropilo o heteroarilo(C_5-C_6).

19, Un compuesto según una de las reivindicaciones 1 a 18, en el que R_7 es H, fluoro, cloro, bromo, metilo, etilo, fenilo, nitrilo, ciclopropilo, tienilo o vinilo.

20. Un compuesto según una de las reivindicaciones 1 a 19, en el que n es 1, 2 o 3.

21. Un compuesto según una de las reivindicaciones 1 a 20, en el que n es 1.

22. Un compuesto según una de las reivindicaciones 1 a 21, en el que R_2 es H, halógeno o alquilo(C_1-C_4).

23. Un compuesto según una de las reivindicaciones 1 a 22, en el que R_2 es H o alquilo(C_1-C_4).

24. Un compuesto según una de las reivindicaciones 1 a 23, en el que R_2 es H, alquilo(C_1-C2).

25. Un compuesto según una de las reivindicaciones 1 a 24, en el que R_6 es H, alquilo(C_1-C_6), R', alquileno(C_1-C_4)-cicloalquil(C_3-C_8), alquileno(C_1-C_4)-heterociclil(C_5-C_{10}), alquileno(C_1-C_4)-C(O)-heterociclil(C_5-C_{10}), alquileno(C_1-C_4)-C(O)-aril(C_6-C_{10}) o alquileno(C_1-C_6)-aril(C_6-C_{10}).

26. Un compuesto según una de las reivindicaciones 1 a 25, en el que R_6 es H, alquilo(C_1-C_6), heterociclil(C_5-C_{10}), alquileno(C_1-C_4)-heterociclil(C_5-C_{10}) o alquileno(C_1-C_6)-aril(C_6-C_{10}).

27. Un compuesto según una de las reivindicaciones 1 a 26, en el que L está unido a la posición 3 o a la posición 4 del anillo de piperidina.

28. Un compuesto según una de las reivindicaciones 1 a 27, en el que L está unido a la posición 4 del anillo de piperidina.

29. Un compuesto según una de las reivindicaciones 1 a 28, en el que L es O-metileno, O-etileno o preferentemente O.

30. Un compuesto según la reivindicación 1, en el que

R_1 es H, alquilo(C_1-C_6), arilo(C_6-C_{10}), NH-alquil(C_1-C_6), NH-aril(C_6-C_{10}), o N[alquil(C_1-C_6)]$_2$;

R_2 es hidrógeno, halógeno, o alquilo(C_1-C_6);

R_3 es H, halógeno, alquileno(C_1-C_4)-R', O-R" o NHR", en el que R' y R" se definen como en la reivindicación 1;

R4 es H, halógeno o alquilo(C_1-C_6);

R_5 es H, alquilo(C_1-C_6), halógeno, CN, arilo(C_6-C_{10}), NH-aril(C_6-C_{10}), alquileno(C_1-C_6)-aril(C_6-C_{10}), heterociclilo(C_5-C_{10}) o alquileno(C_1-C_6)-heterociclil(C_5-C_{10});

R_6 es H, alquilo(C_1-C_6), R', alquileno(C_1-C_4)-heterociclil(C_5-C_{10}), alquileno(C_1-C_6)-C(O)-aril(C_6-C_{10}), alquileno(C_1-C_4)-C(O)-heterociclil(C_5-C_{10}), o alquileno(C_1-C_6)-aril(C_6-C_{10});

R_7 es H, halógeno, CN, alquilo(C_1-C_6), alquenilo(C_2-C_6) o R';

R8 es H, halógeno o alquilo(C_1-C_6);

n es 1, 2 o 3, y

L es O, O-metileno o O-etileno.

31. Un compuesto según la reivindicación 1, en el que

R_1 es H, alquilo(C_1-C_6), arilo(C_6-C_{10}), NH-alquil(C_1-C_6), NH-aril(C_6-C_{10}), o N[alquil(C_1-C_6)]$_2$;

R_2 es H o alquilo(C_1-C_4);

R_3 es H, halógeno o NHR", en el que R" se define como más arriba;

R4 es H, halógeno o alquilo(C_1-C4);

R_5 es H, alquilo(C_1-C_6), halógeno, arilo(C_6-C_{10}), NH-aril(C_6-C_{10}), alquileno(C_1-C_6)-aril(C_6-C_{10}) o heterociclil(C_5-C_{10});

R_6 es H, alquilo(C_1-C_6), R', alquileno(C_1-C_4)-heterociclil(C_5-C_{10}) o alquileno(C_1-C_6)-aril(C_6-C_{10});

R_7 es H, halógeno, CN, alquilo(C_1-C_6), alquenilo(C_2-C_6) o R';

R8 es H, halógeno o alquilo(C_1-C_6);

n es 1, 2 ó 3; y

L es O.

32. Un compuesto según la reivindicación 1, en el que

R_1 es H, alquilo(C_1-C_4), NH-alquil(C_1-C_4), N[alquil(C_1-C_4)]$_2$ o NH-fenil;

R_2 es H, alquilo(C_1-C_4);

R_3 es H, NH-heteroaril(C_5-C_6) o NH-fenil;

R4 es H, halógeno o alquilo(C_1-C4);

R_5 es H, alquilo(C_1-C_4), halógeno, aril(C_6-C_{10}), NH-aril(C_6-C_{10}), alquilo(C_1-C_2)-aril(C_6-C_{10}) o heteroarilo(C_5-C_{10});

R_6 es H, alquilo(C_1-C_6), heterociclilo(C_5-C_{10}), alquileno(C_1-C_4)-heterociclil(C_5-C_{10}), arilo(C_6-C_{10}) o alquileno(C_1-C_6)-aril(C_6-C_{10});

R_7 es H, halógeno, CN, alquilo(C_1-C_4), alquenilo(C_1-C_4), fenilo, ciclopropilo, heteroarilo(C_5-C_6);

R8 es H, halógeno o alquilo(C_1-C4);

n es 1; y

L es O.

33. El uso de por lo menos uno de los compuestos de la fórmula (I) y/o su sal fisiológicamente aceptable según una de las reivindicaciones 1 a 32, para producir un medicamento.

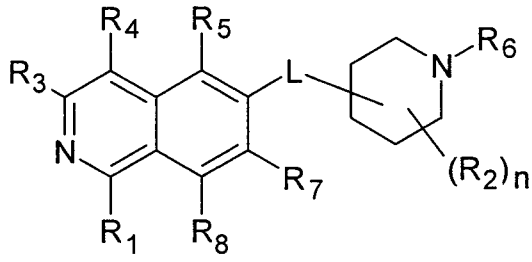
34. El uso de por lo menos uno de los compuestos de la fórmula (I) y/o su sal fisiológicamente aceptable según una de las reivindicaciones 1 a 32, para producir un medicamento para el tratamiento y/o prevención de hipertensión, hipertensión pulmonar, hipertensión ocular, trastorno circulatorio periférico, angina de pecho, vasoespasmo cerebral, asma, parto prematuro, hiperagregabilidad de las plaquetas, Enfermedad Arterial Oclusiva Periférica (PAOD), Enfermedad Pulmonar Obstructiva Crónica (COPD), desarrollo de cáncer, disfunción eréctil, arteriosclerosis, insuficiencia orgánica isquémica (daño del órgano afectado), fibrosis pulmonar, fibrosis hepática, insuficiencia hepática, fibrosis renal, glomeruloesclerosis renal, insuficiencia renal, hipertrofia orgánica, hipertrofia prostática, complicaciones de diabetes, reestenosis de vasos sanguíneos, ateroesclerosis, cáncer, hipertrofia cardiaca, insuficiencia cardiaca, enfermedades isquémicas; inflamación; enfermedades autoinmunitarias; SIDA, osteopatía tal como osteoporosis, trastorno funcional del cerebro, infección de los tubos digestivos con bacterias, sepsis, síndrome de dificultad respiratoria aguda, retinopatía, glaucoma o enfermedad de Alzheimer.

35. Un medicamento que comprende una cantidad eficaz de por lo menos un compuesto según cualquiera de las reivindicaciones 1 a 32, y/o una sal farmacológicamente aceptable del mismo, excipientes y vehículos fisiológicamente tolerados y, en el caso de que sea apropiado, aditivos adicionales y/u otros principios activos.

Resumen

DERIVADOS DE ISOQUINOLINA COMO INHIBIDORES DE RHO-CINASA

La invención se refiere a derivados de isoquinolina sustituidos en posición 6 con piperidinilo de la fórmula (I)



(I),

útiles para el tratamiento y/o prevención de enfermedades asociadas con Rho-cinasa y/o la fosforilación mediada por Rho-cinasa de la fosfatasa de la cadena ligera de miosina, y a composiciones que contienen tales compuestos.

257

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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISION DE NUEVAS CREACIONES
TARJETA ARCHIVO PROPIETARIOS

PATENTE DE INVENCION ___ PCT X MODELO DE UTILIDAD ___ DISEÑO INDUSTRIAL ___

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(71)Solicitante(s) **SANOFI-AVENTIS**

(72) Inventor(es) **OLIVER PLETTENBURG; ARMIN HOFMEISTER; DIETER KADEREIT; STEFAN PEUKERT; SVEN RUF; KURT RITTER; MATTHIAS LÖHN; YURI IVASHCHENKO; PETER MONECKE; MATTHIAS DREYER; AIMO KANNT**

(74) Apoderado: **DR. LUIS PATIÑO LEYVA**

(30) Prioridad	(31) **Nº Prioridad**	32) **Fecha**	(33) **País**
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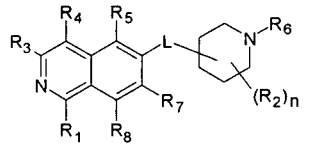
(30) Prioridad (31) Nº Prioridad 32) Fecha (33) País **05013868.4** **28/06/2005** **EP**	(72) Inventor(es) **OLIVER PLETTENBURG Y OTROS**
	(74) Apoderado: **LUIS PATIÑO**
(85) Fecha limite inicio fase nacional: 28/01/2008 (86) Datos relativos a la presentación de la solicitud PCT Fecha de presentación de la solicitud: **13/06/2006** Nº de solicitud **PCT/EP2006/005648**	(87) Publicación internacional Fecha: **04/01/2007** Nº publicación: **WO 2007/000240 A1**
(54) Titulo: **DERIVADOS DE ISOQUINOLINA**	

Reivindicación(es):

1. Un compuesto de la fórmula (I)



(I)

en la que

R_1 es
H,
alquilo(C_1-C_6),
R',
NH-alquil(C_1-C_6),
NHR', o
N[alquil(C_1-C_6)]$_2$;

R_2 es hidrógeno, halógeno o alquilo(C_1-C_6);

R_3 es
H,
halógeno,
alquilo(C_1-C_6),
alquileno(C_1-C_6)-R',
OH,
O-R",
NH_2,
NHR",
NR"R" o
NH-C(O)-R",

R_4 es
H,
halógeno,
hidroxi,
CN,
alquilo(C_1-C_6),
R',
alquileno (C_1-C_6)-R';

R_5 es
H,
halógeno,
CN,
NO_2,
alquilo(C_1-C_6),
alquenilo(C_2-C_6),
R',
alquileno(C_1-C_6)-aril(C_6-C_{10}),
alquenileno(C_1-C_6)-aril(C_6-C_{10}),
alquileno(C_1-C_6)-heterociclil(C_5-C_{10}),
CH(OH)-alquil(C_1-C_6),

NH_2,
NH-R',
NH-SO_2H,
NH-SO_2-alquil(C_1-C_6),
NH-SO_2-R',
NH-C(O)-alquil(C_1-C_6),
NH-C(O)-R',

259

PCT/EP2006/005648

TL

PATENT COOPERATION TREATY

PCT

From the INTERNATIONAL BUREAU

To:

SANOFI-AVENTIS DEUTSCHLAND GMBH
Patentabteilung
Industriepark Höchst, Geb. K801
65926 Frankfurt am Main
ALLEMAGNE

NOTIFICATION OF THE RECORDING OF A CHANGE

(PCT Rule 92*bis*.1 and Administrative Instructions, Section 422)

Date of mailing *(day/month/year)* 25 July 2007 (25.07.2007)	
Applicant's or agent's file reference DE2005/032	**IMPORTANT NOTIFICATION**
International application No. PCT/EP2006/005648	International filing date *(day/month/year)* 13 June 2006 (13.06.2006)

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
SANOFI-AVENTIS DEUTSCHLAND GMBH Brüningstrasse 50 65929 Frankfurt am Main Germany	DE	DE
	Telephone No.	
	Facsimile No.	
	Teleprinter No.	

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

☒ the person ☐ the name ☐ the address ☐ the nationality ☐ the residence

Name and Address	State of Nationality	State of Residence
SANOFI-AVENTIS ,74, avenue de France F-75013 Paris France	FR	FR
	Telephone No.	
	Facsimile No.	
	Teleprinter No.	

3. Further observations, if necessary:

4. A copy of this notification has been sent to:

☒ the receiving Office
☐ the International Searching Authority
☐ 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 82 70	Authorized officer Blanc Veronique e-mail Veronique.Blanc@wipo.int Telephone No. +41 22 338 96 66

1/DBXOQ6DG19

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
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Act. 411 PRESENTACION Folios: 259

Industria y Comercio
SUPERINTENDENCIA

Delegatura de Propiedad Industrial
División de Nuevas Creaciones

REQUISITOS NECESARIOS PARA PRESENTACION Y AGILIZACION DEL TRÁMITE

	USUARIO	RADICADOR
PATENTE DE INVENCION (X) MODELO DE UTILIDAD ( )	(X)	(✓)
- Indicación de que se solicita la concesión de una patente	(X)	(✓)
- Datos de identificación del solicitante o de la persona que presenta la solicitud	(X)	(✓)
- Descripción de la invención	(X)	(✓)
- Dibujos de ser estos pertinentes	( )	( )
- Comprobante de pago de las tasas establecidas	(X)	(✓)

COMPLETA (X) INCOMPLETA ( )

DISEÑO INDUSTRIAL ( )		
- Indicación de que se solicita el registro de Diseño Industrial	( )	( )
- Datos de identificación del solicitante o de la persona que presenta la solicitud	( )	( )
- Representación gráfica y fotográfica del Diseño Industrial o muestra del material que incorpora el diseño	( )	( )
- Comprobante de pago de las tasas establecidas	( )	( )

COMPLETA ( ) INCOMPLETA ( )

EZQUEMA DE TRAZADO ( )		
- Indicación de que se solicita el registro de Diseño Industrial	( )	( )
- Datos de identificación del solicitante o de la persona que presenta la solicitud	( )	( )
- Representación gráfica del Esquema de Trazado	( )	( )
- Comprobante de pago de las tasas establecidas	( )	( )

COMPLETA ( ) INCOMPLETA ( )

Firma responsable: Claudia M Neiva Cortes

Fecha: _____