CSA055696
Organización y Digitalización CSA

QF

PCT

INVENTIVA

Industria y Comercio

SUPERINTENDENCIA

09-106551

DELEGATURA DE PROPIEDAD INDUSTRIAL

DIRECCION DE NUEVAS CREACIONES

SOLICITUD DE PATENTE DE INVENCION

TITULO 3-IMIDAZOLIL-INDOLES PARA EL TRATAMIENTO DE ENFERMEDADES PROLIFERATIVAS

SOLICITANTE NOVARTIS AG

DIRECCION Lichtstrasse 35, CH- 4056 Basel, Suiza

APODERADO CARLOS R OLARTE

BOGOTA 29 de Septiembre de 2009

P2009/000162

FW 29 10 2009

OLARTERAISBECK
OLARTE RAISBECK MOURE & CASTRO LTDA.

Industria y Comercio
SUPERINTENDENCIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 09-106551- -00000-0000
Fecha: 2009-09-29 16:03:55 Dep: 2020 NUECREACIONE
Tra. 11 PATENTEIYII Eve: 379 FASENACIONALII
Act. 411 PRESENTACION Folios: 690

PETITORIO - FORMULARIO Ú
PATENTE P
ENTRADA EN FASE NACIONAL **P2009/000162**

SOLICITUD DE:

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

[ ] Capítulo I. [X] Capítulo II.

(2) **SOLICITANTE (71)**	**Nombre:** NOVARTIS AG **Dirección:** Lichtstrasse 35, CH-4056 Basel **Nacionalidad o Domicilio:** Suiza **Lugar de Constitución:** Suiza **Teléfono:** _____ **Fax:** _____ **E-mail:** _____	**IDENTIFICACIÓN** **C.C.** [ ] **NIT** [ ] **C.E.** [ ] **Otro** [ ] **Cual** _____ **Número** _____
REPRESENTANTE O APODERADO	**Nombre:** CARLOS R. OLARTE **Dirección:** World Trade Center Torre A, Calle 100 No. 8A-37 Piso 10 **Teléfono:** 601-7700 **Fax:** 601-7799 **E-mail:** office@olarteraisbeck.com	**IDENTIFICACIÓN** **C.C.** [X] **NIT** [ ] **C.E.** [ ] **Otro** [ ] **Cual** _____ **Número** 79782747Bta **TP** 74.295
INVENTOR (ES) (72)	**Nombre:** VER PAGINA ADJUNTA **Dirección:** VER PAGINA ADJUNTA **Nacionalidad o Domicilio:** VER PAGINA ADJUNTA	

(5) **PCT (86)**

Solicitud Internacional No. PCT/EP2008/053667 Fecha Marzo 27, 2008

Publicación Internacional No. WO 2008/119741 Fecha octubre 9, 2008

(6) **Título (54)** **3-IMIDAZOLIL-INDOLES PARA EL TRATAMIENTO DE ENFERMEDADES PROLIFERATIVAS**

Clasificación Internacional (51) C07D 403/04, A61K 31/4164, A61P 35/00

Prioridad SI [X] NO [ ]	(33) País de Origen	(32) Fecha	(31) Número de Solicitud
	US	Marzo 29, 2007	07105269.0

(9) **Comprobante de pago No.** 09- **Fecha** 29 de Septiembre 2009

(10) **ANEXOS**

2

- [x] Comprobante de pago de la tasa de presentación de la solicitud.
- [x] Documento que acredita la existencia y representación legal cuando el solicitante sea persona jurídica.
- [x] Poderes, si fuere el caso. Adjunto copia simple ver expediente No. 08-066177
- [x] 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.
- [ ] Arte final 12 x 12.
- [ ] De ser el caso, información sobre otras solicitudes de patente o títulos obtenidos en el extranjero por el mismo titular o su causante, relacionadas parcial o totalmente con la invención de esta solicitud.
- [ ] De ser el caso, *modificaciones efectuadas a la solicitud internacional.*
- [x] Otros. Búsqueda Internacional.

(11) **FIGURA CARACTERÍSTICA:**

(12) Solicito la concesión de la patente,

NOMBRE: CARLOS R. OLARTE FIRMA:

C.C. 79.782.747 Btá T.P. 74.295

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

3

LISTA DE INVENTORES

PCT/EP2008/053667

1. **Andreas BOETTCHER,**
   Röttelerstr. 15,
   CH-4058 Basel
   Suiza
   Nacionalidad: Alemana

2. **Nicole BUSCHMANN,**
   Horburgstrasse 19,
   CH-4057 Basel
   Suiza
   Nacionalidad: Alemana

3. **Pascal FURET,**
   19, rue de la Forêt,
   F-68800 Thann
   Francia
   Nacionalidad: Francesa

4. **Jean-Marc GROELL,**
   Rue de Muespach 4a,
   F-68640 Steinsoultz
   Francia
   Nacionalidad: Francesa

5. **Jörg KALLEN,**
   Kaltbrunnesnstrasse 41,
   CH-4054 Basel
   Suiza
   Nacionalidad: Suiza

6. **Joanna HERGOVICH LISZTWAN,**
   11b rue de Delle,
   F-68640 Steinsoultz
   Francia
   Nacionalidad : Francesa

7. **Keiichi MASUYA,**
   Gemeindeholzweg 30,
   CH-4103 Bottmingen
   Suiza
   Nacionalidad : Japonesa

8. **Lorenz MAYR,**
   Fritz-Schülin-Weg 16,
   79589 Binzen
   Alemania
   Nacionalidad : Alemana

9. **Andrea VAUPEL,**
   Rütiring 23,
   CH-4125 Riehen
   Alemania
   Nacionalidad : Alemana

Nota del traductor:

El documento adjunto de poder de Novartis AG a Carlos R. Olarte y/o J. Ian Raisbeck y/o Ana Maria Frieri y/o Juan Guillermo Moure y/o Natalia Castro lleva los siguientes datos en inglés.

CERTIFICACIÓN NOTARIAL

1. En esta fecha, día 30 de Agosto de 2006, yo, el suscrito Notario Público certifico por medio del presente la autenticidad de las firmas del señor Arthur Canonica, ciudadano de Corticiasca, Suiza, residente en Wisen/SO, Suiza, y del Sr. Pascal Traub, ciudadano de Riehen, Suiza, residente en Basilea, Suiza, ambos personas mayores de edad y con dirección comercial en Lichstrasse 35, 4056, Basilea, Suiza. La autenticidad de la firmas fue establecida por medio de la comparación.
2. Además, yo, el Notario Público, certifico por el presente que las anteriores personas han ejecutado el anterior documento como apoderados de Novartis AG.
3. Además, yo, el Notario Público certifico por el presente que Novartis AG, con su principal lugar de negocios en Basilea, Suiza, está debidamente constituida, está actualmente vigente y que los propósitos para los cuales se otorgó el Documento de Poder están dentro del alcance de sus propósitos corporativos.

Traductor Ofi
JORGE E. SIERRA
Licencia 376 - 1993

4. Además, yo, el Notario Público, certifico por el presente que las anteriores personas tienen la autoridad para ejecutar el documento de Poder y que por este instrumento, su representación es legal.

La base para mis certificaciones de los puntos 2, 3 y 4 fue la exhibición de los siguientes documentos auténticos:

- Documento de Poder de Novartis AG fechado el 19 de junio de 2006 y
- Extracto del Registro de Comercio del Cantón de la ciudad de Basilea para Novartis AG, en Basilea, fechado el 25 de enero de 2006.

Basilea, Suiza, este día 30 de Agosto de 2006.

(Firmado) Dr. Matthias Staehelin, Notario Público del Cantón de la ciudad de Basilea, Suiza.

Mi licencia vence el 11 de Marzo de 2009.

Hay una Apostilla de Suiza, firmada por Heidi Fischer, bajo el No. 8049/13584.

Traductor Offi
JORGE E. SIERRA
Licencia 376 - 1993

Certificación:

Certifico que la presente es una traducción verdadera y completa del documento adjunto: "Novartis"

Fecha: 12 de Septiembre de 2006.

Traductor: Jorge Enrique Sierra Reyes.

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

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

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

E-mail: treseser1@yahoo.com. No. 8346

Traductor Ofi
JORGE E. SIERRA
Licencia 376 - 1993

OLARTE RAISBECK

OLARTE RAISBECK & FRIERI LTDA.

Carlos R. O.
J. Ian Raisl
Ana María F
Juan Guillermo M
Natalia Ca

Zayde Ch
Jacqueline Chap
José Luis Lond
Felipe Men
Simón Sal

Of Cou
Guillermo Chr
Graciela M

Power of Attorney

Poder

The undersigned,

El suscrito,

NOVARTIS AG

domiciled in

domiciliado en

Lichtstrasse 35, CH-4056 Basel / Switzerland

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

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

Signature/Firma:

Arthur Cannon

Pascal Traub

Date/Fecha: June 27, 2006

City,Country/Ciudad,País: Basel, Switzerland

Attestation

1 On this date, the 30th (thirtieth) day of August 2006 (two thousand and six), I, the undersigned Notary Public certify herewith the authenticity of the signatures of **Mr. Arthur Canonica**, citizen of Corticiasca, Switzerland, residing in Wisen/SO, Switzerland and of **Mr. Pascal Traub**, citizen of Riehen, Switzerland, residing in Basel, Switzerland, both of legal age and with business address at, Lichtstrasse 35, 4056 Basel, Switzerland. The authenticity of the signatures was established by means of comparison.

2 Further, I, the Notary Public certify herewith that the foregoing persons have executed the foregoing document as proxy holders for Novartis AG.

3 Further, I, the Notary Public certify herewith that Novartis AG, having its principal place of business located in Basel / Switzerland, is duly incorporated, is currently in existence, and that the purposes for which the Power of Attorney is granted are within the scope of its corporate purposes.

4 Further, I, the Notary Public certify herewith that the foregoing persons have the authority to execute the Power of Attorney and that for this instrument their representation is legal.

The foundation for my certifications contained in points 2 (two), 3 (three) and 4 (four) was the exhibition of the following authentic documents:

- Power of Attorney by Novartis AG dated June 19 (nineteen), 2006 (two thousand and six); and
- Extract from the Register of Commerce of the Canton of Basel-City for Novartis AG, in Basel, dated January 25 (twenty-five), 2006 (two thousand and six).

BASEL, Switzerland, this 30th (thirtieth) day of August 2006 (two thousand and six)

M. Staehelin Notar

Dr. Matthias Staehelin, Notary Public
in the Canton of Basel-City, Switzerland

My license expires on March 11 (eleven), 2009 (two thousand and nine).

Leg.Prot.Nr. 975 /2006

APOSTILLE

(Hague Convention of October 5th, 1961)

1. Country: Switzerland (Schweiz / Suisse)
   This official document
2. is signed by .....
3. in his/her function as .....
4. and certified by the seal of the .....

Certified 24. Aug. 2005

5. in Basel (Bâle) 6. on .....
7. by the State Chancery of the Canton of Basel-Stadt .....
8. no. .....
9. Seal/stamp: 10. Signature:

Heidi Fischer

STATE CHANCERY * BASEL CITY *

2

Box No. VIII (ii) DECLARATION: ENTITLEMENT TO APPLY FOR AND BE GRANTED A PATENT

The declaration must conform to the standardized wording provided for in Section 212; see Notes to Boxes Nos. VIII, VIII (i) to (v) (in general) and the specific Notes to Box No. VIII (ii). If this Box is not used, this sheet should not be included in the request.

Declaration as to the applicant's entitlement, as at the international filing date, to apply for and be granted a patent (Rules 4.17(ii) and 51*bis*.1(a)(ii)), in a case where the declaration under Rule 4.17(iv) is not appropriate:

in relation to this international application,

Novartis AG is entitled to apply for and be granted a patent by virtue of the following:

an assignment from:

Andreas BOETTCHER, citizen of Germany, Röttelerstr. 15, 4058 Basel/CH dated 28.03.08

Nicole BUSCHMANN, citizen of Germany, Horburgstrasse 19, 4057 Basel/CH dated 28.03.08

Pascal FURET, citizen of France, 19, rue de la Forêt, 68800 Thann/FR dated 28.03.08

Jean-Marc GROELL, citizen of France, Rue de Muespach 4a, 68640 Steinsoultz/FR dated 28.03.08

Jörg KALLEN, citizen of Switzerland, Kaltbrunnenstrasse 41, 4054 Basel/CH dated 28.03.08

Joanna HERGOVICH LISZTWAN, citizen of Canada, 11b rue de Delle, 68640 Muespach le Haut/FR dated 28.03.08

Keiichi MASUYA, citizen of Japan, Gemeindeholzweg 30, 4103 Bottmingen/CH dated 28.03.08

Lorenz MAYR, citizen of Germany, Fritz-Schülin-Weg 16, 79589 Binzen/DE dated 29.03.08

Andrea VAUPEL, citizen of Germany, Rütiring 23, 4125 Riehen/CH dated 28.03.08

to Novartis AG

☐ This declaration is continued on the following sheet, "Continuation of Box No. VIII (ii)".

09-162

Caso de Patente: 50849

CESIÓN

Por buena y onerosa consideración, del cual se acusa recibo suficiente, nosotros

Andreas BOETTCHER	Nacionalidad Alemán	Rottelerst. 15 4058 Basilea CH
Nicole BUSCHMANN	Nacionalidad Aleman	Horburgstraasse 19 4057 Basilea CH
Pascal FURET	Nacionalidad Frances	19, rie de la Foret 68800 Thann FR
Jean-Marc GROELL	Nacionalidad Francés	Rue de Muespach 4ª 68640 Steinsoultz FR
Jorg KALLEN	Nacionalidad Suizo	Kaltbrunnenstrasse 41 4054 Basilea CH
Joanna ERGOVICH LISZTWAN	Nacionalidad Canadiense	11b rue de Delle 68640 Muespach le Haut FR
Keiichi MASUYA	Nacionalidad Japon	Gemeindeholzweg 30 4103 Bottmingen CH
Lorenz MAYR	Nacionalidad Alemán	Fritz-Schulin-Weg 16 79589 Binzen DE
Andrea VAUPEL	Nacionalidad Alemán	Rutiring 23 4125 Riehen CH

Por medio de la presente vendemos y transferimos a NOVARTIS AG, una compañía constituida bajo las leyes de la confederación Suiza, de Lichstrasse 35, 4056 Basilea, Suiza y sus sucesores, cesionarios y representantes legales todos nuestros derechos titulo e interés para todos los paises del mundo, excepto Austria, y Novartis Pharma GmbH, una compañía constituida bajo las Leyes de Austria de Bruner Strasse 59, 1230 Vienna, Austria y sus sucesores, cesionarios y representantes legales todos nuestros derechos titulo e interés para Austria (Novartis AG y Novartis Pharma GmbH, llamados de ahora en adelante colectivamente los CESIONARIOS) en y para (1) todos nuestros inventos y descubrimientos descritos en la solicitud de patente titulada:

3-imidazolil-indoles para el tratamiento de enfermedades proliferativas

MAURICE URREGO V
TRADUCTOR E INTERPRETE OFICIAL
INGLES - ESPAÑOL / ESPAÑOL - INGLES
RES. MINJUSTICIA 179[illegible] - 1988

Presentada* en el RO/EP el 27 de marzo, de 2008 , y de acuerdo con la Solicitud de Patente Internacional Numero PCT/EP2008/053667 , (2) dicha solicitud de patente (3) todas las fases nacionales de dicha solicitud de patente internacional, (4) todas las demás solicitudes de patentes en todas las regiones y países que reivindiquen prioridad de la solicitud de patente provisional presentada en la oficina de Marcas y Patentes Europeas el **29 de marzo de 2007** y de acuerdo con las solicitud número **07105269.0**, (5) todas las continuaciones y divisiones de todas las solicitudes de patentes mencionadas (Incluyendo además continuaciones y divisiones como tal, sin limites de continuaciones de continuaciones y continuaciones de divisiones), ((2)-(5) llamados de ahora en adelante colectivamente "solicitudes de patentes"), (6) todas las patentes que sean concedidas de cualquiera de las solicitudes de patentes mencionadas, (7) todos los registros y confirmaciones y certificados de importación basados en una o mas de las patentes mencionadas y (8) todos los re-otorgamientos, renovaciones, y extensiones de dichas patentes, emisión de certificados de reexaminación para dichas patentes y certificados de protección adicional basados en dichas patentes incluyendo el derecho a presentar las solicitudes de patentes de dichos inventos y descubrimientos en nombre del CESIONARIO, sus diseños en cualquier o en todos nuestros nombres, en todas las regiones y países para todas las solicitudes de patentes mencionadas bajo el Convenio Internacional para la Protección de la Propiedad Industrial, y todos los demás acuerdos internacionales similares que sean aplicables) así mismo para se conservada y disfrutada por dichos cesionarios, sus sucesores, cesionarios y representantes legales, proporcionar todos los términos para que todas las patentes puedan ser concedidas, para conservar y disfrutar plenamente y totalmente por nosotros, así mismo como lo harían si esta cesión no hubiera sido vendida y transferida.

*Nosotros por medio del presente autorizamos al CESIONARIO y sus representantes para incorporar en este instrumento el Número de la Solicitud y la fecha de presentación de dicha solicitud cuando esta sea notificada.

Y por medio de la presente nosotros convenimos y acordamos que en cualquier momento, al requerirse y a expensas del CESIONARIO, ejecutaremos y entregaremos cualquier y todos los documentos necesarios o deseables para perfeccionar el título de los anteriores inventos o descubrimientos, solicitudes de patente, registros confirmaciones, certificados de importación, re-otorgamientos, renovaciones, extensiones certificados de reexaminación, certificados de protección adicional a nombre del CESIONARIO, sus cesionarios, sucesores, u otros representantes legales, incluyendo la ejecución y consecución de cualquier y todo documento adicional que evidencie esta cesión y venta según sea necesario o deseable para el registro del mismo ante la Oficina de Patentes u otra oficina de propiedad industrial, agencia o de cualquier región o país en cuestión, y que nosotros, en cualquier momento, al requerirse y a expensas del CESIONARIO, ejecutaremos cualquier solicitud de patente adicional, solicitudes para registros y/o confirmaciones de una o mas de las patentes mencionadas, solicitudes de certificados de importación basada en una o mas de las patentes mencionada, solicitudes de re-otorgamientos renovaciones y extensiones de una o mas de las patentes mencionadas y

MAURICE URREGO V.
TRADUCTOR E INTERPRETE OFICIAL
INGLÉS - ESPAÑOL / ESPAÑOL - INGLÉS
RES. MINJ. [illegible] 1983

certificados de protección adicional basados en una o mas de las patentes mencionadas y realizaremos las declaraciones necesarias juramentadas y realizaremos todos los actos jurídicos necesarios para ello, sin compensación adicional, pero a expensas del CESIONARIO, sus sucesores, cesionarios, u otros representantes legales.

Ejecutado el 28 de marzo de 2008.

Andreas Boettcher, (firma ilegible) L.S.

Ejecutado el 28 de marzo de 2008.

Nicole Buschmann, (firma ilegible) L.S.

Ejecutado el 28 de marzo de 2008.

Pascal Furet, (firma ilegible) L.S.

Ejecutado el 28 de marzo de 2008.

Jean-Marc Groel, (firma ilegible) L.S.

Ejecutado el 28 de marzo de 2008.

Jorg Kalien, (firma ilegible) L.S.

Ejecutado el 28 de marzo de 2008.

Joanna Hergovich Lisztman, (firma ilegible) L.S.

Ejecutado el 28 de marzo de 2008.

Keiichi Masuya, (firma ilegible) L.S.

Ejecutado el 28 de marzo de 2008.

Lorenz May, (firma ilegible) L.S.

Ejecutado el 28 de marzo de 2008.

Andrea Vaupel, (firma ilegible) L.S.

MAURICE URREGO V.
TRADUCTOR E INTERPRETE OFICIAL
INGLES - ESPAÑOL - ESPAÑOL - INGLES
RES. MINJUSTICIA 173 - 1988

ACEPTACION DE LA CESION

En referencia con la cesión realizada a **NOVARTIS AG** de la invención titulada **"3-imidazolil-indoles para el tratamiento de enfermedades proliferativas"**, **firmada por Andreas Boettcher, Nicole Buschmann, Pascal Furet, Jean-Marc** Groell, Jorg Kallen, Joanna Hergovich Lisztwan, Keiichi Masuya, Lorenz Mayr, Andrea Vaupel; esta certificara que **NOVARTIS AG** acepta dicha cesión.

NOVARTIS AG

Por:	[Firma llegible]	[Firma llegible]
Nombre:	Bijana Colovic	Sabine Zeller
Cargo:	Administrador Experto en PI	Administrador Experto en PI
Fecha:	31-03-2008	

TESTIFICACION

Yo, el suscrito, Dr. Thomas Gelzer, notario público de Basilea, Suiza, certifico la autenticidad de las firmas del Sr. Andreas Bottcher, ciudadano Alemán, residente en Basilea, Suiza, el Sr. Nicole Buschmann, ciudadano Alemán, residente en Basilea, Suiza, el Sr. Pascl Furet, ciudadano Francés, residente en Steinsoultz, Francia, el Sr. Joerg Kallen, ciudadano de Futingen (BE), Suiza, residente en Basilea, Suiza; la sra. Joanna Hergovich Lisztwan, ciudadana Canadiense, residente en Muespach le Haut, Francia; el Sr. Keiichi Masuya, ciudadano Japonés, residente en Bottmingen (BL), Suiza; el Sr. Lorenz Mayr, ciudadano Alemán, residente en Binzen, Alemania; y el Dr. Andrea Vaupel, ciudadano Alemán, residente en Riehen, Suiza.

Además, certifico que lo anterior son las firmas autenticas de firmas de la **Sra. Sabine Zeller,** ciudadana Ormalingen/BL, Suiza, residente en Gelterkinden/BL, Suiza, y la Sra. Bijana Colovic, ciudadana Serbia, residente en Basilea/BS, Suiza; ambos actuando por **Novartis AG**, en Basilea, Suiza, como residentes, ambas con firmas conjunta poseedoras.

La autenticidad de la firma fue demostrada bajo comparación.

BASILEA, Suiza, 2 días del mes de abril de 2008

(Firma) llegible
Dr. Th, Gelzer
Notario

Leg.Prot.Nr. 384/2008

MAURICE [illegible]GO V.
TRADUCTOR E INTERPRETE OFICIAL
INGLES - ESPAÑOL - ESPAÑOL - INGLES
RES. MIN. [illegible] 1982

~~764~~
1125 CI
09/162

ASSIGNMENT

For good and valuable consideration, the receipt and adequacy of which is hereby acknowledged, we

1. Andreas BOETTCHER	citizen of Germany	Röttelerstr. 15 4058 Basel CH
2. Nicole BUSCHMANN	citizen of Germany	Horburgstrasse 19 4057 Basel CH
3. Pascal FURET	citizen of France	19, rue de la Forêt 68800 Thann FR
4. Jean-Marc GROELL	citizen of France	Rue de Muespach 4a 68640 Steinsoultz FR
5. Jörg KALLEN	citizen of Switzerland	Kaltbrunnenstrasse 41 4054 Basel CH
6. Joanna HERGOVICH LISZTWAN	citizen of Canada	11b rue de Delle 68640 Muespach le Haut FR
7. Keiichi MASUYA	citizen of Japan	Gemeindeholzweg 30 4103 Bottmingen CH
8. Lorenz MAYR	citizen of Germany	Fritz-Schülin-Weg 16 79589 Binzen DE
9. Andrea VAUPEL	citizen of Germany	Rütiring 23 4125 Riehen CH

do hereby sell, assign and transfer to **Novartis AG**, a company organized under the laws of the Swiss Confederation, of Lichtstrasse 35, 4056 Basel, Switzerland, and its successors, assigns and legal representatives, all our right, title and interest for all countries of the world (Novartis AG hereinafter referred to as the "**ASSIGNEE**") in and to (1) all of our inventions and discoveries described in the patent application(s) entitled

3-Imidazolyl-indoles for the treatment of proliferative diseases

filed* in the RO/ on March 27, 2008, and accorded International Patent Application Number PCT/EP2008/053667, (2) said patent application(s), (3) all national stages of said international patent application, (4) all other patent applications in all countries and regions claiming the priority of the European Procedure, patent application filed on March 29, 2007 and accorded Application Number 07105269.0 (5) all continuations and divisions of all of said patent applications (including further continuations and divisions such as, but not limited to, continuations of continuations and continuations of divisions), ((2)-(5) hereinafter referred to collectively as "patent applications"), (6) all patents that are granted on any of said patent applications, (7) all registrations and confirmations of, and importation certificates based on, one or more of said patents and (8) all reissues, renewals and extensions of said patents, reexamination certificates issued for said patents and supplementary protection certificates based on said

patents (including the right to file patent applications on said inventions and discoveries in the names of **ASSIGNEE**, their designees or in any or all of our names, at their election and in accordance with applicable law in all countries and regions and all rights of priority in all countries and regions for all of said patent applications under the International Convention for the Protection of Industrial Property, and all other applicable similar international agreements), the same to be held and enjoyed by said **ASSIGNEE**, their successors, assigns and legal representatives, to the full ends of the terms for which all patents therefor may be granted, as fully and entirely as the same would have been held and enjoyed by us if this sale, assignment and transfer had not been made.

*We hereby authorize **ASSIGNEE** and their representatives to insert in this instrument the Application Number and the filing date of said patent application when notified thereof.

And we hereby covenant and agree that we will, at any time, upon the request and at the expense of **ASSIGNEE**, execute and deliver all documents that may be necessary or desirable to perfect the title to the foregoing inventions and discoveries, patent applications, patents, registrations, confirmations, importation certificates, reissues, renewals, extensions, reexamination certificates and supplementary protection certificates in **ASSIGNEE**, their successors, assigns or other legal representatives, including the execution and procurement of all further documents evidencing this sale, assignment and transfer as may be necessary or desirable for recording the same in the patent office or other intellectual property office, agency or the like of any country or region, that we will, at any time, upon the request and at the expense of **ASSIGNEE**, execute all additional patent applications, applications for registration and/or confirmation of one or more of said patents, applications for certificates of importation based on one or more of said patents, applications for reissues, renewals and extensions of one or more of said patents and supplemental protection certificates based upon one or more of said patents, and that we will make all rightful oaths and declarations and do all lawful acts requisite for procuring the same or for aiding therein, without further compensation, but at the expense of **ASSIGNEE**, the successors, assigns or other legal representatives.

Executed this 28 day of March, 2008.

Andreas Boettcher L.S.

Name: Andreas Boettcher

Executed this 28 day of March, 2008.

Nicole Buschmann L.S.

Name: Nicole Buschmann

Executed this 28 day of MARCH, 2008.

Pascal Furet L.S.

Name: Pascal Furet

Executed this 28 day of March, 2008.

L.S.

Name: Jean-Marc Groell

Executed this 28 day of March, 2008.

Jörg Kallen L.S.

Name: Jörg Kallen

Executed this 28 day of MARCH, 2008.

_____ L.S.
Name: Joanna Hergovich Lisztwan

Executed this 28 day of March, 2008.

_____ L.S.
Name: Keiichi Masuya

Executed this 29 day of March, 2008.

_____ L.S.
Name: Lorenz Mayr

Executed this 28 day of March, 2008.

_____ L.S.
Name: Andrea Vaupel

ACCEPTANCE OF ASSIGNMENT

With reference to the Assignment to **NOVARTIS AG** of an invention entitled "3-Imidazolyl-indoles for the treatment of proliferative diseases" signed by Andreas Boettcher, Nicole Buschmann, Pascal Furet, Jean-Marc Groell, Jörg Kallen, Joanna Hergovich Lisztwan, Keiichi Masuya, Lorenz Mayr, Andrea Vaupel ; this will certify that **NOVARTIS AG** accepts such Assignment.

NOVARTIS AG

By :

Name : Biljana Colovic Sabine Zeller

Function : Head of Patents Services, NIBR Patents IP Administrative Expert

Date: 31. 03. 08

21

Attestation

I, **Dr. Thomas Gelzer**, the undersigned notary public of Basel, Switzerland, certify herewith the authenticity of the signature of **Mr. Andreas Böttcher**, German citizen, residing in Basel, Switzerland; of **Ms. Nicole Buschmann**, German citizen, residing in Basel, Switzerland; of **Mr. Pascal Furet**, French citizen, residing in Thann, France; of **Mr. Jean-Marc Groell**, French citizen, residing in Steinsoultz, France; of **Mr. Jöerg Kallen**, citizen of Frutingen (BE), Switzerland, residing in Basel, Switzerland; of **Ms. Joanna Hergovich Lisztwan**, Canadian citizen, residing in Muespach le Haut, France; of **Mr. Keiichi Masuya**, Japanese citizen, residing in Bottmingen (BL), Switzerland; of **Mr. Lorenz Mayr**, German citizen, residing in Binzen, Germany; and of **Dr. Andrea Vaupel**, German citizen, residing in Riehen, Switzerland.

I further certify that the above signatures are the genuine signatures of **Ms. Sabine Zeller**, citizen of Ormalingen/BL, Switzerland, residing in Gelterkinden/BL, Switzerland, and **Ms. Biljana Colovic**, citizen of Serbia, residing in Basel, Switzerland, both acting for **Novartis AG**, in Basel, Switzerland, both as proxy holders, both with joint signature.

The authenticity of the signatures was established by comparison.

BASEL, Switzerland, this 2nd (second) day of April 2008 (twothousandandeight)

Dr. Th. Gelzer
Notar

Leg.Prot.Nr. 384 /2008

22

FOR CERTIFIED COPY

I, the undersigned Civil Law Notary in Basel, Switzerland, Dr. Matthias Staehelin, hereby certify that the document attached heretofore is a true and authentic photocopy of the original.

BASEL, Switzerland, this 7th (seventh) day of September 2009 (two thousand and nine)

M. Staehelin, Notar

Dr. M. Staehelin
Notar

Leg.Prot.Nr. 2458/2009

APOSTILLE

(Hague Convention of October 5th, 1961)

1. Country: Switzerland (Schweiz / Suisse)
   This official document
2. is signed by ..... Dr. iur. .....
   ..... M. Staehelin .....
3. in his/her function as ..... notary public .....
4. and certified by the seal of the .....
   ..... above mentioned .....

Certified -7. Sep. 2009

5. in Basel (Bâle) 6. on .....
7. by the State Chancery of the Canton of Basel-Stadt .....
8. no. 6489/12434
9. Seal/stamp: 10. Signature

Helena Schaffner

STATE CHANCERY * BASLE-CITY *

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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
9 October 2008 (09.10.2008)

PCT

(10) International Publication Number
WO 2008/119741 A2

(51) International Patent Classification:
C07D 403/04 (2006.01) *A61P 35/00* (2006.01)
A61K 31/4164 (2006.01)

(21) International Application Number:
PCT/EP2008/053667

(22) International Filing Date: 27 March 2008 (27.03.2008)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
07105269.0 29 March 2007 (29.03.2007) EP

(71) Applicant *(for all designated States except US)*: **NOVARTIS AG** [CH/CH]; Lichtstrasse 35, CH-4056 Basel (CH).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **BOETTCHER, Andreas** [DE/CH]; Röttelerstr. 15, CH-4058 Basel (CH). **BUSCHMANN, Nicole** [DE/CH]; Horburgstrasse 19, CH-4057 Basel (CH). **FURET, Pascal** [FR/FR]; 19, rue de la Forêt, F-68800 Thann (FR). **GROELL, Jean-Marc** [FR/FR]; Rue de Muespach 4a, F-68640 Steinsoultz (FR). **KALLEN, Jörg** [CH/CH]; Kaltbrunnenstrasse 41, CH-4054 Basel (CH). **HERGOVICH LISZTWAN, Joanna** [CA/FR]; 11b rue de Delle, F-68640 Muespach Le Haut (FR). **MASUYA, Keiichi** [JP/CH]; Gemeindeholzweg 30, CH-4103 Bottmingen (CH). **MAYR, Lorenz** [DE/DE]; Fritz-Schülin-Weg 16, 79589 Binzen (DE). **VAUPEL, Andrea** [DE/CH]; Rütiring 23, CH-4125 Riehen (CH).

(74) Agent: **DYER, James**; Novartis Pharma Ag, Patent Department, CH-4002 Basel (CH).

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

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

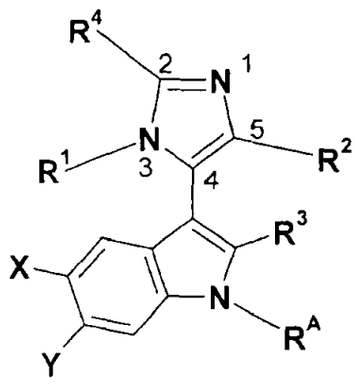
Declaration under Rule 4.17:

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

Published:

— *without international search report and to be republished upon receipt of that report*

(54) Title: 3-IMIDAZOLYL-INDOLES FOR THE TREATMENT OF PROLIFERATIVE DISEASES



(I)

(57) Abstract: The invention relates to 3-heterocyclyl indolyl compounds capable of inhibiting the interaction between p53, or variants thereof, and MDM2 and/or MDM4, or variants thereof, respectively, said compounds having the formula (I) wherein R^1, R^2, R^3, R^4, R^A, Y and Y are as defined in the specification. Due to their activity, the compounds are useful in the treatment of various disorders and diseases mediated by the activity of MDM2 and/or MDM4, or variants thereof, such as inflammatory or proliferative diseases or in the protection of cells.

WO 2008/119741 A2

3-Imidazolyl-indoles for the treatment of proliferative diseases

The present invention relates to 3-heterocyclyl indolyl compounds capable of inhibiting the interaction between p53, or variants thereof, and MDM2 and/or MDM4, or variants thereof, respectively, especially binding to MDM2 and/or MDM4, or variants thereof, a process for the preparation of such compounds, pharmaceutical preparations comprising such compounds, uses and methods of use for such compounds in the treatment (including therapy and/or prophylaxis), and/or related subject matter as specified below. MDM2 refers to all genes and/or proteins encoded thereof with the names MDM2, Mdm2, HDM2, Hdm2. MDM4 refers to all genes and/or proteins encoded thereof with the names MDM4, Mdm4, HDM4, Hdm4, MDMX, MdmX, HDMX, HdmX.

Protein p53 is known as a tumor suppressor protein which helps to control cellular integrity and prevents the proliferation of permanently damaged cells by initiating growth arrest or apoptosis (controlled cell death). p53 mediates its effects in that it is a transcription factor capable of regulating a number of genes that regulate cell cycle and apoptosis. Thus, p53 is an important cell cycle inhibitor. These activities are tightly controlled by MDM2, an important negative regulator of the p53 tumor supressor. "MDM2" (originally from the oncogene "murine double minute") refers both to the name of the gene as well as the protein encoded by that gene. MDM2 protein functions both as a E3 ubiquitin ligase that recognizes the N-terminal trans-activation domain (TAD) of the p53 tumor supressor and thus mediates the ubiquitin-dependent degradation of p53, and as an inhibitor of p53 transcriptional activation.

The original mouse oncogene, which codes for the MDM2 protein, was originally cloned from a transformed mouse cell line. The human homologue of this protein was later identified and is sometimes also called HDM2 (for "human double minute 2"). Further supporting the role of MDM2 as an oncogene, several human tumor and proliferative disease types have been shown to have increased levels of MDM2, including *inter alia* soft tissue sarcomas, bone cancer, e.g. osteosarcomas, breast tumors, bladder cancer, Li-Fraumeni syndrome, brain tumor, rhabdomyosarcoma and adrenocortical carcinoma and the like. Another protein belonging to the MDM2 family is MDM4, also known as MDMX.

Dysregulation of the MDM2/p53 ratio, e.g. due to mutations or molecular defects in the affected cells, can thus be found in many proliferative diseases. MDM2, in view of its

mentioned effects, is capable to inhibit the activity of the tumor suppressor protein p53, thus leading to loss of p53's tumor suppressor activity and inhibiting regulatory mechanisms that impede cells from uncontrolled proliferation. As a consequence, uncontrolled proliferation can take place, leading to tumors, leukemias or other proliferative diseases.

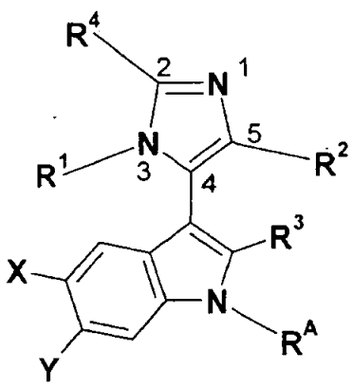
Thus there is a need for new drugs that are capable to interfere with the interaction between p53 and mdm2 or especially oncogenic variants thereof and that thus allow p53 to exert its beneficial effect against uncontrolled tumor growth, allowing it e.g. to accumulate, to arrest the cell cycle and/or to cause apoptosis of affected cells.

Summary of the invention

It has now been found that a novel class of 3-heterocyclyl indoles shows potent inhibition of the MDM2/p53 interaction (this term including MDM2/p53 interaction and/or MDM4/p53 interaction herein) and the corresponding compounds thus represent a novel type of compounds that are useful in the treatment of a number of disorders, such as proliferative diseases. The invention relates therefore to these compounds as well as to the other inventive embodiments indicated above and below.

Detailed Description of the invention

In a first and preferred embodiment, the invention relates to a compound of the formula I,



(I)

wherein

R^1 is unsubstituted or substituted alkyl, unsubstituted or substituted alkenyl or unsubstituted or substituted alkinyl, unsubstituted or substituted aryl or unsubstituted or substituted heterocyclyl;

R^2 is unsubstituted or substituted alkyl, unsubstituted or substituted alkenyl, unsubstituted or substituted alkinyl, unsubstituted or substituted aryl or unsubstituted or substituted heterocyclyl;

R^3 is hydrogen, halogen, unsubstituted or substituted alkyl, unsubstituted or substituted alkenyl, unsubstituted or substituted alkinyl, unsubstituted or substituted aryl, carboxy, cyano, esterified carboxy, unsubstituted or substituted heterocyclyl-carbonyl (heterocyclyl-C)=O)-), unsubstituted or substituted carbamoyl or unsubstituted or substituted heterocyclyl;

R^4 is hydrogen, halogen, unsubstituted or substituted alkyl, unsubstituted or substituted alkenyl, unsubstituted or substituted alkinyl, unsubstituted or substituted aryl, carboxy, cyano, esterified carboxy, unsubstituted or substituted heterocyclyl-carbonyl (heterocyclyl-C)=O)-), unsubstituted or substituted carbamoyl or unsubstituted or substituted heterocyclyl;

R^A is hydrogen or unsubstituted or substituted alkyl or acyl;

X is hydrogen, C_1-C_7-alkyl, halo-C_1-C_7-alkyl, C_1-C_7-alkoxy, halo or cyano; and

Y is C_1-C_7-alkyl, halo-C_1-C_7-alkyl, C_1-C_7-alkoxy, halo or cyano;

and/or a tautomer, an N-oxide and/or a (preferably pharmaceutically acceptable) salt thereof.

The general terms used hereinbefore and hereinafter preferably have within the context of this disclosure the following meanings, unless otherwise indicated, where more general terms whereever used may, independently of each other, be replaced by more specific definitions or remain, thus defining more preferred embodiments of the invention:

The prefix "lower" or "C_1-C_7-" denotes a radical having up to and including a maximum of 7, especially up to and including a maximum of 4 carbon atoms, the radicals in question being either linear or branched with single or multiple branching.

For example, lower alkyl (or C_1-C_7-alkyl) is preferably alkyl with from and including 1 up to and including 7, preferably from and including 1 to and including 4, and is linear or branched; preferably, lower alkyl is butyl, such as n-butyl, sec-butyl, isobutyl, tert-butyl, propyl, such as n-propyl or isopropyl, ethyl or preferably methyl.

The numbering of the positions of substituents at the central imidazole given in the present disclosure (e.g. in the Examples) is usually (though in exceptional cases this may differ) provided in formula I above by the small numbers 1, 2, 3, 4 and 5.

Halogen, halogeno (or halo) is especially fluoro, chloro, bromo, or iodo, especially fluoro, chloro or bromo.

"Lower alkylsulfonyl" stands for alkyl-$S(=O)_2$- (sometimes also referred to as lower alkanesulfonyl).

Compounds of the formula I may have different isomeric forms. For example, any asymmetric carbon atom may be present in the (R)-, (S)- or (R,S)-configuration, preferably in the (R)- or (S)-configuration. Substituents at a double bond or especially a ring may be present in cis- (= Z-) or trans (= E-) form. The compounds may thus be present as mixtures of isomers or preferably as pure isomers, preferably as pure diastereomers or pure enantiomers.

Where the plural form (e.g. compounds, salts) is used, this includes the singular (e.g. a single compound, a single salt). "A compound" does not exclude that (e.g. in a pharmaceutical formulation) more than one compound of the formula I (or a salt thereof) is present, the "a" merely representing the indefinite article. "A" can thus preferably be read as "one or more", less preferably alternatively as "one".

In unsubstituted or substituted alkyl, alkyl (also in alkoxy or the like) preferably has up to 20, more preferably up to 12 carbon atoms, is linear or branched, and is more preferably C_1-C_7-alkyl, especially C_1-C_4-alkyl. Substituted alkyl is preferably C_1- to C_{20}-alkyl, more preferably C_1-C_7-alkyl, especially C_1-C_4-alkyl, that can be linear or branched one or more times (provided the number of carbon atoms allows this), e.g. methyl, ethyl, propyl, n-butyl, sec-butyl, isobutyl, tert-butyl, 2,2-dimethylpropyl, 1,2,2-trimethylpropyl, 1-ethyl-propyl, and that is substituted by one or more, preferably up to three, substitutents independently selected from the group consisting of C_1-C_7-alkyl, hydroxyl-C_1-C_7-alkyl, C_1-C_7-alkoxy-C_1-C_7-alkyl, N-mono- or N,N-di-[C_1-C_7-alkyl, phenyl, C_1-C_7-alkanoyl and/or phenyl-C_1-C_7-alkyl]-amino-C_1-C_7-alkyl (such as –methyl), halo-C_1-C_7-alkyl, such as trifluoromethyl, hydroxy, C_1-C_7-alkoxy, C_1-C_7-alkoxy-C_1-C_7-alkoxy, (C_1-C_7-alkoxy)- C_1-C_7-alkoxy-C_1-C_7-alkoxy, halo-C_1-C_7-alkoxy, halo, especially fluoro, chloro of bromo or iodo, phenoxy, naphthyloxy, phenyl- or naphthyl-C_1-C_7-

alkoxy; amino-C_1-C_7-alkoxy, C_1-C_7-alkanoyloxy, benzoyloxy, naphthoyloxy, oxo (preferably not at the binding carbon), amino, amino-C_1-C_7-alkyl, especially aminomethyl, N-mono- or N,N-di-[C_1-C_7-alkyl, phenyl, C_1-C_7-alkanoyl and/or phenyl-C_1-C_7-alkyl]-amino, N-(heterocyclyl-C_1-C_7-alkyl)- or N-(heterocyclyl-C_1-C_7-alkyl-)-N-(C_1-C_7-alkyl)-amino wherein heterocyclyl preferably has 3 to 14 ring atoms, respectively, of which 1 to 4 are a heteroatom independently selected from N, S, S(=O), $S(=O)_2$ and O and is saturated, especially (pyrrolidinyl, pyrazolidinyl, imidazolidinyl, piperidinyl, azepanyl, piperazinyl, morpholinyl, thiomorpholinyl, S-oxothiomorpholinyl or S,S-dioxothiomorpholinyl)-C_1-C_7-alkylamino, formyl (CHO), carboxy, C_1-C_7-alkoxy-carbonyl, phenyl- or naphthyl-C_1-C_7-alkoxycarbonyl, such as benzyloxycarbonyl; C_2-C_7-alkanoyl, such as acetyl, benzoyl, naphthoyl, carbamoyl, N-mono- or N,N-di-substituted carbamoyl wherein the substitutents are selected from lower alkyl and hydroxy-lower alkyl; amidino, guanidino, ureido, mercapto, C_1-C_7-alkylthio, phenyl- or naphthylthio, phenyl- or naphthyl-C_1-C_7-alkylthio, C_1-C_7-alkyl-phenylthio, C_1-C_7-alkyl-naphthylthio, halogen-C_1-C_7-alkylmercapto, sulfonamido, benzosulfonamido, azido, azido-C_1-C_7-alkyl, especially azidomethyl, nitro, cyano; unsubstituted or substituted heterocyclyl as described below, especially mono- to tricyclic heterocyclyl that is unsaturated or saturated, has 3 to 14 ring atoms of which 1 to 4 are a heteroatom independently selected from N, S, S(=O), $S(=O)_2$ and O, preferably N, such as pyrrolidinyl, pyrazidinyl, imidazolidinyl, piperidinyl, azepanyl, piperazinyl, morpholinyl, thiomorpholinyl, S-oxo-thiomorpholinyl, S,S-dioxo-thiomorpholinyl, indolyl, isoindolyl, indazolyl, quinolinyl, isoquinolinyl, phthalazinyl, quinoxalinyl, quinazolinyl, cinnolinyl, benzofuranyl, isobenzofuranyl, chromenyl, isochromenyl, benzothiophenyl, thiochromenyl or isothiochromenyl, and is unsubstituted or substituted as decribed below for substituted heterocyclyl, especially with one or more, preferably up to three, moieties independently selected from the group consisting of C_1-C_7-alkyl, hydroxy-C_1-C_7-alkyl, hydroxy, oxo, amino or N-mono- or N,N-di-(C_1-C_7-alkyl, {amino or mono- or di-(C_1-C_7-alkyl)-amino}-C_1-C_7-alkyl, C_1-C_7-alkanoyl and/or C_1-C_7-alkoxycarbonyl)-amino, C_1-C_7-alkanoyl, C_1-C_7-alkylsulfonyl and saturated heterocyclyl with 3 to 14 ring atoms and 1 to 4 heteroatoms independently selected from N, S, S(=O), $S(=O)_2$ and O, preferably N, e.g. pyrrolidinyl, pyrazolidinyl, imidazolidinyl, tetrahydrofuranyl, piperidinyl, azepanyl, piperazinyl, morpholinyl, thiomorpholinyl, S-oxo-thiomorpholinyl or S,S-dioxothiomorpholinyl, wherein said saturated heterocyclyl is unsubstituted or substituted by one or more, especially up to three, moieties independently selected from C_1-C_7-alkyl, hydroxy-C_1-C_7-alkyl, C_1-C_7-alkoxy-C_1-C_7-alkyl, oxo, amino, mono- or di-(C_1-C_7-alkyl)-amino), C_1-C_7-alkanoyl and C_1-C_7-alkoxycarbonyl; unsubstituted or substituted aryl as defined below, especially naphthyl or

phenyl each of which is unsubstituted or substituted by one or more, especially up to three, moieties independently selected from C_1-C_7-alkyl, halo-C_1-C_7-alkyl, hydroxyl, C_1-C_7-alkoxy, hydroxy-C_1-C_7-alkoxy, C_1-C_7-alkoxy-C_1-C_7-alkoxy, (C_1-C_7-alkoxy-C_1-C_7-alkoxy)-C_1-C_7-alkoxy, [amino, mono- or di-(C_1-C_7-alkyl)amino]-C_1-C_7-alkoxy, amino, mono- or di-[(C_1-C_7-alkyl, C_1-C_7-alkanoyl, C_1-C_7-alkoxycarbonyl, hydroxy-C_1-C_7-alkyl, C_1-C_7-alkoxy-C_1-C_7alkyl and/or (amino, mono- or di-(C_1-C_7-alkyl)-amino)-C_1-C_7-alkyl]-amino, halo and saturated heterocyclyl, saturated heterocyclyl-C_1-C_7-alkyl or saturated heterocyclyl-C_1-C_7-alkoxy wherein saturated heterocyclyl, respectively, preferably has 3 to 14 ring atoms of which 1 to 4 are a heteroatom independently selected from N, S, S(=O), $S(=O)_2$ and O and is unsubstituted or substituted with one or more, especially up to three, moieties independently selected from C_1-C_7-alkyl, hydroxyl-C_1-C_7-alkyl, C_1-C_7-alkoxy-C_1-C_7-alkyl, hydroxyl, oxo, amino, mono- or di-(C_1-C_7-alkyl)-amino), C_1-C_7-alkanoyl and C_1-C_7-alkoxycarbonyl, especially pyrrolidinyl, pyrazolidinyl, imidazolidinyl, piperidinyl, azepanyl, piperazinyl, [N-(C_1-C_7-alkyl)-piperazinyl or pyrrolidinyl-, pyrazolidinyl-, imidazolidinyl-, piperidinyl-, azepanyl-, piperazinyl- or N-(C_1-C_7-alkyl)-piperazinyl]-C_1-C_7-alkyl or [N-(C_1-C_7-alkyl)-piperazinyl or pyrrolidinyl-, pyrazolidinyl-, imidazolidinyl-, piperidinyl-, azepanyl-, piperazinyl- or N-(C_1-C_7-alkyl)-piperazinyl]-C_1-C_7-alkoxy, nitro or cyano; and unsubstituted or substituted cycloalkyl, especially C_3-C_8-cycloalkyl, that is unsubstituted or substituted by one or more, especially up to three, substitutents independently selected from the substitutents for substituted aryl below;

where each phenyl or naphthyl (also in phenoxy or naphthoxy) mentioned above as substituent or part of a substituent of substituted alkyl (or also of substituted aryl, heterocyclyl etc. mentioned herein) is itself unsubstituted or substituted by one or more, e.g. up to three, preferably 1 or 2, substituents independently selected from C_1-C_7-alkyl, halo-C_1-C_7-alkyl, hydroxyl, C_1-C_7-alkoxy, C_1-C_7-alkoxy-C_1-C_7-alkoxy, halo, especially fluoro, chloro, bromo or iodo, halo-C_1-C_7-alkyl, such as trifluoromethyl, azido, amino, N-mono- or N,N-di-(C_1-C_7-alkyl, phenyl, naphthyl, C_1-C_7-alkanoyl, phenyl-C_1-C_7-alkyl and/or naphthyl-C_1-C_7-alkyl)-amino, carboxy, C_1-C_7-alkoxycarbonyl carbamoyl, sulfamoyl, nitro and cyano.

Unsubstituted or substituted alkenyl is preferably C_2-C_{20}-alkenyl, more preferably C_2-C_{12}-alkenyl, yet more preferably C_2-C_7-alkenyl, which is linear or branched and includes one or more double bonds. The substituents are preferably one or more, especially up to three, substituents independently selected from those mentioned for substituted alkyl, preferably with the proviso that substituents with active hydrogen (such as amino or hydroxyl) can also

be present in tautomeric form (as keto or imino compounds) or are excluded from the substituents where the stability is too low.

Unsubstituted or substituted alkynyl is preferably C_2-C_{20}-alkynyl, more preferably C_3-C_{12}-alkynyl, yet more preferably C_3-C_7-alkynyl, which is linear or branched and includes one or more triple bonds. The substituents are preferably one or more, especially up to three, substituents independently selected from those mentioned for substituted alkyl, preferably with the proviso that substituents with active hydrogen (such as amino or hydroxyl) can also be present in tautomeric form (as keto or imino compounds) or are excluded from the substituents where the stability is too low.

In unsubstituted or substituted aryl, aryl preferably has 6 to 18, more preferably 8 to 14 carbon atoms and is a mono-, di- or polycyclic (preferably up to tricyclic, more preferably up to bicyclic) unsaturated carbocyclic moiety with conjugated double bonds in the ring, especially phenyl, naphthyl, biphenylenyl, indacenyl, acenaphthylenyl, fluorenyl, phenalenyl, phenanthrenyl or anthracenyl. Naphthyl and preferably phenyl are especially preferred. Aryl is unsubstituted or (in the case of substituted aryl) substituted by one or more, e.g. one to three, substitutents preferably independently selected from the group consisting of C_1-C_7-alkyl, such as methyl, ethyl, *n*-propyl, isopropyl, n-butyl, isobutyl, sec-butyl or *tert-butyl*; C_2-C_7-alkenyl; C_2-C_7-alkinyl; C_6-C_{18}-aryl-C_1-C_7-alkyl in which aryl is preferably phenyl, naphthyl, biphenylenyl, indacenyl, acenaphthylenyl, fluorenyl, phenalenyl, phenanthrenyl or anthracenyl and unsubstituted or substituted by C_1-C_7-alkyl, such as methyl or ethyl, by pyrrolidinyl, especially pyrrolidino, by pyrazolidinyl, especially pyrazolidino, by imidazolidinyl, especially imidazolidino, by piperidinyl, especially piperidin-1-yl, by azepanyl, especially azepan-1-yl, piperazinyl, especially piperazino, by amino, by N-mono- and/or N,N-di-C_1-C_7-alkylamino, by halo, by hydroxyl, by C_1-C_7-alkoxy, such as methoxy, and/or by halo-C_1-C_7-alkyl, such as trifluoromethyl; (pyrrolidinyl (especially pyrrolidino), pyridazolidinyl, especially pyridazolidino, imidazolidinyl (especially imidazolidino), piperidinyl (especially piperidino), azepanyl (especially azepan-1-yl), piperazinyl (especially piperazino), morpholino, thiomorpholino, pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, oxazolyl or thiazolyl)-C_1-C_7-alkyl wherein pyrrolidinyl, pyrazolidinyl, imidazolidinyl, piperidinyl, azepanyl, piperazinyl, pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, oxazolyl or thiazolyl are unsubstituted or substituted by C_1-C_7-alkyl, such as methyl or ethyl, by pyrrolidinyl, especially pyrrolidino, by pyrazolidinyl, especially pyrazolidino, by imidazolidinyl, especially imidazolidino, by azepanyl, especially

azepan-1-yl, by piperazinyl, especially piperazino, by amino, by N-mono- and/or N,N-di-C_1-C_7-alkylamino, by halo, by C_1-C_7-alkoxy, such as methoxy, and/or by halo-C_1-C_7-alkyl, such as trifluoromethyl, for example pyrrolidino-C_1-C_7-alkyl, pyrazolidino-C_1-C_7-alkyl, imidazolidino-C_1-C_7-alkyl, piperidino-C_1-C_7-alkyl, azepan-1-yl-C_1-C_7-alkyl, piperazino-C_1-C_7-alkyl, morpholino-C_1-C_7-alkyl, thiomorpholino-C_1-C_7-alkyl, N-C_1-C_7-alkyl-piperazino-C_1-C_7-alkyl, or N-mono- or N,N-di-(C_1-C_7-alkyl)-amino-substituted or unsubstituted pyrrolidino-C_1-C_7-alkyl; (pyrrolidinyl (especially pyrrolidino), pyrazolidinyl, (especially pyrazolidino), imidazolidinyl (especially imidazolidino) piperidinyl (especially piperidino), azepanyl (especially azepan-1-yl), piperazinyl (especially piperazino), pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, oxazolyl or thiazolyl)-oxy-C_1-C_7-alkyl wherein pyrrolidinyl, pyrazolidinyl, imidazolidinyl, piperidinyl, azepanyl, piperazinyl, pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, oxazolyl and thiazolyl are unsubstituted or substituted by C_1-C_7-alkyl, such as methyl or ethyl, by pyrrolidinyl, especially pyrrolidino, by pyrazolidinyl, especially pyrazolidino, by imidazolidinyl, especially imidazolidino, by piperidinyl, especially piperidino, by azepanyl, especially azepan-1-yl, by piperazinyl, especially piperazino, by amino, by N-mono- and/or N,N-di-C_1-C_7-alkylamino, by halo, by C_1-C_7-alkoxy, such as methoxy, and/or by halo-C_1-C_7-alkyl, such as trifluoromethyl; (pyrrolidin (especially pyrrolidino), pyrazolidinyl (especially pyrazolidino), imidazolidinyl (especially imidazolidino), piperidin (especially piperidino), azepan (especially azepan-1-l), piperazin (especially piperazino), pyridin, pyrimidin, pyrazin, pyridazin, oxazoly or thiazol)-carbonyl-C_1-C_7-alkyl wherein pyrrolidin, pyrazolidin, imidazolidin, piperidin, azepan, piperazin, pyridin, pyrimidin, pyridazin, oxazol or pyridazin are unsubstituted or substituted by C_1-C_7-alkyl, such as methyl or ethyl, by pyrrolidinyl, especially pyrrolidino, by pyrazolidinyl, especially pyrazolidino, by imidazolidinyl, especially imidazolidino, by azepanyl, especially azepan-1-yl, by piperazinyl, especially piperazino, by amino, by N-mono- and/or N,N-di-C_1-C_7-alkylamino, by halo, by C_1-C_7-alkoxy, such as methoxy, and/or by halo-C_1-C_7-alkyl, such as trifluoromethyl; halo-C_1-C_7-alkyl, such as trifluoromethyl; hydroxy-C_1-C_7-alkyl, such as hydroxymethyl; C_1-C_7-alkoxy-C_1-C_7-alkyl, such as 3-methoxypropyl or 2-methoxyethyl; C_1-C_7-alkoxy-C_1-C_7-alkoxy-C_1-C_7-alkyl; phenyloxy- or naphthyloxy-C_1-C_7-alkyl; phenyl-C_1-C_7-alkoxy- or naphthyl-C_1-C_7-alkoxy-C_1-C_7-alkyl; amino-C_1-C_7-alkyl, such as aminomethyl; N-mono- or N,N-di-(C_1-C_7-alkyl, C_1-C_7-alkoxy-C_1-C_7-alkyl and/or (mono- or di-(C_1-C_7-alkyl)-amino)-C_1-C_7-alkyl)-amino-C_1-C_7-alkyl; C_1-C_7-alkoxy-C_1-C_7-alkylamino-C_1-C_7-alkyl; mono- or di-[C_6-C_{18}-aryl-C_1-C_7-alkyl in which aryl is preferably phenyl, naphthyl, biphenylenyl, indacenyl, acenaphthylenyl, fluorenyl, phenalenyl, phenanthrenyl or anthracenyl and unsubstituted or substituted by C_1-C_7-alkyl, such as methyl or ethyl, by pyrrolidinyl, especially

pyrrolidino, by pyrazolidinyl, especially pyrazolidino, by imidazolidinyl, especially imidazolidino, by piperidinyl, especially piperidino, by azepanyl, especially azepan-1-yl, by piperazinyl, especially piperazino, by amino, by N-mono- and/or N,N-di-C_1-C_7-alkylamino, by halo, by hydroxyl, by C_1-C_7-alkoxy, such as methoxy, and/or by halo-C_1-C_7-alkyl, such as trifluoromethyl; naphthyl- or phenyl-C_1-C_7-alkyl]-amino-C_1-C_7-alkyl; C_1-C_7-alkanoylamino-C_1-C_7-alkyl; carboxy-C_1-C_7-alkyl; benzoyl- or naphthoylamino-C_1-C_7-alkyl; C_1-C_7-alkylsulfonylamino-C_1-C_7-alkyl; phenyl- or naphthylsulfonylamino-C_1-C_7-alkyl wherein phenyl or naphthyl is unsubstituted or substituted by one or more, especially one to three, C_1-C_7-alkyl moieties; phenyl- or naphthyl-C_1-C_7-alkylsulfonylamino-C_1-C_7-alkyl; halo, especially fluoro (preferred), chloro (preferred) or bromo; hydroxy; C_1-C_7-alkoxy; C_6-C_{18}-aryl-C_1-C_7-alkoxy in which aryl is preferably phenyl, naphthyl, biphenylenyl, indacenyl, acenaphthylenyl, fluorenyl, phenalenyl, phenanthrenyl or anthraxcenyl and unsubstituted or substituted by C_1-C_7-alkyl, such as methyl or ethyl, by C_1-C_7-alkoxy, by pyrrolidinyl, especially pyrrolidino, by pyrazolidinyl, especially parazolidino, by imidazolidinyl, especially imidazolidino, piperidinyl, especially piperidino, by azepanyl, especially azepan-1-yl, by piperazinyl, especially piperazino, by amino, by N-mono- and/or N,N-di-C_1-C_7-alkylamino, by halo, by hydroxyl, by C_1-C_7-alkoxy, such as methoxy, and/or by halo-C_1-C_7-alkyl, such as trifluoromethyl; such as phenyl-C_1-C_7-alkoxy wherein phenyl is unsubstituted or substituted by C_1-C_7-alkoxy and/or halo; halo-C_1-C_7-alkoxy, such as trifluoromethoxy; hydroxy-C_1-C_7-alkoxy; C_1-C_7-alkoxy-C_1-C_7-alkoxy, such as such as 2-(methoxy)-ethoxy; (C_1-C_7-alkoxy-C_1-C_7-alkoxy)-C_1-C_7-alkoxy; [amino, mono- or di-(C_1-C_7-alkyl)amino]-C_1-C_7-alkoxy, N-C_1-C_7-alkanoylamino-C_1-C_7-alkoxy; N-unsubstituted-, N-mono- or N,N-di-(C_1-C_7-alkyl)carbamoyl-C_1-C_7-alkoxy; phenyl- or naphthyloxy; phenyl- or naphthyl-C_1-C_7-alkyloxy; (pyrrolidinyl (especially pyrrolidino), pyrazolidinyl (especially pyrazolidino), imidazolidinyl (especially imidazolidino), piperidinyl (especially piperidino), azepanyl (especially azepan-1-yl), piperazinyl (especially piperazino), pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, oxazolyl or thiazolyl)-C_1-C_7-alkoxy wherein pyrrolidinyl, pyrazolidinyl, imidazolidinyl, piperidinyl, azepanyl, piperazinyl, pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, oxazolyl and thiazolyl are unsubstituted or substituted by C_1-C_7-alkyl, such as methyl or ethyl, by pyrrolidinyl, especially pyrrolidino, by pyrazolidinyl, especially pyrazolidino, by imidazolidinyl, especially imidazolidino, by piperidinyl, especially piperidino, by azepanyl, especially azepan-1-yl, by piperazinyl, especially piperazino, by amino, by N-mono- and/or N,N-di-C_1-C_7-alkylamino, by halo, by C_1-C_7-alkoxy, such as methoxy, and/or by halo-C_1-C_7-alkyl, such as trifluoromethyl; (pyrrolidinyl (especially pyrrolidino), pyrazolidinyl (especially pyrazolidino), imidazolidinyl (especially imidazolidino),

piperidinyl (especially piperidino), azepanyl (especially azepan-1-yl), piperazinyl (especially piperazino), pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, oxazolyl or thiazolyl)-oxy-C_1-C_7-alkoxy wherein pyrrolidinyl, pyrazolidinyl, imidazolidinyl, piperidinyl, azepanyl, piperazinyl, pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, oxazolyl and thiazolyl are unsubstituted or substituted by C_1-C_7-alkyl, such as methyl or ethyl, by pyrrolidinyl, especially pyrrolidino, by pyrazolidinyl, especially pyrazolidino, by imidazolidinyl, especially imidazolidino, by piperidinyl, especially piperidino, by azepanyl, especially azepan-1-yl, by piperazinyl, especially piperazino, by amino, by N-mono- and/or N,N-di-C_1-C_7-alkylamino, by halo, by C_1-C_7-alkoxy, such as methoxy, and/or by halo-C_1-C_7-alkyl, such as trifluoromethyl; C_1-C_7-alkanoyloxy; benzoyl- or naphthoyloxy; C_1-C_7-alkylthio; halo-C_1-C_7-alkylthio, such as trifluoromethylthio; C_1-C_7-alkoxy-C_1-C_7-alkylthio; phenyl- or naphthylthio; phenyl- or naphthyl-C_1-C_7-alkylthio; C_1-C_7-alkanoylthio; benzoyl- or naphthaylthio; nitro; amino; mono- or di-[(C_1-C_7-alkyl, C_1-C_7-alkanoyl, C_1-C_7-alkoxy-carbonyl, hydroxy-C_1-C_7-alkyl, C_1-C_7-alkoxy-C_1-C_7alkyl and/or (amino, mono- or di-(C_1-C_7-alkyl)-amino)-C_1-C_7-alkyl]-amino;; mono- or di-(naphthyl- or phenyl-C_1-C_7-alkyl)-amino; C_1-C_7-alkanoylamino; unsubstituted or amino-, N-mono- or N,N-di-(C_1-C_7-alkyl and/or phenyl- or naphthyl-C_1-C_7alkyl)amino-substituted benzoyl- or naphthoylamino; C_1-C_7-alkoxycarbonylamino; (phenyl or naphthyl)-C_1-C_7-alkoxycarbonylamino; C_1-C_7-alkylsulfonylamino (= C_1-C_7-alkyl-$S(=O)_2$-NH-); phenyl- or naphthylsulfonylamino wherein phenyl or naphthyl is unsubstituted or substituted by one or more, especially one to three, C_1-C_7-alkyl moieties; phenyl- or naphthyl-C_1-C_7-alkylsulfonylamino; C_1-C_7-alkanoyl; C_1-C_7-alkoxy-C_1-C_7-alkanoyl; carboxyl (-COOH); C_1-C_7-alkoxy-carbonyl; phenoxy- or naphthoxycarbonyl; phenyl- or naphthyl-C_1-C_7-alkoxycarbonyl; C_1-C_{10}- especially C_1-C_4-alkylendioxy, such as methylendioxy or 1,2-ethylendioxy; carbamoyl; N-mono- or N,N-di-[C_1-C_7-alkyl, naphthyl-C_1-C_7-alkyl, phenyl-C_1-C_7-alkyl, N'-mono- or N',N'-di-(C_1-C_7alkyl)amino-C_1-C_7-alkyl, pyrrolidinyl (especially pyrrolidino)-C_1-C_7-alkyl, pyrazolidinyl (especially pyrazolidino)-C_1-C_7-alkyl, imidazolidinyl (especially imidazolidino)-C_1-C_7-alkyl, piperidinyl (especially piperidino)-C_1-C_7-alkyl, azepanyl (especially azepan-1-yl)-C_1-C_7-alkyl, piperazinyl- or N-(C_1-C_7-alkyl)piperazinyl(especially piperazino or 4-C_1-C_7-alkylpiperazino)-C_1-C_7-alkyl, mono-C_1-C_7-alkoxy-C_1-C_7-alkyl, (N'-mono- or N',N'-di-(C_1-C_7-alkyl)-amino); phenyl, pyridinyl, oxazolyl or thiazolyl each of which is unsubstituted or substituted by C_1-C_7-alkoxy, by halo, especially fluoro, by pyrrolidino, by pyrazolidino, by imidazolidino, by piperidino, by azepan-1-yl, by piperazino, by hydroxyl-C_1-C_7-alkylamino, by hydroxyl-C_1-C_7-alkyl, by amino or by N-mono- or N,N-di-(C_1-C_7-alkyl)amino; pyrrolidinyl, pyrazolidinyl, imidazolidinyl, piperidinyl, azepanyl, piperazinyl, pyrimidinyl, pyrazinyl and/or pyridazinyl]-amino-carbonyl, such as N- mono- or

N,N-di-(C_1-C_7-alkyl)-aminocarbonyl; N-C_1-C_7-alkoxy-C_1-C_7-alkylcarbamoyl; pyrrolidin-1-carbonyl; amino-N-pyrrolidin-1-carbonyl; N-mono- or N,N-di(C_1-C_7-alkyl)amino-pyrrolidin-1-carbonyl; imidazolidin-1-carbonyl; piperidin-1-carbonylmorpholin-4-carbonyl; thiomorpholin-4-carbonyl; S-oxo-thiomorpholin-4-carbonyl; S,S-dioxothiomorpholin-4-carbonyl; piperazin-1-carbonyl; N-C_1-C_7-alkyl-piperazin-1-carbonyl; N-C_1-C_7-alkoxycarbonyl-piperazin-1-carbonyl; N-mono- or N,N-di-(C_1-C_7-alkyl)-amino-substituted or unsubstituted pyrrolidinyl-C_1-C_7-alkyl; cyano; C_1-C_7-alkenylene or –alkinylene; C_1-C_7-alkylsulfonyl; phenyl- or naphthylsulfonyl wherein phenyl or naphthyl is unsubstituted or substituted by one or more, especially one to three, C_1-C_7-alkyl moieties; phenyl- or naphthyl-C_1-C_7-alkylsulfonyl; sulfamoyl; N-mono or N,N-di-(C_1-C_7-alkyl, phenyl-, naphthyl-, phenyl-C_1-C_7-alkyl-, pyrrolidinyl(especially pyrrolidino)-C_1-C_7-alkyl, pyrazolidinyl(especially pyrazolidino)-C_1-C_7-alkyl, imidazolyl(especially imidazol-1-yl))-C_1-C_7-alkyl, piperidinyl(especially piperidino)-C_1-C_7-alkyl, azepanyl(especially azepan-1-yl))-C_1-C_7-alkyl, piperazinyl(especially piperazino)-C_1-C_7-alkyl, N-C_1-C_7-alkylpiperazinyl(especially 4-C_1-C_7-alkylpiperazino)-C_1-C_7-alkyl, naphthyl-C_1-C_7-alkyl, phenyl which is unsubstituted or substituted by C_1-C_7-alkoxy, by halo, especially fluoro, by pyrrolidino, by pyrazolidino, by imidazolidino, by azepan-1-yl, by piperidino, by piperazino, by hydroxyl-C_1-C_7-alkyl or by N-mono- or N,N-di-(C_1-C_7-alkyl)-C_1-C_7-alkyl; pyrrolidinyl (especially pyrrolidino), pyrazolidinyl (especially pyrazolidino), imidazolidinyl (especially imidazolidino), piperidinyl (especially piperidino), azepanyl (especially azepan-1-yl), piperazinyl (especially piperazino), pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, oxazolyl and/or thiazolyl)-aminosulfonyl, pyrazolyl, pyrazolidinyl, pyrrolyl, pyrrolidinyl, pyridyl that is unsubstituted or substituted by C_1-C_7-alkoxy, such as methoxy, and/or by halo-C_1-C_7-alkyl, such as trifluoromethyl, pyrrolidinyl, pyrazolidinyl, imidazolidinyl, piperidinyl, azepanyl, piperazinyl, morpholinyl, thiomorpholinyl, S-oxo-thiomorpholinyl, S,S-dioxothiomorpholinyl, piperazinyl, N-C_1-C_7-alkyl-piperazinyl, 4-(phenyl-C_1-C_7-alkyl)-piperazinyl, 4-(naphthyl-C_1-C_7-alkyl)-piperazinyl, 4-(C_1-C_7-alkoxycarbonyl)-piperazinyl, 4-(phenyl-C_1-C_7-alkoxycarbonyl)-piperazinyl, 4-(naphthyl-C_1-C_7-alkoxycarbonyl)-piperazinyl, oxazolyl and thiazolyl.

Especially preferably aryl is phenyl or naphthyl, each of which is unsubstituted or substituted as just described, more preferably by one or more, e.g. up to three, substituents independently selected from the group consisting of C_1-C_7-alkyl, hydroxy-C_1-C_7-alkyl, such as hydroxymethyl, C_1-C_7-alkoxy-C_1-C_7-alkyl, such as methoxymethyl, halo-alkyl, such as trifluoromethyl, amino- or mono- or di-(C_1-C_7-alkyl)-amino-C_1-C_7-alkyl, halo, hydroxyl, C_1-C_7-alkoxy, amino, mono- or di-(C_1-C_7-alkyl and/or hydroxyl-C_1-C_7-alkyl)-amino, C_1-C_7 benzoylamino,

aminobenzoylamino, C_1-C_7-alkoxycarbonylamino, (phenyl or naphthyl)-C_1-C_7-alkoxycarbonyl-amino, carbamoyl, N-mono- or N,N-di-(C_1-C_7-alkyl and/or phenyl-C_1-C_7-alkyl)aminocarbonyl, phenylaminocarbonyl, halophenyl-aminocarbonyl, N-[N'-mono- or N',N'-di-(C_1-C_7alkyl)-amino-C_1-C_7-alkyl]-aminocarbonyl, sulfamoyl (= aminosulfonyl) or N-mono- or N,N-di-(C_1-C_7-alkyl and/or phenyl-C_1-C_7-alkyl)aminosulfonyl.

Unsubstituted or substituted heterocyclyl is preferably a heterocyclic radical that is unsaturated (= carrying the highest possible number of conjugated double bonds in the ring(s), then also called heteroaryl), saturated (then also called saturated heterocyclyl herein) or partially saturated and is mono- or polycyclic, preferably a monocyclic or bicyclic or tricyclic ring; and has 3 to 24, more preferably 4 to 16, most preferably 4 to 10 ring atoms; wherein one or more, preferably one to four, especially one to three carbon ring atoms are replaced by a heteroatom independently selected from the group consisting of nitrogen, oxygen and sulfur (including S(=O) or $S(=O)_2$), the bonding ring preferably having 4 to 12, especially 5 to 7 ring atoms; which heterocyclic radical (heterocyclyl) is unsubstituted or substituted by one or more, especially 1 to 3, substituents independently selected from the group consisting of the substituents defined above for substituted alkyl or for substituted aryl; and where heterocyclyl is especially a heterocyclyl radical selected from the group consisting of oxiranyl, azirinyl, aziridinyl, 1,2-oxathiolanyl, thienyl (= thiophenyl), furanyl, tetrahydrofuryl, pyranyl, thiopyranyl, thianthrenyl, isobenzofuranyl, benzofuranyl, chromenyl, 2H-pyrrolyl, pyrrolyl, pyrrolinyl, pyrrolidinyl, imidazolyl, imidazolidinyl, benzimidazolyl, pyrazolyl, pyrazinyl, pyrazolidinyl, thiazolyl, isothiazolyl, dithiazolyl, oxazolyl, isoxazolyl, pyridyl, pyrazinyl, pyrimidinyl, piperidinyl, piperazinyl, pyridazinyl, morpholinyl, thiomorpholinyl, (S-oxo or S,S-dioxo)-thiomorpholinyl, indolizinyl, azepanyl, diazepanyl, especially 1,4-diazepanyl, isoindolyl, 3H-indolyl, indolyl, isoindolyl, indazolyl, benzimidazolyl, cumaryl, triazolyl, tetrazolyl, purinyl, 4H-quinolizinyl, isoquinolyl, isoquinolyl, tetrahydroquinolyl, tetrahydroisoquinolyl, decahydroquinolyl, octahydroisoquinolyl, benzofuranyl, isobenzofuranyl, dibenzofuranyl, benzothiophenyl, dibenzothiophenyl, phthalazinyl, naphthyridinyl, quinoxalyl (= quinoxalinyl), quinazolinyl, quinazolinyl, cinnolinyl, pteridinyl, carbazolyl, beta-carbolinyl, phenanthridinyl, acridinyl, perimidinyl, phenanthrolinyl, furazanyl, phenazinyl, phenothiazinyl, phenoxazinyl, chromenyl, isochromenyl, chromanyl, benzo[1,3]dioxol-5-yl, 2,3-dihydro-benzo[1,4]dioxin-6-yl, thiochromenyl and isothiochromenyl, each of these radicals being unsubstituted or substituted by one or more, preferably up to three, substitutents selected from those mentioned above for substituted alkyl and for aryl and from oxo, especially substituents independently

selected from the group consisting of C_1-C_7-alkyl, hydroxy-C_1-C_7-alkyl, hydroxy, C_1-C_7-alkoxy, hydroxy-C_1-C_7-alkoxy, C_1-C_7-alkoxy-C_1-C_7-alkoxy, (C_1-C_7-alkoxy-C_1-C_7-alkoxy)-C_1-C_7-alkoxy, (amino- mono- or di-(C_1-C_7-alkyl)-amno)-C_1-C_7-alkoxy, oxo, amino, N-mono- or N,N-di-(C_1-C_7-alkyl, {amino or mono- or di-(C_1-C_7-alkyl)-amino}-C_1-C_7-alkyl, C_1-C_7-alkanoyl and/or C_1-C_7-alkoxycarbonyl)-amino, C_1-C_7-alkanoyl, C_1-C_7-alkylsulfonyl and saturated heterocyclyl with 3 to 14 ring atoms and 1 to 4 heteroatoms independently selected from N, S, S(=O), $S(=O)_2$ and O, preferably N , e.g. pyrrolidinyl, imidazolidinyl, piperidinyl, piperazinyl, morpholinyl, thiomorpholinyl, S-oxo-thiomorpholinyl or S,S-dioxothiomorpholinyl, wherein said saturated heterocyclyl is unsubstituted or substituted by one or more, especially up to three, moieties independently selected from C_1-C_7-alkyl, hydroxy-C_1-C_7-alkyl C_1-C_7-alkoxy-C_1-C_7-alkyl, oxo, amino and mono- or di-(C_1-C_7-alkyl)-amino).

Unsubstituted or substituted cycloalkyl is preferably C_3-C_8-cycloalkyl, and is unsubstituted or substituted by one or more, especially up to three, substitutents independently selected from the substitutents for substituted aryl above.

Carboxy is –COOH.

Esterified carboxy is preferably unsubstituted or substituted alkyloxy-carbonyl (= alkyl-O-C(=O)-), unsubstituted or substituted aryloxy-carbonyl (= aryloxy-C(=O)-), unsubstituted or substituted cycloalkyloxy-carbonyl (= cycloalkyl-O-C(=O)-) or unsubstituted or substituted heterocyclyloxy-carbonyl (= heterocyclyl-O-C(=O)-), wherein alkyl, aryl, cycloalkyl and heterocyclyl and their substituted forms are as defined above. More preferably, esterified carboxy is C_1-C_7-alkoxycarbonyl or C_6-C_{14}-aryl-C_1-C_7-alkoxycarbonyl.

In unsubstituted or substituted heterocyclyl-carbonyl (heterocyclyl-C)=O)-), heterocyclyl is preferably a moiety chosen from heterocyclyl as defined above and is unsubstituted or substituted by one or more, especially up to three, substitutents independently selected from those for substituted alkyl and substituted aryl and from oxo, especially from the group consisting of C_1-C_7-alkyl, hydroxy-C_1-C_7-alkyl, hydroxy, C_1-C_7-alkoxy, hydroxy-C_1-C_7-alkoxy, C_1-C_7-alkoxy-C_1-C_7-alkoxy, (C_1-C_7-alkoxy-C_1-C_7-alkoxy)-C_1-C_7-alkoxy, (amino- mono- or di-(C_1-C_7-alkyl)-amno)-C_1-C_7-alkoxy, oxo, amino, N-mono- or N,N-di-(C_1-C_7-alkyl, {amino or mono- or di-(C_1-C_7-alkyl)-amino}-C_1-C_7-alkyl, C_1-C_7-alkanoyl and/or C_1-C_7-alkoxycarbonyl)-amino, C_1-C_7-alkanoyl, C_1-C_7-alkylsulfonyl and saturated heterocyclyl with 3 to 14 ring atoms and 1

to 4 heteroatoms independently selected from N, S, S(=O), $S(=O)_2$ and O, preferably N , e.g. pyrrolidinyl, imidazolidinyl, piperidinyl, piperazinyl, morpholinyl, thiomorpholinyl, S-oxo-thiomorpholinyl or S,S-dioxothiomorpholinyl, wherein said saturated heterocyclyl is unsubstituted or substituted by one or more, especially up to three, moieties independently selected from C_1-C_7-alkyl, hydroxy-C_1-C_7-alkyl C_1-C_7-alkoxy-C_1-C_7-alkyl, oxo, amino and mono- or di-(C_1-C_7-alkyl)-amino). Preferably heterocyclyl in heterocyclyl-carbonyl is unsaturated or preferably saturated, has 3 to 14 ring atoms of which 1 to 4 are a heteroatom independently selected from N, S, S(=O), $S(=O)_2$ and O, preferably N, and is more preferably selected from the group consisting of pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, thiomorpholinyl, S-oxothiomorpholinyl or S,S-dioxothiomorpholinyl, and is unsubstituted or substituted as described above for substituted aryl, substituted alkyl and from oxo, most especially from the substituents mentioned as preferred after "especially" in the preceding sentence.

In unsubstituted or substituted carbamoyl (= unsubstituted or N-substituted carbamoyl), the (N-) substituents (at the nitrogen of the carbamoyl group $-C(=O)-NH_2$) are preferably selected from one or two (meaning that one or two of the hydrogen atoms at the nitrogen are replaced) substituents independently selected from unsubstituted or substituted C_1-C_7-alkyl (as defined above), unsubstituted or substituted aryl (as defined above), unsubstituted or substituted cycloalkyl (as defined above) and from unsubstituted or substituted heterocyclyl (as defined above), where preferably either only one carbamoyl N-substituent is present or one N-substituent is C_1-C_7-alkyl, the other is selected from the group of substituents just mentioned. More preferably, substituted carbamoyl is N-mono- or N,N-di-[C_1-C_7-alkyl, hydroxy-C_1-C_7-alkyl, C_1-C_7-alkoxy-C_1-C_7-alkyl, amino-C_1-C_7-alkyl, mono- or di-(C_1-C_7-alkyl)-amino-C_1-C_7-alkyl, C_6-C_{14}-aryl wherein aryl is unsubstituted or substituted by one or more, especially up to three, moieties independently selected from the group consisting of C_1-C_7-alkyl, C_1-C_7-alkoxy, saturated heterocyclyl with 3 to 14 ring atoms and 1 to 4 heteroatoms independently selected from N, S, S(=O), $S(=O)_2$ and O, preferably N , e.g. pyrrolidinyl, imidazolidinyl, piperidinyl, piperazinyl, azepanyl, morpholinyl, thiomorpholinyl, S-oxo-thiomorpholinyl or S,S-dioxothiomorpholinyl, wherein said saturated heterocyclyl is unsubstituted or substituted with one or more, especially up to three, moieties independently selected from C_1-C_7-alkyl, hydroxy-C_1-C_7-alkyl, hydroxy, oxo and C_1-C_7-alkoxycarbonyl, C_6-C_{14}-aryl-C_1-C_7-alkyl, and saturated heterocyclyl or (saturated heterocyclyl)-C_1-C_7-alkyl wherein saturated heterocyclyl in both cases has 3 to 14 ring atoms and 1 to 4 heteroatoms independently selected from N, S, S(=O), $S(=O)_2$ and O, preferably N, e.g. pyrrolidinyl, imidazolidinyl,

piperidinyl, piperazinyl, azepanyl, morpholinyl, thiomorpholinyl, S-oxo-thiomorpholinyl, S,S-dioxothiomorpholinyl, indolyl or isoindolyl or (pyrrolidinyl, imidazolidinyl, piperidinyl, piperazinyl, azepanyl, morpholinyl, thiomorpholinyl, S-oxo-thiomorpholinyl, S,S-dioxothiomorpholinyl, indolyl or isoindolyl)-C_1-C_7-alkyl, wherein said saturated heterocyclyl is unsubstituted or substituted with one or more, especially up to three, moieties independently selected from C_1-C_7-alkyl, hydroxy-C_1-C_7-alkyl, C_1-C_7-alkoxy-C_1-C_7-alkyl, oxo, C_1-C_7-alkanoyl and C_1-C_7-alkoxycarbonyl]-carbamoyl.

In the case of R^4 unsubstituted or substituted alkyl, halo and unsubstituted or substituted heterocyclyl are preferably as defined above; more preferably, R_4 is C_1-C_7-alkyl, halo, especially chloro or bromo, pyrrolyl, imidazolyl, pyridyl or pyrazinyl.

In the case of R^A , unsubstituted or substituted alkyl is preferably as defined above, more preferably it is C_1-C_7-alkyl,

In the case of Y, C_1-C_7-alkyl, halo or cyano is preferred, more preferably methyl, fluoro, chloro, bromo or cyano; especially chloro or bromo.

Acyl is preferably unsubstituted or substituted aryl-carbonyl (= aryl-CO-; = aroyl) or –sulfonyl (= aryl-$S(O)_2$-), unsubstituted or substituted heterocyclylcarbonyl or -sulfonyl, unsubstituted or substituted cycloalkylcarbonyl or -sulfonyl, formyl or unsubstituted or substituted alkylcarbonyl or -sulfonyl, unsubstituted or substituted alkyloxycarbonyl or –oxysulfonyl, unsubstituted or substituted aryl-oxycarbonyl or -oxysulfonyl, unsubstituted or substituted heterocyclyloxycarbonyl or -oxysulfonyl, unsubstituted or substituted cycloalkyloxycarbonyl or -oxysulfonyl or N-mono- or N,N-di-(unsubstituted or substituted aryl, unsubstituted or substituted heterocyclyl, unsubstituted or substituted cycloalkyl or unsubstituted or substituted alkyl)-aminocarbonyl; wherein unsubstituted or substituted aryl, unsubstituted or substituted heterocyclyl, unsubstituted or substituted cycloalkyl and unsubstituted or substituted alkyl are preferably as described above. Preferred is C_1-C_7-alkanoyl, such as acetyl, unsubstituted or mono-, di- or tri-(halo and/or C_1-C_7-alkyl)-substituted benzoyl or naphthoyl, C_3-C_8-cycloalkylcarbonyl, pyrrolidincarbonyl, especially pyrrolidinocarbonyl, pyrazolidincarbonyl, imidazolidincarbonyl, piperidincarbonyl, piperazincarbonyl, 4-C_1-C_7-alkyl-piperazin-1-yl, C_1-C_7-alkylsulfonyl; such as methylsulfonyl (= methanesulfonyl), (phenyl- or naphthyl)-C_1-C_7-alkylsulfonyl, such as phenylmethansulfonyl, or (unsubstituted, or [C_1-C_7-alkyl-, phenyl-, halo-lower alkyl-,

halo, oxo-C_1-C_7-alkyl- C_1-C_7-alkyloxy-, phenyl-C_1-C_7-alkoxy-, halo-C_1-C_7-alkyloxy-, phenoxy-, C_1-C_7-alkanoylamino-, cyano-, C_1-C_7-alkanoyl- and/or C_1-C_7-alkylsulfonyl-]substituted) (phenyl or naphthyl)-sulfonyl, such as phenylsulfonyl (= benzenesulfonyl), naphthalene-1-sulfonyl, naphthalene-2-sulfonyl or toluene-4-sulfonyl, carbamoyl, N-mono- or N,N-di-(C_1-C_7-alkyl, (unsubstituted or halo-substituted) phenyl or naphthyl, phenyl-C_1-C_7-alkyl, naphthyl-C_1-C_7-alkyl or C_3-C_8-cycloalkyl)-aminocarbonyl, such as N-ethyl-carbamoyl, or (C_1-C_7-alkyl, phenyl, naphthyl, phenyl-C_1-C_7-alkyl and/or napthyl-C_1-C_7-alkyl)-oxycarbonyl, e.g. C_1-C_7-alkoxycarbonyl, such as methoxycarbonyl. Preferred is C_1-C_7-alkanoyl, C_1-C_7-alkoxycarbonyl or (C_6-C_{14}-aryl, such as phenyl or naphthyl)-C_1-C_7-alkoxycarbonyl.

Wherever a compound or compounds of the formula I are mentioned, this is further also intended to include N-oxides of such compounds and/or tautomers thereof.

The term "and/or an N-oxide thereof, a tautomer thereof and/or a (preferably pharmaceutically acceptable) salt thereof" especially means that a compound of the formula I may be present as such or in mixture with its N-oxide, as tautomer (e.g. due to keto-enol, lactam-lactim, amide-imidic acid or enamine-imine tautomerism) or in (e.g. equivalency reaction caused) mixture with its tautomer, or as a salt of the compound of the formula I and/or any of these forms or mixtures of two or more of such forms.

Compounds of the formula I can also be modified by appending appropriate functionalities to enhance selective biological properties. Modifications of this kind are known in the art and include those that increase penetration into a given biological system (e.g. blood, lymphatic system, central nervous system, testis), increase bioavailability, increase solubility to allow parenteral administration (e.g. injection, infusion), alter metabolism and/or alter the rate of secretion. Examples of this type of modifications include but are not limited to esterification, e.g. with polyethylene glycols, derivatisation with pivaloyloxy or fatty acid substituents, conversion to carbamates, hydroxylation of aromatic rings and heteroatom substitution in aromatic rings. Whereever compounds of the formula I, and/or N-oxides, tautomers and/or (preferably pharmaceutically acceptable) salts thereof are mentioned, this comprises such modified formulae, while preferably the molecules of the formula I, their N-oxides, their tautomers and/or their salts are meant.

In view of the close relationship between the novel compounds of the formula I in free form and those in the form of their salts, including those salts that can be used as intermediates, for example in the purification or identification of the novel compounds, any reference to the compounds or a compound of the formula I hereinbefore and hereinafter is to be understood as referring to the compound in free form and/or also to one or more salts thereof, as appropriate and expedient, as well as to one or more solvates, e.g. hydrates.

Salts are formed, for example, as acid addition salts, preferably with organic or inorganic acids, from compounds of formula I with a basic nitrogen atom, especially the pharmaceutically acceptable salts. Suitable inorganic acids are, for example, halogen acids, such as hydrochloric acid, sulfuric acid, or phosphoric acid. Suitable organic acids are, for example, carboxylic, phosphonic, sulfonic or sulfamic acids, for example acetic acid, propionic acid, octanoic acid, decanoic acid, dodecanoic acid, glycolic acid, lactic acid, fumaric acid, succinic acid, malonic acid, adipic acid, pimelic acid, suberic acid, azelaic acid, malic acid, tartaric acid, citric acid, amino acids, such as glutamic acid or aspartic acid, maleic acid, hydroxymaleic acid, methylmaleic acid, cyclohexanecarboxylic acid, adamantanecarboxylic acid, benzoic acid, salicylic acid, 4-aminosalicylic acid, phthalic acid, phenylacetic acid, mandelic acid, cinnamic acid, methane- or ethane-sulfonic acid, 2-hydroxyethanesulfonic acid, ethane-1,2-disulfonic acid, benzenesulfonic acid, 4-toluenesulfonic acid, 2-naphthalenesulfonic acid, 1,5-naphthalene-disulfonic acid, 2- or 3-methylbenzenesulfonic acid, methylsulfuric acid, ethylsulfuric acid, dodecylsulfuric acid, N-cyclohexylsulfamic acid, N-methyl-, N-ethyl- or N-propyl-sulfamic acid, or other organic protonic acids, such as ascorbic acid.

For isolation or purification purposes it is also possible to use pharmaceutically unacceptable salts, for example picrates or perchlorates. For therapeutic use, only pharmaceutically acceptable salts or free compounds are employed (where applicable in the form of pharmaceutical preparations), and these are therefore preferred.

p53 refers to the human protein itself as described by Matlashewski et al. in EMBO J. 3, 3257-62 (1984) (named also p53 wild type herein) or to any variant (e.g. a mutant, fragment or isoform due to deletion, insertion and/or exchange of one or more, e.g. one to 200, of the amino acids) thereof that is still capable to retain preferably at least 1 %, more preferably at least 5 %, yet more preferably at least 10%, 20%, 30%, 40%, 50% or more than 50% of the p53 activity in growth suppression, e.g. in the growth suppression assay described in Pieten-

pol et al., Proc. Nat. Acad. Sci. USA 91, 1998-2002 (1994) and, if compared with the corresponding sequence of p53 wild type, shows at least 20 %, more preferably at least 25 % identity with the full sequence, e.g. at least 90% identity with a partial sequence thereof.

As already indicated above, MDM2 (especially when mentioned as MDM2 or variants thereof) generally refers to all genes and/or proteins encoded thereof with the names MDM2, Mdm2, HDM2, Hdm2, or a variant thereof. MDM4 (especially when mentioned as MDM4 or variants thereof) refers to all genes and/or proteins encoded thereof with the names MDM4, Mdm4, HDM4, Hdm4, MDMX, MdmX, HDMX, HdmX, or a variant thereof.

MDM2 specifically relates to MDM2 as described in EMBO J. 10, 1565-9, Fakharzadeh et al., 1991, a variant thereof refers to a variant thereof which still binds to p53 in the assay system described below (e.g. an isoform, fragment, mutant or oncogene due to deletion, insertion and/or exchange of one or more, e.g. one to 430, of the amino acids), corresponding to the full length proteins as originally described, preferably at least with 0.5 %, more preferably at least with 5%, 10%, 20%, 30%, 40% or especially 50% or more of the affinity of MDM2 to p53, and have at least 20%, more preferably at least 25%, sequence identity to MDM2 or to HDM2 as originally described or as mentioned below specifically. Where not mentioned otherwise, MDM2 generally relates to MDM2, Mdm2, HDM2 or Hdm2, or variants thereof, respectively, as just defined.

MDM4 specifically relates to MDM4 as described in Genomics 43, 34-42, Shvarts et al., 1997, a variant thereof refers to a variant thereof which still binds to p53 in the assay system described below (e.g. an isoform, fragment, mutant or oncogene due to deletion, insertion and/or exchange of one or more, e.g. one to 430, of the amino acids), corresponding to the full length proteins as originally described, preferably at least with 0.5 %, more preferably at least with 5%, 10%, 20%, 30%, 40% or especially 50% or more of the affinity of MDM4 to p53, and have at least 20%, more preferably at least 25%, sequence identity to MDM4, to MDMX, to HDM4 or to HDM2 as originally described or as mentioned below specifically. Where not mentioned otherwise, MDM4 generally relates to MDM4, Mdm4, HDM4, Hdm4, MDMX, MdmX, HDMX or HdmX, or variants thereof, respectively, as just defined.

The percentage of sequence identity, often also termed homology, between a protein and a variant thereof is preferably determined by a computer program commonly employed for this

purpose, such as the Gap program (Wisconsin Sequence Analysis Package, Version 8 for Unix, Genetics Computer Group, University Reseach Park, Madison Wisconsin, USA, which uses the algorithm of Smith and Waterman (Adv. Appl. Math. 2: 482-489 (1981)., especially using an affine gap search with a gap open penalty of 12 and a gap extension penalty of 1.

"Variants thereof" where mentioned means one or more variant(s).

A proto-oncogene is a normal gene that can become an oncogene, either after mutation or increased expression. Proto-oncogenes code for proteins that help to regulate cell growth and differentiation. Proto-oncogenes are often involved in signal transduction and execution of mitogenic signals, usually through their protein products. Upon activation, a proto-oncogene (or its product) becomes a tumor inducing agent, an oncogene.

Quite unexpectedly, it has now been found that the compounds of formula I have advantageous pharmacological properties and disturb the binding interaction (also referred to herein as p53/MDM2 and p53/MDM4 interaction or as p53/MDM2 interaction solely) between p53 on the one side and MDM2 and/or MDM4 or (especially oncogenic) variants thereof which still are capable of binding to p53, on the other side.

The efficacy of the compounds of formula I and salts thereof as modulators affecting the interaction between can be demonstrated as shown in WO 98/01467 (which especially regarding the assays is included herein by reference) or preferably follows:

Fluorescence polarisation assay

The inhibition of p53-Hdm2 interaction is measured by fluorescence polarization. Fluorescence polarization measures the rotational movement of molecules in a homogeneous suspension. For this assay, Hdm2 protein (amino acids 2-185) is combined with a Cy5-labelled p53-derived peptide optimised for Hdm2 binding (*J. Med. Chem.* 2000, *43*, 3205-3208). Upon excitation of the Cy5 fluorescent ligand with linearly polarized light, the peptide rotates faster and emits light which is perpendicularly polarized. If the peptide is bound by Hdm2, rotation will slow down and the perpendicular component will decrease. Disruption of the formation of the peptide-Hdm2 complex due to an inhibitor molecule binding to the p53 binding site of Hdm2 results in faster rotation of the peptide. The

ratiometric polarization assay readout is calculated from the parallel and perpendicular components of the fluorescence light with respect to the polarization of the excitation light.

The test is performed by combining 7µl compounds diluted in dimethyl sulfoxide (DMSO) (10% final concentration) with 31.5µl Hdm2(2-188) (final concentration 3nM) in reaction buffer (PBS, 0.1% CHAPS, 1 mM DTT (dithiothreitol)). The solution is allowed to pre-incubate for 5 minutes at room temperature, followed by addition of 31.5µl peptide in reaction buffer (final concentration 1nM), and a further 5 minutes of incubation. A final volume of 20µl (in triplicate) is distributed into small volume black 384-well plates (Greiner Bio-One GmbH, Frickenhausen, Germany). For measurement of samples, an Analyst AD multimode microplate reader (Molecular Devices Corporation, Sunnyvale, CA, USA) with the following settings is used: Dichroic mirror 650nm, Excitation 630nm, Emission 695nm. Raw values are expressed as percent of DMSO control, where background (reaction buffer with peptide but no Hdm2) is subtracted first from raw values. IC50 values are calculated by curve fitting using XLfit. If not specified, reagents were purchased from Sigma Chemical Co.

Compounds described in the present invention preferably display inhibition of p53-Hdm2 interaction at IC50s ranging from 0.0003 to 25 µM, preferably from 0.0003 to 10 µM.

Time Resolved Fluorescence Energy Transfer (TR-FRET) Assay

The inhibition of p53-Hdm4 interaction is measured by time resolved fluorescence energy transfer (TR-FRET). Fluorescence energy transfer (or Foerster resonance energy transfer) describes an energy transfer between donor and acceptor fluorescent molecules. For this assay, MDM4 protein (amino acids 2-185), tagged with a C-terminal Biotin moiety, is used in combination with a Europium labeled streptavidin (Perkin Elmer, Inc., Waltham, MA, USA) serving as the donor fluorophore. The p53 derived, Cy5 labeled peptide Cy5-TFSDLWKLL (p53 aa18-26) is the energy acceptor. Upon excitation of the donor molecule at 340nm, binding interaction between MDM4 and the p53 peptide induces energy transfer and enhanced response at the acceptor emission wavelength at 665nm. Disruption of the formation of the p53-MDM4 complex due to an inhibitor molecule binding to the p53 binding site of MDM4 results in increased donor emission at 615nm. The ratiometric FRET assay readout is calculated from the raw data of the two distinct fluorescence signals measured in time resolved mode (countrate 665nm/countrate 615nm x 1000).

The test is performed in white 1536w microtiterplates (Greiner Bio-One GmbH, Frickenhausen, Germany) in a total volume of 3.1µl by combining 100nl of compounds diluted in 90% DMSO/10% H_2O (3.2% final DMSO concentration) with 2µl Europium labeled streptavidin (final concentration 2.5nM) in reaction buffer (PBS, 125mM NaCl, 0.001% Novexin (consists of carbohydrate polymers (Novexin polymers), designed to increase the solubility and stability of proteins; Novexin Ltd., Cambridgeshire, United Kingdom), Gelatin 0.01%, 0.2% Pluronic (block copolymer from ethylenoxide and propyleneoxide, BASF, Ludwigshafen, Germany), 1 mM DTT), followed by the addition of 0.5µl MDM4-Bio diluted in assay buffer (final concentration 10nM). Allow the solution to pre-incubate for 15 minutes at room temperature, followed by addition of 0.5µl Cy5-p53 peptide in assay buffer (final concentration 20nM). Incubate at room temperature for 10 minutes prior to reading the plate. For measurement of samples, an Analyst GT multimode microplate reader (Molecular Devices) with the following settings is used: Dichroic mirror 380nm, Excitation 330nm, Emission Donor 615nm and Emission Acceptor 665nm. IC50 values are calculated by curve fitting using XLfit. If not specified, reagents are purchased from Sigma Chemical Co, St. Louis, MO, USA.

The present invention also relates to novel aspects of the above described assays.

Compounds described in the present invention preferably display inhibition of p53-Hdm4 interaction at IC50s of 0.005 to 100 µM, e.g. from 10 nM to 50 µM.

Inhibitions of p53-Hdm2 and p53-Hdm4 by representative compounds in the present invention are displayed in Table 5 hereinbelow.

Having regard to their inhibitory effect on p53/MDM2 and/or p53/MDM4 interaction, compounds of formula (I) in free or pharmaceutically acceptable salt form, are useful in the treatment of conditions which are mediated by the activity (including normal activity or especially overactivity) of MDM2 and/or MDM4, or variants thereof, respectively, as described, such as proliferative and/or inflammatory conditions, e.g. by activation of the P53/MDM2 interaction, and/or that are responsive (meaning especially in a therapeutically beneficial way) to inhibition of the p53/MDM2 interaction, most especially a disease or disorder as mentioned hereinbelow.

"Treatment" in accordance with the invention may be therapeutic, e.g. symptomatic, palliative and/or curative, and/or prophylactic. Preferred is the treatment of warm-blooded animals, especially humans.

Preferred is a compound of formula I for use or the use thereof in the treatment of a disease or disorder that responds to treatment with a compound of the formula I, especially selected from disease that is based on dysregulation of cell cycle or especially apoptosis,: e.g. diseases involving the immune system, e.g. autoimmune diseases or immune diseases resulting due to transplantation (such as rheumatoid arthritis, graft-versus-host disease, systemic lupus erythematosus, Sjögren's syndrome, multiple sclerosis, Hashimoto's thyreoiditis, polymyositis), chronic inflammatory conditions, such as asthma, osteoarthritis, atherosclerosis, Morbus Crohn or inflammatory or allergic conditions of the skin, for example psoriasis, contact dermatitis, atopic dermatitis, alopecia areata, erythema multiforma, dermatitis herpetiformis, scleroderma, vitiligo, hypersensitivity angiitis, urticaria, bullous pemphigoid, pemphigus, epidermolysis bullosa acquisita, or other inflammatory or allergic conditions of the skin, hyperproliferative disorders, (e.g. Li-Fraumeni syndrome, cancer or tumor diseases, such as benign or malignant tumors, sarcomas, such as rhabdomyosarcoma, bone cancer, e.g. osteosarcomas, carcinoma of the brain, e.g. soft tissue brain tumor, kidney, liver, adrenal gland, bladder, breast, stomach, gastric tumors, ovaries, colon, rectum, prostate, pancreas, lung, vagina or thyroid, glioblastomas, multiple myeloma, gastrointestinal cancer, especially colon carcinoma or colorectal adenoma, a tumor of the neck and head, melanoma, prostate hyperplasia, a neoplasia, a neoplasia of epithelial character, a mammary carcinoma, a leukemia, such as B- or T-cell lymphomas adrenocortical carcinoma, including metastasis in other organs, respectively), viral infections (e.g. herpes, papilloma, HIV, viral hepatitis) or other diseases, for example those in which the p53/MDM2 and/or p53/MDM4 interaction is dysregulated and/or that are responsive to inhibition of the p53/MDM2 interaction and/or p53/MDM4.

The invention especially relates to the use of a compound of the formula I (or a pharmaceutical formulation comprising a compound of the formula I) in the treatment of one or more of the diseases mentioned above and below where the disease(s) respond or responds (in a beneficial way, e.g. by partial or complete removal of one or more of its symptoms up to complete cure or remission) to an inhibition of the p53/MDM2 interaction, especially where the involved MDM2 or MDM4 and/or variant shows (e.g.in the context of other regulatory

mechanisms, due to overexpression, to mutation or the like) inadequately high or more higher than normal activity.

Whereever the term "use" or "used" or especially use is mentioned, this is intended to include a compound of the formula I for use in the prophylactic and/or therapeutic treatment of a disease of a warm-blooded animal, especially a human, preferably of one or more diseases mentioned above or below, a method of use or a method of treatment comprising administering a compound of the formula I to a person in need of such treatment in an effective amount for the prophylactic and/or therapeutic treatment of a disease as mentioned above and below, the preparation or a method for the preparation of a pharmaceutical formulation/preparation for use in the prophylactic and therapeutic treatment of a disease or disorder mentioned above and below, especially involving combining a compound of the formula I (as therapeutically active ingredient) with at least one pharmaceutically acceptable carrier material, preferably including making it ready for use in such treatment (e.g. adding an instruction insert (e.g. package leaflet or the like), formulation, appropriate preparation, adaptation for specific uses, customizing and the like), and/or the use of a compound of the formula I for such preparation, and/or all other prophylactic or therapeutic uses mentioned hereinbefore or below. The invention can also relate to the use of a compound of the formula I to induce cell cycle deceleration or preferably arrest and/or apoptosis in cells containing p53 or variants thereof that are still functional, for sensitizing cells to one or more additional pharmaceutically active agents, such as inducers of apoptosis and/or of cell cycle deceleration or arrest, and to chemoprotection of normal cells through the inductoin of cell cycle deceleration or arrest prior to treatment with one or more other chemotherapeutic agents, to the use in rendering normal cells resistant to chemotherapeutic agents and/or treatments, and/or the use in protecting cells from toxic side effects of chemotherapeutic agens or treatments, such as side effects resulting in mucositis, stomatitis, xerostomia, gastrointestinal disorders and/or alopecia.

All these aspects are preferred embodiments of the present invention.

There are also experiments that can demonstrate the antitumor activity of compounds of the formula (I) *in vivo*.

For example, female Harlan (Indianapolis, Indiana, USA) athymic nu/nu mice with s.c. transplanted human osteosarcoma SJSA-1 tumors can be used to determine the anti-tumor activity of p53/MDM2 interaction inhibitors. On day 0, with the animals under peroral Forene® (1-chloro-2,2,2-trifluoroethyldifluormethylether, Abbot, Wiesbaden, Germany) narcosis, 3x106 cells are injected under the skin on the animals' left flank. When tumors reach a volume of 100 mm^3, the mice are divided at random into groups of 6-8 animals and treatment commences. The treatment is carried out for a 2-3 weeks period with peroral, intravenous or intra-peritoneal administration once daily (or less frequently) of a compound of formula (I) in a suitable vehicle at defined doses. The tumors are measured twice a week with a slide gauge and the volume of the tumors is calculated.

As an alternative to cell line SJSA-1, other cell lines may also be used in the same manner, for example,

- the HCT116 colon carcinoma cell line (ATCC No. CCL-247);
- the LNCaP clone FGC prostate carcinoma cell line (ATCC No. CRL-1740);
- the RKO colon carcinoma cell line (ATCC No.CRL-2577);
- the HT1080 fibrosarcoma cell line (ATCC No. CCL-121);
- the A375 malignant melanoma cell line (ATCC No. CRL-1619),
- the NCI-H460 large cell lung carcinoma cell line (ATCC No. HTB-177);

A compound of the formula (I) may also be used to advantage in combination with other anti-proliferative compounds. Such antiproliferative compounds include, but are not limited to aromatase inhibitors; antiestrogens; topoisomerase I inhibitors; topoisomerase II inhibitors; microtubule active compounds; alkylating compounds; histone deacetylase inhibitors; compounds which induce cell differentiation processes; cyclooxygenase inhibitors; MMP inhibitors; mTOR inhibitors,such as RAD001; antineoplastic antimetabolites; platin compounds; compounds targeting/decreasing a protein or lipid kinase activity and further anti-angiogenic compounds; compounds which target, decrease or inhibit the activity of a protein or lipid phosphatase; gonadorelin agonists; anti-androgens; methionine aminopeptidase inhibitors; bisphosphonates; biological response modifiers; antiproliferative antibodies, such as HCD122; heparanase inhibitors; inhibitors of Ras oncogenic isoforms; telomerase inhibitors; proteasome inhibitors; compounds used in the treatment of hematologic malignancies, such as FLUDARABINE; compounds which target, decrease or inhibit the activity of Flt-3, such as PKC412; Hsp90 inhibitors such as 17-AAG (17-allylaminogeldanamycin, NSC330507), 17-

DMAG (17-dimethylaminoethylamino-17-demethoxy-geldanamycin, NSC707545), IPI-504, CNF1010, CNF2024, CNF1010 from Conforma Therapeutics and AUY922; temozolomide (TEMODAL®); kinesin spindle protein inhibitors, such as SB715992 or SB743921 from GlaxoSmithKline, or pentamidine/chlorpromazine from CombinatoRx; PI3K inhibitors, such as BEZ235; RAF inhibitors, such as RAF265; MEK inhibitors such as ARRY142886 from Array PioPharma, AZD6244 from AstraZeneca, PD181461 from Pfizer, leucovorin, EDG binders, antileukemia compounds, ribonucleotide reductase inhibittors, S-adenosylmethionine decarboxylase inhibitors, antiproliferative antibodies or other chemotherapeutic compounds. Further, alternatively or in addition they may be used in combination with other tumor treatment approaches, including surgery, ionizing radiation, photodynamic therapy, implants, e.g. with corticosteroids, hormones, or they may be used as radiosensitizers. Also, in anti-inflammatory and/or antiproliferative treatment, combination with anti-inflammatory drugs is included. Combination is also possible with antihistamine drug substances, bronchodilatatory drugs, NSAID or antagonists of chemokine receptors.

The term "aromatase inhibitor" as used herein relates to a compound which inhibits the estrogen production, i.e. the conversion of the substrates androstenedione and testosterone to estrone and estradiol, respectively. The term includes, but is not limited to steroids, especially atamestane, exemestane and formestane and, in particular, non-steroids, especially aminoglutethimide, roglethimide, pyridoglutethimide, trilostane, testolactone, ketokonazole, vorozole, fadrozole, anastrozole and letrozole. Exemestane can be administered, e.g., in the form as it is marketed, e.g. under the trademark AROMASIN. Formestane can be administered, e.g., in the form as it is marketed, e.g. under the trademark LENTARON. Fadrozole can be administered, e.g., in the form as it is marketed, e.g. under the trademark AFEMA. Anastrozole can be administered, e.g., in the form as it is marketed, e.g. under the trademark ARIMIDEX. Letrozole can be administered, e.g., in the form as it is marketed, e.g. under the trademark FEMARA or FEMAR. Aminoglutethimide can be administered, e.g., in the form as it is marketed, e.g. under the trademark ORIMETEN. A combination of the invention comprising a chemotherapeutic agent which is an aromatase inhibitor is particularly useful for the treatment of hormone receptor positive tumors, e.g. breast tumors.

The term "antiestrogen" as used herein relates to a compound which antagonizes the effect of estrogens at the estrogen receptor level. The term includes, but is not limited to tamoxifen, fulvestrant, raloxifene and raloxifene hydrochloride. Tamoxifen can be admi-

nistered, e.g., in the form as it is marketed, e.g. under the trademark NOLVADEX. Raloxifene hydrochloride can be administered, e.g., in the form as it is marketed, e.g. under the trademark EVISTA. Fulvestrant can be formulated as disclosed in US 4,659,516 or it can be administered, e.g., in the form as it is marketed, e.g. under the trademark FASLODEX. A combination of the invention comprising a chemotherapeutic agent which is an antiestrogen is particularly useful for the treatment of estrogen receptor positive tumors, e.g. breast tumors.

The term "anti-androgen" as used herein relates to any substance which is capable of inhibiting the biological effects of androgenic hormones and includes, but is not limited to, bicalutamide (CASODEX), which can be formulated, e.g. as disclosed in US 4,636,505.

The term "gonadorelin agonist" as used herein includes, but is not limited to abarelix, goserelin and goserelin acetate. Goserelin is disclosed in US 4,100,274 and can be administered, e.g., in the form as it is marketed, e.g. under the trademark ZOLADEX. Abarelix can be formulated, e.g. as disclosed in US 5,843,901.

The term "topoisomerase I inhibitor" as used herein includes, but is not limited to topotecan, gimatecan, irinotecan, camptothecian and its analogues, 9-nitrocamptothecin and the macromolecular camptothecin conjugate PNU-166148 (compound A1 in WO99/ 17804). Irinotecan can be administered, e.g. in the form as it is marketed, e.g. under the trademark CAMPTOSAR. Topotecan can be administered, e.g., in the form as it is marketed, e.g. under the trademark HYCAMTIN.

The term "topoisomerase II inhibitor" as used herein includes, but is not limited to the anthracyclines such as doxorubicin (including liposomal formulation, e.g. CAELYX), daunorubicin, epirubicin, idarubicin and nemorubicin, the anthraquinones mitoxantrone and losoxantrone, and the podophillotoxines etoposide and teniposide. Etoposide can be administered, e.g. in the form as it is marketed, e.g. under the trademark ETOPOPHOS. Teniposide can be administered, e.g. in the form as it is marketed, e.g. under the trademark VM 26-BRISTOL. Doxorubicin can be administered, e.g. in the form as it is marketed, e.g. under the trademark ADRIBLASTIN or ADRIAMYCIN. Epirubicin can be administered, e.g. in the form as it is marketed, e.g. under the trademark FARMORUBICIN. Idarubicin can be administered, e.g. in the form as it is marketed, e.g. under the trademark ZAVEDOS. Mitoxantrone can be administered, e.g. in the form as it is marketed, e.g. under the trademark NOVANTRON.

The term "microtubule active compound" relates to microtubule stabilizing, microtubule destabilizing compounds and microtublin polymerization inhibitors including, but not limited to

taxanes, e.g. paclitaxel and docetaxel, vinca alkaloids, e.g., vinblastine, especially vinblastine sulfate, vincristine especially vincristine sulfate, and vinorelbine, discodermolides, cochicine and epothilones and derivatives thereof, e.g. epothilone B or D or derivatives thereof. Paclitaxel may be administered e.g. in the form as it is marketed, e.g. TAXOL. Docetaxel can be administered, e.g., in the form as it is marketed, e.g. under the trademark TAXOTERE. Vinblastine sulfate can be administered, e.g., in the form as it is marketed, e.g. under the trademark VINBLASTIN R.P.. Vincristine sulfate can be administered, e.g., in the form as it is marketed, e.g. under the trademark FARMISTIN. Discodermolide can be obtained, e.g., as disclosed in US 5,010,099. Also included are Epothilone derivatives which are disclosed in WO 98/10121, US 6,194,181, WO 98/25929, WO 98/08849, WO 99/43653, WO 98/22461 and WO 00/31247. Especially preferred are Epothilone A and/or B.

The term "alkylating compound" as used herein includes, but is not limited to, cyclophosphamide, ifosfamide, melphalan or nitrosourea (BCNU or Gliadel). Cyclophosphamide can be administered, e.g., in the form as it is marketed, e.g. under the trademark CYCLOSTIN. Ifosfamide can be administered, e.g., in the form as it is marketed, e.g. under the trademark HOLOXAN.

The term "histone deacetylase inhibitors" or "HDAC inhibitors" relates to compounds which inhibit the histone deacetylase and which possess antiproliferative activity. This includes compounds such as LDH589 disclosed in WO 02/22577, especially N-hydroxy-3-[4-[[(2-hydroxyethyl)[2-(1H-indol-3-yl)ethyl]-amino]methyl]phenyl]-2E-2-propenamide, N-hydroxy-3-[4-[[[2-(2-methyl-1*H*-indol-3-yl)-ethyl]-amino]methyl]phenyl]-2*E*-2-propenamide and pharmaceutically acceptable salts thereof. It further especially includes Suberoylanilide hydroxamic acid (SAHA).

The term "antineoplastic antimetabolite" includes, but is not limited to, 5-Fluorouracil or 5-FU, capecitabine, gemcitabine, DNA demethylating compounds, such as 5-azacytidine and decitabine, methotrexate and edatrexate, and folic acid antagonists such as pemetrexed. Capecitabine can be administered, e.g., in the form as it is marketed, e.g. under the trademark XELODA. Gemcitabine can be administered, e.g., in the form as it is marketed, e.g. under the trademark GEMZAR..

The term "platin compound" as used herein includes, but is not limited to, carboplatin, cisplatin, cisplatinum and oxaliplatin. Carboplatin can be administered, e.g., in the form as it is marketed, e.g. under the trademark CARBOPLAT. Oxaliplatin can be administered, e.g., in the form as it is marketed, e.g. under the trademark ELOXATIN.

The term "compounds targeting/decreasing a protein or lipid kinase activity"; or a "protein or lipid phosphatase activity"; or "further anti-angiogenic compounds" as used herein includes, but is not limited to, protein tyrosine kinase and/or serine and/or threonine kinase inhibitors or lipid kinase inhibitors, e.g.,

a) compounds targeting, decreasing or inhibiting the activity of the platelet-derived growth factor-receptors (PDGFR), such as compounds which target, decrease or inhibit the activity of PDGFR, especially compounds which inhibit the PDGF receptor, e.g. a N-phenyl-2-pyrimidine-amine derivative, e.g. imatinib, SU101, SU6668 and GFB-111;

b) compounds targeting, decreasing or inhibiting the activity of the fibroblast growth factor-receptors (FGFR);

c) compounds targeting, decreasing or inhibiting the activity of the insulin-like growth factor receptor I (IGF-IR), such as compounds which target, decrease or inhibit the activity of IGF-IR, especially compounds which inhibit the kinase activity of IGF-I receptor, such as those compounds disclosed in WO 02/092599, or antibodies that target the extracellular domain of IGF-I receptor or its growth factors;

d) compounds targeting, decreasing or inhibiting the activity of the Trk receptor tyrosine kinase family, or ephrin B4 inhibitors;

e) compounds targeting, decreasing or inhibiting the activity of the Axl receptor tyrosine kinase family;

f) compounds targeting, decreasing or inhibiting the activity of the Ret receptor tyrosine kinase;

g) compounds targeting, decreasing or inhibiting the activity of the Kit/SCFR receptor tyrosine kinase, i.e C-kit receptor tyrosine kinases - (part of the PDGFR family), such as compounds which target, decrease or inhibit the activity of the c-Kit receptor tyrosine kinase family, especially compounds which inhibit the c-Kit receptor, e.g. imatinib;

h) compounds targeting, decreasing or inhibiting the activity of members of the c-Abl family, their gene-fusion products (e.g. BCR-Abl kinase) and mutants, such as compounds which target decrease or inhibit the activity of c-Abl family members and their gene fusion products, e.g. a N-phenyl-2-pyrimidine-amine derivative, e.g. imatinib or nilotinib (AMN107); PD180970; AG957; NSC 680410; PD173955 from ParkeDavis; or dasatinib (BMS-354825)

i) compounds targeting, decreasing or inhibiting the activity of members of the protein kinase C (PKC) and Raf family of serine/threonine kinases, members of the MEK, SRC,

JAK, FAK, PDK1, PKB/Akt, and Ras/MAPK family members, and/or members of the cyclin-dependent kinase family (CDK) and are especially those staurosporine derivatives disclosed in US 5,093,330, e.g. midostaurin; examples of further compounds include e.g. UCN-01, safingol, BAY 43-9006, Bryostatin 1, Perifosine; Ilmofosine; RO 318220 and RO 320432; GO 6976; Isis 3521; LY333531/LY379196; isochinoline compounds such as those disclosed in WO 00/09495; FTIs; BEZ235 (a P13K inhibitor) or AT7519 (CDK inhibitor);

j) compounds targeting, decreasing or inhibiting the activity of protein-tyrosine kinase inhibitors, such as compounds which target, decrease or inhibit the activity of protein-tyrosine kinase inhibitors include imatinib mesylate (GLEEVEC) or tyrphostin. A tyrphostin is preferably a low molecular weight (Mr < 1500) compound, or a pharmaceutically acceptable salt thereof, especially a compound selected from the benzylidenemalonitrile class or the S-arylbenzenemalonirile or bisubstrate quinoline class of compounds, more especially any compound selected from the group consisting of Tyrphostin A23/RG-50810; AG 99; Tyrphostin AG 213; Tyrphostin AG 1748; Tyrphostin AG 490; Tyrphostin B44; Tyrphostin B44 (+) enantiomer; Tyrphostin AG 555; AG 494; Tyrphostin AG 556, AG957 and adaphostin (4-{[(2,5-dihydroxyphenyl)methyl]amino}-benzoic acid adamantyl ester; NSC 680410, adaphostin);

k) compounds targeting, decreasing or inhibiting the activity of the epidermal growth factor family of receptor tyrosine kinases (EGFR, ErbB2, ErbB3, ErbB4 as homo- or heterodimers) and their mutants, such as compounds which target, decrease or inhibit the activity of the epidermal growth factor receptor family are especially compounds, proteins or antibodies which inhibit members of the EGF receptor tyrosine kinase family, e.g. EGF receptor, ErbB2, ErbB3 and ErbB4 or bind to EGF or EGF related ligands, and are in particular those compounds, proteins or monoclonal antibodies generically and specifically disclosed in WO 97/02266, e.g. the compound of ex. 39, or in EP 0 564 409, WO 99/03854, EP 0520722, EP 0 566 226, EP 0 787 722, EP 0 837 063, US 5,747,498, WO 98/10767, WO 97/30034, WO 97/49688, WO 97/38983 and, especially, WO 96/30347 (e.g. compound known as CP 358774), WO 96/33980 (e.g. compound ZD 1839) and WO 95/03283 (e.g. compound ZM105180); e.g. trastuzumab (Herceptin™), cetuximab (Erbitux™), Iressa, Tarceva, OSI-774, CI-1033, EKB-569, GW-2016, E1.1, E2.4, E2.5, E6.2, E6.4, E2.11, E6.3 or E7.6.3, and 7H-pyrrolo-[2,3-d]pyrimidine derivatives which are disclosed in WO 03/013541; and

l) compounds targeting, decreasing or inhibiting the activity of the c-Met receptor, such as compounds which target, decrease or inhibit the activity of c-Met, especially compounds which inhibit the kinase activity of c-Met receptor, or antibodies that target the extracellular domain of c-Met or bind to HGF.

Further anti-angiogenic compounds include compounds having another mechanism for their activity, e.g. unrelated to protein or lipid kinase inhibition e.g. thalidomide (THALOMID) and TNP-470.

Compounds which target, decrease or inhibit the activity of a protein or lipid phosphatase are e.g. inhibitors of phosphatase 1, phosphatase 2A, or CDC25, e.g. okadaic acid or a derivative thereof.

Compounds which induce cell differentiation processes are e.g. retinoic acid, α- γ- or δ-tocopherol or α- γ- or δ-tocotrienol.

The term cyclooxygenase inhibitor as used herein includes, but is not limited to, e.g. Cox-2 inhibitors, 5-alkyl substituted 2-arylaminophenylacetic acid and derivatives, such as celecoxib (CELEBREX), rofecoxib (VIOXX), etoricoxib, valdecoxib or a 5-alkyl-2-arylaminophenylacetic acid, e.g. 5-methyl-2-(2'-chloro-6'-fluoroanilino)phenyl acetic acid, lumiracoxib.

The term "bisphosphonates" as used herein includes, but is not limited to, etridonic, clodronic, tiludronic, pamidronic, alendronic, ibandronic, risedronic and zoledronic acid. "Etridonic acid" can be administered, e.g., in the form as it is marketed, e.g. under the trademark DIDRONEL. "Clodronic acid" can be administered, e.g., in the form as it is marketed, e.g. under the trademark BONEFOS. "Tiludronic acid" can be administered, e.g., in the form as it is marketed, e.g. under the trademark SKELID. "Pamidronic acid" can be administered, e.g. in the form as it is marketed, e.g. under the trademark AREDIA™. "Alendronic acid" can be administered, e.g., in the form as it is marketed, e.g. under the trademark FOSAMAX. "Ibandronic acid" can be administered, e.g., in the form as it is marketed, e.g. under the trademark BONDRANAT. "Risedronic acid" can be administered, e.g., in the form as it is marketed, e.g. under the trademark ACTONEL. "Zoledronic acid" can be administered, e.g. in the form as it is marketed, e.g. under the trademark ZOMETA.

The term "mTOR inhibitors" relates to compounds which inhibit the mammalian target of rapamycin (mTOR) and which possess antiproliferative activity such as sirolimus (Rapamune®), everolimus (Certican™), CCI-779 and ABT578.

The term "heparanase inhibitor" as used herein refers to compounds which target, decrease or inhibit heparin sulfate degradation. The term includes, but is not limited to, PI-88.

The term " biological response modifier" as used herein refers to a lymphokine or interferons, e.g. interferon γ.

The term "inhibitor of Ras oncogenic isoforms", e.g. H-Ras, K-Ras, or N-Ras, as used herein refers to compounds which target, decrease or inhibit the oncogenic activity of Ras e.g. a "farnesyl transferase inhibitor" e.g. L-744832, DK8G557 or R115777 (Zarnestra).

The term "telomerase inhibitor" as used herein refers to compounds which target, decrease or inhibit the activity of telomerase. Compounds which target, decrease or inhibit the activity of telomerase are especially compounds which inhibit the telomerase receptor, e.g. telomestatin.

The term "methionine aminopeptidase inhibitor" as used herein refers to compounds which target, decrease or inhibit the activity of methionine aminopeptidase. Compounds which target, decrease or inhibit the activity of methionine aminopeptidase are e.g. bengamide or a derivative thereof.

The term "proteasome inhibitor" as used herein refers to compounds which target, decrease or inhibit the activity of the proteasome. Compounds which target, decrease or inhibit the activity of the proteasome include e.g. Bortezomid (Velcade™)and MLN 341.

The term "matrix metalloproteinase inhibitor" or ("MMP" inhibitor) as used herein includes, but is not limited to, collagen peptidomimetic and nonpeptidomimetic inhibitors, tetracycline derivatives, e.g. hydroxamate peptidomimetic inhibitor batimastat and its orally bioavailable analogue marimastat (BB-2516), prinomastat (AG3340), metastat (NSC 683551) BMS-279251, BAY 12-9566, TAA211, MMI270B or AAJ996.

The term "compounds used in the treatment of hematologic malignancies" as used herein includes, but is not limited to, FMS-like tyrosine kinase inhibitors e.g. compounds targeting, decreasing or inhibiting the activity of FMS-like tyrosine kinase receptors (Flt-3R); interferon, 1-b-D-arabinofuransylcytosine (ara-c) and bisulfan; and ALK inhibitors e.g. compounds which target, decrease or inhibit anaplastic lymphoma kinase.

Compounds which target, decrease or inhibit the activity of FMS-like tyrosine kinase receptors (Flt-3R) are especially compounds, proteins or antibodies which inhibit members of the Flt-3R receptor kinase family, e.g. PKC412, TKI258, midostaurin, a staurosporine derivative, SU11248 and MLN518.

The term "HSP90 inhibitors" as used herein includes, but is not limited to, compounds targeting, decreasing or inhibiting the intrinsic ATPase activity of HSP90; degrading, targeting, decreasing or inhibiting the HSP90 client proteins via the ubiquitin proteosome pathway. Compounds targeting, decreasing or inhibiting the intrinsic ATPase activity of HSP90 are especially compounds, proteins or antibodies which inhibit the ATPase activity of HSP90 e.g., 17-allylamino,17-demethoxygeldanamycin (17AAG), a geldanamycin derivative; other geldanamycin related compounds; radicicol and HDAC inhibitors. An example HSP90 inhibitor is AUY922.

The term "antiproliferative antibodies" as used herein includes, but is not limited to, trastuzumab (Herceptin™), Trastuzumab-DM1,erbitux, bevacizumab (Avastin™), rituximab (Rituxan®), PRO64553 (anti-CD40), 2C4 Antibody and HCD122 antibody (anti-CD40). By antibodies is meant e.g. intact monoclonal antibodies, polyclonal antibodies, multispecific antibodies formed from at least 2 intact antibodies, and antibodies fragments so long as they exhibit the desired biological activity.

For the treatment of acute myeloid leukemia (AML), compounds of formula (I) can be used in combination with standard leukemia therapies, especially in combination with therapies used for the treatment of AML. In particular, compounds of formula (I) can be administered in combination with, e.g., farnesyl transferase inhibitors and/or other drugs useful for the treatment of AML, such as Daunorubicin, Adriamycin, Ara-C, VP-16, Teniposide, Mitoxantrone, Idarubicin, Carboplatinum and PKC412.

The term "antileukemic compounds" includes, for example, Ara-C, a pyrimidine analog, which is the 2´-alpha-hydroxy ribose (arabinoside) derivative of deoxycytidine. Also included is the purine analog of hypoxanthine, 6-mercaptopurine (6-MP) and fludarabine phosphate. Compounds which target, decrease or inhibit activity of histone deacetylase (HDAC) inhibitors such as sodium butyrate and suberoylanilide hydroxamic acid (SAHA) inhibit the activity of the enzymes known as histone deacetylases. Specific HDAC inhibitors include MS275, SAHA, FK228 (formerly FR901228), Trichostatin A and compounds disclosed in US 6,552,065, in particular, *N*-hydroxy-3-[4-[[[2-(2-methyl-1*H*-indol-3-yl)-ethyl]-amino]-methyl]phenyl]-2*E*-2-propenamide, or a pharmaceutically acceptable salt thereof and *N*-hydroxy-3-[4-[(2-hydroxyethyl){2-(1*H*-indol-3-yl)ethyl]-amino]methyl]phenyl]-2*E*-2-propen-amide, or a pharmaceutically acceptable salt thereof, especially the lactate salt.

Somatostatin receptor antagonists as used herein refers to compounds which target, treat or inhibit the somatostatin receptor such as octreotide, and SOM230 (pasireotide).

Tumor cell damaging approaches refer to approaches such as ionizing radiation. The term "ionizing radiation" referred to above and hereinafter means ionizing radiation that occurs as either electromagnetic rays (such as X-rays and gamma rays) or particles (such as alpha and beta particles). Ionizing radiation is provided in, but not limited to, radiation therapy and is known in the art. See Hellman, Principles of Radiation Therapy, Cancer, in *Principles and Practice of Oncology*, Devita et al., Eds., 4th Edition, Vol. 1, pp. 248-275 (1993).

The term "EDG binders" as used herein refers a class of immunosuppressants that modulates lymphocyte recirculation, such as FTY720.

The term "ribonucleotide reductase inhibitors" refers to pyrimidine or purine nucleoside analogs including, but not limited to, fludarabine and/or cytosine arabinoside (ara-C), 6-thioguanine, 5-fluorouracil, cladribine, 6-mercaptopurine (especially in combination with ara-C against ALL) and/or pentostatin. Ribonucleotide reductase inhibitors are especially hydroxyurea or 2-hydroxy-1*H*-isoindole-1,3-dione derivatives, such as PL-1, PL-2, PL-3, PL-4, PL-5, PL-6, PL-7 or PL-8 mentioned in Nandy et al., *Acta Oncologica*, Vol. 33, No. 8, pp. 953-961 (1994).

The term "*S*-adenosylmethionine decarboxylase inhibitors" as used herein includes, but is not limited to the compounds disclosed in US 5,461,076.

Also included are in particular those compounds, proteins or monoclonal antibodies of VEGF disclosed in WO 98/35958, e.g. 1-(4-chloroanilino)-4-(4-pyridylmethyl)phthalazine or a pharmaceutically acceptable salt thereof, e.g. the succinate, or in WO 00/09495, WO 00/27820, WO 00/59509, WO 98/11223, WO 00/27819 and EP 0 769 947; those as described by Prewett et al, *Cancer Res*, Vol. 59, pp. 5209-5218 (1999); Yuan et al., *Proc Natl Acad Sci U S A*, Vol. 93, pp. 14765-14770 (1996); Zhu et al., *Cancer Res*, Vol. 58, pp. 3209-3214 (1998); and Mordenti et al., *Toxicol Pathol*, Vol. 27, No. 1, pp. 14-21 (1999); in WO 00/37502 and WO 94/10202; ANGIOSTATIN, described by O'Reilly et al., *Cell*, Vol. 79, pp. 315-328 (1994); ENDOSTATIN, described by O'Reilly et al., *Cell*, Vol. 88, pp. 277-285 (1997); anthranilic acid amides; ZD4190; ZD6474; SU5416; SU6668; bevacizumab; or anti-VEGF antibodies or anti-VEGF receptor antibodies, e.g. rhuMAb and RHUFab, VEGF aptamer e.g. Macugon; FLT-4 inhibitors, FLT-3 inhibitors, VEGFR-2 IgG1 antibody, Angiozyme (RPI 4610) and Bevacizumab (Avastin™).

Photodynamic therapy as used herein refers to therapy which uses certain chemicals known as photosensitizing compounds to treat or prevent cancers. Examples of photodynamic therapy includes treatment with compounds, such as e.g. VISUDYNE and porfimer sodium.

Angiostatic steroids as used herein refers to compounds which block or inhibit angiogenesis, such as, e.g., anecortave, triamcinolone. hydrocortisone, 11-α-epihydrocotisol, cortexolone, 17α-hydroxyprogesterone, corticosterone, desoxycorticosterone, testosterone, estrone and dexamethasone.

Implants containing corticosteroids refers to compounds, such as e.g. fluocinolone, dexamethasone.

"Other chemotherapeutic compounds" include, but are not limited to, plant alkaloids, hormonal compounds and antagonists; biological response modifiers, preferably lymphokines or interferons; antisense oligonucleotides or oligonucleotide derivatives; shRNA or siRNA; or miscellaneous compounds or compounds with other or unknown mechanism of action.

The structure of the active compounds identified by code nos., generic or trade names may be taken from the actual edition of the standard compendium "The Merck Index" or from databases, e.g. Patents International (e.g. IMS World Publications).

None of the quotations of references made within the present disclosure is to be understood as an admission that the references cited are prior art that would negatively affect the patentability of the present invention.

Preferred embodiments of the invention

In the following preferred embodiments of the invention, more general terms may, individually or some or all, be replaced with more specific terms mentioned above or below to define more preferred embodiments of the invention.

A preferred embodiment of the invention relates to a compound of the formula I wherein

R^1 is unsubstituted or substituted alkyl, unsubstituted or substituted alkenyl or unsubstituted or substituted alkinyl;

R^2 is unsubstituted or substituted aryl;

R^3 is hydrogen, unsubstituted or substituted alkyl, carboxy, cyano, esterified carboxy, unsubstituted or substituted heterocyclyl-carbonyl (heterocyclyl-C)=O)-), unsubstituted or substituted carbamoyl, unsubstituted or substituted heterocyclyl or cyano,

R^4 is hydrogen, unsubstituted or substituted alkyl, halo or unsubstituted or substituted heterocyclyl,

R^A is hydrogen or unsubstituted or substituted alkyl or acyl;
X is hydrogen, C_1-C_7-alkyl, halo-C_1-C_7-alkyl, C_1-C_7-alkoxy, halo or cyano; and
Y is C_1-C_7-alkyl, halo-C_1-C_7-alkyl, C_1-C_7-alkoxy, halo or cyano;

and/or a tautomer, an N-oxide and/or a salt thereof.

Preferred is especially a compound of the formula I wherein
R^1 is C_1-C_7-alkyl that is linear or branched and is unsubstituted or substituted by one or more, especially up to three, moieties independently selected from the group consisting of C_1-C_7-alkyl, especially methyl, of hydroxyl, of hydroxyl-C_1-C_7-alkyl, especially hydroxymethyl, of C_1-C_7-alkoxy-C_7-C_7-alkyl, especially 2-methoxy-ethoxy or methoxyethoxy or ethoxy-methoxy, of C_6-C_{14}-aryl, especially phenyl, wherein aryl is unsubstituted or substituted by one or more, especially up to three, moieties independently selected from the group consisting of C_1-C_7-alkyl, especially methyl, halo-C_1-C_7-alkyl, especially trifluoromethyl, hydroxyl, C_1-C_7-alkoxy, C_1-C_7-alkoxy-C_1-C_7-alkoxy, especially 2-methoxyethoxy or 3-methoxypropoxy, [amino, mono- or di-(C_1-C_7-alkyl)-amino]-C_1-C_7-alkoxy, amino, mono- or di-[C_1-C_7-alkyl, hydroxy-C_1-C_7-alkyl, C_1-C_7-alkoxy-C_1-C_7-alkyl, amino-C_1-C_7-alkyl, amino and/or mono- or di-(C_1-C_7-alkyl)-amino-C_1-C_7-alkyl]-amino, halo, especially fluoro, chloro or bromo, and saturated heterocyclyl-C_1-C_7-alkoxy wherein saturated heterocyclyl has 3 to 14 ring atoms of which 1 to 4 are a heteroatom independently selected from N, S, S(=O), $S(=O)_2$ and O and is unsubstituted or substituted with C_1-C_7-alkyl, especially pyrrolidinyl-, piperidinyl-, piperazinyl- or N-(C_1-C_7-alkyl)-piperazinyl-C_1-C_7-alkoxy, and of mono- or bicyclic C_3-C_{14}-heterocyclyl with 3 to 14 ring atoms of which 1 to 4 are a heteroatom independently selected from N, S, S(=O), $S(=O)_2$ and O and is unsubstituted or substituted with C_1-C_7-alkyl, especially corresponding heteroaryl, more especially indolyl, isoindolyl, indazolyl, quinolinyl, isoquinolinyl, phthalazinyl, quinoxalinyl, quinazolinyl, cinnolinyl, benzofuranyl, isobenzofuranyl, chromenyl, isochromenyl, benzothiophenyl, thiochromenyl or isothiochromenyl,

R^2 is C_6-C_{14}-aryl (especially phenyl) that is unsubstituted or substituted by one or more, especially up to three, moieties independently selected from the group consisting of C_1-C_7-alkyl-phenyl, especially methyl, hydroxyl, and halo, especially fluoro or chloro,

R^3 is hydrogen or preferably

C_1-C_7-alkyl that is unsubsituted by one or more, especially up to three, moieties independently selected from the group consisting of hydroxyl, amino and heterocyclyl-C_1-C_7-alkylamino wherein heterocyclyl has 3 to 14 ring atoms of which 1 to 4 are a heteroatom independently selected from N, S, S(=O), $S(=O)_2$ and O and is saturated, especially (morpholinyl, thiomorpholiny, S-oxothiomorpholinyl or S,S-dioxothiomorpholinyl)-C_1-C_7-alkylamino,

cyano, carboxy, C_1-C_7-alkoxycarbonyl or C_6-C_{14}-aryl-C_1-C_7-alkoxycarbonyl;

heterocyclyl-carbonyl (heterocyclyl-C(=O)) wherein heterocyclyl is unsaturated or preferably saturated, has 3 to 14 ring atoms of which 1 to 4 are a heteroatom independently selected from N, S, S(=O), $S(=O)_2$ and O, preferably N, such as pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, thiomorpholinyl, S-oxothiomorpholinyl or S,S-dioxothiomorpholinyl, and is unsubstituted or substituted with one or more, especially one to three, moieties independently selected from the group consisting of C_1-C_7-alkyl, hydroxy-C_1-C_7-alkyl, hydroxy, oxo, amino or N-mono- or N,N-di-(C_1-C_7-alkyl, {amino or mono- or di-C_1-C_7-alkylamino}-C_1-C_7-alkyl, C_1-C_7-alkanoyl and/or C_1-C_7-alkoxycarbonyl)-amino, C_1-C_7-alkanoyl, C_1-C_7-alkylsulfonyl and saturated heterocyclyl with 3 to 14 ring atoms and 1 to 4 heteroatoms independently selected from N, S, S(=O), $S(=O)_2$ and O, preferably N , e.g. pyrrolidinyl, imidazolidinyl, piperidinyl, piperazinyl, morpholinyl, thiomorpholinyl, S-oxo-thiomorpholinyl or S,S-dioxothiomorpholinyl, wherein said saturated heterocyclyl is unsubstituted or substituted by one or more, especially up to three, moieties independently selected from C_1-C_7-alkyl, hydroxy-C_1-C_7-alkyl C_1-C_7-alkoxy-C_1-C_7-alkyl, oxo, amino and mono- or di-(C_1-C_7-alkyl)-amino),

carbamoyl, N-mono- or N,N-di-[C_1-C_7-alkyl, hydroxy-C_1-C_7-alkyl, C_1-C_7-alkoxy-C_1-C_7-alkyl, amino-C_1-C_7-alkyl, mono- or di-(C_1-C_7-alkyl)-amino-C_1-C_7-alkyl, C_6-C_{14}-aryl wherein aryl is unsubstituted or substituted by one or more, especially up to three, moieties independently selected from the group consisting of C_1-C_7-alkyl, C_1-C_7-alkoxy, saturated heterocyclyl with 3 to 14 ring atoms and 1 to 4 heteroatoms independently selected from N, S, S(=O), $S(=O)_2$ and O, preferably N , e.g. pyrrolidinyl, imidazolidinyl, piperidinyl, piperazinyl, azepanyl, morpholinyl, thiomorpholinyl, S-oxo-thiomorpholinyl or S,S-dioxothiomorpholinyl, wherein said saturated heterocyclyl is unsubstituted or substituted with one or more, especially up to three, moieties independently selected from C_1-C_7-alkyl, hydroxy-C_1-C_7-alkyl, hydroxy, oxo and C_1-C_7-alkoxycarbonyl, C_6-C_{14}-aryl-C_1-C_7-alkyl, and saturated heterocyclyl or (saturated heterocyclyl)-C_1-C_7-alkyl wherein saturated heterocyclyl in both cases has 3 to 14 ring atoms and 1 to 4 heteroatoms independently selected from N, S, S(=O), $S(=O)_2$ and O, preferably N , e.g. pyrrolidinyl, imidazolidinyl, piperidinyl, piperazinyl, azepanyl, morpholinyl,

thiomorpholinyl, S-oxo-thiomorpholinyl, S,S-dioxothiomorpholinyl, indolyl or isoindolyl or (pyrrolidinyl, imidazolidinyl, piperidinyl, piperazinyl, azepanyl, morpholinyl, thiomorpholinyl, S-oxo-thiomorpholinyl, S,S-dioxothiomorpholinyl, indolyl or isoindolyl)-C_1-C_7-alkyl, wherein said saturated heterocyclyl is unsubstituted or substituted with one or more, especially up to three, moieties independently selected from C_1-C_7-alkyl, hydroxy-C_1-C_7-alkyl, C_1-C_7-alkoxy-C_1-C_7-alkyl, oxo, C_1-C_7-alkanoyl and C_1-C_7-alkoxycarbonyl]-carbamoyl,

heteroaryl with 3 to 14 ring atoms and 1 to 5 ring heteroatoms independently selected from the group consisting of N, S, S(=O), $S(=O)_2$ and O, especially N, S and O, such as triazolyl or especially tetrazolyl,
or cyano,
R^4 is hydrogen, C_1-C_7-alkyl, halo or heteroaryl with 3 to 14 ring atoms and 1 to 5 heteroatoms independently selected from the group consisting of N, S, S(=O), $S(=O)_2$ and O, especially N, such as pyridyl,
R^A is hydrogen or C_1-C_7-alkyl, preferably hydrogen;
X is hydrogen, C_1-C_7-alkyl, halo or cyano, especially hydrogen or fluoro, and
Y is C_1-C_7-alkyl, halo or cyano, especially methyl, fluoro, chloro, bromo or cyano,

and/or a tautomer, an N-oxide and/or a pharmaceutically acceptable salt thereof.

Highly preferred is a compound of the formula I wherein
R^1 is C_1-C_7-alkyl, especially 3,3-dimethylbutyl, C_1-C_7-alkylbenzyl, especially methyl-benzyl, more especially 4-methylbenzyl, (halo-C_1-C_7-alkyl)-benzyl, especially trifluoromethylbenzyl, more especially 4-trifluoromethylbenzyl, hydroxy-halo-benzyl, especially chloro-hydroxy-benzyl, more especially 4-chloro-2-hydroxybenzyl, halobenzyl, especially bromobenzyl, more especially 4-bromobenzyl, chlorobenzyl, more especially 4-chlorobenzyl, fluorobenzyl, more especially 4-fluorobenzyl, dichlorobenzyl, more especially 3,4- or 2,4-dichlorobenzyl, chloro-fluorobenzyl, more especially 4-chloro-3-fluorobenzyl, 3-chloro-4-fluorobenzyl or 4-chloro-2-fluorobenzyl, (R,S)- or preferably (R)- or (S)-1-(halo-phenyl)-1-(C_1-C_7-alkyl or hydroxy)-C_1-C_7-alkyl, especially (R,S)- or preferably (R)- or (S)-1-(fluorophenyl, chlorophenyl or bromo-phenyl)-1-(methyl or hydroxy)-methyl, more especially (R,S)- or preferably (R)- or (S)-1-(4-fluorophenyl, 4-chlorophenyl or 4-bromophenyl)-1-(methyl or hydroxy)-methyl, (R,S)- or preferably (R)- or (S)-1-(halo-phenyl)-1-[(hydroxy or C_1-C_7-alkoxy)-C_1-C_7-alkyl]-C_1-C_7-alkyl, especially (R,S)- or preferably (R)- or (S)-1-(chlorophenyl)-1-(hydroxymethyl or methoxyme-

thyl)-methyl, more especially (R,S)- or preferably (R)- or (S)-1-(4-chlorophenyl)- 1-(hydroxymethyl or methoxymethyl)-methyl, C_1-C_7-alkyl-halo-benzyl, especially methyl-halo-benzyl, more especially 4-chloro-2-methyl-benzyl, hydroxy-halo-benzyl, especially hydroxy-chloro-benzyl, more especially 4-chloro-2-hydroxybenzyl, C_1-C_7-alkoxy-halo-benzyl, especially methoxy-chloro-benzyl, such as 4-chloro-2-methoxybenzyl, (hydroxy-C_1-C_7-alkoxy or C_1-C_7-alkoxy-C_1-C_7-alkoxy)-halo-benzyl, especially (2-hydroxyethoxy, 3-hydroxypropoxy or 2-methoxy-ethoxy)-chloro-benzyl, more especially 4-chloro-2-(2-hydroxyethoxy, 3-hydroxy-propoxy or 2-methoxy-ethoxy)- benzyl, [amino, N-mono- or N,N-di-(C_1-C_7-alkylamino)-C_1-C_7-alkoxy]-halo-benzyl, especially [2-(N,N-dimethylamino)-ethoxy]-chloro-benzyl, more especially 2-[2-(N,N-dimethylamino)-ethoxy]-4-chloro-benzyl, (hydroxy-C_1-C_7-alkyl-amino)-halo-benzyl, especially [(2-hydroxymethyl- or 3-hydroxypropyl)-amino]-chloro-benzyl, more especially 2-[(2-hydroxymethyl- or 3-hydroxypropyl)-amino]-4-chloro-benzyl, (C_1-C_7-alkoxy-C_1-C_7-alkyl-amino)-halo-benzyl, especially [(2-methoxymethyl- or 3-methoxypropyl)-amino]-chloro-benzyl, more especially 2-[(2-methoxymethyl- or 3-methoxypropyl)-amino]-4-chloro-benzyl, [{amino, N-mono- or N,N-di-(C_1-C_7-alkyl)-amino}-C_1-C_7-alkylamino]-halo-benzyl, especially [(2-dimethylaminoethyl-amino]-chloro-benzyl, more especially 2-(2-dimethylaminoethyl-amino)-4-chloro-benzyl, (pyrrolidinyl-, piperidinyl-, piperazinyl- or N-(C_1-C_7-alkyl)-piperazinyl-C_1-C_7-alkoxy)-halo-benzyl, especially (pyrrolidino-, piperidino-, piperazino- or 4-(C_1-C_7-alkyl)-piperazin-1-yl-C_1-C_7-alkoxy)-halo-benzyl, more especially 4-chloro-2-[2-(pyrrolidino-, piperidino-, piperazino- or 4-(C_1-C_7-alkyl)-piperazin-1-yl)-ethoxy]-benzyl, indolyl-C_1-C_7-alkyl, especially indolylmethyl, more especially indol-6-ylmethyl, benzofuranyl-C_1-C_7-alkyl, especially benzofuranylmethyl, more especially benzofuran-6-ylmethyl, or benzothiophenyl-C_1-C_7-alkyl, especially benzothiophenylmethyl, more especially benzothiophen-6-ylmethyl;

R^2 is phenyl, C_1-C_7-alkyl-phenyl, especially methylphenyl, more especially 2-methylphenyl, hydroxyphenyl, especially 3-hydroxyphenyl, or halophenyl, especially phenyl or fluoro-, chloro- or fluoro-chloro-phenyl, more especially phenyl, 2-fluoropheny, 3-fluorophenyl or 3-chloro-2-fluorophenyl,

R^3 is hydrogen or preferably hydroxyl-C_1-C_7-alkyl, especially hydroxymethyl, amino-C_1-C_7-alkyl, especially 2-aminoethyl, (morpholinyl, thiomorpholiny, S-oxothiomorpholinyl or S,S-dioxothiomorpholinyl)-C_1-C_7-alkylamino-C_1-C_7-alkyl, especially N-(2-morpholinoethyl)-aminomethyl,

cyano, carboxy, C_1-C_7-alkoxycarbonyl, especially methoxycarbonyl or ethoxycarbonyl,

azetidin-carbonyl, especially acetidin-1-ylcarbonyl, pyrrolidin-carbonyl, especially pyrrolidin-1-carbonyl, achiral or (R,S)- or preferably (R)- or (S)-[amino or N'-mono- or N',N'-di-(C_1-C_7-alkyl and/or {amino or mono- or di-C_1-C_7-alkylamino}-C_1-C_7-alkyl)-amino]-pyrrolidin-carbonyl, especially (R,S)- or preferably (R)- or (S)-3-(dimethylamino)-pyrrolidin-1-carbonyl, (R,S)- or preferably (R)- or (S)-3-(diethylamino)-pyrrolidin-1-carbonyl, (R,S)- or preferably (R)- or (S)-3-[N-2-(dimethylamino)-ethyl-amino]-pyrrolidin-1-carbonyl, (R,S)- or preferably (R)- or (S)-3-[N-3-(dimethylamino)-propyl-amino]-pyrrolidin-1-carbonyl, (R,S)- or preferably (R)- or (S)-3-[N-2-(dimethylamino)-ethyl-N-methyl-amino]-pyrrolidin-1-carbonyl, or (R,S)- or preferably (R)- or (S)-3-[N-3-(dimethylamino)-propyl-N-methyl-amino]-pyrrolidin-1-carbonyl or (R,S)-, (R,S)- or preferably (R)- or (S)-pyrrolidinyl-pyrrolidin-carbonyl, especially (R,S)- or preferably (R)- or (S)-3-(pyrrolidin-1-yl)-pyrrolidin-carbonyl, (R,S)- or preferably (R)- or (S)-[(amino, mono- or di-(C_1-C_7-alkyl)-amino)-piperidinyl]-pyrrolidincarbonyl, especially (R,S)- or preferably (R)- or (S)-3-(4-dimethylamino-piperidin-1-yl)-pyrrolidin-1-carbonyl, (R,S)- or preferably (R)- or (S)-[hydroxy-C_1-C_7-alkyl, hydroxy, amino or mono- or di-(C_1-C_7-alkyl, C_1-C_7-alkanoyl, C_1-C_7-alkoxycarbonyl)-amino]-pyrrolidin-carbonyl, especially (R,S)- or preferably (R)- or (S)-3-hydroxy-pyrrolidin-1-carbonyl, especially (R,S)- or preferably (R)- or (S)-3-hydroxymethyl-pyrrolidin-1-carbonyl, (R,S)- or preferably (R)- or (S)-3-amino-pyrrolidin-1-carbonyl, (R,S)- or preferably (R)- or (S)-3-ethylamino-pyrrolidin-1-carbonyl, (R,S)- or preferably (R)- or (S)-3-tert-butoxycarbonylamino-pyrrolidin-1-carbonyl, (R,S)- or preferably (R)- or (S)-3-(N-methyl-N-acetyl-amino)-pyrrolidin-1-carbonyl, (R,S)- or preferably (R)- or (S)-(piperazinyl, C_1-C_7-alkylpiperazinyl, (hydroxy-C_1-C_7-alkyl)-piperazinyl morpholinyl, thiomorpholinyl, S-oxo-thiomorpholinyl or S,S-dioxo-thiomorpholinyl)-pyrrolidin-carbonyl, especially (R,S)- or preferably (R)- or (S)-3-(4-methylpiperazino)-pyrrolidin-1-carbonyl, (R,S)- or preferably (R)- or (S)-3-(4-(2-hydroxyethyl)-piperazino)-pyrrolidin-1-carbonyl, (R,S)- or preferably (R)- or (S)-3-morpholino-pyrrolidin-1-carbonyl or (R,S)- or preferably (R)- or (S)-3-dioxothiomorpholino-pyrrolidin-1-carbonyl,

piperidinyl-carbonyl, especially piperidin-1-carbonyl (piperidin-1-yl-C(=O)-), (hydroxy, hydroxy-C_1-C_7-alkyl, amino or mono- or di-(C_1-C_7-alkyl)amino)-piperidin-carbonyl, especially 4-hydroxymethyl-piperidin-1- carbonyl or 4-dimethylamino-piperidin-1-carbonyl, oxoimidazolidinyl-piperidincarbonyl, especially 4-(2-oxo-imidazolidin-1-yl)-piperidin-1-carbonyl, (phenyl-oxoimidazolidinyl)-piperidincarbonyl, especially 4-(3-phenyl-2-oxo-imidazolidin-1-yl)-piperidin-1-carbonyl, pyrrolidinyl- or oxopyrrolidinyl-piperidincarbonyl, especially 4-(pyrrolidin-1-yl)-piperidin-1 -carbonyl or 4-(2-oxo-pyrrolidin-1-yl-)-piperidin-1 -carbonyl, piperazinyl- or N-(C_1-C_7-alkyl)-piperazinyl-piperidin-carbonyl, especially 4-(4-methyl-piperazin-1-yl)-piperidin-1-

carbonyl, (morpholinyl, thiomorpholinyl, S-oxo-thiomorpholinyl or S,S-dioxo-thiomorpholinyl)-piperidin-carbonyl, especially 4-morpholino-piperidin-1-carbonyl, (oxo-benzoimidazolidinyl)-piperidin-carbonyl, especially (2-oxo-1,3-benzoimidazolidin-1-yl)-piperidin-carbonyl, piperazin-carbonyl, especially piperazin-1-carbonyl, (C_1-C_7-alkyl or hydroxyl-C_1-C_7-alkyl)-piperazin-carbonyl, especially 4-methyl-, 4-(2-hydroxyethyl)- or 4-(3-hydroxypropyl)-piperazin-1-carbonyl, oxopiperazin-carbonyl, especially 2-oxo-piperazin-4-carbonyl, C_1-C_7-alkanoyl-piperazin-carbonyl, especially 1-acetyl-piperazin-4-carbonyl, C_1-C_7-alkylsulfonyl-piperazin-carbonyl, especially 4-methanesulfonyl-piperazin-1- carbonyl,

morpholin-carbonyl (morpholinyl-C(=O)-), especially morpholin-1-carbonyl, (thiomorpholin, S-oxothiomorpholin or S,S-dioxothiomorpholin)-carbonyl, especially S,S-dioxothiomorpholin-1-carbonyl,

carbamoyl (synonymous: amino-carbonyl, -C(=O)-NH_2),

N-mono- or N,N-di-(C_1-C_7-alkyl)-carbamoyl, especially N-methyl-, N,N-dimethyl-, N-ethyl-or N-tert-butyl-carbamoyl,

N-[(hydroxy- or C_1-C_7-alkoxy)-C_1-C_7-alkyl]-carbamoyl, especially N-(2-hydroxyethyl)-carbamoyl, N-(3-hydroxypropyl)-carbamoyl, N-(2-methoxyethyl)-carbamoyl or N-(3-methoxypropyl)-carbamoyl, N-[(amino, mono- or di-(C_1-C_7-alkyl)-amino)-C_1-C_7-alkyl]-carbamoyl, especially N-(2-amino-ethyl)-carbamoyl, N-(2-(methylamino)-ethyl-carbamoyl, 2-(N,N-di-(methyl)-amino)-ethyl-carbamoyl, 3-(N,N-di-(methyl)-amino)-propyl-carbamoyl, N-[2-(N,N-di-(methyl)-amino)-ethyl]-N-methyl-carbamoyl, N-[3-(N,N-di-(methyl)-amino)-propyl]-N-methyl-carbamoyl, 2-(N,N-di-(ethyl)-amino)-ethyl-carbamoyl, 3-(N,N-di-(ethyl)-amino)-propyl-carbamoyl, N-[2-(N,N-di-(ethyl)-amino)-ethyl]-N-methyl-carbamoyl, N-[3-(N,N-di-(ethyl)-amino)-propyl]-N-methyl-carbamoyl, N-phenyl-carbamoyl, N-(C_1-C_7-alkoxy-phenyl)-carbamoyl, especially N-(methoxyphenyl)-carbamoyl, [(pyrrolidinyl, piperidinyl, piperazinyl or 1-(C_1-C_7-alkyl)-piperazinyl)-phenyl]-carbamoyl, especially N-[3-(piperazin-4-yl or 1-methyl-piperazin-4-yl)-phenyl]-carbamoyl, N-(phenyl-C_1-C_7-alkyl)-carbamoyl, especially N-benzyl-carbamoyl, N-(oxoimidazolidinyl-C_1-C_7-alkyl)-carbamoyl, especially N-[2-(2-oxoimidazol-1-yl)-ethyl]-carbamoyl, N-(pyrrolidinyl-C_1-C_7-alkyl)-carbamoyl, especially N-(pyrrolidinomethyl)-carbamoyl, N-(2-pyrrolidino-ethyl)-carbamoyl or N-(3-pyrrolidino-propyl)-carbamoyl, N-(oxopyrrolidinyl-C_1-C_7-alkyl)-carbamoyl, especially N-(2-oxo-pyrrolidinomethyl)-carbamoyl, N-[2-(2-oxopyrrolidino)-ethyl]-carbamoyl or N-[3-(2-oxopyrrolidino)-propyl]-carbamoyl,

N-Piperidinyl-carbamoyl, especially N-piperidin-4-yl-carbamoyl, N-[(C_1-C_7-alkyl)-piperidinyl]-carbamoyl, especially N-(1-methyl-piperidin-4-yl)-carbamoyl, N-[(hydroxyl-C_1-C_7-alkyl)-piperidinyl]-carbamoyl, especially N-[1-(2-hydroxyethyl)-piperidin-4-yl]-carbamoyl, N-[N-(C_1-

C_7-alkoxycarbonyl)-piperidinyl]-carbamoyl, especially N-[1-(tert-butoxycarbonyl) -piperidin-4-yl]-carbamoyl, N-(piperidinyl-C_1-C_7-alkyl)-carbamoyl, especially N-(piperidin-1-yl-methyl)-, N-[2-(piperidin-1-yl-)-ethyl]- or N-[3-(piperidin-1-yl)-propyl]-carbamoyl, N-(azepan-C_1-C_7-alkyl)-carbamoyl, especially N-(azepan-1-yl-methyl)-, N-[2-(piperidin-1-yl-)-ethyl]- or N-[3-(piperidin-1-yl)-propyl]-carbamoyl, N-(piperazinyl-C_1-C_7-alkyl)-carbamoyl, especially N-(piperazin-1-yl-methyl)-, N-[2-(piperazin-1-yl-)-ethyl]- or N-[3-(piperazin-1-yl)-propyl]-carbamoyl, N-(oxopiperazinyl-C_1-C_7-alkyl)-carbamoyl, especially N-[(2-oxo-piperazin-4-yl-)-methyl]-, N-[2-(2-oxo-piperazin-4-yl-)-ethyl]- or N-[3-(2-oxo-piperazin-4-yl)-propyl]-carbamoyl, N-((C_1-C_7-alkyl)-piperazinyl-C_1-C_7-alkyl)-carbamoyl, especially N-[(1-methyl-piperazin-4-yl-)-methyl]-, N-[2-(1-methyl-piperazin-4-yl-)-ethyl]- or N-[3-(1-methyl-piperazin-1-yl)-propyl]-carbamoyl, N-(1-(hydroxyl-C_1-C_7-alkyl)-piperazinyl-C_1-C_7-alkyl)-carbamoyl, especially N-[(1-(2-hydroxyethyl)-piperazin-4-yl-)-methyl]-, N-[2-(1-(2-hydroxyethyl)-piperazin-4-yl-)-ethyl]- or N-[3-(1-(2-hydroxyethyl)-piperazin-1-yl)-propyl]-carbamoyl, N-(1-(C_1-C_7-alkanoyl)-piperazinyl-C_1-C_7-alkyl)-carbamoyl, especially N-[(1-acetyl-piperazin-4-yl-)-methyl]-, N-[2-(1-acetyl-piperazin-4-yl-)-ethyl]- or N-[3-(1-acetyl-piperazin-1-yl)-propyl]-carbamoyl, N-(1-(C_1-C_7-alkoxycarbonyl)-piperazinyl-C_1-C_7-alkyl)-carbamoyl, especially N-[(1-(tert-butoxycarbonyl)-piperazin-4-yl-)-methyl]-, N-[2-(1-(tert-butoxycarbonyl)-piperazin-4-yl-)-ethyl]- or N-[3-(1-(tert-butoxycarbonyl)-piperazin-1-yl)-propyl]-carbamoyl, N-[(morpholinyl, thiomorpholinyl, S-oxo-thiomorpholinyl or S,S-dioxo-thiomorpholinyl)-C_1-C_7-alkyl]-carbamoyl, especially N-morpholinomethyl-, N-(2-morpholino-ethyl)-, N-(3-morpholinopropyl)-carbamoyl, N-(S,S-dioxothiomorpholino)-methyl-, N-[2-(S,S-dioxothiomorpholino)-ethyl]- or N-[3-(S,S-dioxothiomorpholino)-propyl]-carbamoyl, N-[dioxo-1H, 3H-isoindolyl)-C_1-C_7-alkyl)-carbamoyl, especially N-(1,7-dioxo-1H, 7H-isoindolin-2-yl-methyl)-, N-[2-(1,7-dioxo-1H, 7H-isoindolin-2-yl)-ethyl]- or N-[3-(1,7-dioxo-1H, 7H-isoindolin-2-yl)-propyl]-carbamoyl,
triazolyl or tetrazolyl, especially tetrazol-5-yl,
or cyano,

R^4 is hydrogen, C_1-C_7-alkyl, especially methyl, halo, especially bromo or chloro, or pyridyl, especially pyridin-3-, -4- or –2-yl,
R^A is hydrogen or C_1-C_7-alkyl, preferably hydrogen;
X is hydrogen, C_1-C_7-alkyl, halo or cyano, especially hydrogen or fluoro, and
Y is C_1-C_7-alkyl, halo or cyano, especially methyl, fluoro, chloro, bromo or cyano,

and/or a tautomer, an N-oxide and/or a pharmaceutically acceptable salt thereof.

Yet more highly preferred is a compound of the formula I wherein

R^1 is halobenzyl, especially bromobenzyl, more especially 4-bromobenzyl, chlorobenzyl, more especially 4-chlorobenzyl, or fluorobenzyl, more especially 4-fluorobenzyl,

R^2 is phenyl,

R^3 is hydroxyl-C_1-C_7-alkyl, especially hydroxymethyl, carboxy, achiral or (R,S)- or preferably (R)- or (S)-[amino or N'-mono- or N',N'-di-(C_1-C_7-alkyl and/or {amino or mono- or di-C_1-C_7-alkylamino}-C_1-C_7-alkyl)-amino]-pyrrolidin-carbonyl, especially (R,S)- or preferably (R)- or (S)-3-[N-2-(dimethylamino)-ethyl-N-methyl-amino]-pyrrolidin-1-carbonyl, amino or mono- or di-(C_1-C_7-alkyl)amino-piperidin-carbonyl, especially 4-dimethylamino-piperidin-1-carbonyl, carbamoyl, N-C_1-C_7-alkylcarbamoyl, especially N-methyl- or N-ethylcarbamoyl, N-((C_1-C_7-alkyl)-piperazinyl-C_1-C_7-alkyl)-carbamoyl, especially N-[(1-methyl-piperazin-4-yl-)-methyl]-, N-[2-(1-methyl-piperazin-4-yl-)-ethyl]- or N-[3-(1-methyl-piperazin-1-yl)-propyl]-carbamoyl, or N-[(morpholinyl or thiomorpholinyl)-C_1-C_7-alkyl]-carbamoyl, especially N-morpholinomethyl-, N-(2-morpholinoethyl)-, N-(3-morpholinopropyl)-carbamoyl,

R^4 is hydrogen or C_1-C_7-alkyl, especially methyl, or halo, especially bromo or chloro, more preferably hydrogen,

R^A is hydrogen;

X is halo or fluoro, and

Y is halo or cyano, especially chloro or cyano;

and/or a tautomer, an N-oxide and/or a pharmaceutically acceptable salt thereof.

Very preferred are also embodiments of the invention represented in the claims which are therefore incorporated by reference herein.

The invention also preferably relates to a method of manufacture or the USE of any one or more of the compounds of the formula I, and/or tautomers thereof, N-oxides thereof and/or (preferably pharmaceutically acceptable) salts thereof mentioned to be preferred herein, as well as to a pharmaceutical composition comprising it.

The invention relates especially to a compound of the formula I selected from the group of compounds as mentioned below in the examples by their names or formulae, preferably the

isomers shown as formulae, respectively, and/or a tautomer thereof, an N-oxide therof and/or a pharmaceutically acceptable salt thereof, or its use according to the invention, as well as to a pharmaceutical composition comprising it.

Pharmaceutical formulations, uses and methods

The above-mentioned compounds, which can be used in combination with a compound of the formula I, can be prepared and administered as described in the art, such as in the documents cited above.

By "combination", there is meant either a fixed combination in one dosage unit form, or a kit of parts for the combined administration where a compound of the formula I and a combination partner may be administered independently at the same time or separately within time intervals that especially allow that the combination partners show a cooperative, e.g. synergistic effect.

The invention also provides a pharmaceutical preparation, comprising a compound of formula I as defined herein, and/or an N-oxide or a tautomer thereof, and/oror a pharmaceutically acceptable salt of such a compound, or a hydrate or solvate thereof (all referred to often as "a compound of the formula I" merely herein), and at least one pharmaceutically acceptable carrier.

A compound of formula I can be administered alone or in combination with one or more other therapeutic compounds, possible combination therapy taking the form of fixed combinations or the administration of a compound of the invention and one or more other therapeutic (including prophylactic) compounds being staggered or given independently of one another, or the combined administration of fixed combinations and one or more other therapeutic compounds. A compound of formula I can besides or in addition be administered especially for tumor therapy in combination with chemotherapy, radiotherapy, immunotherapy, phototherapy, surgical intervention, or a combination of these. Long-term therapy is equally possible as is adjuvant therapy in the context of other treatment strategies, as described above. Other possible treatments are therapy to maintain the patient's status after tumor regression, or even chemopreventive therapy, for example in patients at risk.

The dosage of the active ingredient depends upon a variety of factors including type, species, age, weight, sex and medical condition of the patient; the severity of the condition to be

treated; the route of administration; the renal and hepatic function of the patient; and the particular compound employed. A physician, clinician or veterinarian of ordinary skill can readily determine and prescribe the effective amount of the drug required to prevent, counter or arrest the progress of the condition. Optimal precision in achieving concentration of drug within the range that yields efficacy requires a regimen based on the kinetics of the drug's availability to target sites. This involves a consideration of the distribution, equilibrium, and elimination of a drug.

The dose of a compound of the formula I or a pharmaceutically acceptable salt thereof to be administered to warm-blooded animals, for example humans of approximately 70 kg body weight, is preferably from approximately 3 mg to approximately 15 g, more preferably from approximately 10 mg to approximately 3 g, yet more preferably from approximately 50 mg to 1.5 g per person per day, undivided in 1 dose or divided preferably into 2 to 4, e.g. 2 or 3, single doses which may, for example, be of the same size. Usually, children receive half of the adult dose.

The compounds of the formula I may be administered by any conventional route, in particular parenterally, for example in the form of injectable solutions or suspensions, enterally, e.g. orally, for example in the form of tablets or capsules, topically, e.g. in the form of lotions, gels, ointments or creams, or in a nasal or a suppository form. Topical administration is e.g. to the skin. A further form of topical administration is to the eye. Pharmaceutical compositions comprising a compound of the invention in association with at least one pharmaceutical acceptable carrier or diluent may be manufactured in conventional manner by mixing with a pharmaceutically acceptable carrier or diluent.

The invention relates also to pharmaceutical compositions comprising an effective amount, especially an amount effective in the treatment of one of the above-mentioned disorders, of a compound of formula I and/or an N-oxide or a tautomer thereof, and/or a pharmaceutically acceptable salt thereof, together with one or more pharmaceutically acceptable carriers that are suitable for topical, enteral, for example oral or rectal, or parenteral administration and that may be inorganic or organic, solid or liquid. There can be used for oral administration especially tablets or gelatin capsules that comprise the active ingredient together with diluents, for example lactose, dextrose, mannitol, and/or glycerol, and/or lubricants and/or polyethylene glycol. Tablets may also comprise binders, for example magnesium aluminum silicate, starches, such as corn, wheat or rice starch, gelatin, methylcellulose, sodium carboxy-

methylcellulose and/or polyvinylpyrrolidone, and, if desired, disintegrators, for example starches, agar, alginic acid or a salt thereof, such as sodium alginate, and/or effervescent mixtures, or adsorbents, dyes, flavorings and sweeteners. It is also possible to use the pharmacologically active compounds of the present invention in the form of parenterally administrable compositions or in the form of infusion solutions. The pharmaceutical compositions may be sterilized and/or may comprise excipients, for example preservatives, stabilisers, wetting compounds and/or emulsifiers, solubilisers, salts for regulating the osmotic pressure and/or buffers. The present pharmaceutical compositions, which may, if desired, comprise other pharmacologically active substances are prepared in a manner known per se, for example by means of conventional mixing, granulating, confectionning, dissolving or lyophilising processes, and comprise approximately from 1% to 99%, especially from approximately 1% to approximately 20%, active ingredient(s).

Additionally, the present invention provides a compound of formula I, and/ or an N-oxide or a tautomer thereof, and/or a pharmaceutically acceptable salt thereof, for use in a method for the treatment of the human or animal body, especially for the treatment of a disease mentioned herein, most especially in a patient requiring such treatment..

The present invention also relates to the use of a compound of formula I and/or an N-oxide or a tautomer thereof, andor a pharmaceutically acceptable salt of such a compound, for the preparation of a medicament for the treatment especially of a proliferative disease.

Furthermore, the invention relates to a method for the treatment of a proliferative disease which responds to an inhibition p53/MDM2 interaction, which comprises administering a compound of formula I, and/or an N-oxide or a tautomer thereof, and/or a pharmaceutically acceptable salt thereof, wherein the radicals and symbols have the meanings as defined above, to a warm-blooded animal requiring such treatment, especially in a quantity effective against said disease and/or capable of inhibiting the p53/MDM2 interaction in said warm-blooded animal.

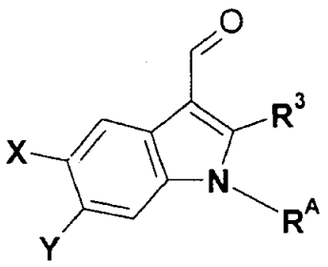
Furthermore, the invention relates to a pharmaceutical composition for treatment of solid or liquid tumours in warm-blooded animals, including humans, comprising an antiproliferativly effective dose of a compound of the formula I as described above or a pharmaceutically acceptable salt of such a compound together with a pharmaceutical carrier.

Manufacturing Process:

The invention relates also to a process for the manufacture of a compound of the formula I, and/or an N-oxide thereof or a tautomer thereof, and/or a salt thereof.

Compounds of the formula I can be prepared according to or in analogy to methods that, in principle and with other educts, intermediates and final products, are known in the art, especially and according to the invention by a process comprising

a) for the manufacture of a compound of the formula I wherein R^4 is hydrogen and R^1, R^2, R^3, R^A, X and Y are as defined for a compound of the formula I, reacting a formylindole derivative of the formula II

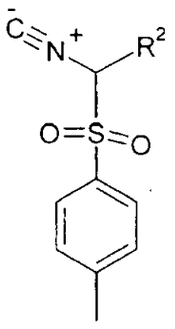


(II)

wherein R^3, R^A, X and Y are as defined for a compound of the formula I, with an amino compound of the formula III,

R^1-NH_2 (III)

wherein R^1 is as defined for a compound of the formula I in the presence of a tosyl-methyl isocyanide of the formula IV,

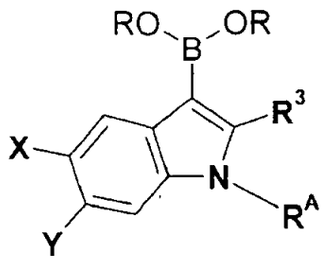


(IV)

wherein $R^2$is as defined for a compound of the formula I;

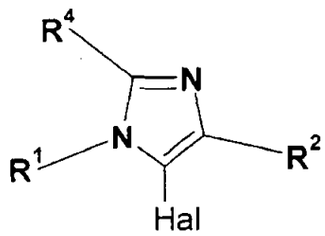
or

b) (for the synthesis of a compound of the formula I) coupling an indole-boronic acid of the formula V,



(V)

wherein R^3, R^A, X and Y are as defined for a compound of the formula I, and each R is aryl, alkenyl or especially alkyl, or wherein the two R form a bridge, especially R is H, lower alkyl or R and R together form 1,1,2,2-tetramethyl-1,2-ethylene, with a halo-imidazole of the formula VI,



(VI)

wherein R^1, R^2 and R^4 are as defined for a compound of the formula I and Hal is halo, especially bromo or more especially iodo,

where in the reaction functional groups in the starting materials can be present in protected form and in the obtainable compounds of the formula I carrying one or more protecting groups such protecting groups are removed;

and, if desired, a compound of the formula I obtainable according to the reaction given above is converted into a different compound of the formula I, an obtainable salt of a compound of the formula I is converted into a different salt thereof, an obtainable free compound of the formula I is converted into a salt thereof, and/or an obtainable isomer of a compound of the formula I is separated from one or more different obtainable isomers of the formula I.

Preferred reaction conditions:

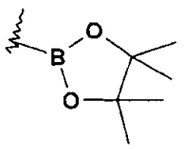
In the following more detailed description of the process, optional reactions and conversions, synthesis of starting materials and intermediates and the like, R^1, R^2, R^3, R^4, R^A, X and Y have the meanings given for a compound of the formula I or the compound mentioned specifically, while other moieties if present are as defined for a compound of the formula II, III, IV, V or VI, respectively.

Variant a) is a cylisation reaction forming the imidazole ring missing in formula II and preferably takes place at elevated temperatures, e.g. at temperatures in the range from 50 to 130 °C, e.g. at about 110 °C, if required in sealed reaction vessels, in an appropriate solvent, e.g. an ether, preferably a cyclic ether, such as tetrahydrofurane. The heating can, for example, be accomplished by a microwave oven.

Variant b) (which not only allows to synthesize also compound of the formula I wherein R^4 is hydrogen but also wherein it has the meanings given for R^4 in compounds of the fomula I wherein R^4 is other than hydrogen)

The reaction preferably takes place under Suzuki-(Miyaura) conditions, that is, by palladium-catalyzed crosscoupling of organoboranes, by reacting the halo- carrying compound of the formula II with the boronic acid of the formula III, or a reactive derivative thereof.

A reactive derivative of a boronic acid of the formula V is preferably one wherein instead of the hydroxyl groups at the boron atom an aryl, alkenyl or especially alkyl moiety is present, or wherein the OH groups are present in bridged form, e.g. , together with the boron atom, forming a group of the formula (A)



(A).

The reaction preferably takes place in a mixture of a polar aprotic solvent, such as dimethylformamide (DMF) or tetrahydrofurane, and water in the presence of a catalyst for the cross-coupling, especially a noble metal catalyst, preferably a palladium catalyst, such as palladium(II) complex, for example bis(triphenylphosphine)palladium (II) dichloride, in the presence of a base, such as potassium carbonate, sodium hydroxide or sodium carbonate,

at a preferred temperature in the range from 60 °C to 130 °C, e.g. at about 80 °C; or according to a another preferred method in an ether solvent, e.g. tetrahydrofurane or 1,2-dimethoxyethane, in the presence of a catalyst for the cross coupling, especially a noble metal catalyst, preferably a palladium (0) complex, for example tris(dibenzylideneacetone)-dipalladium(0) or tetrakis (triphenylphosphin)palladium(0), in the presence of a base, such as sodium hydroxide, potassium carbonate of sodium carbonate, if desired in the presence of an appropriate ligand, such as 2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl (SPhos), at a preferred temperature in the range from 60 to 150 °C, preferably from 70 to 110 °C; if required conducting the reaction in a sealed vessel (e.g. a seal reactor) if the boiling point of the reaction mixture is exceeded and especially if the heating is effected by microwave excitation. Preferably, oxygen is excluded, e.g. by the presence of an inert gas, such as nitrogen or especially argon.

Advantageously, where R^A in a compound of the formula V is hydrogen, this hydrogen is replaced by an N-protecting group, such as tert-butoxycarbonyl, which can, after the reaction with the compound of the formula VI, be removed according to well-known methods, e.g. as described in the references mentioned below.

Where useful or required, the reactions (as well as those forming starting materials or intermediates) can take place under an inert gas, such as nitrogen or argon.

Protecting groups

If one or more other functional groups, for example carboxy, hydroxy, amino, or mercapto, are or need to be protected in a starting material, e.g. in any one or more starting materials of the formula II or III or other starting materials, intermediates and educts mentioned below,, because they should not take part in the reaction or disturb the reaction, these are such groups as are usually used in the synthesis of peptide compounds, and also of cephalosporins and penicillins, as well as nucleic acid derivatives and sugars. Protecting groups are such groups that are no longer present in the final compounds once they are removed, while groups that remain as substitutents are not protecting groups in the sense used here which is groups that are added at a certain intermediate stage and removed to obtain a final compound. For example, tert-butoxy if remaining in a compound of the formula I is a substituent, while if it is removed to obtain the final compound of the formula I it is a protecting group.

The protecting groups may already be present in precursors and should protect the functional groups concerned against unwanted secondary reactions, such as acylations, etherifications, esterifications, oxidations, solvolysis, and similar reactions. It is a characteristic of protecting groups that they lend themselves readily, i.e. without undesired secondary reactions, to removal, typically by acetolysis, protonolysis, solvolysis, reduction, photolysis or also by enzyme activity, for example under conditions analogous to physiological conditions, and that they are not present in the end-products. The specialist knows, or can easily establish, which protecting groups are suitable with the reactions mentioned above and below.

The protection of such functional groups by such protecting groups, the protecting groups themselves, and their removal reactions are described for example in standard reference works, such as J. F. W. McOmie, "Protective Groups in Organic Chemistry", Plenum Press, London and New York 1973, in T. W. Greene, "Protective Groups in Organic Synthesis", Third edition, Wiley, New York 1999, in "The Peptides"; Volume 3 (editors: E. Gross and J. Meienhofer), Academic Press, London and New York 1981, in "Methoden der organischen Chemie" (*Methods of organic chemistry*), Houben Weyl, 4th edition, Volume 15/I, Georg Thieme Verlag, Stuttgart 1974, in H.-D. Jakubke and H. Jescheit, "Aminosäuren, Peptide, Proteine" (*Amino acids, peptides, proteins*), Verlag Chemie, Weinheim, Deerfield Beach, and Basel 1982, and in Jochen Lehmann, "Chemie der Kohlenhydrate: Monosaccharide und Derivate" (*Chemistry of carbohydrates: monosaccharides and derivatives*), Georg Thieme Verlag, Stuttgart 1974.

Optional Reactions and Conversions

A compound of the formula I may be converted into a different compound of the formula I.

For example, a compound of the formula I wherein R^3 is esterified carboxy, especially C_1-C_7-alkoxycarbonyl, may be converted to a compound of the formula I wherein R^3 is a different esterified carboxy, carbamoyl, unsubstituted or substituted heterocyclyl-carbonyl (that is, heterocyclyl-C)=O)-) wherein the heterocyclyl is bound via an (in unprotonated form trivalent) nitrogen, or unsubstituted or substituted carbamoyl by, for the synthesis of a corresponding amide, reaction with a compound of the formula VII,

$$R^a\text{-}NH\text{-}R^b \qquad (VII)$$

wherein each of R^a and R^b, independently of the other, is unsubstituted or substituted C_1-C_7-alkyl, unsubstituted or substituted aryl, unsubstituted or substituted cycloalkyl or unsubstituted or substituted heterocyclyl, or R^a and R^b together with the binding nitrogen are heterocyclyl that is preferably a moiety chosen from heterocyclyl as defined above with an NH- in the ring and which is unsubstituted or substituted;
or, for the synthesis of a corresponding ester, an alcohol of the formula VIII,

$$R^c\text{-OH} \qquad \text{(VIII)}$$

wherein $R^c$is unsubstituted or substituted alkyl, unsubstituted or substituted aryl, unsubstituted or substituted cycloalkylor unsubstituted or substituted heterocyclyl.

The reaction may either take place by first hydrolyising the esterified carboxy, e.g. C_1-C_7-alkoxycarbonyl, to carboxy, e.g. in the presence of an acid or preferably a base, such as an alkali metal hydroxide, such as sodium or potassium hydroxide, in an appropriate solvent, such as an alcohol, e.g. methanol or ethanol, preferably at elevated temperatures, e.g. in the range from 50 °C to the reflux temperature of the reaction mixture, followed then by coupling of the free carboxylic acid of the formula I (which is thus also obtainable by conversion) under appropriate coupling conditions, e.g. in the presence of a coupling agent that forms a reactive derivative of the carboxyl group *in situ*, for example dicyclohexylcarbodiimide/1-hydroxybenzotriazole (DCC/ HOBT); bis(2-oxo-3-oxazolidinyl)phosphinic chloride (BOPCl); *O*-(1,2-dihydro-2-oxo-1-pyridyl)-*N*,*N*,*N*',*N*'-tetramethyluronium tetrafluoroborate (TPTU); O-benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium tetrafluoroborate (TBTU); (benzotriazol-1-yloxy)-tripyrrolidinophosphonium-hexafluorophosphate (PyBOP), O-(1H-6-chlorobenzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate, 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride/hydroxybenzotriazole, O-(7-azabenzotriazol-1-yl)-N,N,N', N'-tetramethyluronium-hexafluorophosphat (HATU) or/1-hydroxy-7-azabenzotriazole (EDC/HOBT or EDC/HOAt) or HOAt alone, or with (1-chloro-2-methyl-propenyl)-dimethylamine. For review of some other possible coupling agents, see e.g. Klauser; Bodansky, *Synthesis* (1972), 453-463. The reaction mixture, which advantageously can comprise an appropriate solvent, e.g. dimethyl formamide or dioxane, and/or N-methylmorpholine, is preferably kept, e.g. stirred, at a temperature of between approximately -20 and 80 °C, especially between 0 °C and 60 °C, e.g. at room temperature or at about 50 °C.

Alternatively, it is also possible to directly replace the original esterifying group, e.g. C_1-C_7-alkoxy, by reaction with a compound of the formula VII or VIII, e.g. at elevated temperatures, for example in the range from 30 °C to the reflux temperature, e.g. at about 60 °C, in the presence of an appropriate solvent, such as a lower alkanol, e.g. methanol or ethanol.

In a compound of the formula I with carbamoyl R^3, this moiety may be converted into cyano, e.g. by reaction of the corresponding compound of the formula I in the presence of trifluoroacetic anhydride in an appropriate solvent, e.g. dichloromethane, e.g. at an elevated temperature in the range from 30 °C to the reflux temperature of the reqction mixture.

In a compound of the formula I with Cyano R^3 (obtainable e.g. according to the preceding paragraph), the cyano may be converted into tetrazolyl R^3 e.g. by reaction with sodium azide in an appropriate solvent, such as 2-methoxy-ethanol, preferably at elevated temperatures, e.g. at about 130 °C.

In a compound of the formula I wherein R^3 is carbamoyl or heterocyclyl-carbonyl wherein heterocyclyl is bound via an (in unprotonated form trivalent) nitrogen atom, the binding –C(=O) may be reduced to a methylene bridge (-CH_2-), for example by reaction with an appropriate reducing agent, such as a hydride, e.g. lithium aluminium hydride, e.g. in the presence of a Lewis acid, such as aluminiumtrichloride, in an appropriate solvent, e.g. an ether, such as tetrahydrofurane, at preferably elevated temperature, e.g. in the range from 50 °C to the reflux temperature of the reaction mixture, thus yielding unsubstituted or substituted alkyl R^3.

In a compound of the formula I wherein R^3 is carboxy, this carboxy can also be reduced to the corresponding hydroxymethyl group R^3 e.g. by reaction with lithium aluminium hydride in an appropriate solvent, such as tehrahydrofurane, at temperatures in the range from 20 ° C to the reflux temperature of the reaction mixture.

A C_1-C_7-alkoxy substituent of aryl, e.g. as substitutent of aryl R^2, can be converted into a corresponding hydroxyl substituent, e.g. by reaction with BBR_3in an appropriate solvent, e.g. dichloromethane, for example at temperatures from 0 to 50 °C.

A nitrogen ring atom within a compound of the formula I, e.g. in the imidazolinylindole core or a nitrogen-containing heterocyclic (e.g. heteroaryl) substituent, can be converted into an N-oxide in the presence of a suitable oxidizing agent, e.g. a peroxide, such as m-chloroperbenzoic acid or hydrogen peroxide, if useful in an appropriate solvent.

Other examples of conversion can be deduced from the Examples, e.g. where a reaction from a starting material that is at the same time also a compound of the formula I involves the removal of a group that corresponds to a protecting group, e.g. the cleavage of an ester, e.g. to convert C_1-C_7-alkoxycarbonyl into carboxyl, the removal of a tert-butoxycarbonyl or methansulfonyl or tert-butyl-dimethylsilyl or the cleavage of isoindol-1,3-dion-2-yl, masking an amino or hydroxy group to give the free hydroxy or amino group, or the cleavage of piperazinyl or N-alkyl-piperazin-1-yl to 2-(N-alkyl-amino)ethyl).

Also in the optional process steps, carried out "if desired", functional groups of the starting compounds which should not take part in the reaction may be present in unprotected form or may be protected for example by one or more of the protecting groups mentioned hereinabove under "protecting groups". The protecting groups are then wholly or partly removed according to one of the methods described there.

Salts of a compound of formula I with a salt-forming group may be prepared in a manner known *per se*. Acid addition salts of compounds of formula I may thus be obtained by treatment with an acid or with a suitable anion exchange reagent, salts with bases by reaction with suitable kation exchange reagents or with corresponding bases, e.g. metal hydroxides or the like.

Salts can usually be converted to free compounds, e.g. acid addition salts by treating with suitable basic compounds, for example with alkali metal carbonates, alkali metal hydrogencarbonates, or alkali metal hydroxides, typically potassium carbonate or sodium hydroxide, salts with bases by reaction with appropriate acids, such as inorganic acids, e.g. hydrochloric acid or sulfuric acid, or sufficiently strong organic acids, e.g. sulfonic acids.

Stereoisomeric mixtures, e.g. mixtures of diastereomers, can be separated into their corresponding isomers in a manner known *per se* by means of suitable separation methods. Diastereomeric mixtures for example may be separated into their individual diastereomers by

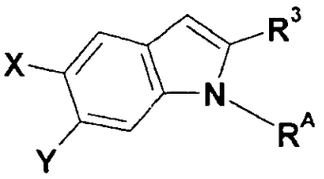
means of fractionated crystallization, chromatography, solvent distribution, and similar procedures. This separation may take place either at the level of a starting compound or in a compound of formula I itself. Enantiomers may be separated through the formation of diastereomeric salts, for example by salt formation with an enantiomer-pure chiral acid, or by means of chromatography, for example by HPLC, using chromatographic substrates with chiral ligands, or by any other method known in the art, e.g. using emulsion crystallization.

It should be emphasized that reactions analogous to the conversions mentioned in this chapter may also take place at the level of appropriate intermediates (and are thus useful in the preparation of corresponding starting materials).

Starting materials:

The starting materials of the formulae II, III, IV, V, VI, VII and VIII, as well as other starting materials, intermediates or educts mentioned herein, e.g. below, can be prepared according to or in analogy to methods that are known in the art, the materials are known in the art and/or are commercially available, or by or in analogy to methods mentioned in the Examples. Novel starting materials, as well as processes for the preparation thereof, are likewise an embodiment of the present invention. In the preferred embodiments, such starting materials are used and the reaction chosen are selected so as to enable the preferred compounds to be obtained.

For example, a formylindole derivative of the formula II may preferably be obtained by formylation of an indole derivative of the formula IX,



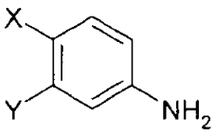
(IX)

wherein R^3, R^A, X and Y are as defined for a compound of the formula I, by reacting it with a dialkyl formamide, such as dimethylformamide, or with N-methyl-N-phenyl-formamide or under Vilsmeier conditions, e.g. in the presence of phosphorous oxychloride in the presence or preferably absence of a further solvent and at temperatures e.g. in the range from about 0 to about 80 °C, or alternatively with hydrogen cyanide (HCN) under Gattermann conditions in the presence of a Lewis catalyst, such as aluminium trichloride, and of hydrogen chloride (HCl), or with Zinc cyanide in the presence of hydrogen chloride (HCl), or under Gattermann-

Koch conditions with carbon monoxide, hydrogen chloride and a Lewis acid, by Rieche formylation or the like.

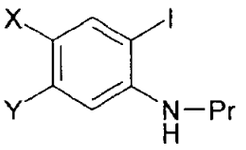
Compounds of the formula IX are known in the art, may be prepared according to methods known in the art, are commercially available and/or can be prepared according or in analogy to methods described in the Examples.

A compound of the formula IX wherein R^3 is esterified carboxy may, for example, be obtained from an aniline compound of the formula X,



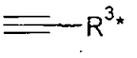
(X)

wherein X and Y are as defined for a compound of the formula I by iodination, e.g. with N-iodo succinimide in the presence of an acid, such as acetic acid, e.g. at temperatures in the range of from 0 to 50 °C, then introduction of a protecting group for the amino function, e.g. by reaction with mesityl chloride in the presence of a base, such as pyridine, in an appropriate solvent, such as dichloromethane, e.g. at temperatures in the range of from 0 to 50 °C, followed by removal of one of the two methansulfonyl groups thus introduced at the amino function with potassium carbonate in an appropriate solvent, such as methanol/tetrahydrofurane, e.g. at temperatures in the range of from 0 to 50 °C, to give a protected iodo aniline derivative of the formula XI,



(XI)

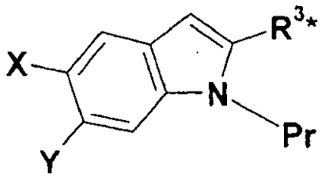
wherein *Pr* is a protecting group, especially methansulfonyl, which compound is then reacted with a propiolate compound of the formula XII,



(XII)

wherein R^{3*} is esterified carboxy, especially methoxycarbonyl, under cyclization in the presence of a base, such as N-ethyl-diisoproplamine, and a catalyst, e.g. tetrakistriphenylphos-

phine palladium, in an appropriate solvent, such as dioxane, at elevated temperatures, e.g. at the reflux temperature of the solvent, to a corresponding compound of the formula XIII,



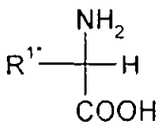
(XIII)

wherein X and Y are as defined for a compound of the formula I and R^{3*} is esterified carboxy, e.g. methoxycarbonyl, which can then be deprotected under removal of the protecting group Pr, e.g. with tetrabutyl ammoniumfluoride in an appropriate solvent, such as tetrahydrofurane, at temperatures e.g. in the range from 0 to 50 °C, to the corresponding compound of the formula IX.

Compounds of the formula X and of the formula XII are known in the art, may be prepared according to methods known in the art, are commercially available and/or can be prepared according or in analogy to methods described in the Examples.

Amino compounds of the formula III are known in the art, can be prepared according to methods that are known in the art, are commercially available and/or can be prepared according or in analogy to methods described in the Examples.

For example, a compound of the formula III wherein R^1 is 1-(unsubstituted or substituted aryl)-1-hydroxymethyl-methyl can be obtained from the corresponding glycine derivative of the formula XIV,



(XIV)

wherein R^{1*} is unsubstituted or substituted aryl, which can be present in (R,S)- or preferably (R)- or (S)- form, by reduction with an appropriate reductant, e.g. lithium aluminium hydride, in an appropriate solvent, e.g. tetrahydrofurane, at preferably elevated temperatures, e.g. at reflux temperature of the reaction mixture, to the corresponding compound wherein a hydroxymethyl is present instead of the carboxy in formula XIV.

Compounds of the formula XIV are known in the art, can be prepared according to methods that are known in the art, are commercially available and/or can be prepared by or in analogy to methods described in the Examples. For example, they can be prepared from aryl boronic acids as described in Tetrahedron, Volume 53, Number 48, 1997, pp. 16463-16470(8).

Compounds of the formula III wherein R^1 is substituted methyl can, for example, be prepared from a cyanide of the formula XV,

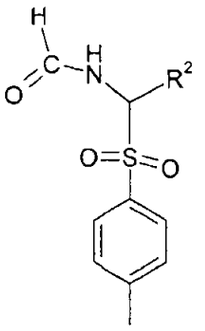
$$R^{1'''}\text{-CN} \qquad \text{(XV)}$$

wherein $R^{1'''}$ is a substitutent as mentioned for substituted alkyl, especially C_1-C_7-alkyl, unsubstituted or substituted heterocyclyl as described above, or unsubstituted or substituted aryl as defined above, by reduction in the presence of an appropriate hydrogenating agent, such as lithium aluminiumhydride, in an appropriate solvent, e.g. tetrahydrofurane, e.g. at temperatures in the range from –10 to +50 °C, e.g. from about 0 °C to about room temperature, to the corresponding compound of the formula III.

The cyanides of the formula XV are known in the art, can be prepared according to methods that are known in the art, are commercially available and/or they can be prepared by or in analogy to methods described in the examples.

Tosyl-methyl isocyanides of the formula IV are known in the art, can be prepared in accordance with methods known in the art, are commercially available and/or can be prepared by or in analogy to methods described in the Examples.

For example, they can be obtained from a tosamide of the formula XVI,



(XVI)

wherein R^2 is as defined for a compound of the formula I by reaction with an inorganic acid halide, especially thionyl chloride or phosphourous oxychloride, in an appropriate solvent, e.g. dimethyl ether, dimethyl formamide or preferably tetrahydrofurane, preferably in the presence of a tertiary amine, such as triethylamine, at temperatures e.g. in the range from –20 to 30 °C, e.g. at about 0 °C.

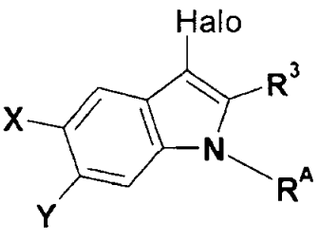
Tosamides of the formula XVI may, for example, be obtained from aldehydes of the formula XVII,

R^2-CHO (XVII)

wherein $R^2$is as defined for a compound of the formula I, by reacting it (in one step or in two steps) with formamide and with p-toluenesulfonic or preferably p-toluenesulfinic acid in an appropriate solvent, e.g. toluene/acetonitrile (with or without dimethylformamide) in the presence of a silyl halogenide, such as trimethylsilyl halogenide, preferably at elevated temperatures, e.g. in the range from 30 to 75 °C. For example, they may be prepared as described in *Chem. Lett.* **1988**, 9, 1531-1534.

Aldehyde compounds of the formula XVII are known in the art, can be prepared according to methods that are known in the art, are commercially available and/or they can be prepared by or in analogy to methods described in the examples.

Indole-boronic acids of the formula V can be obtained from a compound of the formula XVIII,



(XVIII)

wherein X, Y, R^3 and R^A are as defined for a compound of the formula I and Halo is especially bromo or iodo, or is trifluoromethanesulfonyl, by reacting it to a Grignard or preferably (e.g. with alkyl lithium, e.g. butyl lithium) to a lithium compound (Li instead of Halo in formula XVIII) which is then reacted with an trialkoxyborane or a bis(dialkoxyborane) to the corresponding compound of the formula V, e.g. according to the Miyaura Borylation

Reaction, according to the method described in *Org. Lett.*, 2006, 8, 305-307, according to the method described in *Org. Lett.*, 2006, 8, 261-263, or the like.

Halo-imidazoles of the formula VI are known in the art, can be prepared according to methods that are known in the art, are commercially available and/or can be obtained by or in analogy to a method described in the Examples. This is also true for compounds of the formula VII and for alcohols of the formula VIII.

Other starting materials are known in the art, can be prepared according to methods that are known in the art, are commercially available and/or can be prepared according to or in analogy to the methods described in the Examples.

Examples:

The following examples serve to illustrate the invention without limiting the scope thereof. Note that in some cases compounds mentioned as intermediates are also compounds of the formula I according to the invention (it is then mentioned that the compounds fall under formula I).

Abbreviations

Ac	acetyl
AcOH	acetic acid
$AlCl_3$	alminium trichloride
aq.	aqueous
Boc	tert-butoxycarbonyl
Brine	saturated (at rt) sodium chloride solution
^{t}Bu	tert-butyl
CDI	carbonyl diimidazole
Celite	trademark of Celite Corp. (World Minerals Inc.), Santa Barbara, CA, USA, for filtering aid based on kieselguhr
CH_3CN	acetonitrile
conc.	concentrated
DCM	dichloromethane
DMAP	4-dimethylaminopyridine

DMF	N,N-dimethylformamide
DMSO	dimethylsulfoxide
ES-MS	electrospray mass spectrometry
Et	ethyl
Et_3N	triethylamine
Et_2O	diethyl ether
EtOAc	ethyl acetate
EtOH	ethanol
h	hour(s)
HATU	O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium-hexafluorophosphat
HBr	hydrogen bromide
HCl	hydrogen chloride
HOAt	1-hydroxy-7-azabenzotriazole
HPLC	high-pressure liquid chromatography
HyFlo	diatomaceous earth based filtering aid, trademark of Johns Manville Corp., Denver, CO, USA
HV	High vacuum
IPr	isopropyl
K_2CO_3	potassium carbonate
KHMDS	potassium hexamethyldisilazide
KO^tBu	potassium-tert-butoxylate
KOH	potassium hydroxide
K_3PO_4	potassium phosphate
LAH	lithium aluminium hydride
LDA	lithium diisopropylamide
Me	methyl
MeI	methyl iodide
MeOH	methanol
$MgSO_4$	magnesium sulfate
min	minute(s)
mL	milliliter(s)
MS	Mass Spectrometry
MsCl	methanesulfonyl chloride

NaH	sodium hydride
$NaHCO_3$	sodium bicarbonate
Na_2CO_3	sodium carbonate
NaOH	sodium hydroxide
NaOMe	sodium methoxylate
NaOEt	sodium ethoxylate
NaO^tBu	sodium tert-butoxylate
Na_2SO_4	sodium sulfate
NBS	N-bromosuccinimide
NCS	N-chlorosuccinimide
NH_4Cl	ammonium chloride
NIS	N-iodosuccinimide
NMM	4-methylmorpholine
NMR	nuclear magnetic resonance
Ph	phenyl
PG	protecting group
$POCl_3$	phosphorus (III) oxychloride
rt (or RT)	room temperature
TBAF	tetrabutylammonium fluoride
TBAHS	tetrabutylammonium hydrosulfate
TBTU	O-(benzotriazol-1-yl)-N,N,N',N'-tetramethylammonium tetrafluoroborate
TFA	trifluoroacetic acid
TFAA	trifluoroacetic anhydride
THF	tetrahydrofurane
TMS	trimethylsilyl
TMSCl	trimethylsilyl chloride
t_{Ret}	retention time
TsCl	p-toluenesulfonyl chloride
TsOH	p-toluenesulfonic acid
UV	ultraviolet

Where no specific source is indicated, starting materials are obtainable from customary suppliers, such as Sigma-Aldrich, St. Louis, USA, from Fluka, Switzerland, Buchs, from Merck, Darmstadt, FRG, or from providers indicated specifically.

Synthesis

Flash chromatography is performed by using silica gel (Merck; 40 - 63 μm). For thin layer chromatography, pre-coated silica gel (Merck 60 F254; Merck KgaA, Darmstadt, Germany)) plates are used. ^{1}NMR measurements are performed on a Varian Gemini 400 spectrometer using tetramethylsilane as internal standard. Chemical shifts (δ) are expressed in ppm downfield from tetramethylsilane. Electrospray mass spectra are obtained with a Fisons Instruments VG Platform II. Commercially available solvents and chemicals are used for syntheses.

HPLC condition A:

Column: Nucleosil 100-3 C18, 70 x 4.0 mm.

Flow rate: 1.0 mL/min

Mobile phase: A) TFA/water (0.1/100, v/v), B) TFA/CH_3CN (0.1/100,v/v)

Gradient: linear gradient from 20% B to 100% B in 7min

Detection: UV at 215nm

HPLC condition B:

Column: Speed ROD RP18e, 50 x 4.6 mm.

Flow rate: 1.3 ml/min

Mobile phase: A) TFA/water (0.1/100, v/v), B) TFA/ CH_3CN (0.1/100,v/v)

Gradient: linear gradient from 2% B to 100% B in 1 min then 100% B 2 min

Detection: UV at 215nm

HPLC condition C:

Column: Nucleosil 100-3 C 18 HD, 125 x 4.0 mm.

Flow rate: 1.0 mL/min

Mobile phase: A) TFA/water (0.1/100, v/v), B) TFA/ CH_3CN (0.1/100,v/v)

Gradient: linear gradient from 2% B to 100% B in 7 min then 100% B 2 min

Detection: UV at 215nm

HPLC condition D:

Column: Nucleosil 100-3 C 18 HD, 125 x 4.0 mm.

Flow rate: 2.0 mL/min

Mobile phase: A) TFA/water (0.1/100, v/v), B) TFA/ CH_3CN (0.1/100,v/v)

Gradient: gradient from 1% to 20% B in 1min, 20% to 100% B in 2min, then 100% B in 1 min

Detection: UV at 215nm

HPLC condition E:

Column: Speed ROD RP18e, 50 x 4.6 mm.

Flow rate: 1.3 mL/min

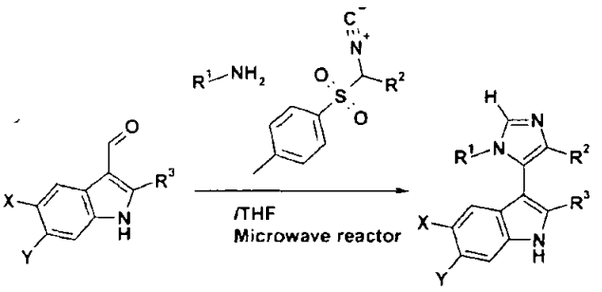
Mobile phase: A) TFA/water (0.1/100, v/v), B) TFA/acetonitrile (0.1/100,v/v)

Gradient: linear gradient from 0% B to 100% B in 6 min then 2 min 100 % B

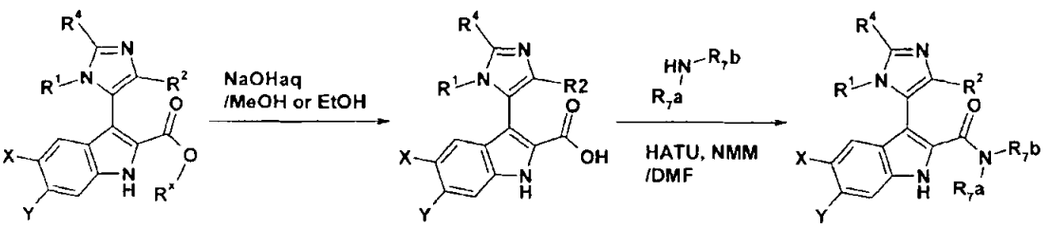
Detection: UV at 215nm

The **HPLC conditions A, B, C, D** and **E** can be identified by the subscript prefixes of the T_{Ret} values given in the examples. For instance, B in ${}_{B}t_{Ret}$ = ... min means condition-B in the case of HPLC.

General Scheme 1

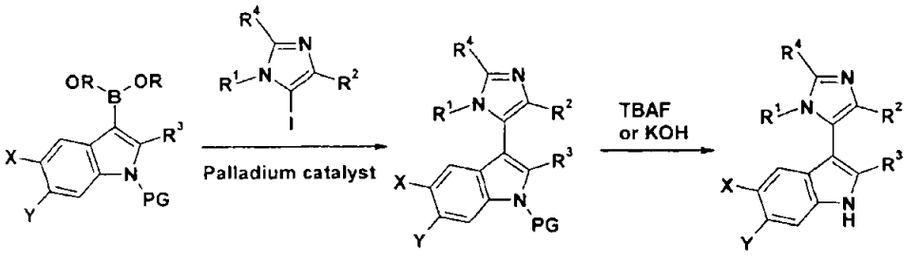


General Scheme 2



Rx = alkyl, e.g. methyl, ethyl; R^{7a}, R^{7b} = H, C_1-C_7-alkyl, phenyl, phenylmethyl or the like, especially as shown in the Examples

General Scheme-3



R = H, lower alkyl or R + R form 1,1,2,2-tetramethyl-1,2-ethylene

Example 1: 6-Chloro-3-[3-(4-chloro-benzyl)-5-phenyl-3H-imidazol-4-yl]-1H-indole

A mixture of **Intermediate 1.1** (100 mg, 0.55 mmol), 4-chlorobenzyl-amine (0.1 mL, 0.83 mmol) and 1-(isocyano-phenyl-methanesulfonyl)-4-methyl-benzene (commercially available from SynChem, Inc., Des Plaines, IL, USA) (227 mg, 0.83 mmol) in THF (2 mL) is sealed and heated by the microwave reactor at 110 °C for 1h. After completion, the reaction mixture is quenched by aqueous $NaHCO_3$, EtOAc is added and the organic layer is washed with brine, dried over $MgSO_4$ and evaporated *in vacuo*. Silica gel flash chromatography of the residue affords the title compound as a colorless powder; ES-MS: M+ = 418.0; HPLC: $_At_{Ret}$ = 4.53 min.

Intermediate 1.1: 6-Chloro-1H-indole-3-carbaldehyde

A mixture of 6-chloro-1H-indole (2.0 g, 13.2 mmol) and $POCl_3$ (1.34 mL, 14.5 mmol) in DMF (5 mL) is heated at 45 °C for 1h. After completion, the reaction mixture is quenched with aqueous $NaHCO_3$, Et_2O is added and the organic layer is washed with brine, dried over $MgSO_4$ and evaporated *in vacuo*. Silica gel flash chromatography of the residue affords the title compound as a colorless powder; ES-MS: M+ = 179.9; HPLC: $_At_{Ret}$ = 3.74 min.

Example 2: 6-Chloro-3-[3-(4-chloro-benzyl)-5-phenyl-3H-imidazol-4-yl]-1H-indole-2-carboxylic acid (2-morpholin-4-yl-ethyl)-amide

A mixture of **Intermediate 2.1** (200 mg, 0.43 mmol), N-(4-aminoethyl)-morpholine (68 mg, 0.52 mmol), NMM (109 mg, 1.08 mmol) and HATU (245 mg, 0.65 mmol) in DMF (2.2 mL) is

heated for 1 h at 50 °C. EtOAc is added and the organic layer is washed with brine, dried over $MgSO_4$ and evaporated in vacuo. Silica gel flash chromatography of the residue affords the title compound as a colorless crystal; ES-MS: M+H = 576.2; HPLC: $_At_{Ret}$ = 3.80 min.

Intermediate 2.1: 6-Chloro-3-[3-(4-chloro-benzyl)-5-phenyl-3H-imidazol-4-yl]-1H-indole-2-carboxylic acid (which is also a compound of the formula I)

A mixture of **Intermediate 2.2** (900 mg, 1.84 mmol) and 2M aqueous NaOH (35 mL) in EtOH (35 mL) is refluxed for 2.5 h. The resulting mixture is poured into a mixture of ice and water, and after neutralized by 4 M aqueous HCl, EtOAc is added and the organic layer is washed with brine, dried over $MgSO_4$. Concentration *in vacuo* affords the title compound as a colorless crystal; ES-MS: M+ = 461.9; HPLC: $_At_{Ret}$ = 4.22 min.

Intermediate 2.2: 6-Chloro-3-[3-(4-chloro-benzyl)-5-phenyl-3H-imidazol-4-yl]-1H-indole-2-carboxylic acid ethyl ester (also an active compound of the formula I)

Method A: A mixture of **Intermediate 2.3** (1.0 g, 3.97 mmol), 4-chlorobenzyl-amine (731 mg, 5.17 mmol) and 1-(isocyano-phenyl-methanesulfonyl)-4-methyl-benzene (1.62 g, 5.96 mmol) in THF (15 mL) is sealed and heated by means of a microwave reactor at 110 °C for 1h. After completion, the reaction mixture is quenched by aqueous $NaHCO_3$, EtOAc is added and the organic layer is washed with brine, dried over $MgSO_4$ and evaporated *in vacuo*. Silica gel flash chromatography of the residue affords the title compound as a colorless powder; ES-MS: M+ = 490.1; HPLC: $_At_{Ret}$ = 4.62 min.

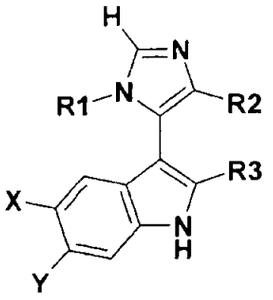
Method B: A mixture of **Intermediate 2.3** (6.09 g, 24.2 mmol), 4-chlorobenzyl-amine (3.55 mL, 29.0 mmol), Et_3N (10.1 mL, 72.6 mmol) and 1-(isocyano-phenyl-methanesulfonyl)-4-methyl-benzene (7.87 g, 29.0 mmol) in EtOH (120 mL) is heated at 60 °C for 3h. After completion, the reaction mixture is concentrated *in vacuo* and quenched by aqueous $NaHCO_3$, EtOAc is added and the organic layer is washed with brine, dried over $MgSO_4$ and evaporated *in vacuo*. Silica gel flash chromatography of the residue affords the title compound as a colorless powder.

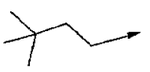
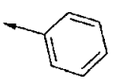
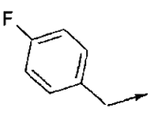
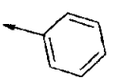
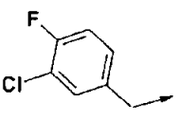
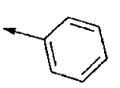
Intermediate 2.3: 6-Chloro-3-formyl-1H-indole-2-carboxylic acid ethyl ester

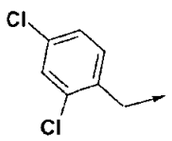
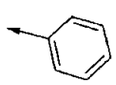
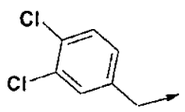
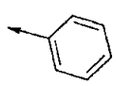
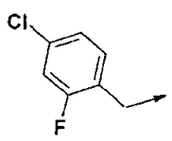
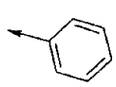
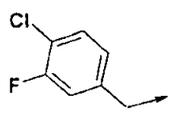
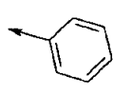
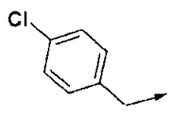
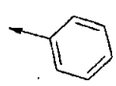
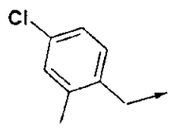
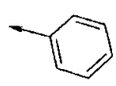
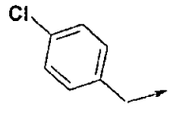
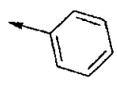
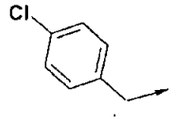
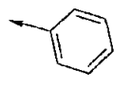
The title compound is prepared according to a published literature procedure (see J. Med.

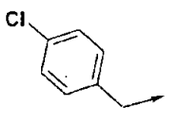
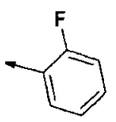
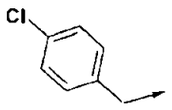
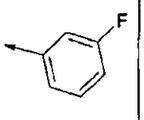
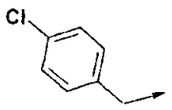
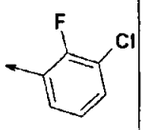
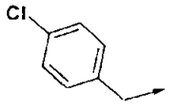
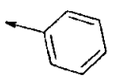
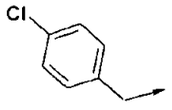
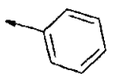
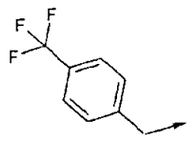
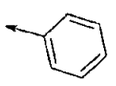
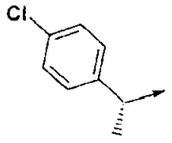
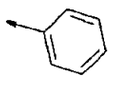
Chem. **2005**, 48, 995-1018.) A solution of 6-chloro-1H-indole-2-carboxylic acid ethyl ester (5.0 g, 22.4 mmol) (commercially available from 3D Medical Systems Inc.) and $POCl_3$ (2.46 mL, 26.8 mmol) in DMF (15 mL) is heated at 50 °C for 28h. After completion, the reaction mixture is quenched by aqueous $NaHCO_3$, Et_2O is added and the organic layer is washed with brine, dried over $MgSO_4$ and evaporated in vacuo. Silica gel flash chromatography of the residue affords the title compound as a colorless powder; ES-MS: M- = 250.1; HPLC: $_At_{Ret}$ = 4.67 min.

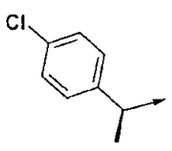
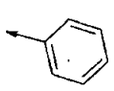
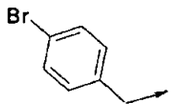
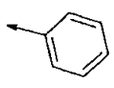
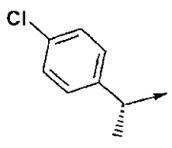
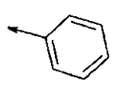
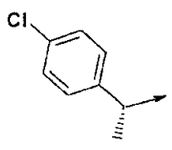
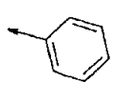
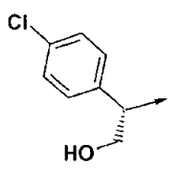
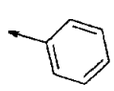
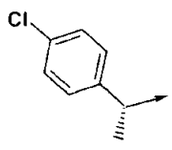
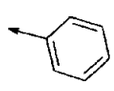
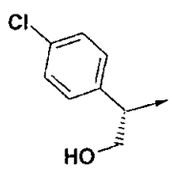
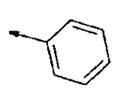
Table 1 of further Examples:

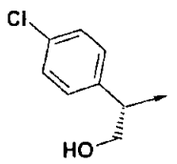
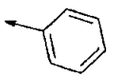
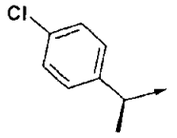
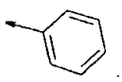
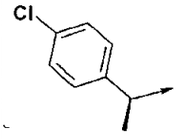
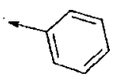
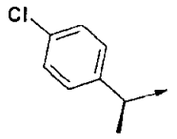
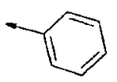
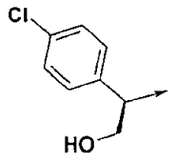
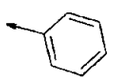
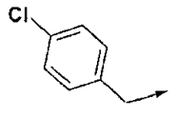
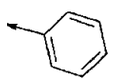
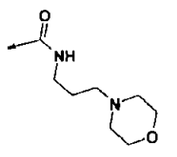
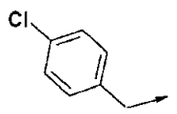
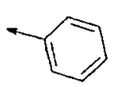
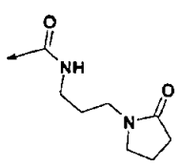


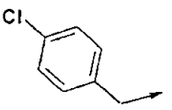
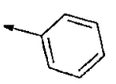
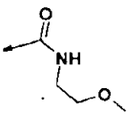
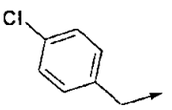
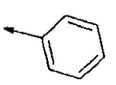
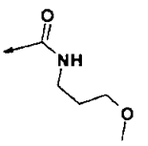
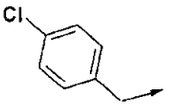
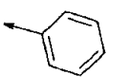
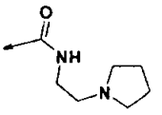
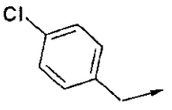
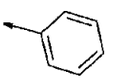
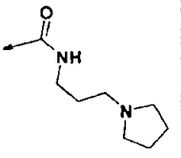
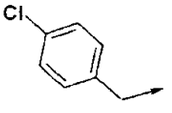
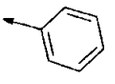
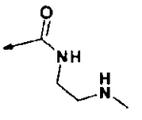
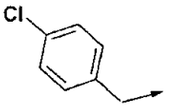
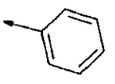
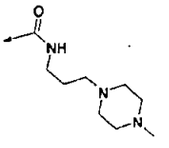
Example	X and Y	R^1	R^2	R^3	Analysis MS/HPLC/NMR
3	X=H Y=Cl			H	M+ = 378.0 $_At_{Ret}$ = 4.61 min
4	X=H Y=Cl			H	M+ = 402.0 $_At_{Ret}$ = 4.37 min
5	X=H Y=Cl			H	M+ = 435.9 $_At_{Ret}$ = 4.49 min

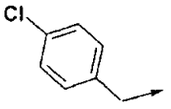
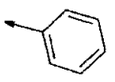
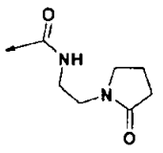
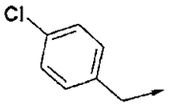
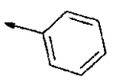
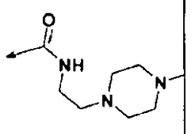
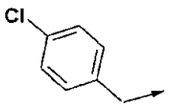
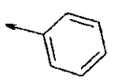
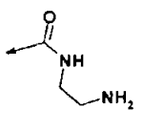
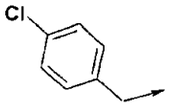
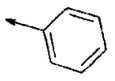
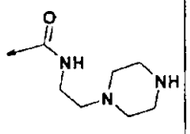
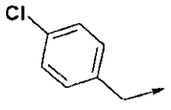
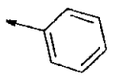
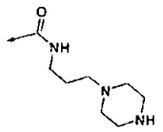
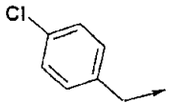
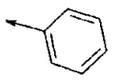
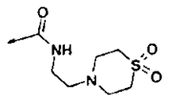
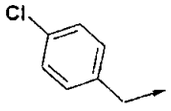
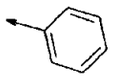
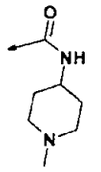
Example	X and Y	R^1	R^2	R^3	Analysis MS/HPLC/NMR
6	X=H Y=Cl			H	M+H= 453.7 $_At_{Ret}$ = 4.65 min
7	X=H Y=Cl			H	M+H= 455.8 $_At_{Ret}$ = 4.65 min
8	X=H Y=Ci			H	M+= 436.0 $_At_{Ret}$ = 4.50 min
9	X=H Y=Cl			H	M- = 436.1 $_At_{Ret}$ = 4.54 min
10	X=F Y=Cl			H	M+= 436.0 $_At_{Ret}$ = 4.53 min
11	X=H Y=Cl			H	M- = 432.1 $_At_{Ret}$ = 4.68 min
12	X=H Y=Br			H	M+= 436.9 $_At_{Ret}$ = 4.61 min
13	X=H Y=Me			H	M- = 398.1 $_At_{Ret}$ = 4.51 min

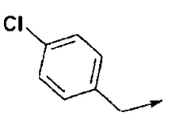
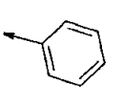
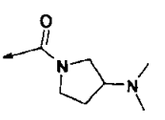
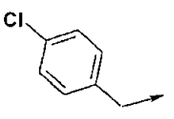
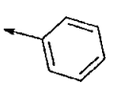
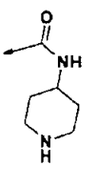
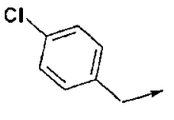
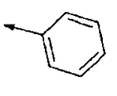
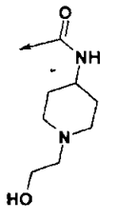
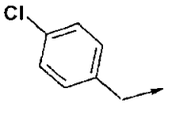
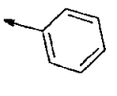
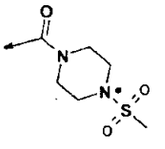
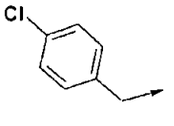
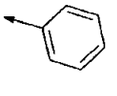
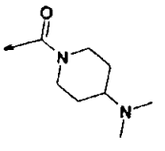
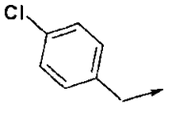
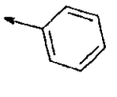
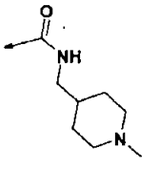
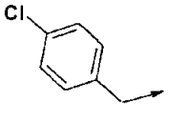
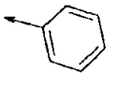
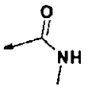
Example	X and Y	R^1	R^2	R^3	Analysis MS/HPLC/NMR
14	X=H Y=Cl			H	M- = 436.0 $_At_{Ret}$ = 4.47 min
15	X=H Y=Cl			H	M+= 436.0 $_At_{Ret}$ = 4.61 min
16	X=H Y=Cl			H	M+H= 471.9 $_At_{Ret}$ = 4.69 min
17	X=H Y=CN			H	M+H= 409.0 $_ct_{Ret}$ = 5.82 min
18	X=F Y=F			H	M+H= 420.0 $_ct_{Ret}$ = 6.20 min
19	X=H Y=Cl			H	M+H= 452.1 $_At_{Ret}$ = 4.60 min
20	X=H Y=Cl			H	M+= 432.1 $_At_{Ret}$ = 4.65 min

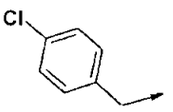
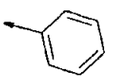
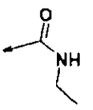
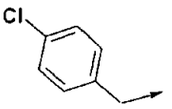
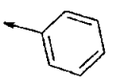
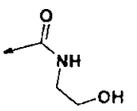
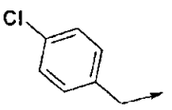
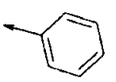
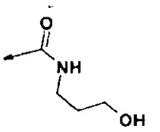
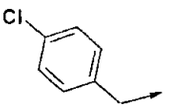
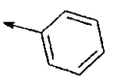
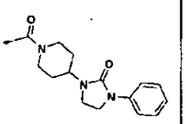
Example	X and Y	R^1	R^2	R^3	Analysis MS/HPLC/NMR
21	X=H Y=Cl			H	M+= 432.1 $_{A}t_{Ret}$ = 4.65 min
22	X=H Y=Cl			H	M+H= 463.9 $_{A}t_{Ret}$ = 4.59 min
23	X=F Y=Cl			H	M+H= 450.0 $_{C}t_{Ret}$ = 6.48 min
24	X=F Y=F			H	M+H= 434.0 $_{C}t_{Ret}$ = 6.25 min
25	X=H Y=Cl			H	M+= 448.0 $_{A}t_{Ret}$ = 4.35 min
26	X=H Y=CN			H	M+= 423.1 $_{A}t_{Ret}$ = 4.14 min
27	X=F Y=Cl			H	M+= 466.0 $_{A}t_{Ret}$ = 4.32 min

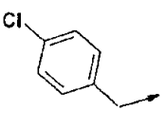
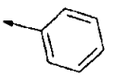
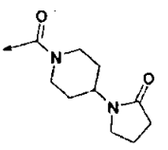
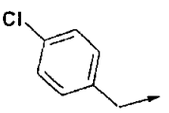
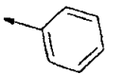
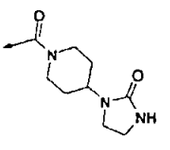
Example	X and Y	R^1	R^2	R^3	Analysis MS/HPLC/NMR
28	X=H Y=CN			H	M+= 439.1 $_{A}t_{Ret}$ = 3.87 min
29	X=F Y=Cl			H	M+= 450.1 $_{A}t_{Ret}$ = 4.59 min
30	X=H Y=CN			H	M+= 423.1 $_{A}t_{Ret}$ = 4.14 min
31	X=F Y=F			H	M+= 434.1 $_{A}t_{Ret}$ = 4.42 min
32	X=F Y=Cl			H	M+= 466.0 $_{A}t_{Ret}$ = 4.33 min
33	X=H Y=Cl				M+= 587.8 $_{A}t_{Ret}$ = 3.96 min
34	X=H Y=Cl				M+= 586.2 $_{A}t_{Ret}$ = 4.35 min

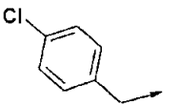
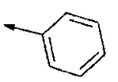
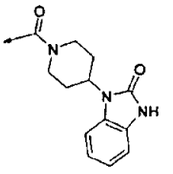
Example	X and Y	R^1	R^2	R^3	Analysis MS/HPLC/NMR
35	X=H Y=Cl				M+= 520.9 $_At_{Ret}$ = 4.34 min
36	X=H Y=Cl				M+= 534.9 $_At_{Ret}$ = 4.41 min
37	X=H Y=Cl				M+= 559.9 $_At_{Ret}$ = 3.91 min
38	X=H Y=Cl				M+= 573.9 $_At_{Ret}$ = 3.87 min
39	X=H Y=Cl				M+= 519.9 $_At_{Ret}$ = 3.76 min
40	X=H Y=Cl				M+= 603.3 $_At_{Ret}$ = 3.51 min

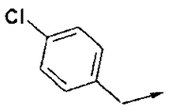
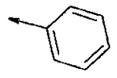
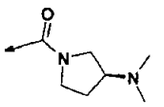
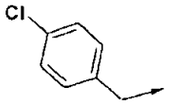
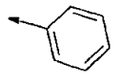
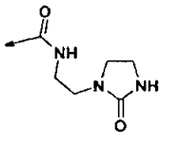
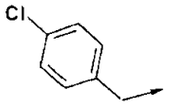
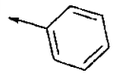
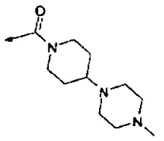
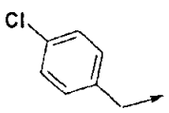
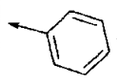
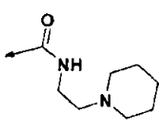
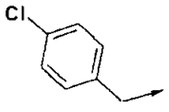
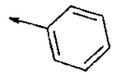
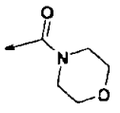
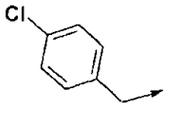
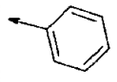
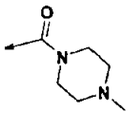
Example	X and Y	R^1	R^2	R^3	Analysis MS/HPLC/NMR
41	X=H Y=Cl				M+= 573.9 $_{A}t_{Ret}$ = 4.22 min
42	X=H Y=Cl				M+= 589.3 $_{A}t_{Ret}$ = 3.61 min
43	X=H Y=Cl				M+= 504.0 $_{A}t_{Ret}$ = 3.67 min
44	X=H Y=Cl				M+= 574.4 $_{A}t_{Ret}$ = 3.52 min
45	X=H Y=Cl				M+= 588.4 $_{A}t_{Ret}$ = 3.49 min
46	X=H Y=Cl				M+= 621.9 $_{A}t_{Ret}$ = 3.97 min
47	X=H Y=Cl				M+= 558.0 $_{A}t_{Ret}$ = 3.78 min

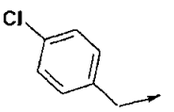
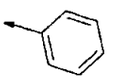
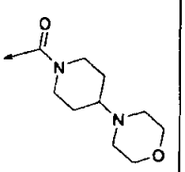
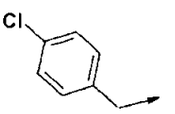
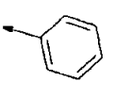
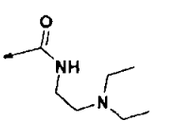
Example	X and Y	R^1	R^2	R^3	Analysis MS/HPLC/NMR
48	X=H Y=Cl				M+= 558.0 $_{A}t_{Ret}$ = 3.73 min
49	X=H Y=Cl				M+= 544.0 $_{A}t_{Ret}$ = 3.71 min
50	X=H Y=Cl				M+= 588.0 $_{A}t_{Ret}$ = 3.73 min
51	X=H Y=Cl				M+= 607.9 $_{A}t_{Ret}$ = 4.36 min
52	X=H Y=Cl				M+= 572.0 $_{A}t_{Ret}$ = 3.78 min
53	X=H Y=Cl				M+= 572.0 $_{A}t_{Ret}$ = 3.81 min
54	X=H Y=Cl				M+= 475.0 $_{C}t_{Ret}$ = 6.09 min

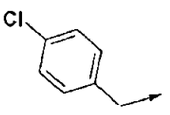
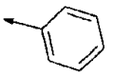
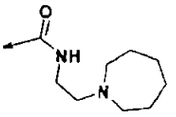
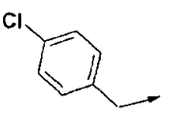
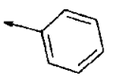
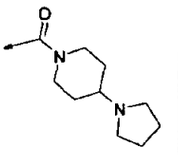
Example	X and Y	R^1	R^2	R^3	Analysis MS/HPLC/NMR
55	X=H Y=Cl				M+= 489.0 ct_{Ret} = 6.24 min
56	X=H Y=Cl				M+= 505.0 ct_{Ret} = 5.91 min
57	X=H Y=Cl				M+= 519.0 ct_{Ret} = 5.97 min
58	X=H Y=Cl				M-H = 689.0; ^{1}HNMR($CDCl_3$) δ 9.98 (s, 1H), 7.81 (s, 1H), 7.82 (d, 2H), 7.54 (d, 2H), 7.43 (s, 1H), 7.39-7.35 (m, 2H), 7.21-7.15 (m, 3H), 7.03-6.89 (m, 5H), 6.79 (d, 2H), 4.99 (d, 1H), 4.81 (d, 1H), 3.89-3.78 (m, 5H), 3.35-3.17 (m, 2H), 2.78-2.57 (m, 2H),

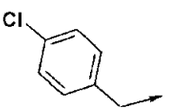
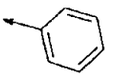
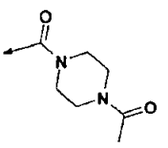
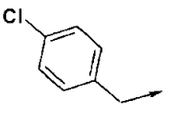
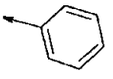
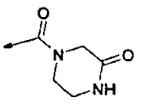
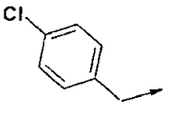
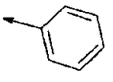
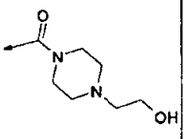
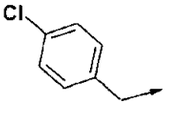
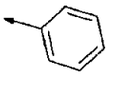
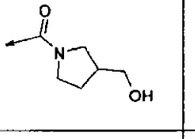
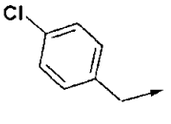
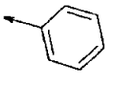
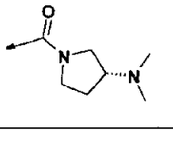
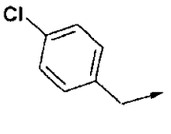
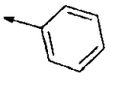
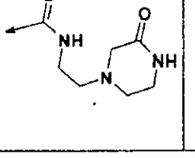
Example	X and Y	R^1	R^2	R^3	Analysis MS/HPLC/NMR
					1.78-1.69 (m, 2H), 1.38-1.07 (m, 2H).
59	X=H Y=Cl				M+H = 615.4; ^{1}HNMR($CDCl_3$) δ 9.21 (s, 1H), 7.81 (s, 1H), 7.60 (d, 2H), 7.42 (s, 1H), 7.19-7.03 (m, 4H), 6.79 (d, 2H), 4.96 (d, 1H), 4.79 (d, 1H), 3.99-3.91 (m, 1H), 3.21-3.04 (m, 2H), 2.78-2.43 (m, 2H), 2.37 (t, 2H), 2.02-1.92 (m, 2H), 1.75-1.55 (m, 4H), 1.43-1.16 (m, 2H).
60	X=H Y=Cl				M+H = 616.4; ^{1}HNMR($CDCl_3$) δ 9.38 (s, 1H), 7.81 (s, 1H),

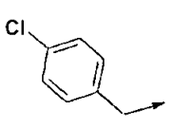
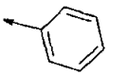
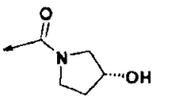
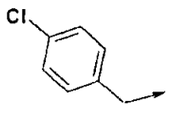
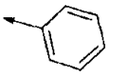
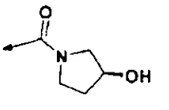
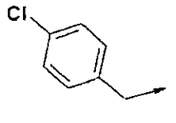
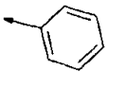
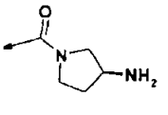
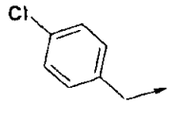
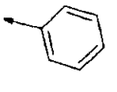
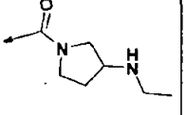
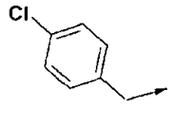
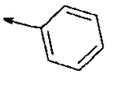
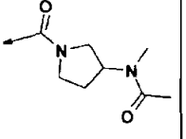
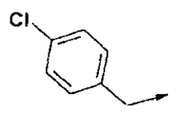
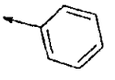
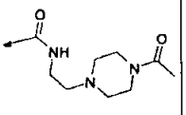
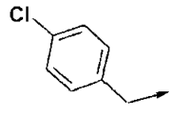
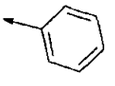
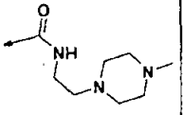
Example	X and Y	R^1	R^2	R^3	Analysis MS/HPLC/NMR
					7.60 (d, 2H), 7.44 (s, 1H), 7.21-7.11 (m, 3H), 7.05-6.89 (m, 4H), 6.78 (d, 2H), 4.95 (d, 1H), 4.79 (d, 1H), 3.78-3.67 (m, 1H), 3.42-3.36 (m, 2H), 3.23-3.18 (m, 2H), 2.79-2.56 (m, 2H), 1.78-1.58 (m, 4H), 1.22-1.04 (m, 2H).
61	X=H Y=Cl				M+H = 690.1; ^{1}HNMR($CDCl_3$) 9.89 (s, 1H), 7.80 (s, 1H), 7.59 (d, 2H), 7.52 (d, 2H), 7.50 (s, 1H), 7.47 (d, 2H), 7.17 (m, 3H), 7.08-6.90 (m, 4H), 6.79 (d, 2H), 4.99 (d, 1H), 4.80 (d, 1H), 4.85-4.65

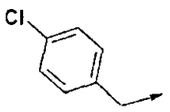
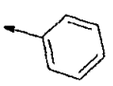
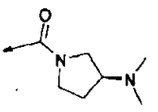
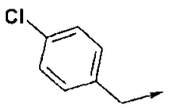
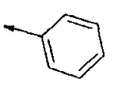
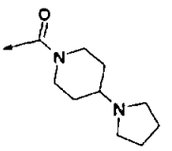
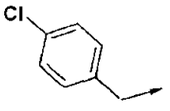
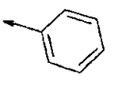
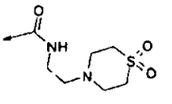
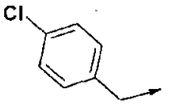
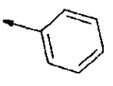
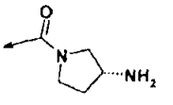
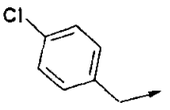
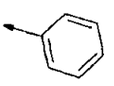
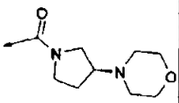
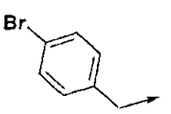
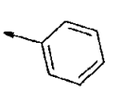
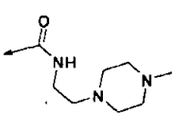
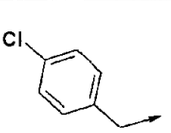
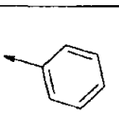
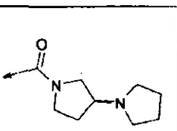
Example	X and Y	R^1	R^2	R^3	Analysis MS/HPLC/NMR
					(m4h), 3.38-3-19 (m, 2H), 2.80-2.65 (m, 3H), 1.71 (m, 2H), 1.41-1.05 (m, 2H).
62	X=H Y=Cl				M+= 558.0 $_{c}t_{Ret}$ = 5.22 min
63	X=H Y=Cl				M+= 573.0 $_{c}t_{Ret}$ = 5.92 min
64	X=H Y=Cl				M+H = 628.3 $_{B}t_{ret}$ = 1.98 min
65	X=H Y=Cl				M+ = 571.9 $_{B}t_{ret}$ = 2.04 min
66	X=H Y=Cl				M+H = 532.7 $_{B}t_{ret}$ = 2.13 min
67	X=H Y=Cl				M+ = 543.9 $_{B}t_{ret}$ = 2.01 min

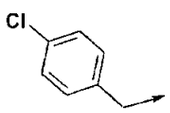
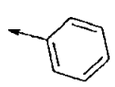
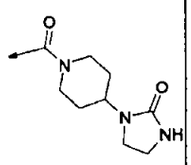
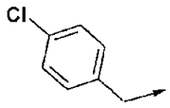
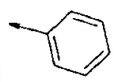
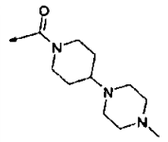
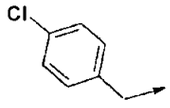
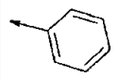
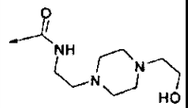
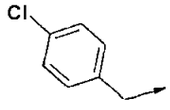
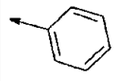
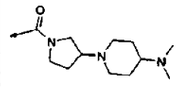
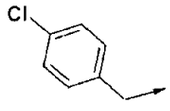
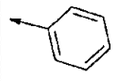
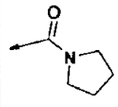
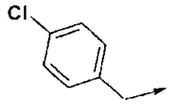
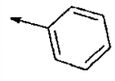
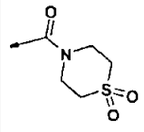
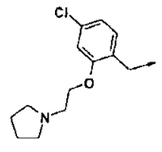
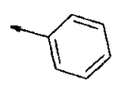
Example	X and Y	R^1	R^2	R^3	Analysis MS/HPLC/NMR
68	X=H Y=Cl				M+ = 614.0 ^{1}HNMR($CDCl_3$) 9.39 (s, 1H), 7.80 (s, 1H), 7.59 (d, 2H), 7.41 (s, 1H), 7.21-7.11 (m, 3H), 6.99-6.91 (m, 4H), 6.78 (d, 2H), 4.92 (d, 1h), 4.79 (d, 1H), 3.71-3.62 (m, 4H), 3.71-3.48 (m, 2H), 2.23-2.19 (m, 1H), 2.79-2.58 (m, 4H), 1.19-1.03 (m, 4H).
69	X=H Y=Cl				M+ = 560.0 ^{1}HNMR($CDCl_3$) 9.80 (s, 1H), 7.86 (1H), 7.54-7.49 (m, 3H), 7.14-7.10 (m, 7H), 6.74 (d, 2H), 6.70 (s, 1H), 4.80 (d, 2H), 4.11 (q,

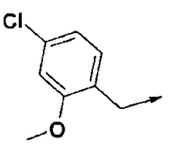
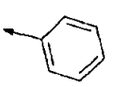
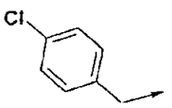
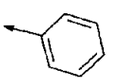
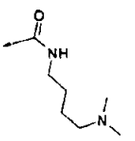
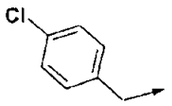
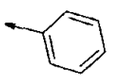
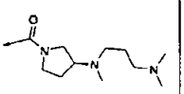
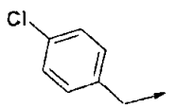
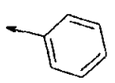
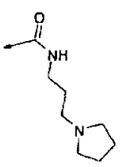
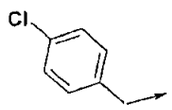
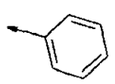
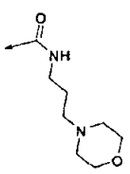
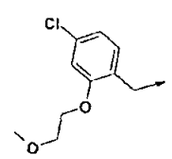
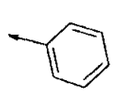
Example	X and Y	R^1	R^2	R^3	Analysis MS/HPLC/NMR
					4H), 3.37-3.19 (m, 2H), 2.40-2.36 (m, 2H), 0.83 (t, 6H).
70	X=H Y=Cl				M+ = 588.7 ^{1}HNMR($CDCl_3$) d 9.98 (s, 1H), 7.98 (s, 1H), 7.57-7.43 (m, 3H), 7.19-7.01 (m, 7H), 6.79 (d, 2H), 6.71(s, 1H), 4.82 (s, 2H), 3.39-3.21 (m, 2H), 2.99-2.64 (m, 6H), 1.81-1.75 (m, 6H).
71	X=H Y=Cl				M+ = 598.0 ^{1}HNMR($CDCl_3$) 9.29 (s, 1H), 7.81 (s, 1H), 7.60 (d, 2H), 7.40 (s, 1H), 7.16-7.12 (m, 3H), 6.99-6.88 (m, 4H), 6.71

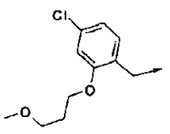
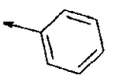
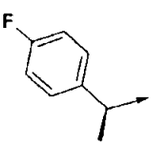
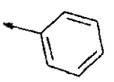
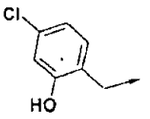
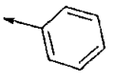
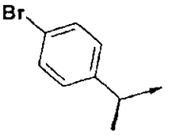
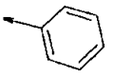
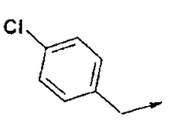
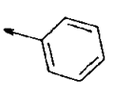
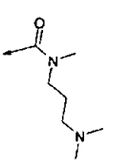
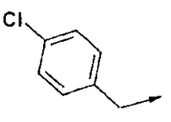
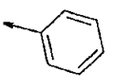
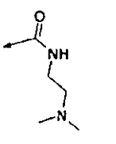
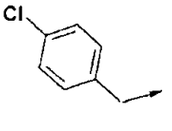
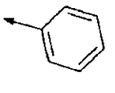
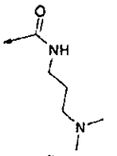
Example	X and Y	R^1	R^2	R^3	Analysis MS/HPLC/NMR
					(d, 2H), 4.92 (bs, 1H), 4,73 (d, 1H), 2.62-2.50 (m, 6H), 2.20-2.11 (m, 1H), 1.84-1.67 (m, 10 H).
72	X=H Y=Cl				M+ H = 573.8 $_Bt_{ret}$ = 2.05 min
73	X=H Y=Cl				M+ H = 545.7 $_Bt_{ret}$ = 2.06 min
74	X=H Y=Cl				M+ = 573.90 $_Bt_{ret}$ = 2.03 min
75	X=H Y=Cl				M+H = 546.8 $_Bt_{ret}$ = 2.09 min
76	X=H Y=Cl				M+ = 557.9 $_Bt_{ret}$ = 1.99 min
77	X=H Y=Cl				M+ = 586.9 $_Bt_{ret}$ = 1.99 min

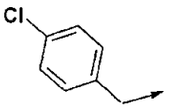
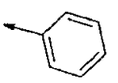
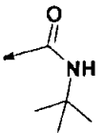
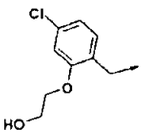
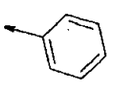
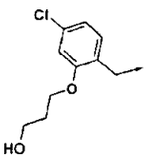
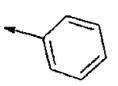
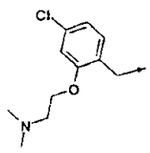
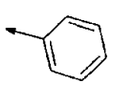
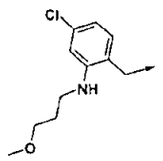
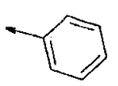
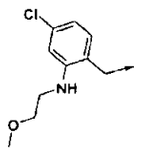
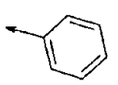
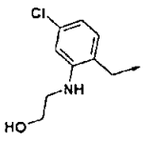
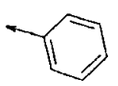
Example	X and Y	R^1	R^2	R^3	Analysis MS/HPLC/NMR
78	X=H Y=Cl				M+H = 532.7 $_{B}t_{ret}$ = 2.09 min
79	X=H Y=Cl				M+ H = 532.7 $_{B}t_{ret}$ = 2.11 min
80	X=H Y=Cl				M+ = 529.9 $_{B}t_{ret}$ = 1.99 min
81	X=H Y=Cl				M+= 558.0 $_{C}t_{Ret}$ = 5.56 min
82	X=H Y=Cl				M+= 586.0 $_{C}t_{Ret}$ = 6.07 min
83	X=H Y=Cl				M+= 615.0 $_{A}t_{Ret}$ = 3.71 min
84	X=F Y=Cl				M+= 607.2 $_{A}t_{Ret}$ = 3.65 min

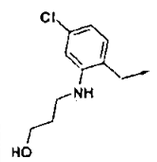
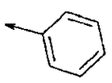
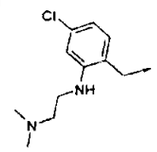
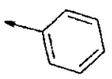
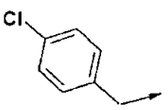
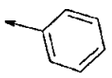
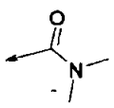
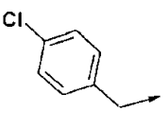
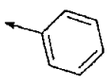
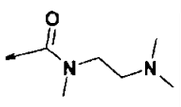
Example	X and Y	R^1	R^2	R^3	Analysis MS/HPLC/NMR
85	X=F Y=Cl				M+= 578.3 $_{A}t_{Ret}$ = 3.72 min
86	X=F Y=Cl				M+= 618.2 $_{A}t_{Ret}$ = 3.85 min
87	X=F Y=Cl				M+= 642.1 $_{A}t_{Ret}$ = 3.95 min
88	X=H Y=Cl				M+ = 529.9 $_{B}t_{ret}$ = 2.05 min
89	X=H Y=Cl				M+ = 599.9 $_{B}t_{ret}$ = 1.99 min
90	X=H Y=Cl				M+= 634.2 $_{A}t_{Ret}$ = 3.64 min
91	X=H Y=Cl				M+ = 584.6 $_{B}t_{ret}$ = 2.04 min

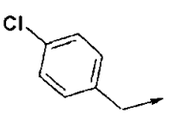
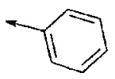
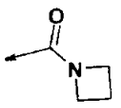
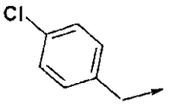
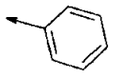
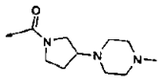
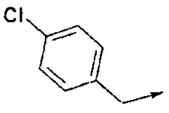
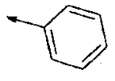
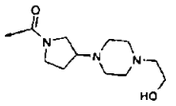
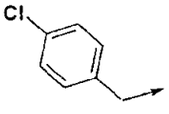
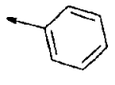
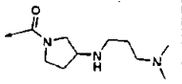
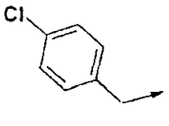
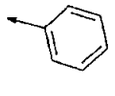
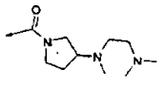
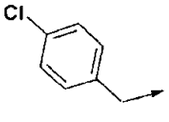
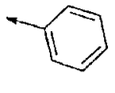
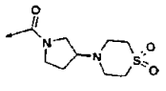
Example	X and Y	R^1	R^2	R^3	Analysis MS/HPLC/NMR
92	X=F Y=Ci				M- = 631.3 $_{A}t_{Ret}$ = 4.18 min
93	X=F Y=Cl				M- = 643.0 $_{A}t_{Ret}$ = 3.69 min
94	X=H Y=Cl				M-H = 651.2 $_{B}t_{ret}$ = 2.00 min
95	X=H Y=Cl				M+ = 641.0 $_{B}t_{ret}$ = 1.96 min
96	X=H Y=Cl				M+ = 515.1 $_{B}t_{ret}$ = 2.13 min
97	X=H Y=Cl				M+ = 578.8 $_{B}t_{ret}$ = 2.13 min
98	X=F Y=Cl			H	M+ = 549.0 $_{A}t_{Ret}$ = 3.87 min

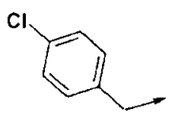
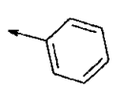
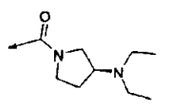
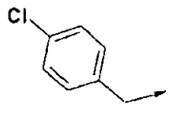
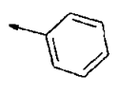
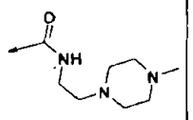
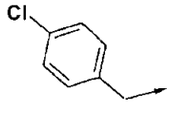
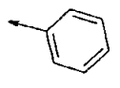
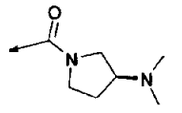
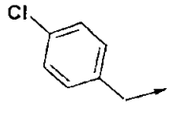
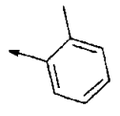
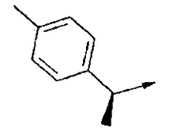
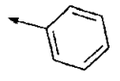
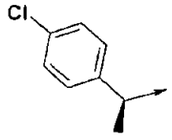
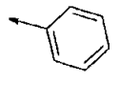
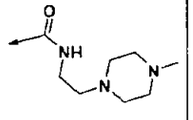
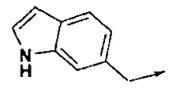
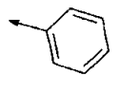
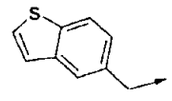
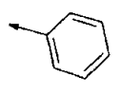
Example	X and Y	R^1	R^2	R^3	Analysis MS/HPLC/NMR
99	X=F Y=Cl			H	M+= 466.0 $_{A}t_{Ret}$ = 4.63 min
100	X=H Y=Cl				M+ = 560.0 $_{C}t_{Ret}$ = 5.57 min
101	X=H Y=Cl				M-H = 637.1 $_{C}t_{ret}$ = 5.46
102	X=F Y=Cl				M+ = 591.5 $_{A}t_{Rel}$ = 3.89 min
103	X=F Y=Cl				M+ = 606.0 $_{A}t_{Rel}$ = 3.78 min
104	X=F Y=Cl			H	M+ = 510.0 $_{A}t_{Rel}$ = 4.65 min

Example	X and Y	R^1	R^2	R^3	Analysis MS/HPLC/NMR
105	X=F Y=Cl			H	M+ = 524.0 $_{A}t_{Ret}$ = 4.75 min
106	X=F Y=Cl			H	M+ = 434.1 $_{A}t_{Ret}$ = 4.45 min
107	X=F Y=Cl			H	M+ = 452.0 $_{A}t_{Ret}$ = 4.36min
108	X=F Y=Cl			H	M+ = 495.8 $_{A}t_{Ret}$ = 4.65 min
109	X=H Y=Cl				M-H = 558.1 $_{B}t_{ret}$ = 2.01 min
110	X=H Y=Cl				M-H = 530.2 $_{B}t_{ret}$ = 2.01 min
111	X=H Y=Cl				M-H = 544.2 $_{B}t_{ret}$ = 2.00 min

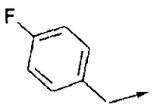
Example	X and Y	R^1	R^2	R^3	Analysis MS/HPLC/NMR
112	X=H Y=Cl				M+H = 518.8 $_{B}t_{ret}$ = 2.17 min
113	X=F Y=Cl			H	M+= 496.0 $_{A}t_{Ret}$ = 4.32 min
114	X=F Y=Cl			H	M+= 510.0 $_{A}t_{Ret}$ = 4.35 min
115	X=F Y=Cl			H	M+= 523.0 $_{A}t_{Ret}$ = 4.81 min
116	X=F Y=Cl			H	M+= 523.0 $_{A}t_{Ret}$ = 4.81 min
117	X=F Y=Cl			H	M+= 509.0 $_{A}t_{Ret}$ = 4.71 min
118	X=F Y=Cl			H	M+= 495.0 $_{A}t_{Ret}$ = 4.35 min

Example	X and Y	R^1	R^2	R^3	Analysis MS/HPLC/NMR
119	X=F Y=Cl			H	M+= 509.0 $_At_{Ret}$ = 4.39 min
120	X=F Y=Cl			H	M+= 522.1 $_At_{Ret}$ = 3.88 min
121	X=H Y=Cl				M-H = 488.1 ^{1}HNMR($CDCl_3$) 9.01 (s, 1H), 7.79 (s, 1H), 7.60 (d, 2H), 7.41 (s, 1H), 7.21-7.17 (m, 3H), 7.03 (d, 2H), 6.97 (s, 2H), 6.79 (d, 2H), 4.89 (d, 1H), 4.79 (d, 1H), 1.59 (s, 1H).
122	X=H Y=Cl				M-H = 544.2 ^{1}HNMR($CDCl_3$) 7.64 (s, 1H), 7.51(d, 2H), 7.39 (s, 1H),

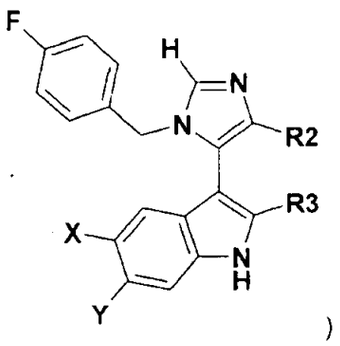
Example	X and Y	R^1	R^2	R^3	Analysis MS/HPLC/NMR
					7.18-7.03 (m, 6H), 6.98-6.87 (m, 4H), 5.00 (s, 2H), 2.82-2.75 (m2H), 2.59-2.41 (m5H), 1.58 (s, 6H).
123	X=H Y=Cl				M+H = 502.8 $_{B}t_{ret}$ = 2.10 min
124	X=H Y=Cl				M+= 613.0 $_{C}t_{Ret}$ = 5.60 min
125	X=H Y=Cl				M-H = 641.3 $_{B}t_{ret}$ = 1.98 min
126	X=H Y=Cl				M+= 615.0 $_{C}t_{Ret}$ = 5.46 min
127	X=H Y=Cl				M-H = 613.3 $_{B}t_{ret}$ = 1.98 min
128	X=H Y=Cl				M-H = 646.2 $_{B}t_{ret}$ = 1.99 min

Example	X and Y	R^1	R^2	R^3	Analysis MS/HPLC/NMR
129	X=H Y=Cl				M-H = 584.2 $_Bt_{ret}$ = 2.01 min
130	X=H Y=CN				M+= 578.1 $_At_{Ret}$ = 3.35 min
131	X=H Y=CN				M+= 549.1 $_At_{Ret}$ = 3.36 min
132	X=F Y=Cl			H	M+= 451.9 $_At_{Ret}$ = 4.60 min
133	X=F Y=Cl			H	M+= 430.0 $_ct_{Ret}$ = 6.56 min
134	X=H Y=Cl				M+= 601.0 $_At_{Ret}$ = 3.79 min
135	X=F Y=Cl			H	M+= 441.0 $_ct_{Ret}$ = 6.26 min
136	X=F Y=Cl			H	M+= 458.0 $_ct_{Ret}$ = 6.46 min

(in the table, the tip of the arrow means the end of the bond at which the respective moiety is bound to the rest of the molecule in the formula; for example, if R^1 has the formula



then the corresponding compound has the formula



Intermediate 10.1: 6-Chloro-5-fluoro-1H-indole-3-carbaldehyde

The title compound is synthesized by formylation of 6-chloro-5-fluoro-1H-indole analogously to the preparation of **Intermediate 1.1** as a white solid; ES-MS: M+ = 198.0; HPLC: $_At_{Ret}$ = 3.98 min.

Intermediate 16.1: 1-Chloro-2-fluoro-3-[isocyano-(toluene-4-sulfonyl)-methyl]-benzene

Intermediate 16.1 is prepared in analogy to a published literature procedure (*Chem. Lett.* **1988**, 9, 1531-1534). $POCl_3$ (0.33 mL, 3.66 mmol) is added to a solution of **Intermediate 16.2** (500 mg, 1.46 mmol) in THF (7 mL) at 0 °C. After 30min, Et_3N (1.32 mL, 9.51 mmol) is added to the reaction mixture, then the mixture is stirred for additional 1h and then quenched by H_2O, EtOAc is added and the organic layer is washed with brine, dried over $MgSO_4$ and evaporated *in vacuo*. Silica gel flash chromatography of the residue affords the title compound as a colorless powder; ES-MS: M+H = 325.0; HPLC: $_At_{Ret}$ = 5.03 min.

Intermediate 16.2: N-[(3-Chloro-2-fluoro-phenyl)-(toluene-4-sulfonyl)-methyl]-formamide

Intermediate 16.2 is prepared in analogy to a published literature procedure (*Chem. Lett.* **1988**, *9*, 1531-1534). A mixture of 3-chloro-2-fluorobenzaldehyde_(2.00 g, 12.6 mmol), p-toluenesulfinic acid (2.96 g, 18.9 mmol), TMSCl (1.75 mL, 13.9 mmol) and formamide (1.25 mL, 31.5 mmol) in toluene (7 mL) and CH_3CN (7 mL) is heated at 50 °C for 5h. After completion, the reaction mixture is quenched by H_2O, EtOAc is added and the organic layer is washed with brine, dried over $MgSO_4$ and evaporated *in vacuo*. Silica gel flash chromatography of the residue affords the title compound as a colorless powder; HPLC: $_At_{Ret}$ = 4.21 min; ^{1}HNMR($CDCl_3$) 8.18 (s, 1H), 7.72 (d, 2H), 7.50-7.45 (m, 1H), 7.40-7.30 (m, 3H), 7.20-7.10 (m, 1H), 7.00 (d, 1H), 6.60 (d, 1H), 2.45 (s, 3H).

Intermediate 17.1: 3-Formyl-1H-indole-6-carbonitrile

The title compound is synthesized by formylation of 1H-indole-6-carbonitrile_analogously to the preparation of **Intermediate 1.1** as a white solid; ES-MS: M-H = 169.0; HPLC: $_ct_{Ret}$ = 4.96 min.

Intermediate 18.1: 5,6-Difluoro-1H-indole-3-carbaldehyde

The title compound is synthesized by formylation of 5,6-difluoro-1H-Indole_analogously to the preparation of **Intermediate 1.1** as a white solid; ES-MS: M-H = 180.0; HPLC: $_ct_{Ret}$ = 5.47 min.

Intermediate 25.1: (S)-2-Amino-2-(4-chloro-phenyl)-ethanol

A mixture of L-4-chloro-phenylglycine_(1.74 g, 9.37 mmol) and LAH (712 mg, 18.75 mmol) in THF (40 mL) is refluxed for 1.5h. After completion, the reaction mixture is quenched by $Na_2SO_4 \cdot 10H_2O$ and the product is isolated by filtration with Celite, washed with THF and dried under reduced pressure to give the title compound as oil; HPLC: $_At_{Ret}$ = 1.46 min; ^{1}HNMR (DMSO-d_6) 7.35 (d, 2H), 7.30 (d, 2H), 4.80 (bs, 1H), 3.85-3.80 (m, 1H), 3.45-3.20 (m, 2H), 1.85 (bs, 2H).

Intermediate 32.1: (R)-2-Amino-2-(4-chloro-phenyl)-ethanol

The title compound is synthesized by reduction of D-4-chloro-phenylglycine analogously to the preparation of **Intermediate 25.1** as a colorless oil; ES-MS: HPLC: $_At_{Rel}$ = 1.47 min; ^{1}HNMR (DMSO-d_6) 7.35 (d, 2H), 7.30 (d, 2H), 4.80 (bs, 1H), 3.85-3.80 (m, 1H), 3.45-3.20 (m, 2H), 1.85 (bs, 2H).

Example 43 is prepared in analogy to a published literature procedure (*J. Med. Chem.* **1989**, *32*, 1728-1732). A mixture of **Intermediate 43.1** (102 mg, 0.16 mmol) and hydrazine hydrate (12 mg, 0.24 mmol) in EtOH (0.8 mL) is refluxed for 2h, After completion, the reaction mixture is quenched by H_2O, EtOAc is added and the organic layer is washed with brine, dried over $MgSO_4$ and evaporated *in vacuo*. Silica gel flash chromatography of the residue affords the title compound as a colorless powder.

Intermediate 43.1: 6-Chloro-3-[3-(4-chloro-benzyl)-5-phenyl-3H-imidazol-4-yl]-1H-indole-2-carboxylic acid [2-(1,3-dioxo-1,3-dihydro-isoindol-2-yl)-ethyl]-amide (also a compound of the formula I)

The title compound is synthesized by condensation of **Intermediate 2.1** and 2-(2-amino-ethyl)-isoindole-1,3-dione analogously to the preparation of **Example 2** as a colorless solid; ES-MS: M+ = 636.1; HPLC: $_At_{Rel}$ = 4.64 min.

Example 44 is prepared in analogy to a published literature procedure (*J. Med. Chem.* **2003**, *46*, 3957-3960). A solution of **Intermediate 44.1** (97 mg, 0.14 mmol) in dioxane (0.5 mL) is treated with 4M dioxane solution of HCl (4 mL) for 14h. After completion, the reaction mixture is quenched by saturated aqueous $NaHCO_3$, EtOAc is added and the organic layer is washed with brine, dried over $MgSO_4$ and evaporated *in vacuo*. Silica gel flash chromatography of the residue affords the title compound as a colorless powder.

Example 45, **49, 80** and **88** are also prepared in analogy to **Example 44**.

Intermediate 44.1: 4-[2-({6-Chloro-3-[3-(4-chloro-benzyl)-5-phenyl-3H-imidazol-4-yl]-1H-indole-2-carbonyl}-amino)-ethyl]-piperazine-1-carboxylic acid tert-butyl ester (also a compound of the formula I)

The title compound is synthesized by condensation of **Intermediate 2.1** and 4-(2-amino-ethyl)-piperazine-1-carboxylic acid tert-butyl ester analogously to the preparation of **Example 2** as a colorless solid; ES-MS: M+ = 675.3; HPLC: $_At_{Rel}$ = 4.29 min.

Intermediate 45.1: 4-[3-({6-Chloro-3-[3-(4-chloro-benzyl)-5-phenyl-3H-imidazol-4-yl]-1H-indole-2-carbonyl}-amino)-propyl]-piperazine-1-carboxylic acid tert-butyl ester (also a compound of the formula I)

The title compound is synthesized by condensation of **Intermediate 2.1** and 4-(3-amino-propyl)-piperazine-1-carboxylic acid tert-butyl ester analogously to the preparation of **Example 2** as a colorless solid; ES-MS: M+ = 689.3; HPLC: $_At_{Rel}$ = 4.24 min.

Intermediate 49.1: 4-({6-Chloro-3-[3-(4-chloro-benzyl)-5-phenyl-3H-imidazol-4-yl]-1H-indole-2-carbonyl}-amino)-piperidine-1-carboxylic acid tert-butyl ester (also a compound of the formula I)

The title compound is synthesized by condensation of **Intermediate 2.1** and 4-amino-piperidine-1-carboxylic acid tert-butyl ester analogously to the preparation of **Example 2** as a colorless solid; ES-MS: M+ = 643.7; HPLC: $_At_{Rel}$ = 4.88 min.

Example 56 is prepared in analogy to a published literature procedure (J. Org. Chem. **2006**, 71, 1442-1448). A solution of **Intermediate 56.1** (142 mg, 0.22 mmol) in DCM (1.5 mL) is treated with 1M THF solution of TBAF (0.45 mL) for 47h. After completion, the reaction mixture is quenched by saturated aqueous $NaHCO_3$, EtOAc is added and the organic layer is washed with brine, dried over $MgSO_4$ and evaporated in vacuo. Silica gel flash chromatography of the residue affords the title compound as a colorless powder.

Example 57 is also prepared in analogy to **Example 56**.

Intermediate 56.1: 6-Chloro-3-[3-(4-chloro-benzyl)-5-phenyl-3H-imidazol-4-yl]-1H-indole-2-carboxylic acid [2-(tert-butyl-dimethyl-silanyloxy)-ethyl]-amide (also a compound of the formula I)

The title compound is synthesized by condensation of **Intermediate 2.1** and 2-(tert-butyl-dimethyl-silanyloxy)-ethylamine analogously to the preparation of **Example 2** as a colorless solid; ES-MS: M+ = 619.0; HPLC: $_{ct}t_{Ret}$ = 7.37 min.

Intermediate 56.2: 2-(tert-Butyl-dimethyl-silanyloxy)-ethylamine

A mixture of ethanolamine (0.5 mL, 8.1 mmol), tert-butyldimethylchlorosilane (1.42 g, 8.9 mmol), Et_3N (1.25 mL, 8.9 mmol) and DMAP (51 mg, 0.41 mmol) in DCM (25 mL) is stirred at RT for 18 h. The reaction mixture is quenched by H_2O, DCM is added and the organic layer is washed with brine, dried over $MgSO_4$ and evaporated *in vacuo*. Silica gel flash chromatography of the residue affords the title compound as a colorless oil; ES-MS: M+ = 176.2; ^{1}HNMR ($CDCl_3$) 3.95-3.85 (m, 2H), 3.15-3.10 (m, 2H), 0.90 (s, 9H), 0.05 (s, 6H), NH_2 is missing.

Intermediate 57.1: 6-Chloro-3-[3-(4-chloro-benzyl)-5-phenyl-3H-imidazol-4-yl]-1H-indole-2-carboxylic acid [3-(tert-butyl-dimethyl-silanyloxy)-propyl]-amide (also a compound of the formula I)

The title compound is synthesized by condensation of **Intermediate 2.1** and 2-(tert-butyl-dimethyl-silanyloxy)-propylamine analogously to the preparation of **Example 2** as a colorless solid; ES-MS: M+ = 633.0; HPLC: $_{ct}t_{Ret}$ = 7.52 min.

Intermediate 57.2: 2-(tert-Butyl-dimethyl-silanyloxy)-propylamine

The title compound is synthesized by condensation of 3-amino-1-propanol and tert-butyldimethylchlorosilane analogously to the preparation of **Intermediate 56.2** as a colorless oil; ES-MS: M+ = 190.2; ^{1}HNMR ($CDCl_3$) 3.80-3.70 (m, 2H), 3.10-3.05 (m, 2H), 1.95-1.85 (m, 2H), 0.90 (s, 9H), 0.03 (s, 6H), NH_2 is missing.

Intermediate 80.1: ((S)-1-{6-Chloro-3-[3-(4-chloro-benzyl)-5-phenyl-3H-imidazol-4-yl]-1H-indole-2-carbonyl}-pyrrolidin-3-yl)-carbamic acid tert-butyl ester (also a compound of the formula I)

The title compound is synthesized by condensation of **Intermediate 2.1** and (S)-pyrrolidin-3-yl-carbamic acid tert-butyl ester analogously to the preparation of **Example 2** as a colorless solid; ES-MS: M+H = 531.8; HPLC: $_{Bt}t_{Ret}$ = 2.17 min.

Intermediate 84.1: 6-Chloro-3-[3-(4-chloro-benzyl)-5-phenyl-3H-imidazol-4-yl]-5-fluoro-1H-indole-2-carboxylic acid (also a compound of the formula I)

The title compound of is synthesized by hydrolysis of **Intermediate 84.2** analogously to the preparation of **Intermediate 2.1** as a colorless solid; ES-MS: M+ = 480.0; HPLC: $_At_{Ret}$ = 4.23 min.

Intermediate 84.2: 6-Chloro-3-[3-(4-chloro-benzyl)-5-phenyl-3H-imidazol-4-yl]-5-fluoro-1H-indole-2-carboxylic acid methyl ester (also a compound of the formula I)

The title compound is synthesized by condensation of **Intermediate 84.3**, 4-chloro-benzylamine and 1-(isocyano-phenyl-methanesulfonyl)-4-methyl-benzene analogously to the preparation of **Intermediate 2.2** as a colorless solid; ES-MS: HPLC: $_At_{Ret}$ = 4.51 min; ^{1}HNMR (DMSO-d_6) 12.5 (s, 1H), 8.05 (s, 1H), 7.58 (d, 1H), 7.35-7.30 (m, 2H), 7.10-7.00 (m, 5H), 6.75-6.65 (m, 3H), 5.00 (d, 1H), 4.85 (d, 1H), 3.65 (s, 3H).

Intermediate 84.3: 6-Chloro-5-fluoro-3-formyl-1H-indole-2-carboxylic acid methyl ester

The title compound is synthesized by formylation of **Intermediate 84.4** analogously to the preparation of **Intermediate 2.3** as a white solid; $_At_{Ret}$ = 4.47 min; ^{1}HNMR (DMSO-d_6) 13.1 (bs, 1H), 10.5 (s, 1H), 8.05 (d, 1H), 7.70 (d, 1H), 4.00 (s, 3H).

Intermediate 84.4: 6-Chloro-5-fluoro-1H-indole-2-carboxylic acid methyl ester

Intermediate 84.4 is prepared in analogy to published literature procedure (*Org. Lett.* **2004**, *6*, 2953-2956.). A mixture of **Intermediate 84.5** (330 mg, 1.08 mmol) and 1M THF solution of TBAF (5.0 mL, 5.0 mmol) is stirred at RT for 1.5 h. The reaction mixture is quenched by saturated aqueous NH_4Cl, EtOAc is added and the organic layer is washed with brine, dried over $MgSO_4$ and evaporated *in vacuo*. Silica gel flash chromatography of the residue affords the title compound as a colorless powder; ES-MS: M- = 226.1; HPLC: $_At_{Ret}$ = 4.71 min.

Intermediate 84.5: 6-Chloro-5-fluoro-1-methanesulfonyl-1H-indole-2-carboxylic acid methylester

Intermediate 84.5 is prepared in analogy to published literature procedure (*Org. Lett.* **2004**, *6*, 2953-2956.). A mixture of **Intermediate 84.6** (3.00 g, 8.58 mmol), methyl propiolate (1.4 mL, 17.16 mmol), N-ethyldiisopropylamine (8.8mL, 51.4 mmol), zinc bromide (5.8 g, 25.7 mmol) and tetrakistriphenylphosphine palladium (300 mg, 0.26 mmol) in dioxane (60mL) is heated to reflux for 2 h. The reaction mixture is quenched by H_2O, EtOAc is added and the organic layer is washed with brine, dried over $MgSO_4$ and evaporated *in vacuo*. Silica gel flash chromatography of the residue affords the title compound as a colorless powder; ES-MS: M+ = 306.0; HPLC: ${}_At_{Ret}$ = 4.85 min.

Intermediate 84.6: N-(5-Chloro-4-fluoro-2-iodo-phenyl)-methanesulfonamide

A mixture of 3-chloro-4-fluoroaniline (12.9 g, 88.9 mmol) and NIS (22.0 g, 97.8 mmol) in AcOH (90 mL) is stirred at RT for 1.5h. After completion, the reaction mixture is quenched by H_2O, DCM is added and the organic layer is washed with brine, dried over $MgSO_4$ and evaporated *in vacuo*. Silica gel flash chromatography of the residue affords 5-chloro-4-fluoro-2-iodoaniline as a colorless powder; HPLC: ${}_At_{Ret}$ = 4.75 min; ^{1}HNMR ($CDCl_3$) 7.40 (d, 1H), 6.75 (d, 1H), 4.00 (bs, 2H).

MsCl (11.8 mL, 152.0 mmol) is added to a mixture of 5-chloro-4-fluoro-2-iodoaniline (15.8 g, 58.4 mmol) and pyridine (16.5 mL, 204.6 mmol) in DCM (200 mL) at RT, and is heated to 50 °C for 18h. The reaction mixture is quenched by saturated aqueous $NaHCO_3$, DCM is added and the organic layer is washed with brine. The washing is repeatedly extracted with DCM and combined extracts are washed with brine, dried and concentrated to give N-(5-chloro-4-fluoro-2-iodo-phenyl)-bis-methanesulfonamide as a yellow solid, which is submitted to the next step without further purification.

A mixture of N-(5-chloro-4-fluoro-2-iodo-phenyl)-bis-methanesulfonamide and K_2CO_3 (10.5 g, 76.0 mmol) in MeOH (100 mL) and THF (100 mL) is stirred at RT for 18h. The reaction mixture is quenched by saturated aqueous NH_4Cl, EtOAc is added and the organic layer is washed with brine, dried over $MgSO_4$ and evaporated *in vacuo*. Silica gel flash chromatography of the residue affords the title compound as a colorless powder; HPLC: ${}_At_{Ret}$ = 4.11 min; ^{1}HNMR (DMSO-d_6) 9.50(s, 1H), 7.95 (d, 1H), 7.50 (d, 1H), 3.00 (s, 3H).

Intermediate 88.1: ((R)-1-{6-Chloro-3-[3-(4-chloro-benzyl)-5-phenyl-3H-imidazol-4-yl]-1H-indole-2-carbonyl}-pyrrolidin-3-yl)-carbamic acid tert-butyl ester (also a compound of the formula I)

The title compound is synthesized by condensation of **Intermediate 2.1** and (R)-pyrrolidin-3-yl-carbamic acid tert-butyl ester analogously to the preparation of **Example 2** as a colorless solid; ES-MS: M+H = 531.8; HPLC: $_{B}t_{Ref}$ = 2.18 min.

Intermediate 89.1: (S)-4-Pyrrolidin-3-yl-morpholine·2HBr salt

Intermediate 89.1 is prepared in analogy to published literature procedure (*J. Org. Chem.* **1998**, *63*, 8266-8275.). **Intermediate 89.2** is dissolved in a 33 % HBr/AcOH solution and heated to reflux for 2.5 h. The reaction is then allowed to cool to RT, whereupon the product precipitates. It is isolated by filtration, subsequently washed with AcOH, EtOAc and dried to give the title compound as a yellow powder. ES-MS: M+H = 157.4 (free base); ^{1}HNMR (MeOH-d4) δ 4.18-4.01 (m, 2H), 3.99-3.90 (m, 4H), 3.86-3.82 (m, 2H), 3.71-3.62 (m, 2H), 3.48-3.37 (m, 2H), 2.63.2.56 (m2H), 2.42-2.35 (m, 2H).

Intermediate 89.2: 4-[(S)-1-(Toluene-4-sulfonyl)-pyrrolidin-3-yl]-morpholine

Intermediate 89.3 (1.0 g, 2.5 mmol) is dissolved in morpholine (5 mL) and heated to 85 °C in an oil bath for 12 h. After completion the reaction mixture is allowed to cool to RT, diluted with EtOAc and washed with 4M aqueous NaOH solution. The washing is repeatedly extracted with EtOAc and combined extracts are washed with brine, dried and concentrated to give the title compound as a yellow oil, which is submitted to the next step without further purification. ^{1}HNMR ($CDCl_3$) δ 7.78 (d, 2H), 7.58 (d, 2H), 3.69-3.61 (m, 4H), 3.55 (dd, 1H), 3.38 (dd, 1H), 3.29-3.21 (m, 1H), 2.98 (dd, 1H), 2.76 (m, 1H), 2.44 (s, 3H), 2.43-2.21 (m, 4H), 2.02-1.98 (m, 1H), 1.71-1.64 (m, 1H). ; HPLC: $_{B}t_{Ret}$ = 1.87 min.

Intermediate 89.3

R-Prolinol (7.0 g, 80.3 mmol, 1 equiv) is dissolved in DCM (40 mL). Pyridine (33 mL) and DMAP (980 mg, 8.0 mmol, 0.1 equiv) are added at RT and the reaction is cooled in an ice bath followed by addition of TsCl (38.3 g, 200.8 mmol, 2.5 equiv). The reaction is then

allowed to reach RT and stirred for 2 days. It is concentrated and suspended with hexanes/diethylether (1:1, 150 mL). The solid product is isolated by filtration and dried. It is subsequently dissolved in diethylether/THF (3:1, 600 mL), washed with brine, dried and concentrated to give the title compound as a light yellow powder. ES-MS: M+H = 397.3; HPLC: $_{B}t_{Ret}$ = 2.33 min.

Intermediate 90.1: 3-[3-(4-Bromo-benzyl)-5-phenyl-3H-imidazol-4-yl]-6-chloro-1H-indole-2-carboxylic acid (also a compound of the formula I)

The title compound is synthesized by hydrolysis of **Intermediate 90.2** analogously to the preparation of **Intermediate 2.1** as a colorless solid; HPLC: $_{A}t_{Ret}$ = 4.28 min.; ^{1}HNMR (DMSO-d_6) 12.4 (s, 1H), 7.45-7.05 (m, 10H), 6.90 (s, 1H), 6.75 (d, 2H), 5.10 (d, 1H), 4.90 (d, 1H).

Intermediate 90.2: 3-[3-(4-Bromo-benzyl)-5-phenyl-3H-imidazol-4-yl]-6-chloro-1H-indole-2-carboxylic acid ethyl ester (also a compound of the formula I)

The title compound is synthesized by condensation of **Intermediate 2.3**, 4-bromo-benzylamine and 1-(isocyano-phenyl-methanesulfonyl)-4-methyl-benzene analogously to the preparation of **Intermediate 2.2** as a colorless solid; HPLC: $_{A}t_{Ret}$ = 4.71 min.; .; ^{1}HNMR (DMSO-d_6) 12.3 (s, 1H), 8.05 (s, 1H), 7.50-7.00 (m, 9H), 6.95 (s, 1H), 6.65 (d, 2H), 5.05 (d, 1H), 4.90 (d, 1H), 4.00 (q, 2H), 1.00 (t, 3H).

Intermediate 91.1.: (S)-[1,3']Bipyrrolidinyl·2HBr salt

The title compound is synthesized by condensation of **Intermediate 89.3** and pyrrolidine analogously to the preparation of **Intermediate 89.1** as a yellow powder; ES-MS: M+H = 141.5 (free base); ^{1}HNMR (DMSO-d_6) δ 9.19 (s, 1H), 4.17-3.99 (m, 1H), 3.69-3-49 (m, 2H), 3.43-3.35 (m, 2H), 3.24-3.19 (m, 1H), 3.18-2.99 (m, 2H), 2.60-2.49 (m, 1H), 2.21-2.10 (m, 1H), 2.05-1.95 (m, 2H), 1.94-1.78 (m, 3H).

Intermediate 94.1.: 2-[4-(2-Amino-ethyl)-piperazin-1-yl]-ethanol

2-{2-[4-(2-Hydroxy-ethyl)-piperazin-1-yl]-ethyl}-isoindole-1,3-dione (370 mg, 1.2 mmol) is dissolved in EtOH (8 mL) and hydrazine hydrate (88mL, 1.8 mmol) is added at RT. The

reaction mixture is then refluxed for 3h and allowed to cool to RT again. The precipitated product is isolated by filtration, washed subsequently with cold EtOH and dried in HV to give the title compound ass a white powder. ES-MS: M+H = 174.2. ^{1}HNMR (MeOH-d4) δ 4.24 (bs, 2H), 3.41 (t, 2H), 2.62 (t, 2H), 2.54-2.50 (m, 2H), 2-39-2.201 (m, 10H).

Intermediate 94.2.: 2-{2-[4-(2-Hydroxy-ethyl)-piperazin-1-yl]-ethyl}-isoindole-1,3-dione

2-Piperazin1-yl-ethanol (510 mg, 3.9 mmol) is dissolved in CH_3CN (5 mL). N-(2-Bromoethyl)-phthalimid (995 mg, 3.9 mmol) and anhydrous K_2CO_3 (1.1 g, 7.8 mmol) are added at RT and then the reaction mixture is refluxed for 5 h. The reaction mixture is allowed to cool to RT again and the precipitated crude product is isolated by filtration. It is then purified by flash chromatography (SiO_2; DCM/MeOH, gradient 1-5 % MeOH) to give the title compound as a white powder. : M+H = 304.1; HPLC: $_ct_{Ret}$ = 1.73 min.

Intermediate 95.1.: Dimethyl-((S)-1-pyrrolidin-3-yl-piperidin-4-yl)-amine 2HBr salt

The title compound is synthesized by condensation of **Intermediate 89.3** and dimethyl-piperidin-4-yl-amine analogously to the preparation of **Intermediate 89.1** as a yellow powder; ES-MS: M+H = 198.4 (free base); ^{1}HNMR (DMSO-d_6) δ 9.87 (s, 1H), 3.99 (m 1H), 3.45-3.34 (m, 5H), 3.23-2.95 (m, 4H), 2.48-2.03 (m, 4H), 1.99-1.78 (m, 2H).

Intermediate 98.1: 4-Chloro-2-(2-pyrrolidin-1-yl-ethoxy)-benzylamine

A mixture of 4-chloro-2-fluoro-benzonitrile (869 mg, 5.58 mmol) and 2-pyrrolidin-1-yl-ethanol (0.80 mL, 6.70 mmol) in THF (30 mL) is treated with a 0.5 M toluene solution of KHMDS (13.4 mL, 6.7 mmol) at 0 °C. After completion of the reaction at RT, the reaction mixture is quenched by H_2O. EtOAc is added and the organic layer is washed with brine, dried over $MgSO_4$. Concentration *in vacuo* affords the corresponding 4-chloro-2-(2-pyrrolidin-1-yl-ethoxy)-benzonitrile. A THF (7 mL) solution of 4-chloro-2-(2-pyrrolidin-1-yl-ethoxy)-benzonitrile is added to a suspension of LAH (293 mg, 7.71 mmol) in THF (50 mL) at 0 °C. The reaction is allowed to stir for 2 h at ambient temperature and then quenched by $Na_2SO_4 \cdot 10H_2O$, and the product is isolated by filtration with Celite and washed with THF and dried under reduced pressure to give the title compound as oil; ES-MS: M+ = 255.2; HPLC: $_At_{Ret}$ = 1.22 min.

Intermediate 99.1: 4-Chloro-2-methoxy-benzylamine

The title compound is synthesized by coupling followed by reduction of 4-chloro-2-fluoro-benzonitrile and methanol analogously to the preparation of **Intermediate 98.1** as a colorless oil; HPLC: $_At_{Ret}$ = 2.24 min; ^{1}HNMR ($CDCl_3$) δ 7.20-7.10 (m, 1H), 7.00-6.80 (m 2H), 3.90-3.80 (m, 5H), 1.80 (bs, 2H).

Intermediate 101.1.: N,N,N'-Trimethyl-N'-(S)-pyrrolidin-3-yl-propane-1,3-diamine 3HBr salt

The title compound is synthesized by condensation of **Intermediate 89.3** and N,N,N'-trimetyl-propane-1,3-diamine analogously to the preparation of **Intermediate 89.1** as a yellow powder; ES-MS: M+H = 186.2 (free base); ^{1}HNMR (DMSO-d_6) δ 9.19 (s, 1H), 4.09-4.03 (m, 1H), 3.65-3.59 (m, 1H), 3.31-3.02 (m, 5H), 3.83 (s, 3H), 3.79 (s, 6H), 2.42-2.36 (m, 2H), 2.22-2.03 (m, 4H).

Intermediate 104.1: 4-Chloro-2-(2-methoxy-ethoxy)-benzylamine

The title compound is synthesized by coupling followed by reduction of 4-chloro-2-fluoro-benzonitrile and 2-methoxy-ethanol analogously to the preparation of **Intermediate 98.1** as a colorless solid; ES-MS: M+ = 216.1; HPLC: $_At_{Ret}$ = 2.51 min.

Intermediate 106.1: 4-Chloro-2-(3-methoxy-propoxy)-benzylamine

The title compound is synthesized by coupling followed by reduction of 4-chloro-2-fluoro-benzonitrile and 3-methoxy-propanol analogously to the preparation of **Intermediate 98.1** as a colorless solid; ES-MS: M+ = 230.1; HPLC: $_At_{Ret}$ = 2.81 min.

Intermediate 107.1: 3-[3-(2-tert-Butoxy-4-chloro-benzyl)-5-phenyl-3H-imidazol-4-yl]-6-chloro-5-fluoro-1H-indole (also a compound of the formula I)

The title compound is synthesized by condensation of **Intermediate 10.1**, **Intermediate 107.2** and 1-(isocyano-phenyl-methanesulfonyl)-4-methyl-benzene analogously to the preparation of **Example 1** as a colorless solid; ES-MS: M+ = 508.0; HPLC: $_At_{Ret}$ = 4.98 min.

Intermediate 107.2: 2-tert-Butoxy-4-chloro-benzylamine

The title compound of **Intermediate 113.1** is synthesized by coupling followed by reduction of 4-chloro-2-fluoro-benzonitrile and ^{t}butanol analogously to the preparation of **Intermediate 98.1** as a colorless oil; ES-MS: M+H-^{t}Bu = 158.0; HPLC: $_At_{Ret}$ = 3.19 min.

Intermediate 113.1: 2-(2-Aminomethyl-5-chloro-phenoxy)-ethanol

A mixture of 4-chloro-2-fluoro-benzonitrile (1.00 g, 6.43 mmol), ethylene glycol (3.59 mL, 64.3 mmol) and K_2CO_3 (1.33 g, 9.64 mmol) in DMF (30 mL) is stirred at RT for 12h. The reaction mixture is quenched by H_2O. EtOAc is added and the organic layer is washed with brine, dried over $MgSO_4$. Concentration *in vacuo* affords the corresponding 4-chloro-2-(2-hydroxy-ethoxy)-benzonitrile. A THF (6 mL) solution of 4-chloro-2-(2-hydroxy-ethoxy)-benzonitrile (875 mg, 4.43 mmol) is added to a suspension of LAH (504 mg, 13.2 mmol) in THF (45 mL) at 0 °C. The reaction is allowed to stir for 2 h at ambient temperature and then quenched by $Na_2SO_4 \cdot 10H_2O$, and the product is isolated by filtration with Celite and washed with THF and dried under reduced pressure to give the title compound as colorless solid; ES-MS: M+ = 202.1; HPLC: $_At_{Ret}$ = 1.90 min

Intermediate 114.1: 3-(2-Aminomethyl-5-chloro-phenoxy)-propan-1-ol

The title compound is synthesized by coupling followed by reduction of 4-chloro-2-fluoro-benzonitrile and 1,3-propane-diol analogously to the preparation of **Intermediate 113.1** as a colorless solid; ES-MS: M+ = 216.1; HPLC: $_At_{Ret}$ = 2.23 min.

Intermediate 115.1: [2-(2-Aminomethyl-5-chloro-phenoxy)-ethyl]-dimethyl-amine

The title compound is synthesized by coupling followed by reduction of 4-chloro-2-fluoro-benzonitrile and 2-dimethylamino-ethanol analogously to the preparation of **Intermediate 113.1**. colorless oil; ES-MS: M+ = 229.2; HPLC: $_At_{Ret}$ = 1.18 min.

Intermediate 116.1: (2-Aminomethyl-5-chloro-phenyl)-(3-methoxy-propyl)-amine

The title compound is synthesized by coupling followed by reduction of 4-chloro-2-fluoro-benzonitrile and 3-methoxy-propylamine analogously to the preparation of **Intermediate 113.1**. colorless oil; ES-MS: M- = 227.1; HPLC: $_At_{Ret}$ = 2.97 min.

Intermediate 117.1: (2-Aminomethyl-5-chloro-phenyl)-(2-methoxy-ethyl)-amine

The title compound is synthesized by coupling followed by reduction of 4-chloro-2-fluoro-benzonitrile and 3-methoxy-ethylamine analogously to the preparation of **Intermediate 113.1** as a colorless oil; ES-MS: M- = 213.2; HPLC: $_At_{Ret}$ = 2.73 min.

Intermediate 118.1: 2-(2-Aminomethyl-5-chloro-phenylamino)-ethanol

The title compound is synthesized by coupling followed by reduction of 4-chloro-2-fluoro-benzonitrile and 2-amino-ethanol analogously to the preparation of **Intermediate 113.1**. colorless powder; ES-MS: M- = 199.1; HPLC: $_At_{Ret}$ = 1.90 min.

Intermediate 119.1: 3-(2-Aminomethyl-5-chloro-phenylamino)-propan-1-ol

The title compound is synthesized by coupling followed by reduction of 4-chloro-2-fluoro-benzonitrile and 3-amino-propanol analogously to the preparation of **Intermediate 113.1**. colorless oil; ES-MS: M- = 213.1; HPLC: $_At_{Ret}$ = 2.27 min.

Intermediate 120.1: N-(2-Aminomethyl-5-chloro-phenyl)-N',N'-dimethyl-ethane-1,2-diamine

The title compound is synthesized by coupling followed by reduction of 4-chloro-2-fluoro-benzonitrile and 2-dimethylamino-ethylamine analogously to the preparation of **Intermediate 113.1** as a colorless oil; ^{1}HNMR ($CDCl_3$) δ 9.20 (bs, 1H), 7.18-7.10 (m, 2H), 6.95 (d, 1H), 4.60 (s, 2H), 3.80 (s, 2H), 3.25-3.05 (m, 4H), 2.25 (s, 6H). ;HPLC: $_At_{Ret}$ = 1.26 min.

Intermediate 124.1.: 1-Methyl-4-(S)-pyrrolidin-3-yl-piperazine 2HBr salt

The title compound is synthesized by condensation of **Intermediate 89.3** and 1-methylpiperazine analogously to the preparation of **Intermediate 89.1** as a yellow powder; ES-MS: M+H = 170.2 (free base); ^{1}HNMR (DMSO-d_6) δ 9.48 (s, 1H), 4.76-4.59 (m, 1H), 3.42 (d, 2H), 3.39-3-22 (m, 2H), 3.18-2.82 (m, 6H), 2.79 (s, 3H), 2.43-2.14 (m2H), 2.09-2.03 (m, 1H), 1.79-1.72 (m, 1H).

Intermediate 125.1.: 2-((S)-4-Pyrrolidin-3-yl-piperazin-1-yl)-ethanol 2HBr salt

The title compound is synthesized by condensation of **Intermediate 89.3** and 2-piperazin-1-yl-ethanol analogously to the preparation of **Intermediate 89.1** as a yellow powder; ES-MS: M+2H = 402.0; ^{1}HNMR (MeOH-d_4) δ 4.42-4.40 (m, 2H), 3.98-3.94 (m, 1H), 3.79-3.76 (m, 1H), 3.65-3.61 (m, 1H), 3.59-3.39 (m, 6H), 3.21-2.99 (m, 4H), 2.39-2.23 (m, 2H), 2.19-2.14 (m, 2H).

Intermediate 126.1.: N,N-Dimethyl-N'-(S)-pyrrolidin-3-yl-propane-1,3-diamine·3HBr salt

The title compound is synthesized by condensation of **Intermediate 89.3** and 3-dimethylamino-propylamine analogously to the preparation of **Intermediate 89.1** as a yellow powder; ES-MS: ES-MS: M+H = 158.1;. ^{1}HNMR (MeOH-d_4) δ 4.29.4.19 (m, 1H), 3.84 (dd, 1H), 3.69-3.60 (m, 3H), 3.49-3.41 (m, 1H), 3.39-3.25 (m, 4H), 2.97 (s, 6H), 2.62-2.57 (m, 1H), 2.42-2.37 (m, 1H), 2.35-2.21 (m, 2H).

Intermediate 127.1.: N,N,N'-Trimethyl-N'-(S)-pyrrolidin-3-yl-ethane-1,2-diamine·3HBr salt

The title compound is synthesized by condensation of **Intermediate 89.3** and 2-dimethylamino-ethylamine analogously to the preparation of **Intermediate 89.1** as a yellow powder; ES-MS: M+H = 172.1; ^{1}HNMR (MeOH-d_4) δ 4.47-4.39 (m, 1H), 3.95-3.94 (m, 1H), 3.81-3.73 (m, 5H), 3.68-3.62 (m, 1H), 3.45-3.38 (m, 1H), 3.08-2.97 (m, 9H), 2.70-2.62 (m, 1H), 2.50-2.43 (m, 1H).

Intermediate 128.1.: (S)-4-Pyrrolidin-3-yl-thiomorpholine 1,1-dioxide·2HBr salt

The title compound is synthesized by condensation of **Intermediate 89.3** and thiomorpholine 1,1-dioxide analogously to the preparation of **Intermediate 89.1** as a yellow powder; ES-MS: M+H = 201.5..

Intermediate 129.1.: Diethyl-(S)-pyrrolidin-3-yl-amine·2HBr salt

The title compound is synthesized by condensation of **Intermediate 89.3** and diethylamine analogously to the preparation of **Intermediate 89.1** as a yellow powder; ES-MS: M+H = 143.1; ^{1}HNMR (MeOH-d_4) δ 4.37 (quin, 1H), 3.91-3.83 (m, 1H), 3.69-3.61 (m, 2H), 3.44-3.23 (m, 5H), 2.62-2.58 (m, 1H), 2.39-2.28 (m, 2H), 1.39 (t, 6H).

Intermediate 130.1: 3-[3-(4-Chloro-benzyl)-5-phenyl-3H-imidazol-4-yl]-6-cyano-1H-indole-2-carboxylic acid (which is also a compound of the formula I according to the invention)

The title compound is synthesized by hydrolysis of **Intermediate 130.2** analogously to the preparation of **Intermediate 2.1** as a colorless solid; ES-MS: M+ = 453.1; HPLC: $_At_{Ret}$ = 3.81 min.

Intermediate 130.2: 3-[3-(4-Chloro-benzyl)-5-phenyl-3H-imidazol-4-yl]-6-cyano-1H-indole-2-carboxylic acid methyl ester (which is also a compound of the formula I according to the invention)

The title compound is synthesized by condensation of **Intermediate 130.3**, 4-chloro-benzylamine and 1-(isocyano-phenyl-methanesulfonyl)-4-methyl-benzene analogously to the preparation of **Intermediate 2.2** as a brown solid; ES-MS: M+ = 467.1; HPLC: $_At_{Ret}$ = 4.08 min.

Intermediate 130.3: 6-Cyano-3-formyl-1H-indole-2-carboxylic acid methyl ester

The title compound is synthesized by formylation of 6-cyano-1H-indole-2-carboxylic acid methyl ester analogously to the preparation of **Intermediate 2.3** as a white solid; ES-MS: M- = 227.1; HPLC: $_At_{Ret}$ = 3.79 min.

Intermediate 132.1: 1-[isocyano-(toluene-4-sulfonyl)-methyl]-2-methyl benzene

The title compound is synthesized by condensation of 2-methylbenzaldehyde analogously to the preparation of **Intermediate 16.1** as a white solid; ES-MS: M- = 284.1; HPLC: $_At_{Ret}$ = 4.94 min.

Intermediate 134.1: 6-Chloro-3-{3-[(S)-1-(4-chloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carboxylic acid (which is also a compound of the formula I according to the invention)

The title compound is synthesized by hydrolysis of **Intermediate 134.2** analogously to the preparation of **Intermediate 2.1** as a colorless solid; ES-MS: M+ = 476.0; HPLC: $_At_{Ret}$ = 4.33 min.

Intermediate 134.2: 6-Chloro-3-{3-[(S)-1-(4-chloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carboxylic acid ethyl ester (which is also a compound of the formula I according to the invention)

The title compound is synthesized by condensation of **Intermediate 2.3**, (S)-1-(4-chloro-phenyl)-ethylamine and 1-(isocyano-phenyl-methanesulfonyl)-4-methyl-benzene analogously to the preparation of **Intermediate 2.2** as a brown solid; ES-MS: M+ = 504.0; HPLC: $_At_{Ret}$ = 4.77 min.

Example 137: 6-Chloro-3-[3-(3,3-dimethyl-butyl)-5-phenyl-3H-imidazol-4-yl]-1H-indole-2-carboxylic acid amide

A mixture of **Intermediate 137.1** (50 mg, 0.11 mmol) and 7M MeOH solution of ammonia (2 mL, 14 mmol) is heated to 60 °C. After completion the reaction mixture is allowed to cool to RT, diluted with EtOAc and washed with with brine, dried over $MgSO_4$ and evaporated *in vacuo*. Silica gel flash chromatography of the residue affords the title compound as a colorless powder; ES-MS: M+ = 421.1; HPLC: $_At_{Ret}$ = 4.18 min.

Intermediate 137.1: 6-Chloro-3-[3-(3,3-dimethyl-butyl)-5-phenyl-3H-imidazol-4-yl]-1H-indole-2-carboxylic acid ethyl ester (which is also a compound of the formula I according to the invention)

The title compound is synthesized by condensation of **Intermediate 2.3**, 3,3-dimethyl-butylamine and 1-(isocyano-phenyl-methanesulfonyl)-4-methyl-benzene analogously to the preparation of **Intermediate 2.2** as a colorless solid; ES-MS: M+ = 450.0; HPLC: $_At_{Ret}$ = 4.77 min.

Example 138: 6-Chloro-3-[3-(3,3-dimethyl-butyl)-5-phenyl-3H-imidazol-4-yl]-1H-indole-2-carboxylic acid amide

The title compound is synthesized by condensation of **Intermediate 2.2** analogously to the preparation of **Example 137** as a colorless solid; ES-MS: M+ = 462.9; HPLC: $_At_{Ret}$ = 4.17 min.

Example 139: 6-Chloro-3-[3-(4-chloro-benzyl)-5-phenyl-3H-imidazol-4-yl]-2-(1H-tetrazol-5-yl)-1H-indole

A mixture of **Example 139.1** (37 mg, 0.08 mmol) and sodium azide (16 mg, 0.25 mol) in 2-methoxy-ethanol (0.5 mL) is heated to 130 °C. After completion the reaction mixture is allowed to cool to RT, diluted with EtOAc and washed with with brine, dried over $MgSO_4$ and evaporated *in vacuo*. Silica gel flash chromatography of the residue affords the title compound as a colorless powder; ES-MS: M+H = 487.9; HPLC: $_At_{Ret}$ = 4.32 min.

Intermediate 139.1: 6-Chloro-3-[3-(4-chloro-benzyl)-5-phenyl-3H-imidazol-4-yl]-1H-indole-2-carbonitrile (at the same time a compound of the formula I according to the invention)

A mixture of **Example 138** (150 mg, 0.33 mmol) and TFAA (1.5 mL) in DCM (1.5 mL) is heated to reflux. After completion the reaction mixture is quenched by saturated aqueous $NaHCO_3$. DCM is added and the organic layer is washed with brine, dried over $MgSO_4$ and evaporated *in vacuo*. Silica gel flash chromatography of the residue affords the title compound as a colorless powder; ES-MS: M+H = 444.9: $_At_{Ret}$ = 4.44.

Example 140: {6-Chloro-3-[3-(4-chloro-benzyl)-5-phenyl-3H-imidazol-4-yl]-1H-indol-2-yl}-methanol

A mixture of **Intermediate 2.2** (470 mg, 0.92 mmol) and LAH (70 mg, 1.84 mmol) in THF (4.8 mL) is stirred at RT for 1h and then refluxed for 2h. EtOAc is added and the organic layer is washed with brine, dried over $MgSO_4$ and evaporated *in vacuo*. Silica gel flash chromatography of the residue affords the title compound as a colorless powder; ES-MS: M+H = 449.9; HPLC: ${}_At_{Rel}$ = 4.29 min.

Example 141: {6-Chloro-3-[3-(4-chloro-benzyl)-5-phenyl-3H-imidazol-4-yl]-1H-indol-2-ylmethyl}-(2-morpholin-4-yl-ethyl)-amine

A mixture of **Example 2** (101 mg, 0.18 mmol), $AlCl_3$ (117 mg, 0.88 mmol) and LAH (33 mg, 0.88 mmol) in THF (2 mL) is refluxed. After completion the reaction mixture is quenched by sodium-potassium tartarate and neutralized by saturated aqueous $NaHCO_3$. EtOA is added and the organic layer is washed with brine, dried over $MgSO_4$ and evaporated *in vacuo*. Silica gel flash chromatography of the residue affords the title compound as a colorless powder; ES-MS: M+H = 561.8: ${}_At_{Rel}$ = 3.74 min.

Example 142: 3-[1-(4-Chloro-benzyl)-5-(6-chloro-5-fluoro-1H-indol-3-yl)-1H-imidazol-4-yl]-phenol

A solution of **Intermediate 142.1** (40 mg, 0.08 mmol) in DCM (2 mL) is treated by 1M solution of BBr_3 (0.34 mL, 0.34 mmol) in DCM at RT and is heated to 40 °C. After completion the reaction mixture is quenched by MeOH, and neutralized by saturated aqueous $NaHCO_3$. DCM is added and the organic layer is washed with brine, dried over $MgSO_4$ and evaporated *in vacuo*. Silica gel flash chromatography of the residue affords the title compound as a colorless powder; ES-MS: M+ = 452.0: ${}_At_{Rel}$ = 4.20

Intermediate 142.1: 6-Chloro-3-[3-(4-chloro-benzyl)-5-(3-methoxy-phenyl)-3H-imidazol-4-yl]-5-fluoro-1H-indole (at the same time a compound of the formula I according to the invention)

The title compound is synthesized by condensation of **Intermediate 10.1**, 4-chloro-benzylamine and **Intermediate 142.2** analogously to the preparation of **Intermediate 2.2** as a colorless solid; ES-MS: M+ = 466.0; HPLC: $_At_{Ret}$ = 4.55 min.

Intermediate 142.2: 1-[isocyano-(toluene-4-sulfonyl)-methyl]-3-methoxy benzene

The title compound is synthesized by condensation of 3-methoxybenzaldehyde analogously to the preparation of **Intermediate 16.1** as a colorless solid; ^{1}HNMR (DMSO-d_6) δ 7.65 (d, 2H), 7.50 (d, 2H), 7.40 (t, 1H), 7.10-7.05 (m, 1H), 6.90-6.80 (m, 3H), 3.70 (s, 3H), 2.40 (s, 3H) ;HPLC: $_At_{Ret}$ = 4.75 min.

Example 143: {6-Chloro-3-[3-(4-chloro-benzyl)-5-(3-hydroxy-phenyl)-3H-imidazol-4-yl]-1H-indol-2-yl}-((S)-3-dimethylamino-pyrrolidin-1-yl)-methanone

The title compound is synthesized by dealkylation of **Intermediate 143.1** analogously to the preparation of **Example 142** as a colorless solid; ES-MS: M+ = 574.0; HPLC: $_At_{Ret}$ = 3.56 min.

Intermediate 143.1: {6-Chloro-3-[3-(4-chloro-benzyl)-5-(3-methoxy-phenyl)-3H-imidazol-4-yl]-1H-indol-2-yl}-((S)-3-dimethylamino-pyrrolidin-1-yl)-methanone (at the same time a compound of the formula I according to the invention)

The title compound is synthesized by condensation of **Intermediate 143.2**, 4-chloro-benzylamine and **Intermediate 142.2** analogously to the preparation of **Intermediate 2.2** as a colorless solid; ES-MS: M+ = 588.0; HPLC: $_At_{Ret}$ = 3.80 min.

Intermediate 143.2: 6-Chloro-2-((S)-3-dimethylamino-pyrrolidine-1-carbonyl)-1H-indole-3-carbaldehyde

The title compound is synthesized by formylation of **Intermediate 143.3** analogously to the preparation of **Intermediate 2.3** as a brown solid; ES-MS: M+ = 320.2; HPLC: $_At_{Ret}$ = 2.91 min.

Intermediate 143.3: (6-Chloro-1H-indol-2-yl)-((S)-3-dimethylamino-pyrrolidin-1-yl)-methanone

The title compound is synthesized by condensation of 6-chloro-1H-indole-2-carboxylic acid and dimethyl-(S)-pyrrolidin-3-yl-amine analogously to the preparation of **Example 2** as a colorless solid; ES-MS: M+ = 292.2; HPLC: $_{A}t_{Ret}$ = 3.15 min.

Example 144: 6-Chloro-3-[3-(4-chloro-benzyl)-2-methyl-5-phenyl-3H-imidazol-4-yl]-1H-indole

Intermediate 144.1 (100 mg, 0.24 mmol) and **Intermediate 144.3** (127 mg, 0.29 mmol) are dissolved in 1,2 dimethoxethane (1 mL). $Pd(PPh_3)_4$ (14.6 mg, 0.012 mmol), K_3PO_4 (210 mg, 0.96 mmol) and H_2O (0.5 mL) are added, the reaction vessel is sealed and heated to 100 °C for 3 h. The mixture is then allowed to cool to RT and diluted with EtOAc. The organic layer is repeatedly washed with brine and combined aqueous washings are extracted with EtOAc . Combined extracts are dried and concentrated to give the crude product which is purified by trituration with hexanes/EtOAc to give the title compound as off-white powder. ES-MS: M+H = 590.0, ^{1}HNMR (DMSO-d6) δ 8.02 (s, 1H), 7.92 (s, 1H), 7.85 (d, 2H), 7.37 (d, 2H), 7.29-7.26 (m, 2H), 7.12-7.09 (m, 3H), 7.04-7.02 (m, 3H), 6.83 (d, 1H), 6.65 (d, 2H), 4.92 (s, 2H), 2.35 (s, 3H), 2.32 (s, 3H).

Intermediate 144.1: 6-Chloro-3-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-1-(toluene-4-sulfonyl)-1H-indole

Intermediate 144.2 (1.0 g, 2.3 mmol) is dissolved in DMSO (20 mL). Bis(pinacolato)diboron (0.89 g, 3.5 mmol), $Pd(dppf)Cl_2$ (0.21 g, 0.23 mmol) and KOAc (0.68 g, 6.9 mmol) are added. The reaction vessel is sealed and heated with stirring to 100 °C for 2 h. It is allowed to cool to RT again , diluted with EtOAc and the organic layer is repeatedly washed with sat. aqueous $NaHCO_3$ solution. After drying and evaporation of the solvents the crude product is purified by flash chromatography (SiO_2; hexanes/EtOAc, gradient 0-30 % EtOAc) to give the title compound as a white powder. ^{1}HNMR ($CDCl_3$) δ 7.95 (s, 2H), 7.84-7.79 (m, 3H), 7.27-7.20 (m, 3H), 1.35 (s, 12H).

Intermediate 144.2: 6-Chloro-3-iodo-1-(toluene-4-sulfonyl)-1H-indole

A mixture of 6-chloro-1H-indole (2.0 g, 13.2 mmol) and NIS (4.45 g, 19.8 mmol) in THF (60 mL) is stirred at 0 °C. After completion the reaction mixture is quenched by H_2O. EtOAc is added and the organic layer is washed with brine, dried over $MgSO_4$ and evaporated *in vacuo*. Silica gel flash chromatography of the residue affords 6-chloro-3-iodo-1H-indole as a colorless powder. A mixture of 6-chloro-3-iodo-1H-indole (4.14 g, 13.2 mmol), TsCl (3.77 g, 19.8 mmol), TBAHS (672 mg, 1.98 mmol) and NaOH (16.0 g, 400 mmol) in THF (60 mL) and H_2O (25 mL) is stirred at RT. After completion the reaction mixture is quenched by H_2O. EtOAc is added and the organic layer is washed with brine, dried over $MgSO_4$ and evaporated *in vacuo*. Re-crystalization from EtOAc of the residue affords the title compound as a colorless powder; ES-MS: M-H = 430.0: ${}_{C}t_{Ret}$ = 8.66 min.

Intermediate 144.3: 1-(4-Chloro-benzyl)-5-iodo-2-methyl-4-phenyl-1H-imidazole

A mixture of **Intermediate 144.4** (1.0 g, 3.53 mmol) and NIS (872 mg, 3.88 mmol) in CH_3CN (18 mL) is stirred at 50 °C. After completion the reaction mixture is quenched by H_2O. EtOAc is added and the organic layer is washed with brine, dried over $MgSO_4$ and evaporated *in vacuo*. Silica gel flash chromatography of the residue affords the title compound as a colorless powder; ES-MS: M+ = 409.0: ${}_{A}t_{Ret}$ = 4.06 min.

Intermediate 144.4: 1-(4-Chloro-benzyl)-2-methyl-4-phenyl-1H-imidazole

A mixture of 2-methyl-4-phenyl-1H-imidazole HCl salt (1.51 g, 7.75 mmol), 4-chlorobenzyl bromide (1.75 g, 8.53 mmol) and NaH (745 mg, 18.6 mmol) in DMF (20 mL) is stirred at RT. After completion the reaction mixture is quenched by H_2O. EtOAc is added and the organic layer is washed with brine, dried over $MgSO_4$ and evaporated *in vacuo*. Silica gel flash chromatography of the residue affords the title compound as a colorless powder; ES-MS: M+ = 283.1: ${}_{A}t_{Ret}$ = 3.93 min.

Example 145: 6-Bromo-3-[2-chloro-3-(4-chloro-benzyl)-5-phenyl-3H-imidazol-4-yl]-1H-indole-2-carboxylic acid ethyl ester

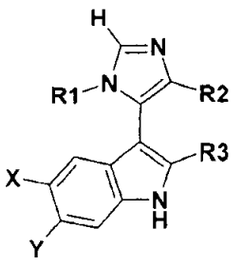
A mixture of **Intermediate 2.2** (98 mg, 0.20 mmol) and NBS (39 mg, 0.22 mmol) in THF (1.0 mL) is stirred at RT for 3h. After completion the reaction mixture is quenched by aqueous

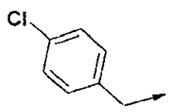
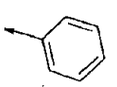
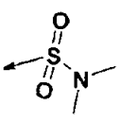
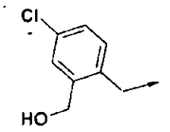
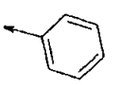
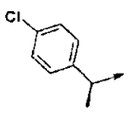
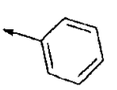
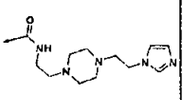
saturated $NaHCO_3$. EtOAc is added and the organic layer is washed with brine, dried over $MgSO_4$ and evaporated *in vacuo*. Silica gel flash chromatography of the residue affords the title compound as a colorless powder; ES-MS: M+ = 569.7: $_At_{Rel}$ = 5.76 min.

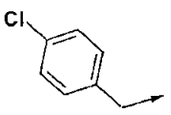
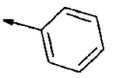
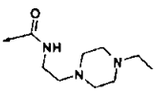
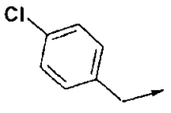
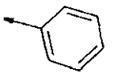
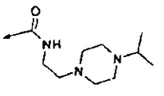
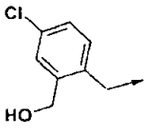
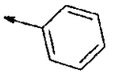
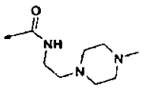
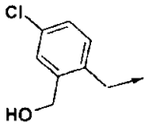
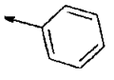
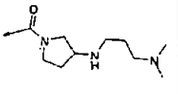
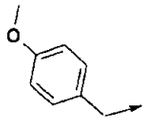
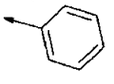
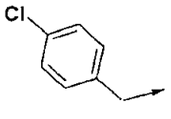
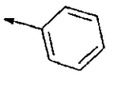
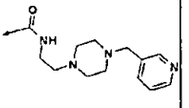
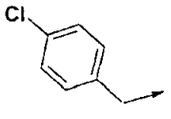
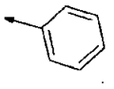
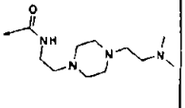
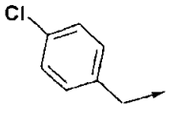
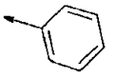
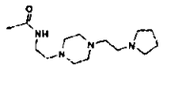
Example 146: 6-Chloro-3-[2-chloro-3-(4-chloro-benzyl)-5-phenyl-3H-imidazol-4-yl]-1H-indole-2-carboxylic acid ethyl ester

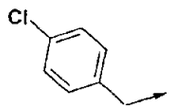
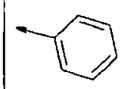
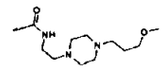
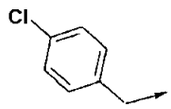
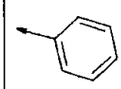
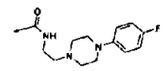
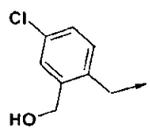
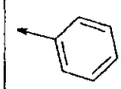
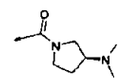
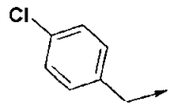
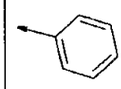
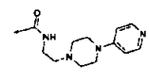
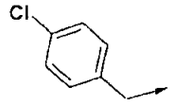
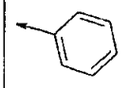
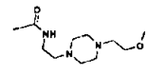
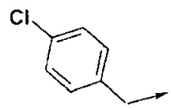
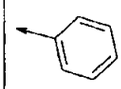
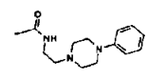
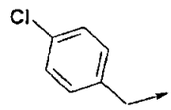
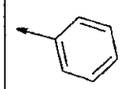
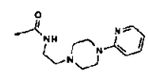
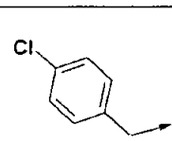
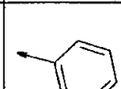
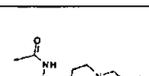
A mixture of **Intermediate 2.2** (151 mg, 0.31 mmol) and NCS (90 mg, 0.67 mmol) in THF (1.5 mL) is stirred at 60 °C for 1h. After completion the reaction mixture is quenched by aqueous saturated $NaHCO_3$. EtOAc is added and the organic layer is washed with brine, dried over $MgSO_4$ and evaporated *in vacuo*. Silica gel flash chromatography of the residue affords the title compound as a colorless powder; ES-MS: M+H = 525.8: $_At_{Rel}$ = 5.83 min.

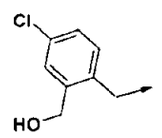
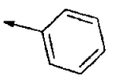
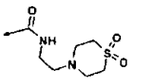
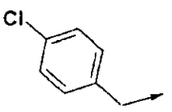
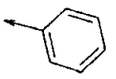
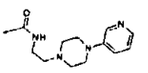
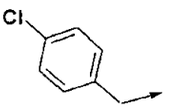
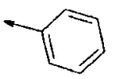
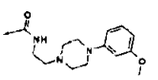
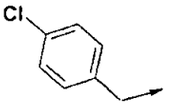
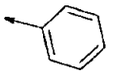
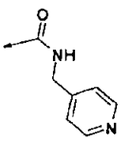
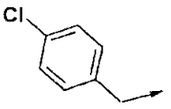
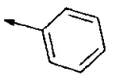
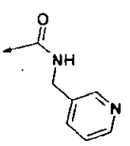
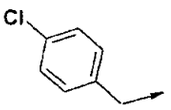
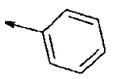
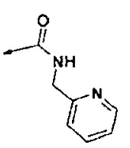
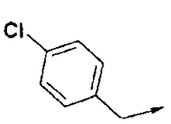
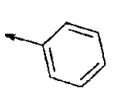
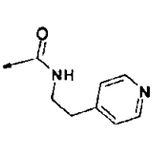
Table 2 of further Examples:

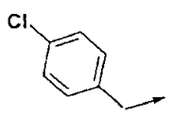
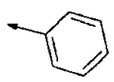
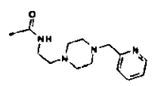
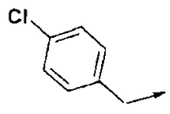
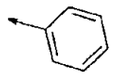
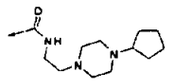
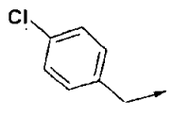
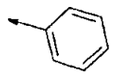
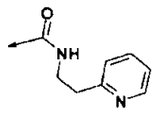
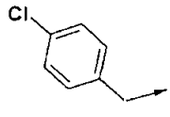
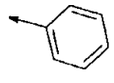
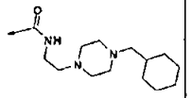
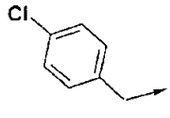
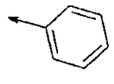
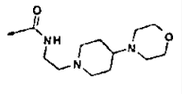
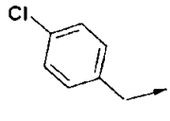
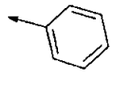
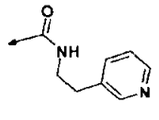
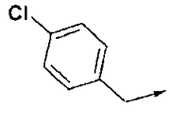
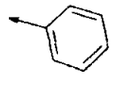
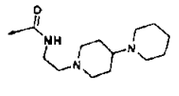
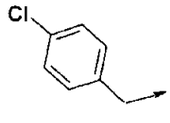
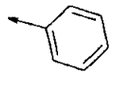
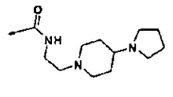


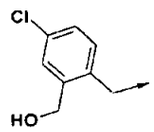
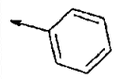
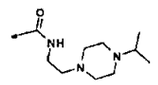
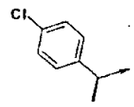
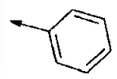
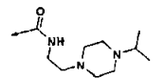
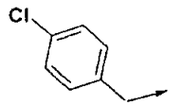
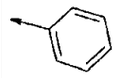
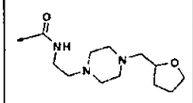
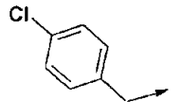
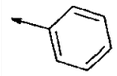
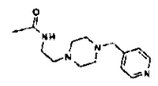
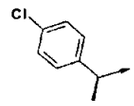
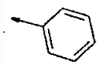
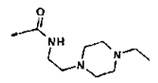
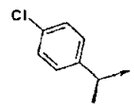
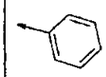
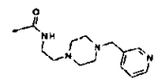
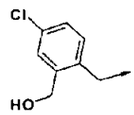
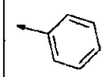
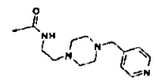
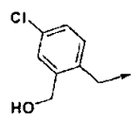
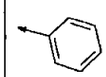
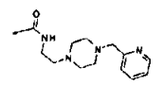
Example	X and Y	R^1	R^2	R^3	Analysis MS/HPLC/NMR
147	X=H Y=Cl				M+= 525.0 $_At_{Rel}$ = 4.51 min
148	X=F Y=Cl			H	M+H= 466.0 $_ct_{Rel}$ = 6.07 min
149	X=H Y=Cl				M+H= 681.0 $_ct_{Rel}$ = 5.45 min

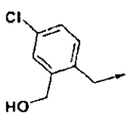
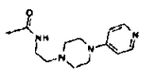
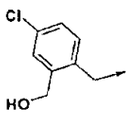
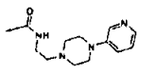
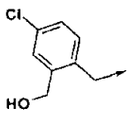
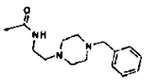
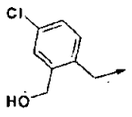
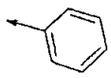
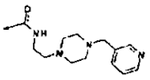
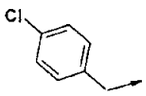
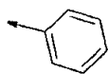
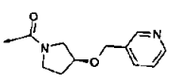
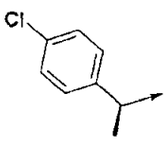
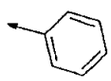
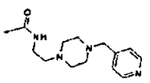
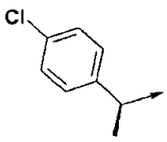
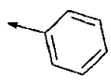
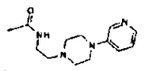
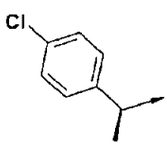
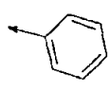
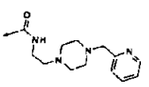
Example	X and Y	R^1	R^2	R^3	Analysis MS/HPLC/NMR
150	X=H Y=Cl				M+= 601.0 $_{A}t_{Ret}$ = 3.69 min
151	X=H Y=Cl				M+= 615.0 $_{A}t_{Ret}$ = 3.67 min
152	X=H Y=Cl				M+H= 617.0 $_{C}t_{Ret}$ = 5.26 min
153	X=H Y=Cl				M+H= 659.0 $_{C}t_{Ret}$ = 5.12 min
154	X=F Y=Cl			H	M+H= 432.1 $_{C}t_{Ret}$ = 6.18 min
155	X=H Y=Cl				M+= 664.0 $_{A}t_{Ret}$ = 3.59 min
156	X=H Y=Cl				M+= 643.9 $_{A}t_{Ret}$ = 3.67 min
157	X=H Y=Cl				M+= 670.0 $_{A}t_{Ret}$ = 3.66 min

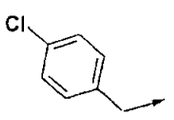
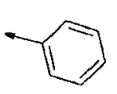
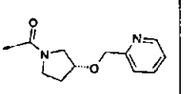
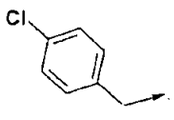
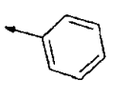
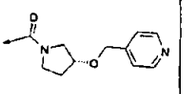
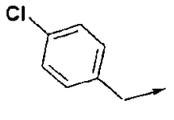
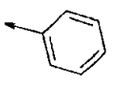
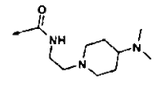
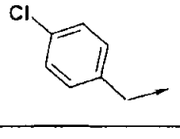
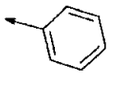
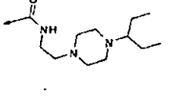
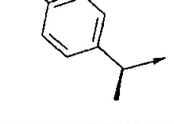
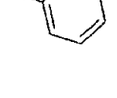
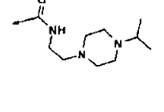
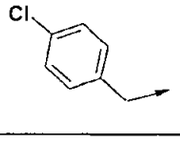
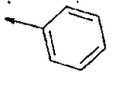
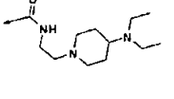
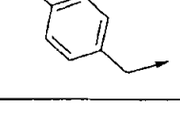
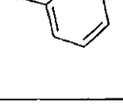
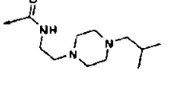
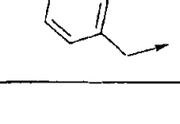
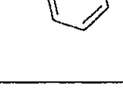
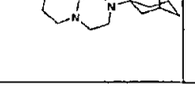
Example	X and Y	R^1	R^2	R^3	Analysis MS/HPLC/NMR
158	X=H Y=Cl				M+= 645.1 $_{A}t_{Ret}$ = 3.77 min
159	X=H Y=Cl				M+= 666.9 $_{A}t_{Ret}$ = 4.34 min
160	X=H Y=Cl				M+H= 588.0 $_{C}t_{Ret}$ = 5.31 min
161	X=H Y=Cl				M+= 650.0 $_{A}t_{Ret}$ = 3.66 min
162	X=H Y=Cl				M+= 631.0 $_{A}t_{Ret}$ = 3.69 min
163	X=H Y=Cl				M+= 648.9 $_{A}t_{Ret}$ = 4.23 min
164	X=H Y=Cl				M+= 649.9 $_{A}t_{Ret}$ = 3.65 min
165	X=H Y=Cl				M+= 662.9 $_{A}t_{Ret}$ = 3.99 min

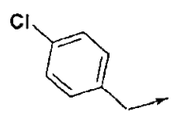
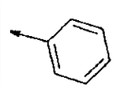
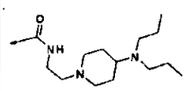
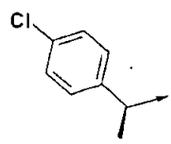
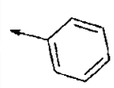
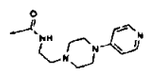
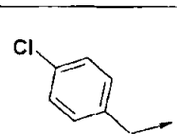
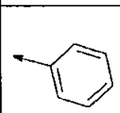
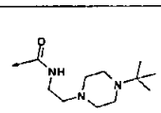
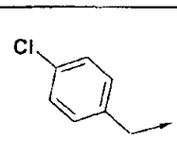
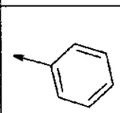
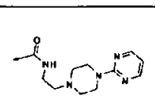
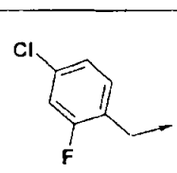
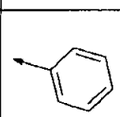
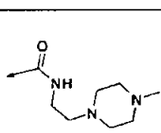
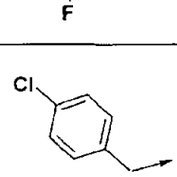
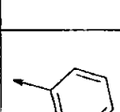
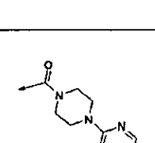
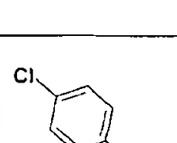
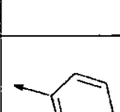
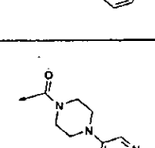
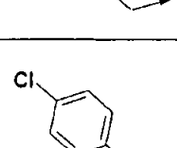
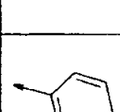
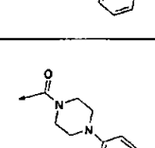
Example	X and Y	R^1	R^2	R^3	Analysis MS/HPLC/NMR
166	X=H Y=Cl				M+H= 651.9 $_{C}t_{Ret}$ = 5.57 min
167	X=H Y=Cl				M+= 649.9 $_{A}t_{Ret}$ = 3.58 min
168	X=H Y=Cl				M+= 678.9 $_{A}t_{Ret}$ = 4.30 min
169	X=H Y=Cl				M+= 551.9 $_{A}t_{Ret}$ = 3.71 min
170	X=H Y=Cl				M+= 551.9 $_{A}t_{Ret}$ = 3.73 min
171	X=H Y=Cl				M+= 551.9 $_{A}t_{Ret}$ = 3.81 min
172	X=H Y=Cl				M+= 565.9 $_{A}t_{Ret}$ = 3.74 min

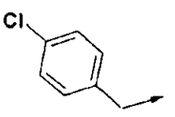
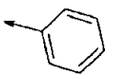
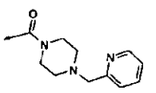
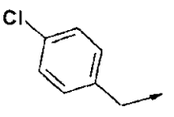
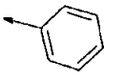
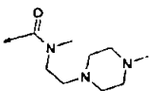
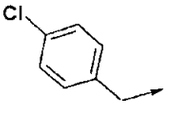
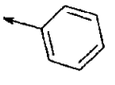
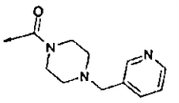
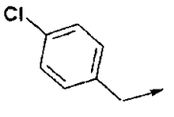
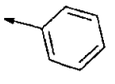
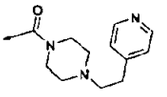
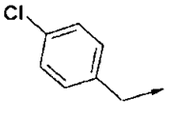
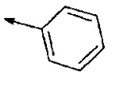
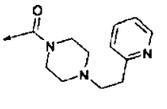
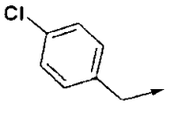
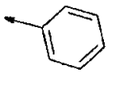
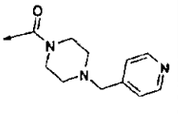
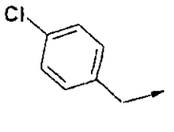
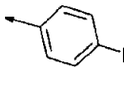
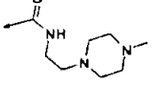
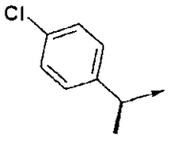
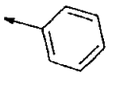
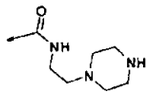
Example	X and Y	R^1	R^2	R^3	Analysis MS/HPLC/NMR
173	X=H Y=Cl				M+= 664.0 $_At_{Ret}$ = 3.72 min
174	X=H Y=Cl				M+= 641.0 $_At_{Ret}$ = 3.91 min
175	X=H Y=Cl				M+= 566.0 $_At_{Ret}$ = 3.80 min
176	X=H Y=Cl				M+= 669.0 $_At_{Ret}$ = 4.11 min
177	X=H Y=Cl				M+= 656.9 $_At_{Ret}$ = 3.61 min
178	X=H Y=Cl				M+= 565.9 $_At_{Ret}$ = 3.82 min
179	X=H Y=Cl				M+= 655.0 $_At_{Ret}$ = 3.67 min
180	X=H Y=Cl				M+= 641.0 $_At_{Ret}$ = 3.62 min

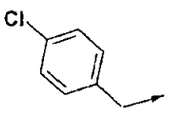
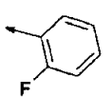
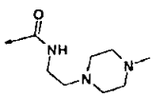
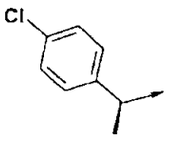
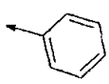
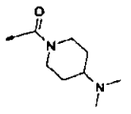
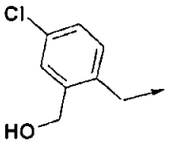
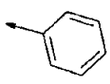
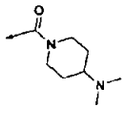
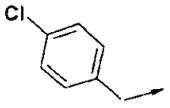
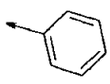
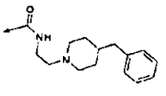
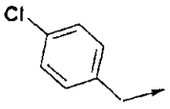
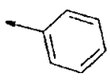
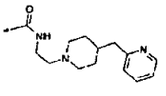
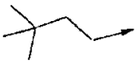
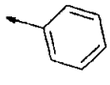
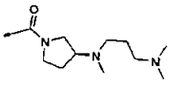
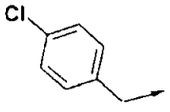
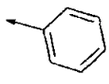
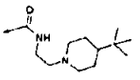
Example	X and Y	R^1	R^2	R^3	Analysis MS/HPLC/NMR
181	X=H Y=Cl				M+H= 644.9 ct_{Ret} = 5.36 min
182	X=H Y=Cl				M+H= 629.0 ct_{Ret} = 5.70 min
183	X=H Y=Cl				M+= 656.9 At_{Ret} = 3.82 min
184	X=H Y=Cl				M+= 663.9 At_{Ret} = 3.50 min
185	X=H Y=Cl				M+H= 614.9 ct_{Ret} = 5.64 min
186	X=H Y=Cl				M+H= 677.9 ct_{Ret} = 5.53 min
187	X=H Y=Cl				M+= 693.9 At_{Ret} = 3.33 min
188	X=H Y=Cl				M+= 693.9 At_{Ret} = 3.44 min

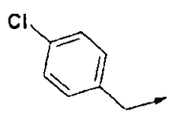
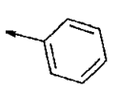
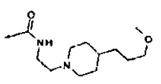
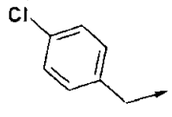
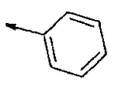
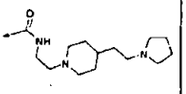
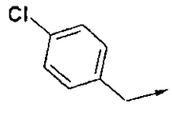
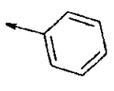
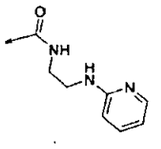
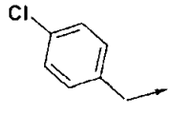
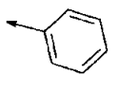
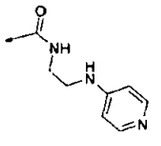
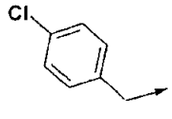
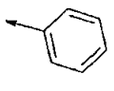
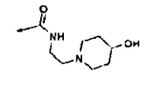
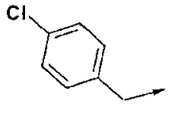
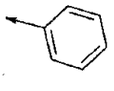
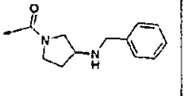
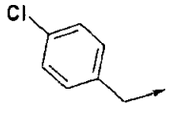
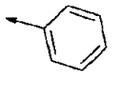
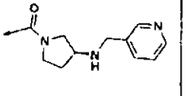
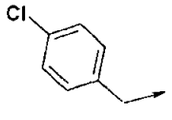
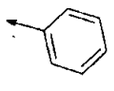
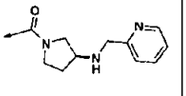
Example	X and Y	R^1	R^2	R^3	Analysis MS/HPLC/NMR
189	X=H Y=Cl				M+= 680.0 $_At_{Ret}$ = 3.32 min
190	X=H Y=Cl				M+= 679.9 $_At_{Ret}$ = 3.31 min
191	X=H Y=Cl				M+= 692.9 $_At_{Ret}$ = 3.86 min
192	X=H Y=Cl				M+= 693.9 $_At_{Ret}$ = 3.37 min
193	X=H Y=Cl				M+= 621.9 $_At_{Ret}$ = 3.82 min
194	X=H Y=Cl				M+H= 678.0 $_Ct_{Ret}$ = 5.53 min
195	X=H Y=Cl				M+H= 664.0 $_Ct_{Ret}$ = 5.55 min
196	X=H Y=Cl				M+H= 678.1 $_Ct_{Ret}$ = 5.59 min

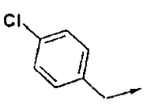
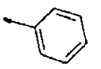
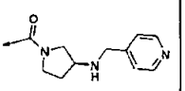
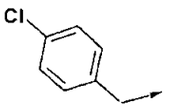
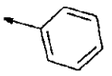
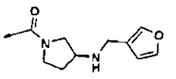
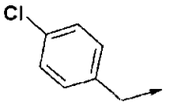
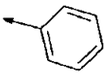
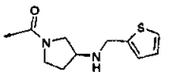
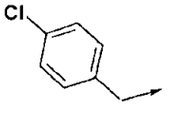
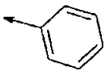
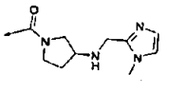
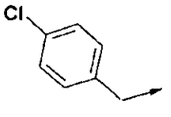
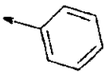
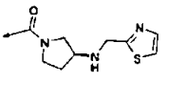
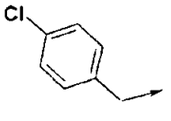
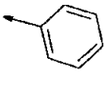
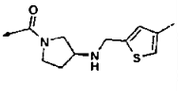
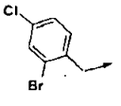
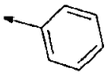
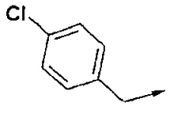
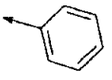
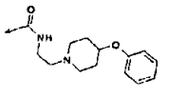
Example	X and Y	R^1	R^2	R^3	Analysis MS/HPLC/NMR
197	X=H Y=Cl				M+= 621.9 $_{A}t_{Ret}$ = 3.87 min
198	X=H Y=Cl				M+= 622.0 $_{A}t_{Ret}$ = 3.79 min
199	X=H Y=Cl				M+= 615.0 $_{A}t_{Ret}$ = 3.54 min
200	X=H Y=Cl				M+= 643.0 $_{A}t_{Ret}$ = 3.94 min
201	X=H Y=Cl				M+H= 629.0 $_{C}t_{Ret}$ = 5.47 min
202	X=H Y=Cl				M+= 643.0 $_{A}t_{Ret}$ = 3.75 min
203	X=H Y=Cl				M+= 629.0 $_{A}t_{Ret}$ = 3.91 min
204	X=H Y=Cl				M+= 707.0 $_{A}t_{Ret}$ = 4.20 min

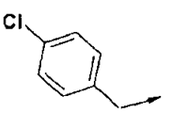
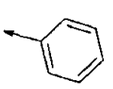
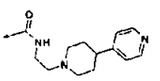
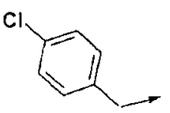
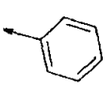
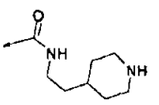
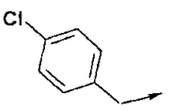
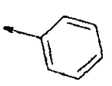
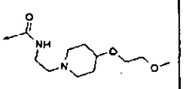
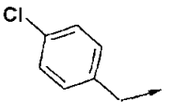
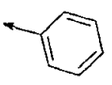
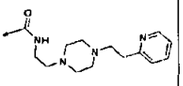
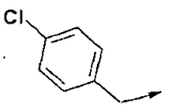
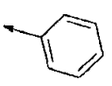
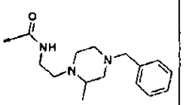
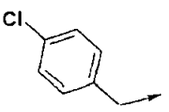
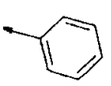
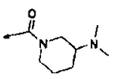
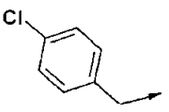
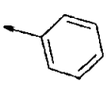
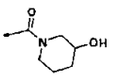
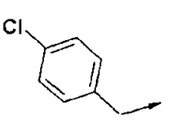
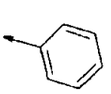
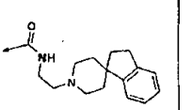
Example	X and Y	R^1	R^2	R^3	Analysis MS/HPLC/NMR
205	X=H Y=Cl				M+= 671.0 $_At_{Ret}$ = 3.96 min
206	X=H Y=Cl				M+H= 663.9 $_Ct_{Ret}$ = 5.66 min
207	X=H Y=Cl				M+= 628.9 $_At_{Ret}$ = 3.72 min
208	X=H Y=Cl				M+= 651.0 $_At_{Ret}$ = 4.01 min
209	X=H Y=Cl				M+H= 604.8 $_Ct_{Ret}$ = 5.69 min
210	X=H Y=Cl				M+H= 607.0 $_Ct_{Ret}$ = 5.77 min
211	X=H Y=Cl				M+H= 607.0 $_Ct_{Ret}$ = 5.72 min
212	X=H Y=Cl				M+H= 607.0 $_Ct_{Ret}$ = 5.72 min

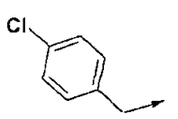
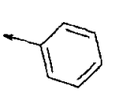
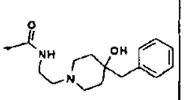
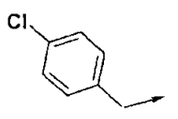
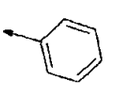
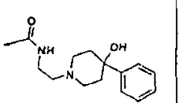
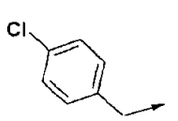
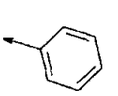
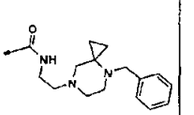
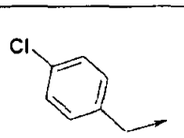
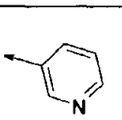
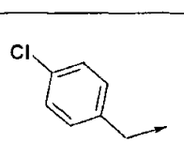
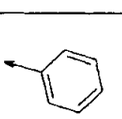
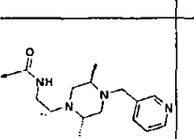
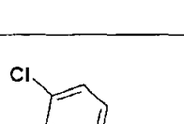
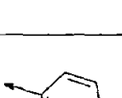
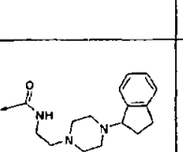
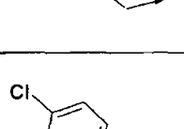
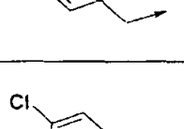
Example	X and Y	R^1	R^2	R^3	Analysis MS/HPLC/NMR
213	X=H Y=Cl				M+H= 621.0 ct_{Ret} = 5.81 min
214	X=H Y=Cl				M+H= 601.0 ct_{Ret} = 5.54 min
215	X=H Y=Cl				M+H= 621.0 ct_{Ret} = 5.56 min
216	X=H Y=Cl				M+H= 635.0 ct_{Ret} = 5.40 min
217	X=H Y=Cl				M+H= 635.0 ct_{Ret} = 5.56 min
218	X=H Y=Cl				M+H= 621.0 ct_{Ret} = 5.61 min
219	X=H Y=Cl				M+H= 605.0 ct_{Ret} = 5.58 min
220	X=H Y=Cl				M+H= 587.1 ct_{Ret} = 5.52 min

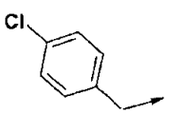
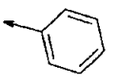
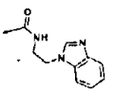
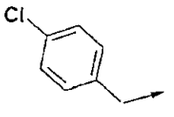
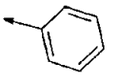
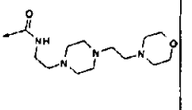
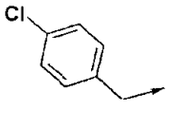
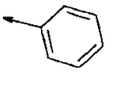
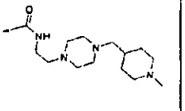
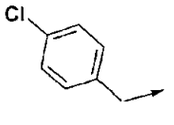
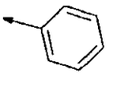
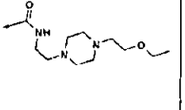
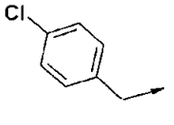
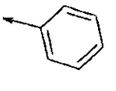
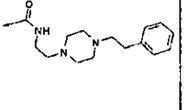
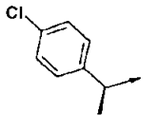
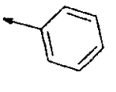
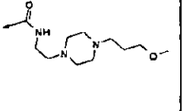
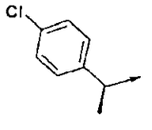
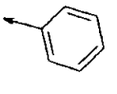
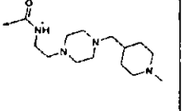
Example	X and Y	R^1	R^2	R^3	Analysis MS/HPLC/NMR
221	X=H Y=Cl				M+H= 605.0 ct_{Ret} = 5.48 min
222	X=H Y=Cl				M+H= 586.0 ct_{Ret} = 5.76 min
223	X=H Y=Cl				M+H= 602.0 ct_{Ret} = 5.38 min
224	X=H Y=Cl				M+= 662.0 $_At_{Ret}$ = 4.52 min
225	X=H Y=Cl				M+= 663.0 $_At_{Ret}$ = 3.60 min
226	X=H Y=Cl				M+H= 589.2 ct_{Ret} = 5.35 min
227	X=H Y=Cl				M+H= 628.1 ct_{Ret} = 6.38 min

Example	X and Y	R^1	R^2	R^3	Analysis MS/HPLC/NMR
228	X=H Y=Cl				M+H= 644.0 ct_{Ret} = 6.00 min
229	X=H Y=Cl				M+H= 669.0 ct_{Ret} = 5.52 min
230	X=H Y=Cl				M+H= 581.0 ct_{Ret} = 5.79 min
231	X=H Y=Cl				M+H= 581.0 ct_{Ret} = 5.62 min
232	X=H Y=Cl				M+H= 588.0 ct_{Ret} = 5.56 min
233	X=H Y=Cl				M-H = 618.0 Et_{ret} = 4.16 min
234	X=H Y=Cl				M-H = 620.0 Et_{ret} = 3.77 min
235	X=H Y=Cl				M-H = 619.0 Et_{ret} = 3.97 min

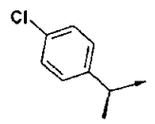
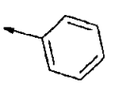
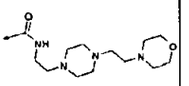
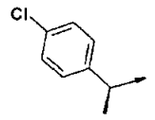
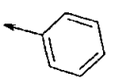
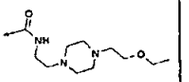
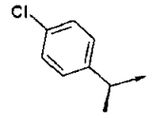
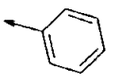
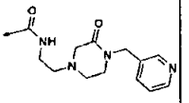
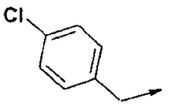
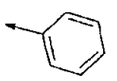
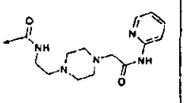
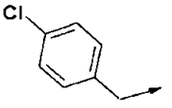
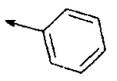
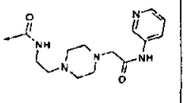
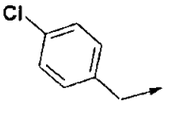
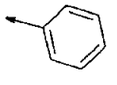
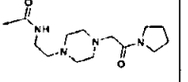
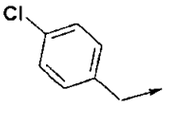
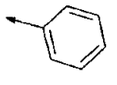
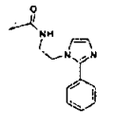
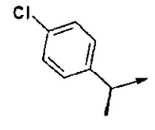
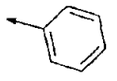
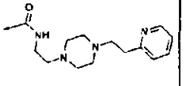
Example	X and Y	R^1	R^2	R^3	Analysis MS/HPLC/NMR
236	X=H Y=Cl				M-H = 619.2 $_{E}t_{ret}$ = 3.79 min
237	X=H Y=Cl				M-H = 608.1 $_{E}t_{ret}$ = 4.03 min
238	X=H Y=Cl				M-H = 624.0 $_{E}t_{ret}$ = 4.00 min
239	X=H Y=Cl				M-H = 622.1 $_{E}t_{ret}$ = 3.79 min
240	X=H Y=Cl				M-H = 625.0 $_{E}t_{ret}$ = 3.98 min
241	X=H Y=Cl				M-H = 638.0 $_{E}t_{ret}$ = 4.22 min
242	X=F Y=Cl			H	M+H= 515.8 $_{C}t_{Rel}$ = 6.55 min
243	X=H Y=Cl				M+H= 664.0 $_{C}t_{Rel}$ = 5.25 min

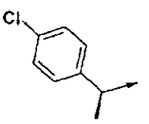
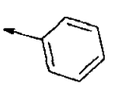
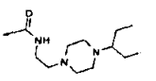
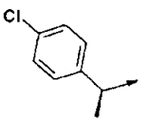
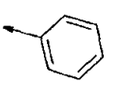
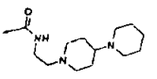
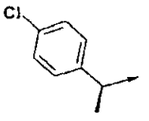
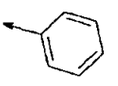
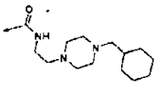
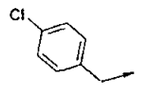
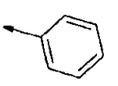
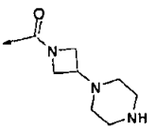
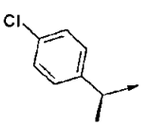
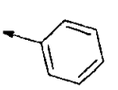
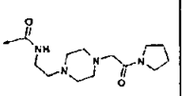
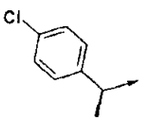
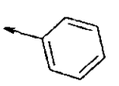
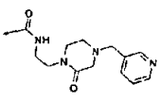
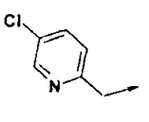
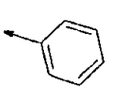
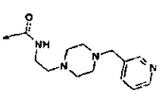
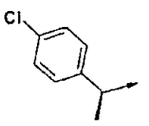
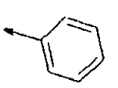
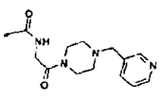
Example	X and Y	R^1	R^2	R^3	Analysis MS/HPLC/NMR
244	X=H Y=Cl				M+H= 649.0 $_{C}t_{Ret}$ = 5.42 min
245	X=H Y=Cl				M+H= 572.0 $_{C}t_{Ret}$ = 5.58 min
246	X=H Y=Cl				M+= 646.0 $_{A}t_{Ret}$ = 3.91 min
247	X=H Y=Cl				M+H= 678.0 $_{C}t_{Ret}$ = 5.44 min
248	X=H Y=Cl				M+H= 677.0 $_{C}t_{Ret}$ = 5.95 min
249	X=H Y=Cl				M+= 572.0 $_{A}t_{Ret}$ = 3.85 min
250	X=H Y=Cl				M+= 545.0 $_{A}t_{Ret}$ = 4.29 min
251	X=H Y=Cl				M+= 674.0 $_{A}t_{Ret}$ = 4.55 min

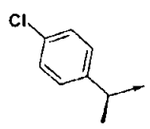
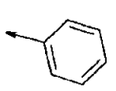
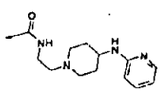
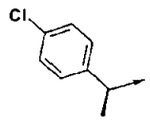
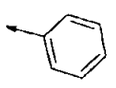
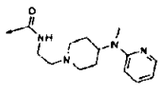
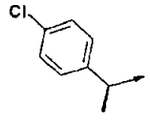
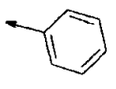
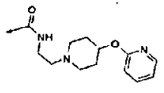
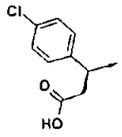
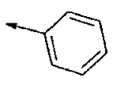
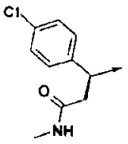
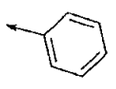
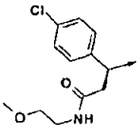
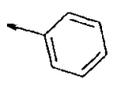
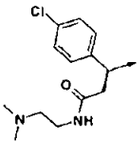
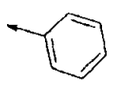
Example	X and Y	R^1	R^2	R^3	Analysis MS/HPLC/NMR
252	X=H Y=Cl				M+H= 678.0 ct_{Ret} = 6.09 min
253	X=H Y=Cl				M+H= 664.0 ct_{Ret} = 6.06 min
254	X=H Y=Cl				M+H= 689.1 ct_{Ret} = 6.23 min
255	X=F Y=Cl			H	M+H= 437.0 ct_{Ret} = 5.57 min
256	X=H Y=Cl				M+H= 692.0 ct_{Ret} = 5.42 min
257	X=H Y=Cl				M+H= 689.0 ct_{Ret} = 5.95 min
258	X=H Y=Cl				M+H= 667.0 ct_{Ret} = 5.39 min
259	X=H Y=Cl				M+H= 693.0 ct_{Ret} = 5.97 min

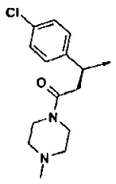
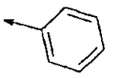
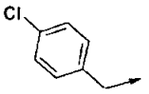
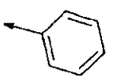
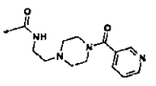
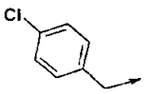
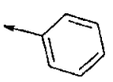
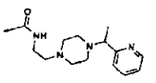
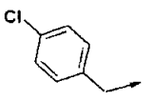
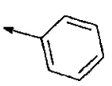
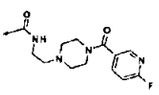
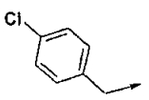
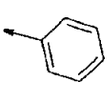
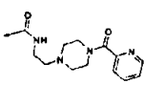
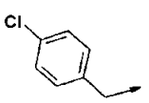
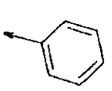
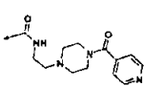
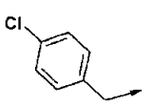
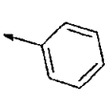
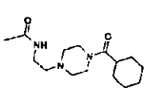
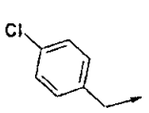
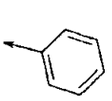
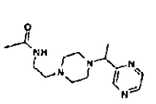
Example	X and Y	R^1	R^2	R^3	Analysis MS/HPLC/NMR
260	X=H Y=Cl				M+H= 605.0 ct_{Ret} = 5.74 min
261	X=H Y=Cl				M+H= 686.0 ct_{Ret} = 5.40 min
262	X=H Y=Cl				M+H= 684.0 ct_{Ret} = 5.34 min
263	X=H Y=Cl				M+H= 645.0 ct_{Ret} = 5.61 min
264	X=H Y=Cl				M+H= 677.0 ct_{Ret} = 5.92 min
265	X=H Y=Cl				M+H= 659.0 ct_{Ret} = 5.67 min
266	X=H Y=Cl				M+H= 698.0 ct_{Ret} = 5.44 min

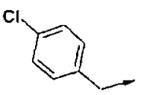
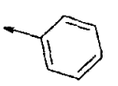
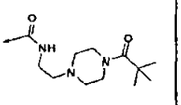
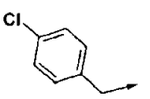
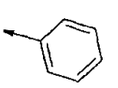
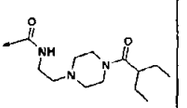
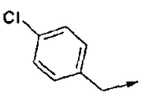
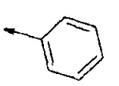
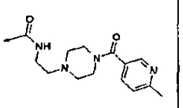
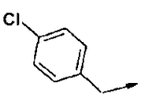
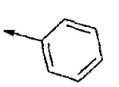
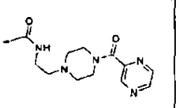
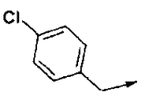
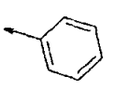
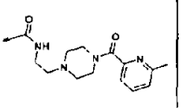
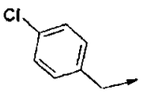
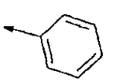
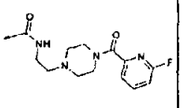
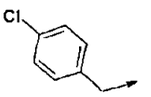
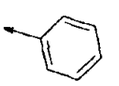
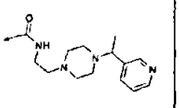
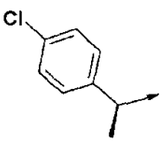
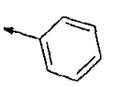
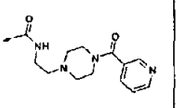
150

Example	X and Y	R^1	R^2	R^3	Analysis MS/HPLC/NMR
267	X=H Y=Cl				M+H= 700.0 ct_{Ret} = 5.51 min
268	X=H Y=Cl				M+H= 659.0 ct_{Ret} = 5.74 min
269	X=H Y=Cl				M+H= 691.9 ct_{Ret} = 5.49 min
270	X=H Y=Cl				M+H= 707.0 ct_{Ret} = 5.50 min
271	X=H Y=Cl				M+H= 707.0 ct_{Ret} = 5.35 min
272	X=H Y=Cl				M+H= 684.0 ct_{Ret} = 5.62 min
273	X=H Y=Cl				M+H= 631.0 ct_{Ret} = 5.75 min
274	X=H Y=Cl				M+H= 692.0 ct_{Ret} = 5.54 min

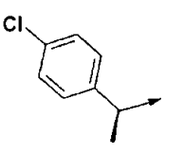
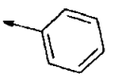
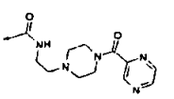
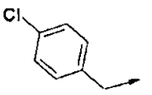
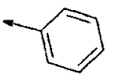
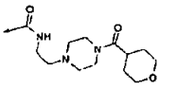
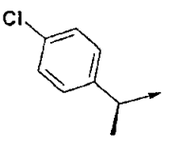
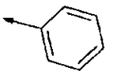
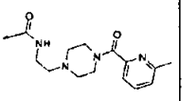
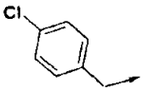
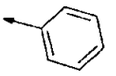
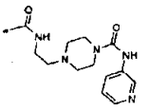
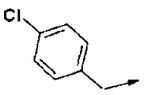
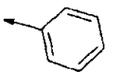
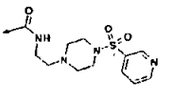
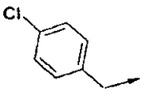
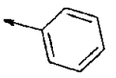
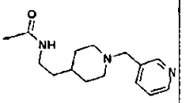
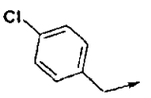
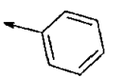
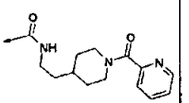
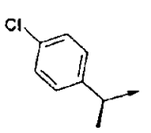
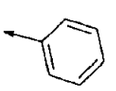
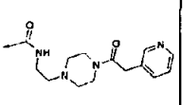
Example	X and Y	R^1	R^2	R^3	Analysis MS/HPLC/NMR
275	X=H Y=Cl				M+H= 657.1 ct_{Ret} = 5.82 min
276	X=H Y=Cl				M+H= 669.0 ct_{Ret} = 5.57 min
277	X=H Y=Cl				M+H= 683.0 ct_{Ret} = 6.03 min
278	X=H Y=Cl				M+= 585.0 $_{A}t_{Ret}$ = 3.60 min
279	X=H Y=Cl				M+H= 698.0 ct_{Ret} = 5.72 min
280	X=H Y=Cl				M+H= 691.8 ct_{Ret} = 5.63 min
281	X=H Y=Cl				M+H= 664.8 ct_{Ret} = 5.10 min
282	X=H Y=Cl				M+H= 692.0 ct_{Ret} = 5.41 min

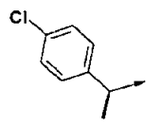
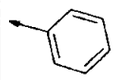
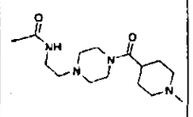
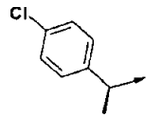
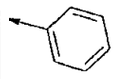
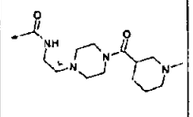
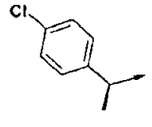
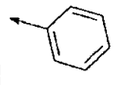
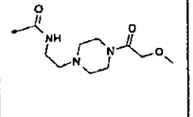
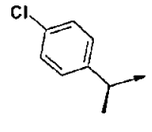
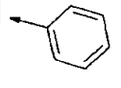
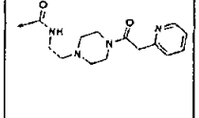
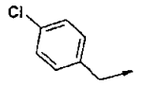
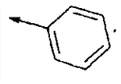
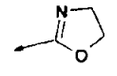
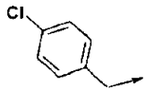
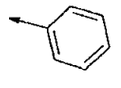
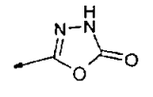
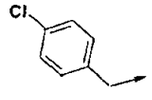
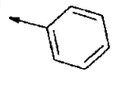
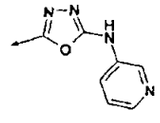
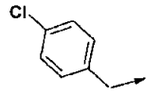
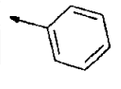
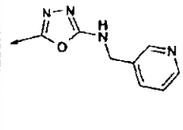
Example	X and Y	R^1	R^2	R^3	Analysis MS/HPLC/NMR
283	X=H Y=Cl				M+H= 678.0 $_{A}t_{Ret}$ = 5.41 min
284	X=H Y=Cl				M+H= 691.9 $_{A}t_{Ret}$ = 5.41 min
285	X=H Y=Cl				M+H= 679.0 $_{D}t_{Ret}$ = 2.88 min
286	X=F Y=Cl			H	M+H= 495.7 $_{A}t_{Ret}$ = 4.28 min
287	X=F Y=Cl			H	M+H= 507.0 $_{C}t_{Ret}$ = 6.17 min
288	X=F Y=Cl			H	M+H= 551.0 $_{C}t_{Ret}$ = 6.23 min
289	X=F Y=Cl			H	M+H= 564.0 $_{C}t_{Ret}$ = 5.72 min

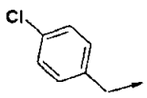
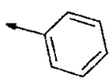
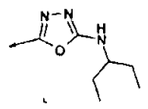
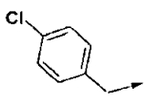
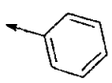
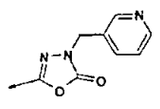
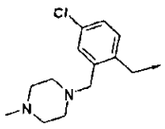
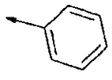
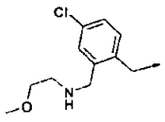
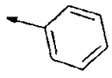
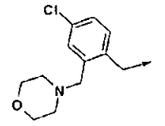
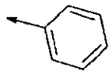
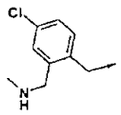
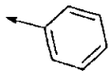
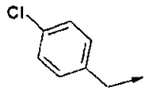
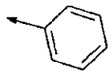
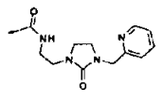
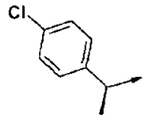
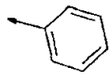
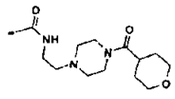
Example	X and Y	R^1	R^2	R^3	Analysis MS/HPLC/NMR
290	X=F Y=Cl			H	M+H= 576.0 $_{C}t_{Ret}$ = 5.73 min
291	X=H Y=Cl				M+= 677.8 $_{A}t_{Ret}$ = 3.71 min
292	X=H Y=Cl				M+= 677.9 $_{A}t_{Ret}$ = 3.65 min
293	X=H Y=Cl				M+= 695.9 $_{A}t_{Ret}$ = 3.92 min
294	X=H Y=Cl				M+= 678.0 $_{A}t_{Ret}$ = 3.82 min
295	X=H Y=Cl				M+= 677.9 $_{A}t_{Ret}$ = 3.59 min
296	X=H Y=Cl				M+= 683.0 $_{A}t_{Ret}$ = 4.24 min
297	X=H Y=Cl				M+= 679.0 $_{A}t_{Ret}$ = 3.80 min

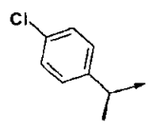
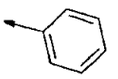
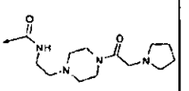
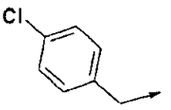
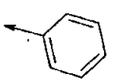
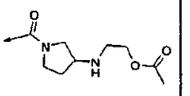
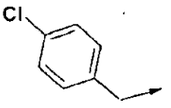
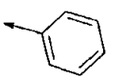
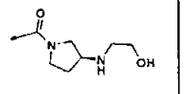
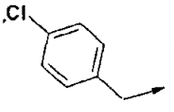
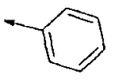
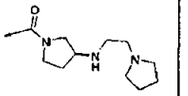
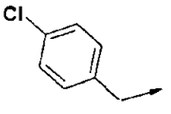
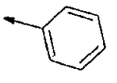
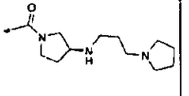
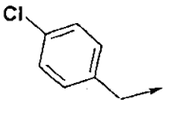
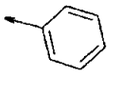
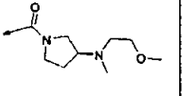
Example	X and Y	R^1	R^2	R^3	Analysis MS/HPLC/NMR
298	X=H Y=Cl				M+= 657.0 $_{A}t_{Ret}$ = 4.05 min
299	X=H Y=Cl				M-H= 670.6 $_{A}t_{Ret}$ = 4.15 min
300	X=H Y=Cl				M+= 691.9 $_{A}t_{Ret}$ = 3.58 min
301	X=H Y=Cl				M+= 678.9 $_{A}t_{Ret}$ = 3.78 min
302	X=H Y=Cl				M+= 692.0 $_{A}t_{Ret}$ = 3.82 min
303	X=H Y=Cl				M+= 695.9 $_{A}t_{Ret}$ = 3.96 min
304	X=H Y=Cl				M+= 678.0 $_{A}t_{Ret}$ = 3.60 min
305	X=H Y=Cl				M+= 692.9 $_{A}t_{Ret}$ = 3.75 min

155

Example	X and Y	R^1	R^2	R^3	Analysis MS/HPLC/NMR
306	X=H Y=Cl				M+= 692.9 $_At_{Ret}$ = 3.88 min
307	X=H Y=Cl				M+= 685.0 $_At_{Ret}$ = 3.78 min
308	X=H Y=Cl				M+= 706.0 $_At_{Ret}$ = 3.97 min
309	X=H Y=Cl				M+= 693.0 $_At_{Ret}$ = 3.55 min
310	X=H Y=Cl				M+= 713.9 $_At_{Ret}$ = 4.02 min
311	X=H Y=Cl				M+H= 663.0 $_Ct_{Ret}$ = 5.51 min
312	X=H Y=Cl				M+H= 677.0 $_Ct_{Ret}$ = 6.15 min
313	X=H Y=Cl				M+H= 706.0 $_Ct_{Ret}$ = 5.35 min

Example	X and Y	R^1	R^2	R^3	Analysis MS/HPLC/NMR
314	X=H Y=Cl				M+H= 712.0 $_{c}t_{Ret}$ = 5.34 min
315	X=H Y=Cl				M+H= 712.0 $_{c}t_{Ret}$ = 5.38 min
316	X=H Y=Cl				M+H= 659.0 $_{c}t_{Ret}$ = 5.59 min
317	X=H Y=Cl				M+H= 706.0 $_{c}t_{Ret}$ = 5.38 min
318	X=H Y=Cl				M+H = 487.0 $_{c}t_{Ret}$ = 6.27 min
319	X=H Y=Cl				M+ = 502.0. $_{A}t_{Ret}$ = 4.23 min
320	X=H Y=Cl				M+ = 578.0 $_{A}t_{Ret}$ = 3.86 min
321	X=H Y=Cl				M+ = 592.0 $_{A}t_{Ret}$ = 3.72 min

Example	X and Y	R^1	R^2	R^3	Analysis MS/HPLC/NMR
322	X=H Y=Cl				M+ = 571.0 $_At_{Ret}$ = 4.70 min
323	X=H Y=Cl				M+ = 592.9 $_At_{Ret}$ = 3.87 min
324	X=F Y=Cl			H	M+H= 548.1 $_ct_{Ret}$ = 5.59 min
325	X=F Y=Cl			H	M+H= 523.0 $_ct_{Ret}$ = 5.50 min
326	X=F Y=Cl			H	M+H= 535.0 $_ct_{Ret}$ = 5.45 min
327	X=F Y=Cl			H	M+H= 479.0 $_ct_{Ret}$ = 5.38 min
328	X=H Y=Cl				M+H= 664.0 $_ct_{Ret}$ = 5.63 min
329	X=H Y=Cl				M+H= 698.9 $_ct_{Ret}$ = 5.63 min

Example	X and Y	R^1	R^2	R^3	Analysis MS/HPLC/NMR
330	X=H Y=Cl				M+H= 691.9 $_{C}t_{Rel}$ = 5.23 min
331	X=H Y=Cl				M-H= 614.0 $_{E}t_{Rel}$ = 4.00 min
332	X=H Y=Cl				M-H= 601.9 $_{E}t_{Rel}$ = 3.89 min
333	X=H Y=Cl				M-H= 625.0 $_{E}t_{Rel}$ = 3.79 min
334	X=H Y=Cl				M-H= 639.1 $_{E}t_{Rel}$ = 3.77 min
335	X=H Y=Cl				M-H= 601.9 $_{E}t_{Rel}$ = 3.89 min

Example 147 is synthesized by condensation of 4-Chlorobenzyl-amine, **Intermediate 147.1** and 1-(isocyano-phenyl-methanesulfonyl)-4-methyl-benzene analogously to the preparation of **Intermediate 2.2** as a colorless solid.

Intermediate 147.1: 6-Chloro-3-formyl-1H-indole-2-sulfonic acid dimethylamide

The title compound is synthesized by formylation of **Intermediate 147.2** analogously to the preparation of **Intermediate 1.1** as a white solid; ES-MS: M+ = 287.1; HPLC: $_{A}t_{Rel}$ = 4.33 min.

Intermediate 147.2: 6-Chloro-1H-indole-2-sulfonic acid dimethylamide

Step 1; A solution of **Intermediate 147.3** (1.0 g, 3.27 mmol) in the mixture of hexane (11 mL) and Et_2O (11 mL) is treated with 2M THF/heptane solution of LDA (1.8 mL, 3.6 mmol) for 1h at 0 °C. The reaction mixture is cooled to -30 °C, and is treated with sulfuryl chloride (0.52 mL, 6.5 mmol) for 4h. The reaction mixture is quenched by H_2O and diluted with EtOAc, then the organic layer is dried over Na_2SO_4 and evaporated *in vacuo* to provide crude product, which is submitted to the next step without further purification.

Step 2; A solution of 6-Chloro-1-(toluene-4-sulfonyl)-1H-indole-2-sulfonyl chloride in THF (17 mL) is treated with the excess of 2M THF solution of dimethylamine (17.3 mL, 34.6 mmol) at RT. After completion the reaction mixture is quenched with saturated aqueous $NaHCO_3$ and diluted with EtOAc. The organic layer is dried over Na_2SO_4 and evaporated *in vacuo*. Silica gel flash chromatography of the residue affords 6-Chloro-1-(toluene-4-sulfonyl)-1H-indole-2-sulfonic acid dimethylamide as a red solid; ES-MS: M+ = 413.0: ${}_At_{Ref}$ = 5.36.

Step 3; A mixture of 6-Chloro-1-(toluene-4-sulfonyl)-1H-indole-2-sulfonic acid dimethylamide (160 mg, 0.39 mmol) and 1M THF solution of TBAF (1.8 mL) is stirred at RT. After completion, the reaction mixture is quenched by saturated aqueous NH_4Cl, EtOAc is added and the organic layer is washed with brine, dried over $MgSO_4$ and evaporated *in vacuo*. Silica gel flash chromatography of the residue affords the title compound as a white powder; ES-MS: M+ = 259.1: ${}_At_{Ref}$ = 4.43.

Intermediate 147.3: 6-Chloro-1-(toluene-4-sulfonyl)-1H-indole

Intermediate 147.3 is prepared in analogy to a published literature procedure (*J. Med. Chem.* **2006**, 49, 3101-3115). 55% of NaH in mineral oil (881 mg, 20.2 mmol) is added to a solution of 6-Chloroindole (3.0 g, 19.8 mmol) in THF (28 mL) at 0 °C. After 1h, TsCl (3.85 g, 20.2 mmol) is added, and the reaction mixture is stirred at RT. After completion, the reaction mixture is quenched by saturated aqueous $NaHCO_3$ and diluted with Et_2O. The organic layer is dried over Na_2SO_4 and evaporated *in vacuo* to provide crude solid. The crude product is washed with small amount of Et_2O to give the title compound as orange crystal; ES-MS: M+ = 306.1: ${}_At_{Ref}$ = 5.60.

Example 148 is synthesized by condensation of **Intermediate 148.1**, **Intermediate 10.1** and 1-(isocyano-phenyl-methanesulfonyl)-4-methyl-benzene analogously to the preparation of **Intermediate 2.2** as a colorless solid.

Intermediate 148.1: (2-Aminomethyl-5-chloro-phenyl)-methanol

Intermediate 148.1 is prepared in analogy to a published literature procedure (*J. Org. Chem.* **2004**, 69, 3620-3627).

Step 1; A mixture of methyl 2-bromo-5-chlorobenzoate (3 g, 12.0 mmol) and copper cyanide (1.2 g, 13.2 mmol) in DMF (15 mL) is heated at 90 °C for 4h and then cooled to 10 °C. Toluene (15 mL) is added followed by the slow addition of a 9:1 aqueous solution (15ml) of 10% (w/v) NH_4Cl/30% NH_4OH to maintain the internal temperature <25 °C. The reaction mixture is exposed to air and the resulting biphasic mixture stirred for 14h. Then blue aquous layer is removed and this process is repeated until the aqueous layer is no longer blue. The organic layer is dried over Na_2SO_4 and evaporated *in vacuo* to provide crude solid. Silica gel flash chromatography of the residue affords 5-Chloro-2-cyano-benzoic acid methyl ester as a yellow solid; $_ct_{Ret}$ = 6.82.

Step2; A mixture of $ZnCl_2$ (338 mg, 2.43 mmol) and $LiBH_4$ (117 mg, 5.11 mmol) in THF (5.2 mL) is heated at 60 °C for 90min followed by the slow addition of toluene (2.6 ml) solution of 5-Chloro-2-cyano-benzoic acid methyl ester (500 mg, 2.56 mmol) and stirred for 12h. The resulting mixture is cooled to 10 °C and quenched by 3N HCl and this biphasic mixture is then heated to 40°C for 30min. This mixture is neutlized by 10N NaOH to pH 12, and toluene layer is concentrated *in vacuo*. Silica gel flash chromatography of the residue affords the title compound as a yellow solid; ES-MS: M+H = 172.0: $_ct_{Ret}$ = 3.88.

Intermediate 149.1: 2-[4-(2-Imidazol-1-yl-ethyl)-piperazin-1-yl]-ethylamine

A solution of **Intermediate 149.2** (1.1 g, 5.0 mmol) in THF (15 mL) is treated by LAH (393 mg, 10.0 mmol) at 0 °C. After completion the reaction mixture is quenched by $Na_2SO_4 \cdot 10H_2O$ (8.4 g, excess) and stirred for 30 min. The product is isolated by filtration with Celite and washed with THF and dried under reduced pressure to give the title compound as oil; ES-MS: M+H = 224.2: $_ct_{Ret}$ = 1.58.

Intermediate 149.2: [4-(2-Imidazol-1-yl-ethyl)-piperazin-1-yl]-acetonitrile

A mixture of 1-(2-Imidazol-1-yl-ethyl)-piperazine (commercially available from CHESS GmbH) (1.0 g, 5.44 mmol), bromoacetonitrile (740mg, 6.0 mmol) and K_2CO_3 (1.65 g, 12.0 mmol) in CH_3CN (15 mL) is stirred at RT. After completion the product is isolated by filtration with Celite and washed with CH_3CN and dried under reduced pressure to give the title compound as oil; ES-MS: M+H = 220.2: $_{ct}t_{Ret}$ = 1.70.

Intermediate 150.1: 2-(4-Ethyl-piperazin-1-yl)-ethylamine

The title compound is synthesized by reduction of **Intermediate 150.2** analogously to the preparation of **Intermediate 149.1** as a orange oil; ES-MS: M+H= 158.2: ^{1}HNMR(DMSO-d_6) 2.60-2.20 (*m*, 16H), 0.95 (t, 3H).

Intermediate 150.2: (4-Ethyl-piperazin-1-yl)-acetonitrile

The title compound is synthesized by coupling of 1-Ethyl-piperazine and bromoacetonitrile analogously to the preparation of **Intermediate 149.2** as a orange oil; ES-MS: M+ = 154.1: ^{1}HNMR(DMSO-d_6) 3.70 (s, 2H), 2.40-2.20 (m, 10H), 0.95 (t, 3H).

Intermediate 151.1: 2-(4-Isopropyl-piperazin-1-yl)-ethylamine

The title compound is synthesized by reduction of **Intermediate 151.2** analogously to the preparation of **Intermediate 149.1** as a colorless oil; ES-MS: M+ = 172.2: ^{1}HNMR(DMSO-d_6) 2.60-2.20 (m, 15H), 0.95 (d, 6H).

Intermediate 151.2: (4-Isopropyl-piperazin-1-yl)-acetonitrile

The title compound is synthesized by coupling of 1-Isopropyl-piperazine and bromoacetonitrile analogously to the preparation of **Intermediate 149.2** as a colorless oil; ES-MS: M+ = 168.1; ^{1}HNMR(DMSO-d_6) 3.70 (s, 2H), 2.70-2.40 (m, 9H), 0.95 (d, 6H).

Intermediate 152.1: 6-Chloro-3-[3-(4-chloro-2-hydroxymethyl-benzyl)-5-phenyl-3H-imidazol-4-yl]-1H-indole-2-carboxylic acid (which is also a compound of the formula I according to the invention)

The title compound is synthesized by hydrolysis of **Intermediate 152.2** analogously to the preparation of **Intermediate 2.1** as a colorless solid; ES-MS: M+H = 492.0: ct_{Rel} = 5.85.

Intermediate 152.2: 6-Chloro-3-[3-(4-chloro-2-hydroxymethyl-benzyl)-5-phenyl-3H-imidazol-4-yl]-1H-indole-2-carboxylic acid ethyl ester (which is also a compound of the formula I according to the invention)

The title compound is synthesized by condensation of **Intermediate 2.3**, **Intermediate 148.1** and 1-(isocyano-phenyl-methanesulfonyl)-4-methyl-benzene analogously to the preparation of **Intermediate 2.2** as a colorless solid; ES-MS: M+H = 520.0: ct_{Rel} = 6.20.

Intermediate 155.1: 2-(4-Pyridin-3-ylmethyl-piperazin-1-yl)-ethylamine

The title compound is synthesized by reduction of **Intermediate 155.2** analogously to the preparation of **Intermediate 149.1** as a colorless oil; ES-MS: M+ = 221.2: ^{1}HNMR(DMSO-d_6) 8.45-8.40 (m, 2H), 7.65-7.60 (m, 1H), 7.45-7.30 (m, 1H), 3.45 (s, 2H), 2.55 (t, 2H), 2.40-2.20 (m, 12H).

Intermediate 155.2: (4-Pyridin-3-ylmethyl-piperazin-1-yl)-acetonitrile

The title compound is synthesized by coupling of 1-Pyridin-3ylmethyl-piperazine (commercially available from CHESS GmbH) and bromoacetonitrile analogously to the preparation of **Intermediate 149.2** as a colorless oil; ES-MS: M+ = 217.2.

Intermediate 156.1: 2-[4-(2-Dimethylamino-ethyl)-piperazin-1-yl]-ethylamine

The title compound is synthesized by reduction of **Intermediate 156.2** analogously to the preparation of **Intermediate 149.1** as a colorless oil; ES-MS: M+H = 201.3.

Intermediate 156.2: [4-(2-Dimethylamino-ethyl)-piperazin-1-yl]-acetonitrile

The title compound is synthesized by coupling of Dimethyl-(2-piperazin-1-yl-ethyl)-amine (commercially available from CHESS GmbH) and bromoacetonitrile analogously to the preparation of **Intermediate 149.2** as a colorless oil; ES-MS: M+ = 197.2.

Intermediate 157.1: 2-[4-(2-Pyrrolidin-1-yl-ethyl)-piperazin-1-yl]-ethylamine

The title compound is synthesized by reduction of **Intermediate 157.2** analogously to the preparation of **Intermediate 149.1** as a colorless oil; ES-MS: M+H = 227.3.

Intermediate 157.2: [4-(2-Pyrrolidin-1-yl-ethyl)-piperazin-1-yl]-acetonitrile

The title compound is synthesized by coupling of 1-(2-Pyrrolidin-1-yl-ethyl)-piperazine (commercially available from ABCR GmbH) and bromoacetonitrile analogously to the preparation of **Intermediate 149.2** as a colorless solid; ES-MS: M+H = 223.3.

Intermediate 158.1: 2-[4-(3-Methoxy-propyl)-piperazin-1-yl]-ethylamine

The title compound is synthesized by reduction of **Intermediate 158.2** analogously to the preparation of **Intermediate 149.1** as a colorless oil; ES-MS: M+ = 202.2: ^{1}HNMR(DMSO-d_6) 3.30 (t, 2H), 3.20 (s, 3H), 2.55 (t, 2H), 2.40-2.20 (m, 14H), 1.65-1.55 (m, 2H).

Intermediate 158.2: [4-(3-Methoxy-propyl)-piperazin-1-yl]-acetonitrile

The title compound is synthesized by coupling of 1-(3-Methoxy-propyl)-piperazine (commercially available from CHESS GmbH) and bromoacetonitrile analogously to the preparation of **Intermediate 149.2** as a colorless oil; ES-MS: M+ = 198.2: ^{1}HNMR(DMSO-d_6) 3.65 (s, 2H), 3.30 (s, 3H), 2.45-2.20 (m, 12H), 1.65-1.55 (m, 2H).

Intermediate 159.1: 2-[4-(4-Fluoro-phenyl)-piperazin-1-yl]-ethylamine

The title compound is synthesized by reduction of **Intermediate 159.2** analogously to the preparation of **Intermediate 149.1** as a colorless oil; ES-MS: M+ = 224.2: $_At_{Rel}$ = 1.54.

Intermediate 159.2: 4-(4-Fluoro-phenyl)-piperazin-1-yl]-acetonitrile

The title compound is synthesized by coupling of 1-(4-Fluoro-phenyl)-piperazine and bromoacetonitrile analogously to the preparation of **Intermediate 149.2** as a colorless oil; ES-MS: M+ = 220.2: $_At_{Rel}$ = 2.48.

Intermediate 161.1: 2-(4-Pyridin-4-yl-piperazin-1-yl)-ethylamine

The title compound is synthesized by reduction of **Intermediate 161.2** analogously to the preparation of **Intermediate 149.1** as a colorless oil; ES-MS: M+ = 207.2.

Intermediate 161.2: (4-Pyridin-4-yl-piperazin-1-yl)-acetonitrile

The title compound is synthesized by coupling of 1-Pyridin-4-yl-piperazine and bromoacetonitrile analogously to the preparation of **Intermediate 149.2** as a colorless oil; ES-MS: M+ = 202.2: ^{1}HNMR(DMSO-d_6) 8.15 (d, 2H), 6.80 (d, 2H), 3.80 (s, 1H), 3.35 (t, 4H), 2.50 (t, 4H).

Intermediate 162.1: 2-[4-(2-Methoxy-ethyl)-piperazin-1-yl]-ethylamine

The title compound is synthesized by reduction of **Intermediate 162.2** analogously to the preparation of **Intermediate 149.1** as a colorless oil; ES-MS: M+ = 188.2.

Intermediate 162.2: [4-(2-Methoxy-ethyl)-piperazin-1-yl]-acetonitrile
The title compound is synthesized by coupling of 1-(2-Methoxy-ethyl)-piperazine and bromoacetonitrile analogously to the preparation of **Intermediate 149.2** as a colorless oil; ES-MS: M+ = 184.2.

Intermediate 163.1: 2-[4-Phenyl-piperazin-1-yl]-ethylamine

The title compound is synthesized by reduction of **Intermediate 163.2** analogously to the preparation of **Intermediate 149.1** as a colorless oil; ES-MS: M+ = 206.2: $_At_{Ret}$ = 1.20.

Intermediate 163.2: (4-Phenyl-piperazin-1-yl)-acetonitrile

The title compound is synthesized by coupling of 1-Phenyl-piperazine and bromoacetonitrile analogously to the preparation of **Intermediate 149.2** as a white solid; ES-MS: M+ = 202.2: $_At_{Ret}$ = 1.95.

Intermediate 164.1: 2-(4-Pyridin-2-yl-piperazin-1-yl)-ethylamine

The title compound is synthesized by reduction of **Intermediate 164.2** analogously to the preparation of **Intermediate 149.1** as a colorless oil; ES-MS: M+ = 207.2.

Intermediate 164.2: (4-Pyridin-2-yl-piperazin-1-yl)-acetonitrile

The title compound is synthesized by coupling of 1-Pyridin-2-yl-piperazine and bromoacetonitrile analogously to the preparation of **Intermediate 149.2** as a colorless oil; ES-MS: M+ = 203.2: ^{1}HNMR(DMSO-d_6) 8.05 (dd, 1H), 7.50 (dd, 1H), 6.80 (d, 1H), 6.60 (dd, 1H), 3.80 (s, 1H), 3.50 (t, 4H), 2.50 (t, 4H).

Intermediate 165.1: 2-(4-Benzyl-piperazin-1-yl)-ethylamine

The title compound is synthesized by reduction of **Intermediate 165.2** analogously to the preparation of **Intermediate 149.1** as a colorless oil; ES-MS: M+ = 220.2: $_At_{Ret}$ = 1.10.

Intermediate 165.2: (4-Benzyl-piperazin-1-yl)-acetonitrile

The title compound is synthesized by coupling of 1-Benzyl-piperazine and bromoacetonitrile analogously to the preparation of **Intermediate 149.2** as a white solid; ES-MS: M+ = 216.2: $_At_{Ret}$ = 1.50.

Intermediate 167.1: 2-(4-Pyridin-3-yl-piperazin-1-yl)-ethylamine

The title compound is synthesized by reduction of **Intermediate 167.2** analogously to the preparation of **Intermediate 149.1** as a colorless oil; ES-MS: M+ = 207.2.

Intermediate 167.2: (4-Pyridin-3-yl-piperazin-1-yl)-acetonitrile

The title compound is synthesized by coupling of 1-Pyridin-3-yl-piperazine and bromoacetonitrile analogously to the preparation of **Intermediate 149.2** as a white solid; ES-MS: M+ = 203.2: $_At_{Ret}$ = 1.10.

Intermediate 168.1: 2-[4-(3-Methoxy-phenyl)-piperazin-1-yl]-ethylamine

The title compound is synthesized by reduction of **Intermediate 168.2** analogously to the preparation of **Intermediate 149.1** as a colorless oil; ES-MS: M+ = 236.2: $_At_{Ret}$ = 1.44.

Intermediate 168.2: [4-(3-Methoxy-phenyl)-piperazin-1-yl]-acetonitrile

The title compound is synthesized by coupling of 1-(3-Methoxy-phenyl)-piperazine and bromoacetonitrile analogously to the preparation of **Intermediate 149.2** as a white solid; ES-MS: M+ = 232.2: $_{A}t_{Rel}$ = 2.62.

Intermediate 173.1: 2-(4-Pyridin-2-ylmethyl-piperazin-1-yl)-ethylamine

The title compound is synthesized by reduction of **Intermediate 173.2** analogously to the preparation of **Intermediate 149.1** as a colorless oil; ES-MS: M+ = 221.2.

Intermediate 173.2: (4-Pyridin-2-ylmethyl-piperazin-1-yl)-acetonitrile

The title compound is synthesized by coupling of 1-Pyridin-2ylmethyl-piperazine (commercially available from CHESS GmbH) and bromoacetonitrile analogously to the preparation of **Intermediate 149.2** as a brown solid; ES-MS: M+ = 217.2: ^{1}HNMR(DMSO-d_6) 8.45 (dd, 1H), 7.75 (td, 1H), 7.40 (d, 1H), 7.25-7.20 (m, 1H), 3.70 (s, 2H), 3.60 (s, 2H), 2.50-2.35 (m, 8H).

Intermediate 174.1: 2-(4-Cyclopentyl-piperazin-1-yl)-ethylamine

The title compound is synthesized by reduction of **Intermediate 174.2** analogously to the preparation of **Intermediate 149.1** as a colorless oil; ES-MS: M+ = 198.2: ^{1}HNMR(DMSO-d_6) 2.55 (t, 2H), 2.40-2.30 (m, 10H), 2.25 (t, 2H), 1.80-1.70 (m, 2H), 1.60-1.40 (m, 4H), 1.30-1.20 (m, 3H).

Intermediate 174.2: (4-Cyclopentyl-piperazin-1-yl)-acetonitrile

The title compound is synthesized by coupling of 1-Cyclopentyl-piperazine (commercially available from CHESS GmbH) and bromoacetonitrile analogously to the preparation of **Intermediate 149.2** as a colorless oil; ES-MS: M+ = 194.2: ^{1}HNMR(DMSO-d_6) 3.65 (s, 2H), 2.45-2.20 (m, 9H), 1.80-1.20 (m, 8H).

Intermediate 176.1: 2-(4-Cyclohexylmethyl-piperazin-1-yl)-ethylamine

The title compound is synthesized by reduction of **Intermediate 176.2** analogously to the preparation of **Intermediate 149.1** as a colorless oil; ES-MS: M+ = 226.3: ^{1}HNMR(DMSO-d_6)

2.25 (t, 2H), 2.40-2.20 (m, 12H), 2.00 (d, 2H), 1.70-1.55 (m, 5H), 1.50-1.40 (m, 1H), 1.20-1.05 (m, 3H), 0.85-0.70 (m, 2H).

Intermediate 176.2: (4-Cyclohexylmethyl-piperazin-1-yl)-acetonitrile

The title compound is synthesized by coupling of 1-Cyclohexylmethyl-piperazine piperazine (commercially available from Fluorochem Ltd) and bromoacetonitrile analogously to the preparation of **Intermediate 149.2** as a colorless oil; ES-MS: M+ = 222.2: ^{1}HNMR(DMSO-d_6) 3.65 (s, 2H), 2.45-2.20 (m, 8H), 2.00 (d, 2H), 1.70-1.55 (m, 5H), 1.50-1.40 (m, 1H), 1.20-1.05 (m, 3H), 0.85-0.70 (m, 2H).

Intermediate 177.1: 2-(4-Morpholin-4-yl-piperidin-1-yl)-ethylamine

The title compound is synthesized by reduction of **Intermediate 177.2** analogously to the preparation of **Intermediate 149.1** as a colorless oil; ES-MS: M+ = 214.3: : ^{1}HNMR(DMSO-d_6) 3.55 (t, 4H), 3.30 (bs, 2H), 2.55 (t, 2H), 2.40 (t, 4H), 2.20 (t, 2H), 2.10-2.00 (m, 1H), 1.85-1.80 (m, 2H), 1.80-1.70 (m, 2H), 1.40-1.20 (m, 2H).

Intermediate 177.2: (4-Morpholin-4-yl-piperidin-1-yl)-acetonitrile

The title compound is synthesized by coupling of 4-Piperidin-4-yl-morpholine (commercially available from CHESS GmbH) and bromoacetonitrile analogously to the preparation of **Intermediate 149.2** as a colorless oil; ES-MS: M+ = 210.1: ^{1}HNMR(DMSO-d_6) 3.65 (s, 2H), 3.55 (t, 4H), 2.80-2.75 (m, 2H), 2.40 (t, 4H), 2.15-2.00 (m, 3H), 1.80-1.70 (m, 2H), 1.40-1.30 (m, 2H).

Intermediate 179.1: 2-[1,4']Bipiperidinyl-1'-yl-ethylamine

The title compound is synthesized by reduction of **Intermediate 179.2** analogously to the preparation of **Intermediate 149.1** as a colorless oil; ES-MS: M+ = 212.3: ^{1}HNMR(DMSO-d_6) 3.30 (bs, 2H), 2.85-2.80 (m, 2H), 2.55 (t, 2H), 2.40 (t, 4H), 2.20 (t, 2H), 2.10-2.05 (m, 1H), 1.85-1.75 (m, 2H), 1.65-1.55 (m, 2H), 1.45-1.30 (m, 8H).

Intermediate 179.2: [1,4']Bipiperidinyl-1'-yl-acetonitrile

The title compound is synthesized by coupling of [1,4']Bipiperidinyl (commercially available from Fluorochem Ltd) and bromoacetonitrile analogously to the preparation of **Intermediate 149.2** as a colorless oil; ES-MS: M+ = 208.2.

Intermediate 180.1: 2-(4-Pyrrolidin-1-yl-piperidin-1-yl)-ethylamine

The title compound is synthesized by reduction of **Intermediate 180.2** analogously to the preparation of **Intermediate 149.1** as a colorless oil; ES-MS: M+ = 198.2: ^{1}HNMR(DMSO-d_6) 3.30 (bs, 2H), 2.80-2.75 (m, 2H), 2.55 (t, 2H), 2.45-2.35 (m, 4H), 2.20 (t, 2H), 1.90-1.55 (m, 9H), 1.40-1.30 (m, 2H).

Intermediate 180.2: (4-Pyrrolidin-1-yl-piperidin-1-yl)-acetonitrile

The title compound is synthesized by coupling of 4-Pyrrolidin-1-yl-piperidine (commercially available from CHESS GmbH) and bromoacetonitrile analogously to the preparation of **Intermediate 149.2** as a white solid; ES-MS: M+ = 194.1: ^{1}HNMR(DMSO-d_6) 3.65 (s, 2H), 2.75-2.70 (m, 2H), 2.45-2.40 (m, 4H), 2.20-2.10 (m, 2H), 1.90-1.75 (m, 3H), 1.65-1.60 (m, 4H), 1.45-1.30 (m, 2H).

Intermediate 183.1: 2-[4-(Tetrahydro-furan-2-ylmethyl)-piperazin-1-yl]-ethylamine

The title compound is synthesized by reduction of **Intermediate 183.2** analogously to the preparation of **Intermediate 149.1** as a colorless oil; ES-MS: M+ = 214.3.

Intermediate 183.2: [4-(Tetrahydro-furan-2-ylmethyl)-piperazin-1-yl]-acetonitrile

The title compound is synthesized by coupling of 1-(Tetrahydro-furan-2-ylmethyl)-piperazine (commercially available from CHESS GmbH) and bromoacetonitrile analogously to the preparation of **Intermediate 149.2** as a white solid; ES-MS: M+ = 210.2.

Intermediate 184.1: 2-(4-Pyridin-4-ylmethyl-piperazin-1-yl)-ethylamine

The title compound is synthesized by reduction of **Intermediate 184.2** analogously to the preparation of **Intermediate 149.1** as a colorless oil; ES-MS: M+ = 221.2: ^{1}HNMR($CDCl_3$) 8.50 (d, 2H), 7.20 (d, 2H), 3.50 (s, 2H), 2.80 (t, 2H), 2.60-2.30 (m, 12H).

Intermediate 184.2: (4-Pyridin-4-ylmethyl-piperazin-1-yl)-acetonitrile

The title compound is synthesized by coupling of 1-Pyridin-4ylmethyl-piperazine (commercially available from ABCR GmbH) and bromoacetonitrile analogously to the preparation of **Intermediate 149.2** as a colorless oil; ES-MS: M+ = 217.2: ^{1}HNMR($CDCl_3$) 8.55 (d, 2H), 7.25 (d, 2H), 3.50 (s, 4H), 2.70-2.40 (m, 8H).

Intermediate 193.1: 3-((R)-Pyrrolidin-3-yloxymethyl)-pyridine 2HCl salt

Intermediate 193.2 (609 mg, 2.19 mmol) is treated with 1M EtOH solution of HCl (10 mL) at RT. After 5h, the reaction mixture is evaporated *in vacuo* to provide the title compound as a white solid with high purity, which is submitted to the next step without further purification; ES-MS: M+ = 179.1; ^{1}HNMR(DMSO-d_6) 9.50 (bs, 2H), 8.95 (s, 1H), 8.80 (d, 1H), 8.50 (d, 1H), 7.95 (dd, 1H), 4.70 (s, 2H), 4.35 (t, 1H), 3.40-3.10 (m, 5H), 2.10-1.95 (m, 2H).

Intermediate 193.2: (R)-3-(Pyridin-3-ylmethoxy)-pyrrolidine-1-carboxylic acid tert-butyl ester

55% of NaH in mineral oil (160 mg, 6.68 mmol) is added to a solution of (R)-3-Hydroxy-pyrrolidine-1-carboxylic acid tert-butyl ester (500 mg, 2.67 mmol) in THF (8 mL) at 0 °C. After 15min, 3-chloromethyl-pyridine HCl salt (526 mg, 3.20 mmol) is added, and the reaction mixture is stirred at 40 °C. After completion, the reaction mixture is quenched by H_2O, EtOAc is added and the organic layer is washed with brine, dried over $MgSO_4$ and evaporated *in vacuo*. Silica gel flash chromatography of the residue affords the title compound as a white powder; ES-MS: M+ = 279.2: $_At_{Ret}$ = 2.80.

Intermediate 197.1: 2-((R)-Pyrrolidin-2-yloxymethyl)-pyridine 2HCl salt

The title compound is synthesized by deprotection of **Intermediate 197.2** analogously to the preparation of **Intermediate 193.1** as a white solid; ES-MS: M+ = 179.1; ^{1}HNMR(DMSO-d_6) 9.60 (bs, 1H), 9.40 (bs, 1H), 8.75 (d, 1H), 8.35 (t, 1H), 7.90 (d, 1H), 7.80 (dd, 1H), 4.80 (s, 2H), 4.40 (t, 1H), 3.50-3.10 (m, 5H), 2.10-1.90 (m, 2H).

Intermediate 197.2: (R)-3-(Pyridin-2-ylmethoxy)-pyrrolidine-1-carboxylic acid tert-butyl ester

The title compound is synthesized by coupling of (R)-3-Hydroxy-pyrrolidine-1-carboxylic acid tert-butyl ester and 2-chloromethyl-pyridine HCl salt analogously to the preparation of **Intermediate 193.2** as a white solid; ES-MS: M+ = 279.2: $_At_{Rel}$ = 2.81.

Intermediate 198.1: 4-((R)-Pyrrolidin-4-yloxymethyl)-pyridine

The title compound is synthesized by deprotection of **Intermediate 198.2** analogously to the preparation of **Intermediate 193.1** as a white solid; ES-MS: M+ = 179.1; ^{1}HNMR(DMSO-d_6) 9.50 (bs, 2H), 8.85 (d, 2H), 7.95 (d, 2H), 4.80 (s, 2H), 4.40 (t, 1H), 3.40-3.15 (m, 5H), 2.20-1.90 (m, 2H).

Intermediate 198.2: (R)-3-(Pyridin-4-ylmethoxy)-pyrrolidine-1-carboxylic acid tert-butyl ester

The title compound is synthesized by coupling of (R)-3-Hydroxy-pyrrolidine-1-carboxylic acid tert-butyl ester and 4-chloromethyl-pyridine HCl salt analogously to the preparation of **Intermediate 193.2** as a white solid; ES-MS: M+ = 279.2: $_At_{Rel}$ = 2.84.

Intermediate 199.1: [1-(2-Amino-ethyl)-piperidin-4-yl]-dimethyl-amine

The title compound is synthesized by reduction of **Intermediate 199.2** analogously to the preparation of **Intermediate 149.1** as a colorless oil; ES-MS: M+ = 172.1: ^{1}HNMR(DMSO-d_6) 3.30 (s, 2H), 2.85-2.75 (m, 2H), 2.55 (t, 2H), 2.20 (t, 2H), 2.10 (s, 6H), 2.00-1.95 (m, 1H), 1.90-1.80 (m, 2H), 1.70-1.60 (m, 2H), 1.40-1.20 (m, 2H).

Intermediate 199.2: (4-Dimethylamino-piperidin-1-yl)-acetonitrile

The title compound is synthesized by coupling of Dimethyl-piperidin-4-yl-amine and bromoacetonitrile analogously to the preparation of **Intermediate 149.2** as a colorless oil; ES-MS: M+ = 168.1: ^{1}HNMR(DMSO-d_6) 3.65 (s, 2H), 2.80-2.75 (m, 2H), 2.15-2.05 (m, 8H, including a singlet at 2.10), 2.00-1.95 (m, 1H), 1.75-1.65 (m, 2H), 1.40-1.30 (m, 2H).

Intermediate 200.1: 2-[4-(1-Ethyl-propyl)-piperazin-1-yl]-ethylamine

The title compound is synthesized by reduction of **Intermediate 200.2** analogously to the

preparation of **Intermediate 149.1** as a colorless oil; ES-MS: M+ = 200.3: ^{1}HNMR(DMSO-d_6) 3.30 (bs, 2H), 2.55 (t, 2H), 2.40-2.25 (m, 8H), 2.20 (t, 2H), 2.10-2.00 (m, 1H), 1.45-1.35 (m, 2H), 1.25-1.05 (m, 2H), 0.90 (t, 6H).

Intermediate 200.2: 4-(1-Ethyl-propyl)-piperazin-1-yl]-acetonitrile

The title compound is synthesized by coupling of 1-(1-Ethyl-propyl)-piperazine (commercially available from CHESS GmbH) and bromoacetonitrile analogously to the preparation of **Intermediate 149.2** as a colorless oil; ES-MS: M+ = 196.2: ^{1}HNMR(DMSO-d_6) 3.65 (s, 2H), 2.50-2.35 (m, 8H), 2.15-2.05 (m, 1H), 1.45-1.35 (m, 2H), 1.25-1.05 (m, 2H), 0.90 (t, 6H).

Intermediate 202.1: [1-(2-Amino-ethyl)-piperidin-4-yl]-diethyl-amine

The title compound is synthesized by reduction of **Intermediate 202.2** analogously to the preparation of **Intermediate 149.1** as a colorless oil; ES-MS: M+ = 200.3: ^{1}HNMR(DMSO-d_6) 3.30 (bs, 2H), 2.85-2.75 (m, 2H), 2.55 (t, 2H), 2.45-2.30 (m, 5H), 2.20 (t, 2H), 1.90-1.80 (m, 2H), 1.60-1.55 (m, 2H), 1.40-1.30 (m, 2H), 0.95 (t, 6H).

Intermediate 202.2: (4-Diethylamino-piperidin-1-yl)-acetonitrile

The title compound is synthesized by coupling of Diethyl-piperidin-4-yl-amine (commercially available from CHESS GmbH) and bromoacetonitrile analogously to the preparation of **Intermediate 149.2** as a colorless oil; ES-MS: M+ = 196.2: ^{1}HNMR(DMSO-d_6) 3.65 (s, 2H), 2.80-2.75 (m, 2H), 2.45-2.30 (m, 5H), 2.15-2.05 (m, 2H), 1.70-1.60 (m, 2H), 1.45-1.35 (m, 2H), 0.95 (t, 6H).

Intermediate 203.1: 2-(4-Isobutyl-piperazin-1-yl)-ethylamine

The title compound is synthesized by reduction of **Intermediate 203.2** analogously to the preparation of **Intermediate 149.1** as a colorless oil; ES-MS: M+ = 186.2: : ^{1}HNMR(DMSO-d_6) 3.30 (bs, 2H), 2.50 (t, 2H), 2.40-2.20 (m, 10H), 1.95 (d, 2H), 1.75-1.65 (m, 1H), 0.95 (d, 6H).

Intermediate 203.2: (4-Isobutyl-piperazin-1-yl)-acetonitrile

The title compound is synthesized by coupling of 1-Isobutyl-piperazine amine (commercially

available from CHESS GmbH) and bromoacetonitrile analogously to the preparation of **Intermediate 149.2** as a colorless oil; ES-MS: M+ = 182.2: ^{1}HNMR(DMSO-d_6) 3.65 (s, 2H), 2.45-2.20 (m, 8H), 2.00 (d, 2H), 1.80-1.70 (m, 1H), 0.90 (d, 6H).

Intermediate 204.1: 2-(4-Adamantan-1-yl-piperazin-1-yl)-ethylamine

The title compound is synthesized by reduction of **Intermediate 204.2** analogously to the preparation of **Intermediate 149.1** as a colorless oil; ES-MS: M+ = 264.4: ^{1}HNMR(DMSO-d_6) 3.30 (bs, 2H), 2.60-2.50 (m, 6H), 2.40-2.20 (m, 6H), 2.00 (bs, 3H), 1.60-1.50 (m, 12H).

Intermediate 204.2: (4-Adamantan-1-yl-piperazin-1-yl)-acetonitrile

The title compound is synthesized by coupling of 1-Adamantyl-piperazine (commercially available from CHESS GmbH) and bromoacetonitrile analogously to the preparation of **Intermediate 149.2** as a colorless oil; ES-MS: M+ = 260.3: ^{1}HNMR(DMSO-d_6) 3.65 (s, 2H), 2.60-2.50 (m, 4H), 2.45-2.40 (m, 4H), 2.00 (bs, 3H), 1.60-1.50 (m, 12H).

Intermediate 205.1: [1-(2-Amino-ethyl)-piperidin-4-yl]-dipropyl-amine

The title compound is synthesized by reduction of **Intermediate 205.2** analogously to the preparation of **Intermediate 149.1** as a colorless oil; ES-MS: M+ = 228.3: ^{1}HNMR(DMSO-d_6) 3.30 (bs, 2H), 2.85-2.80 (m, 2H), 2.60 (t, 2H), 2.40-2.25 (m, 5H), 2.20 (t, 2H), 1.85-1.80 (m, 2H), 1.60-1.50 (m, 2H), 1.40-1.25 (m, 6H), 0.90 (t, 6H).

Intermediate 205.2: (4-Dipropylamino-piperidin-1-yl)-acetonitrile

The title compound is synthesized by coupling of Dipropyl-piperidin-4-yl-amine (commercially available from CHESS GmbH) and bromoacetonitrile analogously to the preparation of **Intermediate 149.2** as a colorless oil; ES-MS: M+ = 224.3: ^{1}HNMR(DMSO-d_6) 3.65 (s, 2H), 2.80-2.75 (m, 2H), 2.40-2.30 (m, 5H), 2.15-2.05 (m, 2H), 1.65-1.60 (m, 2H), 1.50-1.30 (m, 6H), 0.90 (t, 6H).

Intermediate 207.1: 2-(4-tert-Butyl-piperazin-1-yl)-ethylamine

The title compound is synthesized by reduction of **Intermediate 207.2** analogously to the preparation of **Intermediate 149.1** as a colorless oil; ES-MS: M+ = 186.2; ^{1}HNMR(DMSO-d_6)

2.60 (t, 2H), 2.50-2.20 (m, 10H), 1.40 (bs, 2H), 0.95 (s, 9H).

Intermediate 207.2: (4-^{t}Butyl-piperazin-1-yl)-acetonitrile

The title compound is synthesized by coupling of 1-^{t}Butyl-piperazine (commercially available from Wako Pure Chemical Industries, Ltd) and bromoacetonitrile analogously to the preparation of **Intermediate 149.2** as a colorless oil; ES-MS: M+ = 182.2: ^{1}HNMR(DMSO-d_6) 3.65 (s, 2H), 2.50-2.40 (m, 8H), 1.00 (s, 9H).

Intermediate 208.1: 2-(4-Pyrimidin-2-yl-piperazin-1-yl)-ethylamine

The title compound is synthesized by reduction of **Intermediate 208.2** analogously to the preparation of **Intermediate 149.1** as a colorless oil; ES-MS: M+ = 208.2.

Intermediate 208.2: (4-Pyrimidin-2-yl-piperazin-1-yl)-acetonitrile

The title compound is synthesized by coupling of 2-Piperazin-1-yl-pyrimidine and bromoacetonitrile analogously to the preparation of **Intermediate 149.2** as a white solid; ES-MS: M+ = 204.2: ^{1}HNMR(DMSO-d_6) 8.35 (d, 2H), 6.60 (t, 1H), 3.80-3.70 (m, 6H), 2.45-2.40 (m, 4H).

Intermediate 209.1: 6-Chloro-3-[3-(4-chloro-2-fluoro-benzyl)-5-phenyl-3H-imidazol-4-yl]-1H-indole-2-carboxylic acid (at the same time a compound of the formula I according to the invention)

The title compound is synthesized by hydrolysis of **Intermediate 209.2** analogously to the preparation of **Intermediate 2.1** as a colorless solid; ES-MS: M+ = 480.0: $_At_{Ret}$ = 4.23.

Intermediate 209.2: 6-Chloro-3-[3-(4-chloro-2-fluoro-benzyl)-5-phenyl-3H-imidazol-4-yl]-1H-indole-2-carboxylic acid ethyl ester (which is also a compound of the formula I according to the invention)

The title compound is synthesized by condensation of **Intermediate 2.3**, 4-chloro-2-fluoro-benzylamine and 1-(isocyano-phenyl-methanesulfonyl)-4-methyl-benzene analogously to the preparation of **Intermediate 2.2** as a colorless solid; ES-MS: M+ = 508.0: $_At_{Ret}$ = 4.63.

Intermediate 219.1: 6-Chloro-3-[3-(4-chloro-benzyl)-5-(4-fluoro-phenyl)-3H-imidazol-4-yl]-1H-indole-2-carboxylic acid (which is also a compound of the formula I according to the invention)

The title compound is synthesized by hydrolysis of **Intermediate 219.2** analogously to the preparation of **Intermediate 2.1** as a colorless solid; ES-MS: M+H = 480.0: HPLC $_{ct}t_{Ret}$ = 6.24.

Intermediate 219.2: 6-Chloro-3-[3-(4-chloro-benzyl)-5-(4-fluoro-phenyl)-3H-imidazol-4-yl]-1H-indole-2-carboxylic acid ethyl ester (which is also a compound of the formula I according to the invention)

The title compound is synthesized by condensation of **Intermediate 2.3**, 4-chloro-benzylamine and 1-(isocyano-4-fluoro-phenyl-methanesulfonyl)-4-methyl-benzene (commercially available from SynChem, Inc) analogously to the preparation of **Intermediate 2.2** as a colorless solid; ES-MS: M+H = 508.0: HPLC $_{ct}t_{Ret}$ = 6.59.

Example 220 is synthesized by deprotection of **Intermediate 220.1** analogously to the preparation of **Example 44** as a colorless solid; ES-MS: M+H = 587.0; HPLC: $_{ct}t_{Ret}$ = 5.36 min.

Intermediate 220.1: 4-{2-[(6-Chloro-3-{3-[(S)-1-(4-chloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carbonyl)-amino]-ethyl}-piperazine-1-carboxylic acid tert-butyl ester (which is also a compound of the formula I according to the invention)

The title compound is synthesized by condensation of **Intermediate 134.1** and 4-(2-amino-ethyl)-piperazine-1-carboxylic acid tert-butyl ester analogously to the preparation of **Example 2** as a colorless solid; ES-MS: M+H = 687.0; HPLC: $_{ct}t_{Ret}$ = 6.12 min.

Intermediate 221.1: 6-Chloro-3-[3-(4-chloro-benzyl)-5-(2-fluoro-phenyl)-3H-imidazol-4-yl]-1H-indole-2-carboxylic acid (which is also a compound of the formula I according to the invention)

The title compound is synthesized by hydrolysis of **Intermediate 221.2** analogously to the preparation of **Intermediate 2.1** as a colorless solid; ES-MS: M+H = 480.0: $_{c}t_{Ret}$ = 6.12.

Intermediate 221.2: 6-Chloro-3-[3-(4-chloro-benzyl)-5-(2-fluoro-phenyl)-3H-imidazol-4-yl]-1H-indole-2-carboxylic acid ethyl ester (which is also a compound of the formula I according to the invention)

The title compound is synthesized by condensation of **Intermediate 2.3**, 4-chloro-benzylamine and 1-(isocyano-2-fluoro-phenyl-methanesulfonyl)-4-methyl-benzene (commercially available from SpeedChemical Corp. Ltd) analogously to the preparation of **Intermediate 2.2** as a colorless solid; ES-MS: M+H = 508.0: $_{c}t_{Ret}$ = 6.50.

Intermediate 224.1: 2-(4-Benzyl-piperidin-1-yl)-ethylamine

The title compound is synthesized by reduction of **Intermediate 224.2** analogously to the preparation of **Intermediate 149.1** as a colorless oil; ES-MS: M+H = 219.3: $_{A}t_{Ret}$ = 2.04.

Intermediate 224.2: (4-Benzyl-piperidin-1-yl)-acetonitrile

The title compound is synthesized by coupling of 4-Benzyl-piperidine and bromoacetonitrile analogously to the preparation of **Intermediate 149.2** as a colorless oil; ES-MS: M+ = 215.2: $_{A}t_{Ret}$ = 2.90.

Intermediate 225.1: 2-(4-Pyridin-2-ylmethyl-piperidin-1-yl)-ethylamine

The title compound is synthesized by reduction of **Intermediate 225.2** analogously to the preparation of **Intermediate 149.1** as a colorless oil; ES-MS: M+ = 220.3.

Intermediate 225.2: (4-Pyridin-2-ylmethyl-piperidin-1-yl)-acetonitrile

The title compound is synthesized by coupling of 2-Piperidin-4-ylmethyl-pyridine (commercially available from Array Biopharma) and bromoacetonitrile analogously to the preparation of **Intermediate 149.2** as a colorless oil; ES-MS: M+ = 216.2.

Intermediate 226.1: 6-Chloro-3-[3-(3,3-dimethyl-butyl)-5-phenyl-3H-imidazol-4-yl]-1H-indole-2-carboxylic acid (which is also a compound of the formula I according to the invention)

The title compound is synthesized by hydrolysis of **Intermediate 137.1** analogously to the preparation of **Intermediate 2.1** as a colorless solid; ES-MS: M+ = 422.0: $_At_{Rel}$ = 4.30.

Intermediate 227.1: 2-(4-^{t}Butyl-piperidin-1-yl)-ethylamine

The title compound is synthesized by reduction of **Intermediate 227.2** analogously to the preparation of **Intermediate 149.1** as a colorless oil; ES-MS: M+H = 185.3; ^{1}HNMR(DMSO-d_6) 3.40 (bs, 2H), 2.90-2.80 (m, 2H), 2.55 (t, 2H), 2.20 (t, 2H), 1.80-1.70 (m, 2H), 1.60-1.50 (m, 2H), 1.25-1.05 (m, 2H), 1.00-0.90 (m, 1H), 0.80 (s, 9H).

Intermediate 227.2: (4-^{t}Butyl-piperidin-1-yl)-acetonitrile

The title compound is synthesized by coupling of 4-^{t}Butyl-piperidine (commercially available from Matrix Scientific) and bromoacetonitrile analogously to the preparation of **Intermediate 149.2** as a colorless oil; ES-MS: M+ = 181.2; ^{1}HNMR(DMSO-d_6) 3.65 (s, 2H), 2.80-2.75 (m, 2H), 2.05-2.00 (m, 2H), 1.65-1.60 (m, 2H), 1.25-1.05 (m, 2H), 1.00-0.90 (m, 1H), 0.80 (s, 9H).

Intermediate 228.1: 2-[4-(3-Methoxy-propyl)-piperidin-1-yl]-ethylamine

The title compound is synthesized by reduction of **Intermediate 228.2** analogously to the preparation of **Intermediate 149.1** as a colorless oil; ES-MS: M+H = 201.3.

Intermediate 228.2: [4-(3-Methoxy-propyl)-piperidin-1-yl]-acetonitrile

The title compound is synthesized by coupling of 4-(3-Methoxy-propyl)-piperidine (commercially available from ChemBridge Corporation) and bromoacetonitrile analogously to the preparation of **Intermediate 149.2** as a colorless oil; ES-MS: M+ = 197.2; ^{1}HNMR(DMSO-d_6) 3.65 (s, 2H), 3.30 (t, 2H), 3.00 (s, 3H), 2.75-2.70 (m, 2H), 2.10-2.00 (m, 2H), 1.65-1.40 (m, 4H), 1.20-1.00 (m, 5H).

Intermediate 229.1: 2-[4-(2-Pyrrolidin-1-yl-ethyl)-piperidin-1-yl]-ethylamine

The title compound is synthesized by reduction of **Intermediate 229.2** analogously to the preparation of **Intermediate 149.1** as a colorless oil; ES-MS: M+ = 226.3; ^{1}HNMR(DMSO-d_6) 2.75 (d, 2H), 2.55 (t, 2H), 2.40-2.30 (m, 6H), 2.20 (t, 2H), 1.80-1.75 (m, 2H), 1.65-1.50 (m, 6H), 1.30-1.00 (m, 7H).

Intermediate 229.2: 4-(2-Pyrrolidin-1-yl-ethyl)-piperidin-1-yl]-acetonitrile
The title compound is synthesized by coupling of 4-(2-Pyrrolidin-1-yl-ethyl)-piperidine (commercially available from ABCR GmbH) and bromoacetonitrile analogously to the preparation of **Intermediate 149.2** as a colorless oil; ES-MS: M+ = 222.3; ^{1}HNMR($CDCl_3$) 3.45 (s, 2H), 2.70 (d, 2H), 2.45-2.20 (m, 8H), 1.80-1.60 (m, 6H), 1.40-1.20 (m, 5H).

Example 233: ((S)-3-Benzylamino-pyrrolidin-1-yl)-{6-chlorobenzyl)-5-phenyl-3H imidazol-4-yl]-1H-indol-2yl}metanone

Sodium cyano borohydride (9 mg, 0.12 mmol) is added to a solution of **Example 80** (50 mg, 0.09 mmol) in 1,2-dichloroethan (2 mL) at RT. After 1 h of stirring the reaction mixture is quenched by addition of DCM and saturated $NaHCO_3$ solution. The organic layer is separated and washed with H_2O and brine, dried and concentrated. Silica gel flash chromatography of the crude product affords the title compound as a white solid. ES-MS: M-H = 618.0; HPLC: $_Et_{Ret}$ = 4.16 min.

Example 234, 235, 236, 237, 238, 239, 240 and **241** are also prepared in analogy to **Example 233**.

Intermediate 243.1: 2-(4-Phenoxy-piperidin-1-yl)-ethylamine

The title compound is synthesized by reduction of **Intermediate 243.2** analogously to the preparation of **Intermediate 149.1** as a colorless oil; ES-MS: M+H = 221.2: $_ct_{Ret}$ = 3.95.

Intermediate 243.2: (4-Phenoxy-piperidin-1-yl)-acetonitrile

The title compound is synthesized by coupling of 4-Phenoxy-piperidine (commercially available from Alfa Aesar) and bromoacetonitrile analogously to the preparation of **Intermediate 149.2** as a colorless oil; ES-MS: M+H = 217.2: $_{ct}t_{Ret}$ = 4.80.

Intermediate 244.1: 2-(3,4,5,6-Tetrahydro-2H-[4,4']bipyridinyl-1-yl)-ethylamine

The title compound is synthesized by reduction of **Intermediate 244.2** analogously to the preparation of **Intermediate 149.1** as a colorless oil; ES-MS: M+H = 206.2: $_{ct}t_{Ret}$ = 1.60.

Intermediate 244.2: (3,4,5,6-Tetrahydro-2H-[4,4']bipyridinyl-1-yl)-acetonitrile

The title compound is synthesized by coupling of 1,2,3,4,5,6-Hexahydro-[4,4']bipyridinyl (commercially available from CHESS GmbH) and bromoacetonitrile analogously to the preparation of **Intermediate 149.2** as a colorless oil; ES-MS: M+H = 202.2: $_{ct}t_{Ret}$ = 2.41.

Example 245 is synthesized by deprotection of **Intermediate 245.1** analogously to the preparation of **Example 44** as a colorless solid; ES-MS: M+H = 572.0; HPLC: $_{ct}t_{Ret}$ = 5.58 min.

Intermediate 245.1: 4-[2-({6-Chloro-3-[3-(4-chloro-benzyl)-5-phenyl-3H-imidazol-4-yl]-1H-indole-2-carbonyl}-amino)-ethyl]-piperidine-1-carboxylic acid tert-butyl ester (which is also a compound of the formula I according to the invention)

The title compound is synthesized by condensation of **Intermediate 2.1** and 4-(2-Amino-ethyl)-piperidine-1-carboxylic acid tert-butyl ester analogously to the preparation of **Example 2** as a colorless solid; ES-MS: M+H = 672.0; HPLC: $_{ct}t_{Ret}$ = 6.93 min.

Intermediate 246.1: 2-[4-(2-Methoxy-ethoxy)-piperidin-1-yl]-ethylamine

The title compound is synthesized by reduction of **Intermediate 246.2** analogously to the preparation of **Intermediate 149.1** as a colorless oil; ES-MS: M+ = 203.2; ^{1}HNMR(DMSO-d_6) 3.45 (dd, 2H), 3.40 (dd, 2H), 3.25-3.20 (m, 4H), 2.70-2.50 (m, 4H), 2.20 (t, 2H), 2.05-1.70 (m, 4H), 1.40-1.20 (m, 4H).

Intermediate 246.2: 2-[4-(2-Methoxy-ethoxy)-piperidin-1-yl]-acetonitrile

The title compound is synthesized by coupling of 4-(2-Methoxy-ethoxy)-piperidine (commercially available from ChemBridge Corporation) and bromoacetonitrile analogously to the preparation of **Intermediate 149.2** as a colorless oil; ES-MS: M+ = 199.2; ^{1}HNMR(DMSO-d_6) 3.65 (s, 2H), 3.50 (dd, 2H), 3.40 (dd, 2H), 3.30-3.25 (m, 1H), 3.20 (s, 3H), 2.70-2.60 (m, 2H), 2.25-2.20 (m, 2H), 1.85-1.80 (m, 2H), 1.50-1.40 (m, 2H).

Intermediate 247.1: 2-[4-(2-Pyridin-2-yl-ethyl)-piperazin-1-yl]-ethylamine

The title compound is synthesized by reduction of **Intermediate 247.2** analogously to the preparation of **Intermediate 149.1** as a colorless oil; ES-MS: M+H = 235.2: $_Ct_{Ret}$ = 1.81.

Intermediate 247.2: [4-(2-Pyridin-2-yl-ethyl)-piperazin-1-yl]-acetonitrile

The title compound is synthesized by coupling of 1-(2-Pyridin-2-yl-ethyl)-piperazine (commercially available from ABCR GmbH) and bromoacetonitrile analogously to the preparation of **Intermediate 149.2** as a colorless oil; ES-MS: M+H = 231.2: $_Ct_{Ret}$ = 2.17.

Intermediate 248.1: 2-(4-Benzyl-2-methyl-piperazin-1-yl)-ethylamine

The title compound is synthesized by reduction of **Intermediate 248.2** analogously to the preparation of **Intermediate 149.1** as a colorless oil; ES-MS: M+ = 234.3; ; ^{1}HNMR(DMSO-d_6) 7.35-7.20 (m, 5H), 3.40 (dd, 2H), 2.70-2.50 (m, 6H), 2.40-2.00 (m, 4H), 1.80 (t, 1H), 1.20 (bs, 2H), 0.90 (d, 3H).

Intermediate 248.2: (4-Benzyl-2-methyl-piperazin-1-yl)-acetonitrile

The title compound is synthesized by coupling of 4-Benzyl-2-methyl-piperazine (commercially available from CHESS GmbH) and bromoacetonitrile analogously to the preparation of **Intermediate 149.2** as a colorless oil; ES-MS: M+ = 230.2: $_At_{Ret}$ = 1.86.

Intermediate 251.1:

The title compound is synthesized by reduction of **Intermediate 251.2** analogously to the preparation of **Intermediate 149.1** as a colorless oil; ES-MS: M+ = 231.3: $_At_{Ret}$ = 2.27.

Intermediate 251.2:

The title compound is synthesized by coupling of 2,3-Dihydrospiro[indene-1,4'-piperidine] (commercially available from Parkway Scientific) and bromoacetonitrile analogously to the preparation of **Intermediate 149.2** as a colorless oil; ES-MS: M+ = 227.2: $_{A}t_{Ret}$ = 3.10.

Intermediate 252.1: 1-(2-Amino-ethyl)-4-benzyl-piperidin-4-ol

The title compound is synthesized by reduction of **Intermediate 252.2** analogously to the preparation of **Intermediate 149.1** as a colorless oil; ES-MS: M+ = 235.2: $_{A}t_{Ret}$ = 1.27.

Intermediate 251.2: (4-Benzyl-4-hydroxy-piperidin-1-yl)-acetonitrile

The title compound is synthesized by coupling of 4-Benzyl-4-hydroxy-piperidine (commercially available from ABCR GmbH) and bromoacetonitrile analogously to the preparation of **Intermediate 149.2** as a colorless oil; ES-MS: M+ = 231.2: $_{A}t_{Ret}$ = 1.81.

Intermediate 253.1: 1-(2-Amino-ethyl)-4-phenyl-piperidin-4-ol

The title compound is synthesized by reduction of **Intermediate 253.2** analogously to the preparation of **Intermediate 149.1** as a colorless oil; ES-MS: M+ = 221.2; ^{1}HNMR(DMSO-d_6) 7.50-7.40 (m, 2H), 7.30-7.10 (m, 3H), 3.30 (s, 2H), 2.70-2.60 (m, 4H), 2.40-2.20 (m, 4H), 1.95-1.70 (m, 3H), 1.60-1.50 (m, 2H).

Intermediate 253.2: (4-Hydroxy-4-phenyl-piperidin-1-yl)-acetonitrile

The title compound is synthesized by coupling of 4-Hydroxy-4-phenyl-piperidine and bromoacetonitrile analogously to the preparation of **Intermediate 149.2** as a colorless oil; ES-MS: M+ = 217.2: $_{A}t_{Ret}$ = 1.51.

Intermediate 254.1: 2-(4-Benzyl-4,7-diaza-spiro[2.5]oct-7-yl)-ethylamine

The title compound is synthesized by reduction of **Intermediate 254.2** analogously to the preparation of **Intermediate 149.1** as a colorless oil; ES-MS: M+H = 246.3: $_{C}t_{Ret}$ = 3.81.

Intermediate 254.2: (4-Benzyl-4,7-diaza-spiro[2.5]oct-7-yl)-acetonitrile

The title compound is synthesized by coupling of 4-Benzyl-4,7-diaza-spiro[2.5]octane (which prepared in analogy to a published literature procedure (WO030828859)) and bromoacetonitrile analogously to the preparation of **Intermediate 149.2** as a colorless oil; ES-MS: M+H = 242.2: $_{c}t_{Ret}$ = 3.84.

Intermediate 255.1: 3-[Isocyano-(toluene-4-sulfonyl)-methyl]-pyridine

The title compound is synthesized by condensation of Pyridine-3-carbaldehyde analogously to the preparation of **Intermediate 16.1** as a colorless solid; ES-MS: M+H = 273.1: $_{c}t_{Ret}$ = 5.45.

Intermediate 256.1: 2-((2S,5R)-2,5-Dimethyl-4-pyridin-3-ylmethyl-piperazin-1-yl)-ethylamine

The title compound is synthesized by reduction of **Intermediate 256.2** analogously to the preparation of **Intermediate 149.1** as a colorless oil; ES-MS: M+H = 249.2; ^{1}HNMR(DMSO-d_6) 8.50 (s, 1H), 8.40 (d, 1H), 7.65 (d, 1H), 7.35 (dd, 1H), 4.00 (d, 1H), 3.05 (d, 1H), 2.80-1.70 (m, 12H), 1.05 (d, 3H), 0.90 (d, 3H).

Intermediate 256.2: ((2S,5R)-2,5-Dimethyl-4-pyridin-3-ylmethyl-piperazin-1-yl)-acetonitrile

The title compound is synthesized by coupling of **Intermediate 256.3** and bromoacetonitrile analogously to the preparation of **Intermediate 149.2** as a colorless oil; ES-MS: M+H = 245.2: $_{c}t_{Ret}$ = 2.88.

Intermediate 256.3: (2R,5S)-2,5-Dimethyl-1-pyridin-3-ylmethyl-piperazine

The title compound is synthesized by deprotection of **Intermediate 256.4** analogously to the preparation of **Example 44** as a colorless solid; ES-MS: M+H = 206.2; HPLC: $_{c}t_{Ret}$ = 2.56 min.

Intermediate 256.4: (2S,5R)-2,5-Dimethyl-4-pyridin-3-yl methyl-piperazine-1-carboxylic acid tert-butyl ester

The title compound is synthesized by alkylation of **Intermediate 256.5** with 3-Picolyl chloride hydrochloride analogously to the preparation of **Intermediate 149.2** as a colorless solid; ES-MS: M+H = 306.3; HPLC: ct_{Ret} = 5.14 min.

Intermediate 256.5: (2S,5R)-2,5-Dimethyl-piperazine-1-carboxylic acid tert-butyl ester

A mixture of trans-2,5-Dimethyl-piperazine (1.0 g, 8.76 mmol) (commercially available from ABCR GmbH), $(Boc)_2O$ (1.91 g, 8.76 mmol) and Et_3N (2.44 mL, 17.5 mmol) in DCM (50 mL) is stirred for 16 h at RT. After completion, the reaction mixture is quenched by H_2O, DCM is added and the organic layer is washed with brine, dried over $MgSO_4$ and evaporated *in vacuo*. Silica gel flash chromatography of the residue affords the title compound as a colorless oil; ES-MS: M+H = 215.2: ^{1}HNMR(DMSO-d_6) 3.95-3.90 (m, 1H), 3.35 (dd, 1H), 3.20 (bs, 1H), 3.05 (dd, 1H), 3.00-2.90 (m, 2H), 2.30 (dd, 1H), 1.40 (s, 9H), 1.05 (d, 3H), 1.00 (d, 3H).

Intermediate 257.1: 2-(4-Indan-1-yl-piperazin-1-yl)-ethylamine

The title compound is synthesized by reduction of **Intermediate 257.2** analogously to the preparation of **Intermediate 149.1** as a colorless oil; ES-MS: M+H = 246.3: ct_{Ret} = 3.69.

Intermediate 257.2: (4-Indan-1-yl-piperazin-1-yl)-acetonitrile

The title compound is synthesized by coupling of 1-Indan-1-yl-piperazine (commercially available from CHESS GmbH) and bromoacetonitrile analogously to the preparation of **Intermediate 149.2** as a colorless oil; ES-MS: M+H = 242.2: ct_{Ret} = 4.25.

Intermediate 259.1: 2-[4-(2-Phenoxy-ethyl)-piperazin-1-yl]-ethylamine

The title compound is synthesized by reduction of **Intermediate 259.2** analogously to the preparation of **Intermediate 149.1** as a colorless oil; ES-MS: M+H = 250.2: ct_{Ret} = 3.78.

Intermediate 259.2: 2-[4-(2-Phenoxy-ethyl)-piperazin-1-yl]-acetonitrile

The title compound is synthesized by coupling of 1-(2-Phenoxy-ethyl)-piperazine (commercially available from CHESS GmbH) and bromoacetonitrile analogously to the preparation of **Intermediate 149.2** as a colorless oil; ES-MS: M+H = 246.2: $_{ct}t_{Ret}$ = 4.31.

Intermediate 260.1: 2-Benzoimidazol-1-yl-ethylamine

The title compound is synthesized by reduction of **Intermediate 260.2** analogously to the preparation of **Intermediate 149.1** as a colorless oil; ES-MS: M+H = 162.1: $_{ct}t_{Ret}$ = 3.45.

Intermediate 260.2: Benzoimidazol-1-yl-acetonitrile

The title compound is synthesized by coupling of Benzimidazole and bromoacetonitrile analogously to the preparation of **Intermediate 149.2** as a colorless solid; ES-MS: M+H = 158.0: $_{ct}t_{Ret}$ = 3.42.

Intermediate 261.1: 2-[4-(2-Morpholin-4-yl-ethyl)-piperazin-1-yl]-ethylamine

The title compound is synthesized by reduction of **Intermediate 261.2** analogously to the preparation of **Intermediate 149.1** as a colorless oil; ES-MS: M+H = 243.0; ^{1}HNMR(DMSO-d_6) 7.95 (bs, 2H), 3.80-3.60 (m, 4H), 3.40-2.70 (m, 20H).

Intermediate 261.2: [4-(2-Morpholin-4-yl-ethyl)-piperazin-1-yl]-acetonitrile

The title compound is synthesized by coupling of 4-(2-Piperazin-1-yl-ethyl)-morpholine (commercially available from ABCR GmbH) and bromoacetonitrile analogously to the preparation of **Intermediate 149.2** as a colorless oil; ES-MS: M+H = 239.3; ^{1}HNMR(DMSO-d_6) 3.70 (s, 2H), 3.30 (bs, 4H), 2.60-2.30 (m, 16H).

Intermediate 262.1: 2-[4-(1-Methyl-piperidin-4-ylmethyl)-piperazin-1-yl]-ethylamine

The title compound is synthesized by reduction of **Intermediate 262.2** analogously to the preparation of **Intermediate 149.1** as a colorless oil; ES-MS: M+H = 241.0; ^{1}HNMR(DMSO-d_6) 2.70-2.50 (m, 5H), 2.40-2.20 (m, 10H), 2.10 (s, 3H), 2.15-2.00 (m, 2H), 1.75 (t, 2H), 1.60 (d, 2H), 1.40-1.30 (m, 2H), 10.5 (dq, 2H).

Intermediate 262.2: [4-(1-Methyl-piperidin-4-ylmethyl)-piperazin-1-yl]-acetonitrile

The title compound is synthesized by coupling of 1-(1-Methyl-piperidin-4-ylmethyl)-piperazine (commercially available from CHESS GmbH) and bromoacetonitrile analogously to the preparation of **Intermediate 149.2** as a colorless oil; ES-MS: M+H = 237.3.

Intermediate 263.1: 2-[4-(2-Ethoxy-ethyl)-piperazin-1-yl]-ethylamine

The title compound is synthesized by reduction of **Intermediate 263.2** analogously to the preparation of **Intermediate 149.1** as a colorless oil; ES-MS: M+H = 202.2; ^{1}HNMR(DMSO-d_6) 3.40 (q, 2H), 3.35 (q, 2H), 2.55 (t, 2H), 2.40-2.20 (m, 14H), 1.05 (t, 3H).

Intermediate 263.2: [4-(2-Ethoxy-ethyl)-piperazin-1-yl]-acetonitrile

The title compound is synthesized by coupling of 4-(2-Ethoxy-ethyl)-piperazine (commercially available from ABCR GmbH) and bromoacetonitrile analogously to the preparation of **Intermediate 149.2** as a colorless oil; ES-MS: M+H = 198.2; ^{1}HNMR(DMSO-d_6) 3.70 (s, 2H), 3.45 (q, 2H), 3.40 (q, 2H), 2.40-2.30 (m, 10H), 1.05 (t, 3H).

Intermediate 264.1: 2-(4-Phenethyl-piperazin-1-yl)-ethylamine

The title compound is synthesized by reduction of **Intermediate 264.2** analogously to the preparation of **Intermediate 149.1** as a colorless oil; ES-MS: M+H = 234.3: $_Ct_{Ret}$ = 3.74.

Intermediate 264.2: (4-Phenethyl-piperazin-1-yl)-acetonitrile

The title compound is synthesized by coupling of 4-Phenylethyl-piperazine (commercially available from ABCR GmbH) and bromoacetonitrile analogously to the preparation of **Intermediate 149.2** as a colorless oil; ES-MS: M+H = 230.2: $_Ct_{Ret}$ = 4.20.

Intermediate 269.1: 4-(2-Amino-ethyl)-1-pyridin-3-ylmethyl-piperazin-2-one

The title compound is synthesized by deprotection of **Intermediate 269.2** analogously to the preparation of **Example 44** as a colorless oil; ES-MS: M+H = 235.2: $_Ct_{Ret}$ = 1.76.

Intermediate 269.2: [2-(3-Oxo-4-pyridin-3-ylmethyl-piperazin-1-yl)-ethyl]-carbamic acid tert-butyl ester

A mixture of **Intermediate 269.3** (1.7 g, 6.44 mmol), 2-Boc-aminoethyl-bromide (1.58 g, 7.08 mmol) and K_2CO_3 (5.34 g, 38.6 mmol) in DMF (30 mL) is stirred at RT. After completion, the reaction mixture is quenched by H_2O, EtOAc is added and the organic layer is washed with brine, dried over $MgSO_4$ and evaporated *in vacuo*. Silica gel flash chromatography of the residue affords the title compound as a colorless oil; ES-MS: M+H = 335.3: ${}_ct_{Ret}$ = 3.73.

Intermediate 269.3: 1-Pyridin-3-ylmethyl-piperazin-2-one 2HCl salt

A solution of **Intermediate 269.4** (2.03 g, 6.97 mmol) in Dioxane (25 mL) is treated by 4M Dioxane solution of HCl (25 mL) at RT. After completion, the reaction mixture is concentrated *in vacuo* to provide crude product, which is submitted to the next step without further purification; ES-MS: M+H = 192.1: ${}_ct_{Ret}$ = 1.40.

Intermediate 269.4: 3-Oxo-4-pyridin-3-ylmethyl-piperazine-1-carboxylic acid tert-butyl ester

A mixture of 3-Oxo-piperazine-1-carboxylic acid tert-butyl ester (2.0 g, 9.99 mmol) and 3-Picolyl chloride hydrochloride (1.63 g, 9.99 mmol) in DMF (20 mL) is treated by 60% NaH in mineral oil (0.80 g, 19.98 mmol) at 0 °C. After completion, the reaction mixture is quenched by H_2O, EtOAc is added and the organic layer is washed with brine, dried over $MgSO_4$ and evaporated *in vacuo*. Silica gel flash chromatography of the residue affords the title compound as a colorless oil; ES-MS: M+H = 292.2 t_{et} = 4.15.

Intermediate 270.1: 2-[4-(2-Amino-ethyl)-piperazin-1-yl]-N-pyridin-2-yl-acetamide

The title compound is synthesized by deprotection of **Intermediate 270.2** analogously to the preparation of **Example 44** as a colorless oil; ES-MS: M+H = 264.2: ${}_ct_{Ret}$ = 2.70.

Intermediate 270.2: {2-[4-(Pyridin-2-ylcarbamoylmethyl)-piperazin-1-yl]-ethyl}-carbamic acid tert-butyl ester

The title compound is synthesized by coupling of 2-Piperazin-1-yl-N-pyridin-2-yl-acetamide trihydrochloride dehydrate (commercially available from ABCR GmbH) and (2-Bromo-ethyl)-

carbamic acid tert-butyl ester analogously to the preparation of **Intermediate 269.2** as a colorless oil; ES-MS: M+H = 364.3: $_{ct}t_{Ret}$ = 4.07.

Intermediate 271.1: 2-[4-(2-Amino-ethyl)-piperazin-1-yl]-N-pyridin-3-yl-acetamide

The title compound is synthesized by deprotection of **Intermediate 271.2** analogously to the preparation of **Example 44** as a colorless oil; ES-MS: M+H = 264.2: $_{ct}t_{Ret}$ = 1.62.

Intermediate 271.2: {2-[4-(Pyridin-3-ylcarbamoylmethyl)-piperazin-1-yl]-ethyl}-carbamic acid tert-butyl ester

The title compound is synthesized by coupling of 2-Piperazin-1-yl-N-pyridin-2-yl-acetamide trihydrochloride (commercially available from CHESS GmbH) and (2-Bromo-ethyl)-carbamic acid tert-butyl ester analogously to the preparation of **Intermediate 269.2** as a colorless oil; ES-MS: M+H = 364.2: $_{ct}t_{Ret}$ = 3.88.

Intermediate 272.1: 2-[4-(2-Amino-ethyl)-piperazin-1-yl]-1-pyrrolidin-1-yl-ethanone

The title compound is synthesized by deprotection of **Intermediate 272.2** analogously to the preparation of **Example 44** as a colorless oil; ES-MS: M+H = 241.3: $_{ct}t_{Ret}$ = 2.88.

Intermediate 272.2: {2-[4-(2-Oxo-2-pyrrolidin-1-yl-ethyl)-piperazin-1-yl]-ethyl}-carbamic acid tert-butyl ester

The title compound is synthesized by coupling of 2-Piperazin-1-yl-1-pyrrolidin-1-yl-ethanone (commercially available from CHESS GmbH) and (2-Bromo-ethyl)-carbamic acid tert-butyl ester analogously to the preparation of **Intermediate 269.2** as a colorless oil; ES-MS: M+H = 341.3: $_{ct}t_{Ret}$ = 4.08.

Intermediate 273.1: 2-(2-Phenyl-imidazol-1-yl)-ethylamine

The title compound is synthesized by reduction of **Intermediate 273.2** analogously to the preparation of **Intermediate 149.1** as a colorless oil; ES-MS: M+H = 188.1: $_{ct}t_{Ret}$ = 2.37.

Intermediate 273.2: (2-Phenyl-imidazol-1-yl)-acetonitrile

The title compound is synthesized by coupling of 2-Phenyl-1H-imidazole and bromoacetonitrile analogously to the preparation of **Intermediate 269.4** as a colorless oil; ES-MS: M+H = 184.1: $_{C}t_{Ret}$ = 3.48.

Example 278 is synthesized by deprotection of **Intermediate 278.1** analogously to the preparation of **Example 44** as a colorless solid.

Intermediate 278.1: 4-(1-{6-Chloro-3-[3-(4-chloro-benzyl)-5-phenyl-3H-imidazol-4-yl]-1H-indole-2-carbonyl}-azetidin-3-yl)-piperazine-1-carboxylic acid tert-butyl ester (which is also a compound of the formula I according to the invention)

The title compound is synthesized by condensation of **Intermediate 2.1** and **Intermediate 278.2** analogously to the preparation of **Example 2** as a colorless solid; ES-MS: M+ = 685.0; HPLC: $_{A}t_{Ret}$ = 4.21 min.

Intermediate 278.2: 4-Azetidin-3-yl-piperazine-1-carboxylic acid tert-butyl ester

A mixture of **Intermediate 278.3** (1.0 g, 2.45 mmol) and 5% Pd/C (200 mg) in MeOH is shaken under a H_2-atmosphere (1 bar). After 22h, the reaction mixture is filtered through Celite and carefully washed with THF. Concentration *in vacuo* to provide crude product, which is submitted to the next step without further purification; ES-MS: M+ = 242.3.

Intermediate 278.3: 4-(1-Benzhydryl-azetidin-3-yl)-piperazine-1-carboxylic acid tert-butyl ester

The title compound is synthesized by condensation of Piperazine-1-carboxylic acid tert-butyl ester and Methanesulfonic acid 1-benzhydryl-azetidin-3-yl ester (commercially available from Fluorochem Ltd) analogously to the preparation of **Intermediate 149.2** as a white solid; ES-MS: M+ = 408.3; HPLC: $_{A}t_{Ret}$ = 3.84 min.

Intermediate 280.1: 1-(2-Amino-ethyl)-4-pyridin-3-ylmethyl-piperazin-2-one

The title compound is synthesized by deprotection of **Intermediate 280.2** analogously to the preparation of **Example 44** as a colorless oil; ES-MS: M+H = 235.1: $_{C}t_{Ret}$ = 1.86.

Intermediate 280.2: [2-(2-Oxo-4-pyridin-3-ylmethyl-piperazin-1-yl)-ethyl]-carbamic acid tert-butyl ester

The title compound is synthesized by coupling of **Intermediate 280.3** and (2-Bromo-ethyl)-carbamic acid tert-butyl ester analogously to the preparation of **Intermediate 269.2** as a colorless oil; ES-MS: M+H = 335.2: $_{ct}t_{Ret}$ = 4.06.

Intermediate 280.3: 4-Pyridin-3-ylmethyl-piperazin-2-one

The title compound is synthesized by coupling of Piperazin-2-one and Picolyl chloride hydrochloride analogously to the preparation of **Intermediate 269.2** as a white solid; ES-MS: M+H = 192.1: $_{ct}t_{Ret}$ = 1.74.

Intermediate 281.1: 6-Chloro-3-[3-(5-chloro-pyridin-2-ylmethyl)-5-phenyl-3H-imidazol-4-yl]-1H-indole-2-carboxylic acid (which is also a compound of the formula I according to the invention)

The title compound is synthesized by hydrolysis of **Intermediate 281.2** analogously to the preparation of **Intermediate 2.1** as a colorless solid; ES-MS: M+H = 462.8: $_{ct}t_{Ret}$ = 5.77.

Intermediate 281.2: 6-Chloro-3-[3-(5-chloro-pyridin-2-ylmethyl)-5-phenyl-3H-imidazol-4-yl]-1H-indole-2-carboxylic acid ethyl ester (which is also a compound of the formula I according to the invention)

The title compound is synthesized by condensation of **Intermediate 2.3**, **Intermediate 281.3** and 1-[isocyano-(toluene-4-sulfonyl)-methyl]-2-fluoro-benzene analogously to the preparation of **Intermediate 2.2** as a colorless solid; ES-MS: M+H = 490.8: $_{ct}t_{Ret}$ = 6.14.

Intermediate 281.3: C-(5-Chloro-pyridin-2-yl)-methylamine

A mixture of 5-Chloro-2-cyanopyridine (1.5 g, 10.8 mmol) and 10% Pd/C (0.4 g) in EtOH (40 mL) and conc HCl (1.2 mL) is shaken under a H_2-atmosphere (1 bar). After 2h, the reaction mixture is filtered through Celite and carefully washed with THF. Concentration *in vacuo* and silica gel flash chromatography of the residue affords the title compound as a white solid; ES-MS: M+H = 143.0: $_{ct}t_{Ret}$ = 3.33.

Intermediate 282.1: 2-Amino-1-(4-pyridin-3-ylmethyl-piperazin-1-yl)-ethanone

The title compound is synthesized by deprotection of **Intermediate 282.2** analogously to the preparation of **Example 44** as a colorless oil; ES-MS: M+H = 235.2: $_{C}t_{Ret}$ = 1.62.

Intermediate 282.2: [2-Oxo-2-(4-pyridin-3-ylmethyl-piperazin-1-yl)-ethyl]-carbamic acid tert-butyl ester

The title compound is synthesized by condensation of 1-Pyridin-3-ylmethyl-piperazine and N-Boc-glycine analogously to the preparation of **Example 2** as a colorless solid; ES-MS: M+H = 335.3; HPLC: $_{A}t_{Ret}$ = 3.93 min.

Intermediate 283.1: [1-(2-Amino-ethyl)-piperidin-4-yl]-pyridin-2-yl-amine

The title compound is synthesized by reduction of **Intermediate 283.2** analogously to the preparation of **Intermediate 149.1** as a colorless oil; ES-MS: M+H = 221.0: $_{A}t_{Ret}$ = 2.29.

Intermediate 283.2: [4-(Pyridin-2-ylamino)-piperidin-1-yl]-acetonitrile

The title compound is synthesized by coupling of **Intermediate 283.3** and bromoacetonitrile analogously to the preparation of **Intermediate 149.2** as a colorless oil; ES-MS: M+H = 217.1: $_{A}t_{Ret}$ = 3.11.

Intermediate 283.3: Piperidin-4-yl-pyridin-2-yl-amine 3HCl

The title compound is synthesized by deprotection of **Intermediate 283.4** analogously to the preparation of **Intermediate 193.1** as a colorless oil; ES-MS: M+H = 178.0: $_{A}t_{Ret}$ = 2.48.

Intermediate 283.4: 4-(Pyridin-2-ylamino)-piperidine-1-carboxylic acid tert-butyl ester

A mixture of 4-Amino-1-Boc-piperidine (2.0 g, 9.7 mmol), 2-Bromo-pyridine (1.93 mL, 19.4 mmol), NaO^{t}Bu (2.7 g, 27.1 mmol), 2-Dicyclohexylphosphino-2'-(N,N-dimethylamino)biphenyl (472 mg, 1.16 mmol) and Tris(dibenzylideneacetone)dipalladium Chloroforme Complex (620 mg, 0.58 mmol) in dioxane (10 mL) is heated to 90 °C. After completion, the reaction mixture is quenched by H_2O, DCM is added and the organic layer is washed with brine, dried over

$MgSO_4$ and evaporated *in vacuo*. Silica gel flash chromatography of the residue affords the title compound as a white powder; ES-MS: M+H = 278.3: $_At_{Ret}$ = 4.75.

Intermediate 284.1: [1-(2-Amino-ethyl)-piperidin-4-yl]-methyl-pyridin-2-yl-amine

The title compound is synthesized by reduction of **Intermediate 284.2** analogously to the preparation of **Intermediate 149.1** as a colorless oil; ES-MS: M+H = 253.3: $_At_{Ret}$ = 2.31.

Intermediate 284.2: [4-(Methyl-pyridin-2-yl-amino)-piperidin-1-yl]-acetonitrile

The title compound is synthesized by coupling of **Intermediate 284.3** and bromoacetonitrile analogously to the preparation of **Intermediate 149.2** as a colorless oil; ES-MS: M+H = 231.3: $_At_{Ret}$ = 3.29.

Intermediate 284.3: Methyl-piperidin-4-yl-pyridin-2-yl-amine

The title compound is synthesized by deprotection of **Intermediate 284.4** analogously to the preparation of **Intermediate 193.1** as a colorless oil; ES-MS: M+H = 192.2: $_At_{Ret}$ = 2.62.

Intermediate 284.4: 4-(Methyl-pyridin-2-yl-amino)-piperidine-1-carboxylic acid tert-butyl ester

A mixture of **Intermediate 283.4** (1.14 g, 4.0 mmol) and MeI (0.37 mL, 6.0 mmol) in DMF (10 mL) is treated with 60% NaH in mineral oil (240 mg, 6.0 mmol) at RT. After completion, the reaction mixture is quenched by H_2O, EtOAc is added and the organic layer is washed with brine, dried over $MgSO_4$ and evaporated *in vacuo*. Silica gel flash chromatography of the residue affords the title compound as a white powder; ES-MS: M+H = 232.3: $_At_{Ret}$ = 4.87.

Intermediate 285.1: 2-[4-(Pyridin-2-yloxy)-piperidin-1-yl]-ethylamine
The title compound is synthesized by reduction of **Intermediate 285.2** analogously to the preparation of **Intermediate 149.1** as a colorless oil; ES-MS: M+H = 222.3: $_Dt_{Ret}$ = 1.46.

Intermediate 285.2: [4-(Pyridin-2-yloxy)-piperidin-1-yl]-acetonitrile

The title compound is synthesized by coupling of **Intermediate 285.3** and bromoacetonitrile analogously to the preparation of **Intermediate 149.2** as a colorless oil; ES-MS: M+H = 218.3: $_{D}t_{Ret}$ = 1.78.

Intermediate 285.3: 2-(Piperidin-4-yloxy)-pyridine

The title compound is synthesized by deprotection of **Intermediate 285.4** analogously to the preparation of **Intermediate 193.1** as a colorless oil; ES-MS: M+ =179.1: $_{D}t_{Ret}$ = 1.47.

Intermediate 285.4: 4-(Pyridin-2-yloxy)-piperidine-1-carboxylic acid tert-butyl ester

A mixture of tert-Butyl-4-hydroxy-1-piperidine-carboxylate (2.0 g, 9.64 mmol) and 2-Fluoro-pyridine (0.93 mL, 10.6 mmol) in DMF (10 mL) is treated with 60% NaH in mineral oil (600 mg, 12.5 mmol) at RT. After completion, the reaction mixture is quenched by H_2O, EtOAc is added and the organic layer is washed with brine, dried over $MgSO_4$ and evaporated *in vacuo*. Silica gel flash chromatography of the residue affords the title compound as a white powder; ES-MS: M+H = 279.0: $_{D}t_{Ret}$ = 2.82.

Example 286 is synthesized by condensation of (S)-3-Amino-3-(4-chloro-phenyl)-propionic acid, **Intermediate 10.1** and 1-(isocyano-phenyl-methanesulfonyl)-4-methyl-benzene analogously to the preparation of **Example 1** as a colorless solid; ES-MS: M+H = 495.7; HPLC: $_{A}t_{Ret}$ = 4.28 min.

Example 287: (S)-3-[5-(6-Chloro-5-fluoro-1H-indol-3-yl)-4-phenyl-imidazol-1-yl]-3-(4-chloro-phenyl)-N-methyl-propionamide

The title compound is synthesized by condensation of **Example 286** and methylamine HCl salt analogy to the preparation of **Example 2** as a white solid.

Example 288, 289 and **290** are also prepared in analogy to **Example 287**.

Example 291: 6-Chloro-3-[3-(4-chloro-benzyl)-5-phenyl-3H-imidazol-4-yl]-1H-indole-2-carboxylic acid {2-[4-(pyridine-3-carbonyl)-piperazin-1-yl]-ethyl}-amide

A solution of **Example 44** (109 mg, 0.19 mmol) in pyridine (1.0 mL) is treated with nicotinyl chloride hydrochloride salt (41 mg, 0.23 mmol) at RT. After completion, the reaction mixture is quenched by H_2O, EtOAc is added and the organic layer is washed with brine, dried over $MgSO_4$ and evaporated *in vacuo*. Silica gel flash chromatography of the residue affords the title compound as a white powder.

Example 294, 295, 296, 298, 299, 305, 309, 310 and **312** are also prepared in analogy to **Example 291**.

Example 292: 6-Chloro-3-[3-(4-chloro-benzyl)-5-phenyl-3H-imidazol-4-yl]-1H-indole-2-carboxylic acid {2-[4-(1-pyridin-2-yl-ethyl)-piperazin-1-yl]-ethyl}-amide

A mixture of **Example 44** (80 mg, 0.14 mmol), K_2CO_3 (39 mg, 0.28 mmol) and **Intermediate 292.1** in toluene (0.5 mL) and CH_3CN (0.5 mL) is heated to at 85 °C. After completion, the reaction mixture is quenched by H_2O, EtOAc is added and the organic layer is washed with brine, dried over $MgSO_4$ and evaporated *in vacuo*. Silica gel flash chromatography of the residue affords the title compound as a white powder.

Example 297, 304 and **311** are also prepared in analogy to **Example 292**.

Intermediate 292.1: Methanesulfonic acid 1-pyridin-2-yl-ethyl ester

A mixture of **Intermediate 292.2** (1.0 g, 8.12 mmol) and Et_3N (2.3 mL, 16.2 mmol) in DCM (10 mL) is treated by methansulfonylchloride (0.66 ml, 8.53 mmol) at 0 °C. After completion, the reaction mixture is quenched by H_2O, DCM is added and the organic layer is washed with brine, dried over $MgSO_4$ and evaporated *in vacuo* to provide crude product, which is submitted to the next step without further purification; ES-MS: M+ = 202.1; $_At_{Ret}$ = 1.37.

Intermediate 292.2: 1-Pyridin-2-yl-ethanol

A solution of 2-Acetyl-pyridine (2.0 g, 16.5 mmol) in MeOH (33 mL) is treated by $NaBH_4$ (624 mg, 16.5 mmol) at 0 °C. After completion, the reaction mixture is quenched by H_2O, EtOAc is added and the organic layer is washed with brine, dried over $MgSO_4$ and evaporated *in vacuo* to provide crude product, which is submitted to the next step without further

purification; ES-MS: M+ = 124.0; ^{1}HNMR(DMSO-d_6) 8.45 (d, 1H), 7.75 (td, 1H), 7.50 (d, 1H), 7.20 (dd, 1H), 5.30 (d, 1H), 4.70-4.60 (m, 1H), 1.30 (d, 3H).

Example 293: 6-Chloro-3-[3-(4-chloro-benzyl)-5-phenyl-3H-imidazol-4-yl]-1H-indole-2-carboxylic acid {2-[4-(6-fluoro-pyridine-3-carbonyl)-piperazin-1-yl]-ethyl}-amide

The title compound is synthesized by condensation of **Example 44** (100 mg, 0.17 mmol) and 6-Fluoro-nicotinic acid (37 mg, 0.26 mmol) analogy to the preparation of **Example 2** as a white solid.

Example 300, 301, 302, 303, 306, 307, 308, 313, 314, 315, 316, 317, 329 and **330** are also prepared in analogy to **Example 293**.

Intermediate 297.1: Methanesulfonic acid 1-pyrazin-2-yl-ethyl ester

The title compound is synthesized by methansulfonylation of **Intermediate 297.2** analogously to the preparation of **Intermediate 292.1** as a colorless oil; ES-MS: M+ = 203.1: $_At_{Ret}$ = 1.77.

Intermediate 297.2: 1-Pyrazin-2-yl-ethanol

The title compound is synthesized by reduction of Acetylpyrazine analogously to the preparation of **Intermediate 292.2** as a colorless oil; ES-MS: M+ = 125.0; ^{1}HNMR(DMSO-d_6) 8.75 (s, 1H), 8.55-8.50 (m, 2H), 5.60 (d, 1H), 4.85-4.75 (m, 1H), 1.40 (d, 3H).

Intermediate 304.1:

The title compound is synthesized by methansulfonylation of **Intermediate 304.2** analogously to the preparation of **Intermediate 292.1** as a colorless oil; ES-MS: M+ = 202.1: $_At_{Ret}$ = 1.10.

Intermediate 304.2:

The title compound is synthesized by reduction of 3-Acetyl-pyridine analogously to the

preparation of **Intermediate 292.2** as a colorless oil; ES-MS: M+ = 124.0; ^{1}HNMR(DMSO-d_6) 8.50 (d, 1H), 8.40 (dd, 1H), 7.70 (td, 1H), 7.30 (dd, 1H), 5.30 (d, 1H), 4.80-4.70 (m, 1H), 1.35 (d, 3H).

Example 318: 6-Chloro-3-[3-(4-chloro-benzyl)-5-phenyl-3H-imidazol-4-yl]-2-(4,5-dihydro -oxazol-2-yl)-1H-indole

A mixture of **Intermediate 2.1** (600 mg, 1.3 mmol), CDI (260 mg, 1.56 mmol), 2-Bromoethylamine hydrobromide (411 mg, 1.95 mmol) and Et_3N (0.55 mL, 3.89 mmol) in THF (6 mL) is heated to reflux. After completion, the reaction mixture is quenched by H_2O, EtOAc is added and the organic layer is washed with brine, dried over $MgSO_4$ and evaporated *in vacuo*. Silica gel flash chromatography of the residue affords the title compound as a white powder.

Example 319: 5-{6-Chloro-3-[3-(4-chloro-benzyl)-5-phenyl-3H-imidazol-4-yl]-1H-indol-2-yl}-3H-[1,3,4]oxadiazol-2-one

A mixture of **Intermediate 319.1** (200 mg, 0.42 mmol), CDI (89 mg, 0.54 mmol) and Et_3N (0.1 mL, 0.71 mmol) in THF (3.6 mL) and DMF (0.4 mL) is heated to reflux. After completion, the reaction mixture is quenched by H_2O, EtOAc is added and the organic layer is washed with brine, dried over $MgSO_4$ and evaporated *in vacuo*. Silica gel flash chromatography of the residue affords the title compound as a white powder.

Intermediate 319.1: 6-Chloro-3-[3-(4-chloro-benzyl)-5-phenyl-3H-imidazol-4-yl]-1H-indole-2-carboxylic acid hydrazide (which is also a compound of the formula I according to the invention)

A mixture of **Intermediate 2.2** (1.0 g, 2.0 mmol) and hydrazine (0.49 mL, 10.2 mmol) in EtOH (50 mL) is heated to reflux. After completion, the reaction mixture is concentrated *in vacuo*, DCM is added and the organic layer is washed with brine, dried over $MgSO_4$ and evaporated *in vacuo*. Silica gel flash chromatography of the residue affords the title compound as a white powder. ES-MS: M+ = 476.1: $_At_{Rel}$ = 3.88.

Example 320: (5-{6-Chloro-3-[3-(4-chloro-benzyl)-5-phenyl-3H-imidazol-4-yl]-1H-indol-2-yl}-[1,3,4]oxadiazol-2-yl)-pyridin-3-yl-amine

A mixture of **Intermediate 319.1** (400 mg, 0.84 mmol), 3-Isothiocyanato-pyridine (94 µL, 0.84 mmol) and pyridine (0.14 mL, 1.76 mmol) in THF (2.8 mL) is heated to at 50 °C. After 15min, TsCl (198 mg, 1.0 mmol) and pyridine (0.14 mLl, 1.76 mmol) are added and stirred for 16h at 70 °C. After completion, the reaction mixture is concentrated *in vacuo*, EtOAc is added and the organic layer is washed with brine, dried over $MgSO_4$ and evaporated *in vacuo*. Silica gel flash chromatography of the residue affords the title compound as a white powder.

Example 321 and **322** are also prepared in analogy to **Example 320**.

Example 323: 5-{6-Chloro-3-[3-(4-chloro-benzyl)-5-phenyl-3H-imidazol-4-yl]-1H-indol-2-yl}-3-pyridin-3-ylmethyl-3H-[1,3,4]oxadiazol-2-one

The title compound is synthesized by coupling of **Example 319** and 3-Chloromethyl-pyridine HCl salt analogy to the preparation of **Example 292** as a white solid.

Example 324: 6-Chloro-3-{3-[4-chloro-2-(4-methyl-piperazin-1-ylmethyl)-benzyl]-5-phenyl-3H-imidazol-4-yl}-5-fluoro-1H-indole

A mixture of **Intermediate 324.1** (100 mg, 0.177 mmol), 1-Methylpiperazine (30 µL 0.266 mmol) and K_2CO_3 (36.8 mg, 0.266 mmol) in DMF (2 mL) is stirred at RT. After completion, the reaction mixture is concentrated *in vacuo*, EtOAc is added and the organic layer is washed with brine, dried over $MgSO_4$ and evaporated *in vacuo*. Silica gel flash chromatography of the residue affords the title compound as a white powder.

Example 325, 326 and **327** are also prepared in analogy to **Example 324**.

Intermediate 324.1: 6-Chloro-3-[3-(4-chloro-2-chloromethyl-benzyl)-5-phenyl-3H-imidazol-4-yl]-5-fluoro-1H-indole

A mixture of **Example 148** (1.1 g, 2.36 mmol) and Et_3N (0.49 mL, 3.53 mmol) in DMF (25 mL) is treated by MsCl (0.20 mL, 2.59 mmol) at 0 °C. After completion, the reaction mixture is concentrated *in vacuo*, EtOAc is added and the organic layer is washed with brine, dried over $MgSO_4$ and evaporated *in vacuo*. Silica gel flash chromatography of the residue affords the title compound as a white powder. ES-MS: M+H = 485.9: $_ct_{Ret}$ = 6.52.

Example 328: 6-Chloro-3-[3-(4-chloro-benzyl)-5-phenyl-3H-imidazol-4-yl]-1H-indole-2-carboxylic acid [2-(2-oxo-3-pyridin-2-ylmethyl-imidazolidin-1-yl)-ethyl]-amide

A mixture of **Intermediate 328.1** (24 mg, 0.038 mmol) and CDI (6.7 mg, 0.041 mmol) in DCM (0.5 mL) is stirred at RT. After completion, DCM is added to the reaction mixture and the organic layer is washed with brine, dried over $MgSO_4$ and evaporated *in vacuo*. Silica gel flash chromatography of the residue affords the title compound as a white powder. ES-MS: M+H = 664.0: $_ct_{Ret}$ = 5.63.

Intermediate 328.1: 6-Chloro-3-[3-(4-chloro-benzyl)-5-phenyl-3H-imidazol-4-yl]-1H-indole-2-carboxylic acid (2-{2-[(pyridin-2-ylmethyl)-amino]-ethylamino}-ethyl)-amide (which is also a compound of the formula I according to the invention)

The title compound is synthesized by reductive amination of **Intermediate 328.2** and pyridine-2-carbaldehyde analogously to the preparation of **Example 233** as a colorless solid; ES-MS: M+H = 638.0; HPLC: $_ct_{Ret}$ = 5.50 min.

Intermediate 328.2: 6-Chloro-3-[3-(4-chloro-benzyl)-5-phenyl-3H-imidazol-4-yl]-1H-indole-2-carboxylic acid [2-(2-amino-ethylamino)-ethyl]-amide (which is also a compound of the formula I according to the invention)

The title compound is synthesized by deprotection of **Intermediate 328.3** analogously to the preparation of **Example 44** as a colorless solid; ES-MS: M+H = 547.1; HPLC: $_ct_{Ret}$ = 5.29 min.

Intermediate 328.3: {2-[2-({6-Chloro-3-[3-(4-chloro-benzyl)-5-phenyl-3H-imidazol-4-yl]-1H-indole-2-carbonyl}-amino)-ethylamino]-ethyl}-carbamic acid tert-butyl ester (which is also a compound of the formula I according to the invention)

The title compound is synthesized by condensation of **Intermediate 2.1** and [2-(2-Amino-ethylamino)-ethyl]-carbamic acid tert-butyl ester analogously to the preparation of **Example 2** as a colorless solid; ES-MS: M+H = 647.0; HPLC: $_{c}t_{Rel}$ = 6.02 min.

Intermediate 331.1: Acetic acid 2-((S)-pyrrolidin-3-ylamino)-ethyl ester 2HBr salt

The title compound is synthesized according to the procedure described for **Intermediate 89.1** as the the corresponding HBr salt; ES-MS: M+H = 173.1.

Example 332: {6-Chloro-3-[3-(4-chloro-benzyl)-5-phenyl-3H-imidazol-4-yl]-1H-indol-2-yl}-[(S)-3-(2-hydroxy-ethylamino)-pyrrolidin-1-yl]-methanone

K_2CO_3 (17 mg, 0.12 mmol) is added to a solution of **Example 331** (50 mg, 0.08 mmol) in MeOH (1 mL) at RT. H_2O (0.5 mL) is added and the reaction mixture is stirred under reflux for 3h. It is allowed to cool to rt and carefully neutralized by addition of 0.1M aqueous HCl solution followed by aqueous work up. The crude product is recrystallized from EtOAc/CH_2Cl_2 to afford the title compound as a white solid.

Intermediate 333.1: (S)-Pyrrolidin-3-yl-(2-pyrrolidin-1-yl-ethyl)-amine 3HBr salt

The title compound is synthesized according to the procedure described for **Intermediate 89.1** as the the corresponding HBr salt; ES-MS: M+H = 184.2.

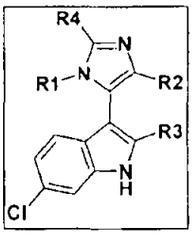
Intermediate 334.1: (S)-Pyrrolidin-3-yl-(3-pyrrolidin-1-yl-propyl)-amine 3HBr salt

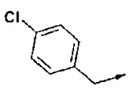
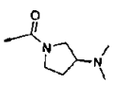
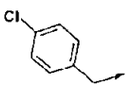
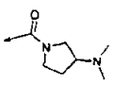
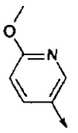
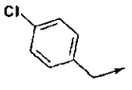
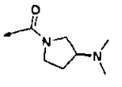
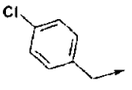
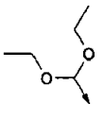
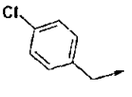
The title compound is synthesized according to the procedure described for **Intermediate 89.1** as the the corresponding HBr salt; ES-MS: M+H = 198.3.

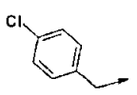
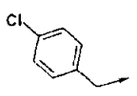
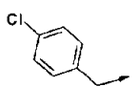
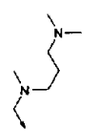
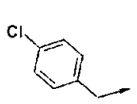
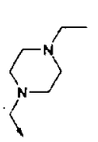
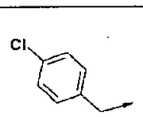
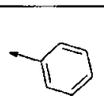
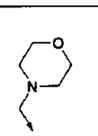
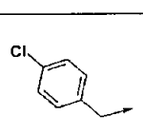
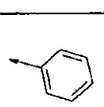
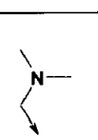
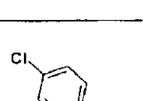
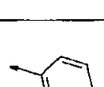
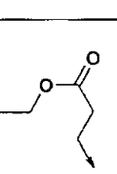
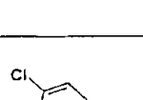
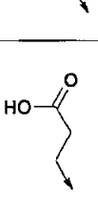
Intermediate 335.1: (2-Methoxy-ethyl)-methyl-(S)-pyrrolidin-3-yl-amine 2HBr salt

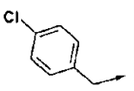
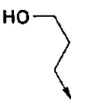
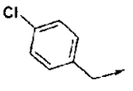
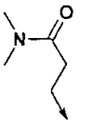
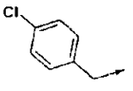
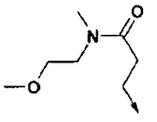
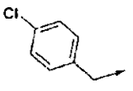
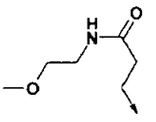
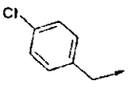
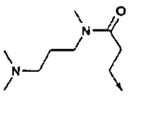
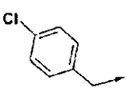
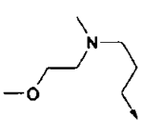
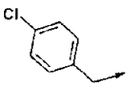
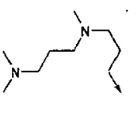
The title compound is synthesized according to the procedure described for **Intermediate 89.1** as the the corresponding HBr salt; ES-MS: M+H = 159.2; ^{1}HNMR($CDCl_3$) 3.43 (t, 2H), 3.38 (s, 3H), 3.17-3.03 (m, 2H), 2.99-2.91 (m, 2H), 2.80 (dd, 1H), 2.67-2.57 (m, 3H), 2.24 (s, 3H).

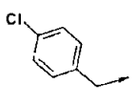
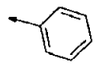
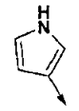
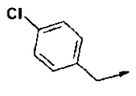
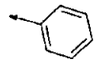
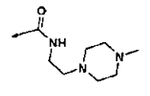
Table 3 for further examples



Example	R^1	R^2	R^3	R^4	Analysis MS/HPLC/NMR
336					M+= 635.0 $_{A}t_{Ret}$ = 3.83 min
337					M+= 665.0 $_{A}t_{Ret}$ = 4.07 min
338					M+= 635.9 $_{A}t_{Ret}$ = 3.97 min
339			H		M+H = 521.8 $_{E}t_{ret}$ = 5.16 min
340			H		M+H = 449.9 $_{E}t_{ret}$ = 4.53 min

Example	R^1	R^2	R^3	R^4	Analysis MS/HPLC/NMR
341			H		M-H = 493.1 $_{E}t_{ret}$ = 4.65 min
342			H		M+H = 463.9 $_{E}t_{ret}$ = 4.51 min
343			H		M-H = 545.2 $_{E}t_{ret}$ = 4.03 min
344			H		M-H = 542.2 $_{E}t_{ret}$ = 4.09 min
345			H		M-H = 519.0 $_{E}t_{ret}$ = 4.68 min
346			H		M-H = 473.1 $_{E}t_{ret}$ = 4.57 min
347			H		M-H = 516.0 $_{E}t_{ret}$ = 4.89 min
348			H		M-H = 488.9 $_{E}t_{ret}$ = 4.55 min

Example	R^1	R^2	R^3	R^4	Analysis MS/HPLC/NMR
349			H		M+H = 478.2 $_{E}t_{ret}$ = 4.51 min
350			H		M-H = 519.2 $_{E}t_{ret}$ = 4.61 min
351			H		M-H = 559.0 $_{E}t_{ret}$ = 4.67 min
352			H		M-H = 549.2 $_{E}t_{ret}$ = 4.55 min
353			H		M-H = 590.2 $_{E}t_{ret}$ = 4.11 min
354			H		M-H = 545.1 $_{E}t_{Ret}$ = 4.13 min
355			H		M-H = 572.2 $_{E}t_{Ret}$ = 3.99 min

Example	R^1	R^2	R^3	R^4	Analysis MS/HPLC/NMR
356			H		M-H = 481.1 ^{1}HNMR($CDCl_3$) δ 8.36 (bs 1H), 8.31 (bs, 1H), 7.61 (d, 2H), 7.39 (s, 1H), 7.21-7.12 (m, 7H), 6.99 (d, 1H), 6.89 (d, 1H), 6.86 (d, 2H), 6.80-6,76 (m, 1H), 6.49-6.46 (m, 1H), 5.07 (s, 2H).
357				Me	M-H = 599.0 $_E t_{Ret}$ = 3.88 min

All compounds without **Example 336, 337, 338** obtained by KOH or TBAF mediated deprotection of corresponding N-Tosyl protected precursors

Typical procedure for TBAF mediated deprotection:

The N-protected intermediate (0.1 mmol) is added to a 3 M solution of TBAF in THF at rt and stirred until completion of the reaction. Aqueous workup and silicagel flash chromatography of the crude material affords the final examples.

Typical procedure for KOH mediated deprotction:

The N-protected intermediate (0.1 mmol, 1.0 equiv) is dissolved in MeOH (5 mL) and ttreated with powdered KOH (0.15 mmol , 1.5 equiv) at rt. The reaction is then warmed to 65 °C and stirred until completion. It is cooled in an ice bath and carefully neutralized by addition of 0.1 M aqueous HCl solution followed by aqueous workup and silica gel flash chromatography of the crude material to afford the final examples.

Example 336: {6-Chloro-3-[3-(4-chloro-benzyl)-5-phenyl-2-pyridin-3-yl-3H-imidazol-4-yl]-1H-indol-2-yl}-((S)-3-dimethylamino-pyrrolidin-1-yl)-methanone

A mixture of **Intermediate 336.1** (100 mg, 0.15 mmol), Pyridine-3-boronic acid (38 mg, 0.31 mmol), $Pd(PPh_3)_4$ (18 mg, 0.015 mmol) and K_2CO_3 (85 mg, 0.62 mmol) in dioxane (0.8 mL) and H_2O (0.4 mL) is heated at 90 °C. After completion, the reaction mixture is quenched by H_2O, EtOAc is added and the organic layer is washed with brine, dried over $MgSO_4$ and evaporated *in vacuo*. Silica gel flash chromatography of the residue affords the title compound as a white powder.

Example 337 and **338** are also prepared in analogy to **Example 336**.

Intermediate 336.1: {3-[2-Bromo-3-(4-chloro-benzyl)-5-phenyl-3H-imidazol-4-yl]-6-chloro-1H-indol-2-yl}-((S)-3-dimethylamino-pyrrolidin-1-yl)-methanone (which is also a compound of the formula I according to the invention)

The title compound is synthesized by condensation of **Intermediate 336.2** and Dimethyl-(S)-pyrrolidin-3-yl-amine analogously to the preparation of **Example 2** as a colorless solid; ES-MS: M+ = 637.7; HPLC: $_At_{Ret}$ = 4.67 min

Intermediate 336.2: 3-[2-Bromo-3-(4-chloro-benzyl)-5-phenyl-3H-imidazol-4-yl]-6-chloro-1H-indole-2-carboxylic acid (which is also a compound of the formula I according to the invention)

The title compound is synthesized by hydrolysis of **Example 145** analogously to the preparation of **Intermediate 2.1** as a colorless solid; ES-MS: M+ = 541.7; HPLC: $_At_{Ret}$ = 5.10 min.

Intermediate 339.1: 6-Chloro-3-[3-(4-chlorobenzyl)-2-diethoxymethyl-5-phenyl-3H-imidazol-4-yl]-1-(toluene-4-sulfonyl)-1H-indole

A solution of **intermediate 144.1** (1.7 g, 3.4 mmol), **intermediate 339.2** (1.8 g , 4.2 mmol), $Pd(PPh_3)_4$ (410 mg, 0.34 mmol), K_3PO_4 (1.9 g, 8.7 mmol) in dioxane/H_2O (3:1; 40 mL) is heated to 100 °C in a sealed tube under argon atmosphere for 30 min. It then allowed to

cool to rt and diluted to EtOAc. The organic layer is washed with H_2O , aqueous citric acid solution (15 % wt) and brine, dried and concentrated. Silica gel flash chromatography of the crude product affords the title compound as a greenish solid. ES-MS: M+H = 677.2: $_{Et}t_{Ret}$ = 5.91 min.

Intermediate 339.2: 1-(4-Chlorobenzyl)-2-diethoxymethyl-5-iodo-4-phenyl-1H-imidazole

NIS (5.5 g, 24 mmol) is added to a solution of **intermediate 339.3** (5.9 g, 15.9 mmol) in CH_3CN (60 mL) at rt. The reaction mixture is then warmed to 85 °C and stirred for 3 d. After completion it is allowed to cool to rt and diluted with EtOAc. The organic layer is washed repeatedly with sat. aqueous $NaHCO_3$ solution, dried and concentrated. Silica gel flash chromatograpy of the crude product affords the title compound as a yellow oil. ES-MS: M+H = 498.3: $_{Et}t_{Ret}$ = 5.40 min.

Intermediate 339.3: 1-(4-Chlorobenzyl)-2-diethoxymethyl-4-phenyl-1H-imidazole

60% of NaH in mineral oil (0.83 g, 20.8 mmol) is added to a solution of **intermediate 339.4** (3.9 g, 16.0 mmol) in THF (20 mL) at RT. The reaction is allowed to stir for 20 min followed by addition of 4-chloro benzylbromide (3.4 g, 16.0 mmol). Stirring is continued for 1 h at RT and then the reaction is quenched by addition of EtOAc and H_2O . The organic layer is separated, washed with brine, dried and concentrated to give the title compound which was submitted without further purification to the next stage. ES-MS: M+H = 371.2: $_{Et}t_{Ret}$ = 4.65 min.

Intermediate 339.4: 2-Diethoxymethyl-4phenyl-1H-imidazole

NaOMe (18% wt solution in MeOH; 2.83 g, 51 mmol) is added to a solution of diethoxyacetonitrile (4.9 mL, 34.3 mmol) in MeOH(60 mL) and stirred for 1 h at rt. Phenylacylamine hydrochloride (3.0 g, 17.1 mmol) is then added to the reaction mixture followed by NaOMe (18% wt solution in MeOH; 2.83 g, 51 mmol). After 2 h of stirring at rt the reaction mixture is diluted with EtOAc and the organic layer is washed with H_2O and brine. The organic layer is then dried and concentrated. The crude product is the purified by tituration with EtOAc/hexanes. Yellow solid. ES-MS: M+H = 247.1: ^{1}HNMR (DMSO d6) δ

7.73 (d, 2H), 7.52 (s, 1H), 7.30 (dd, 2H), 7.27 (dd, 1H), 5.51 (s, 1H), 3.60 (q, 2H), 3.54 (q, 2H), 1.14 (t, 6H).

Intermediate 340.1: {1-(4-Chlorobenzyl)-5-[6-chloro-1-(toluene-4-sulfonyl)-1H-indol-3-yl]-4-phenyl-1H-imidazol-2-yl}-methanol

A solution of **intermediate 340.2** (43 mg, 0.06 mmol) in THF (2 mL) is treated with LAH (2M solution in THF; 30 µL, 0.06 mmol) at 0°C. The reaction mixture is allowed to warm to RT and stirred for 15 min. It is quenched by addition of EtOAc. The organic layer is washed with aqueous citric acid (15 % wt) and brine, dried and concentrated to give the title compound as an off white solid. ES-MS: M-H = 600.4: $_{E}t_{Rel}$ = 5.31 min.

Intermediate 340.2: 1-(4-Chlorobenzyl)-5-[6-chloro-1-(toluene-4-sulfonyl)-1H-indol-3-yl]-4-phenyl-1H-imidazole-2-carbaldehyd

A solution of **intermediate 339.1** (1.5 g, 2.2 mmol) in THF (30 mL) ia treated with HCl (1M solution in H_2O; 11 mL) at RT. The reaction mixture is then warmed to reflux and stirred for 1h. After cooling to rt it is diluted with EtOAc and the organic layer is washed with saturated aqueous $NaHCO_3$ solution and brine, dried and concentrated to give the title compound as a white solid. ES-MS: M-H = 599.2: $_{E}t_{Rel}$ = 6.67 min.

Example 341 is synthesized by coupling of **Intermediate 144.1** and 4-Pyridineboronic acid analogously to the preparation of **Example 144** as a white solid.

Intermediate 342.1: {1-(4-Chlorobenzyl)-5-[6-chloro-1-(toluene-4-sulfonyl)-1H-indol-3-yl]-4-phenyl-1H-imidazol-2-yl}-ethanol

A solution of **intermediate 340.2** (70 mg, 0.12 mmol) in THF (1 mL) is treated with MeMgBr (3M solution in THF; 120 µL) at rt. The reaction mixture is allowed to stir for 1 h and is then quenched by addition of EtOAc. The organic layer is repeatedly washed with aqueous citric acid (15 % wt) and brine, dried and concentrated to give the title compound as a yellow solid. ES-MS: M-CH_3 = 600.0: $_{E}t_{Rel}$ = 5.33 min.

Intermediate 343.1: N-{1-(4-Chlorobenzyl)-5-[6-chloro-1-(toluene-4-sulfonyl)-1H-indol-3-yl]-4-phenyl-1H-imidazol-2-ylmethyl}-N,N^,N^-trimethylpropane-1,3-diamine

AcOH (5 µL, 0.08 mmol) and sodium cyano borohydride (8 mg, 0.12 mmol) are added to a solution of **intermediate 340.2** (50 mg , 0.08 mmol) and N,N;N-trimethylpropane diamine (13 µL, 0.09 mmol) in THF (2 mL) at RT. The reaction mixture is stirred for 12 h and then diluted with EtOAc. The organic layer is washed with satureated aqueous $NaHCO_3$ solution, H_2O and brine, dried and concentrated. Silica gel flash chromatography of the crude product affords the title compound as a white foam. $_Et_{Ret}$ = 5.50 min.

Intermediate 344.1: 6-Chloro-3-[3-(4-chlorobenzyl)-4-ethyl-piperazin-1-ylmethyl-5-phenyl-3H-imidazole-4-yl]-1-(toluene-4-sulfonyl)-1H-indole

The title compound is synthesized by reductive amination analogously to the preparation of **Intermediate 343.1** as a colorless solid; ES-MS: M+H = 772.0: $_Et_{Ret}$ = 4.87 min.

Intermediate 345.1: 6-Chloro-3-[3-(4-chlorobenzyl)-2-morpholin-4-ylmethyl-5-phenyl-3H-imidazole-4-yl]-1-(toluene-4-sulfonyl)-1H-indole

The title compound is synthesized by reductive amination analogously to the preparation of **Intermediate 343.1** as a colorless solid; ES-MS: M+H = 773.2: $_Et_{Ret}$ = 5.40 min.

Intermediate 346.1: {1-(4-Chlorobenzyl)-5-[6-chloro-1-(toluene-4-sulfonyl)-1H-indol-3-yl]-4-phenyl-1H-imidazol-2-ylmethyl}-dimethylamine

The title compound is synthesized by reductive amination analogously to the preparation of **Intermediate 343.1** as a colorless solid; ES-MS: M+H = 631.1: $_Et_{Ret}$ = 5.39 min.

Intermediate 347.1: 3-[1-(4-Chloro-benzyl)-5-[6-chloro-1-(toluene-4-sulfonyl)-1H-indol-3-yl]-4-phenyl-1H-imidazol-2-yl]-propionic acid ethyl ester

$ZnBr_2$ (280 mg, 1.2 mmol) and Pd-C (5 % , Engelhard 4709, 260 mg) are added to a solution of **Intermediate 347.2** (910 mg, 1.2 mmol) in EtOAc (20 mL) at RT. The reaction mixture is stirred under an atmosphere of H_2 at RT for 1 d. It is then diluted with EtOAc and filtered

over a plug of celite and concentrated. Silica gel flash chromatography of the crude product affords the title compound as a yellow solid. ES-MS: M+H = 674.2: $_{Et}t_{Ret}$ = 5.57min.

Intermediate 347.2: (E)-3-{1-(4-Chloro-benzyl)-5-[6-chloro-1-(toluene-4-sulfonyl)-1H-indol-3-yl]-4-phenyl-1H-imidazol-2-yl}-acrylic acid ethyl ester

A solution of triethyl phosphono acetate (320 µL, 1.6 mmol) in THF (10 mL) is treated with 60% of NaH in mineral oil (62 mg, 1.6 mmol) at 0°C. The solution is stirred for 5 min and then added via a canula to a solution of **intermediate 340.2** (845 mg, 1.4 mmol) in THF (10 mL) at RT. The resulting reaction mixture is stirred for 30 min at rt and then diluted with EtOAc. The organic layer is washed with H_2O and brine, dried and concentrated to give the title compound as a yellow solid. ES-MS: M-H = 669.9: $_{Et}t_{Ret}$ = 6.27min.

Example 348: 3-[1-(4-Chlorobenzyl)-5-(6-chloro-1H-indol-3yl)-4-phenyl-1H-imidazol-2-yl]—N-(2-methoxy-ethyl)-carboxylic acid

Powdered KOH (140 mg, 2.2 mmol) is added to a solution of **intermediate 347.1** (583 mg, 0.87 mmol) in EtOH (10 mL) at RT. The reaction mixture is then heated to 80 °C for 20 h. After cooling to RT it is transferred to an ice bath and acidified by careful addition of aqueous HCl solution (5M). Stirring is continued for 30 min at 0°C and the resulting precipitate of the title compound is isolated by filtration and dried under reduced pressure to give a yellow solid.

Intermediate 349.1: 3-[1-(4-Chloro-benzyl)-5-[6-chloro-1-(toluene-4-sulfonyl)-1H-indol-3-yl]-4-phenyl-1H-imidazol-2-yl]-propan-1-ol

A solution of **intermediate 347.1** (150 mg, 0.22 mmol) in THF (5 mL) is treated with LAH (2M solution in THF; 224 µL, 0.44 mmol) at 0°C. The reaction mixture is allowed to warm to RT and stirred for 30 min. It is quenched by addition of EtOAc. The organic layer is washed with aqueous citric acid (15 % wt) and brine, dried and concentrated to give the title compound as an off white solid. ES-MS: M-H = 628.0: $_{Et}t_{Ret}$ = 5.27 min.

Example 350: 3-[1-(4-Chlorobenzyl)-5-(6-chloro-1H-indol-3yl)-4-phenyl-1H-imidazol-2-yl]-N,N-dimethyl-propionamide

N-Methylmorpholine (67 µL, 0.61 mmol) and HATU (93 mg, 0.24 mmol) are added to a solution of **Example 348** (100 mg, 0.2 mmol) in THF (5 mL) at RT .The reaction mixture is stirred for 5 min followed by addition of N,N dimethyl amine (2M solution in THF, 310 µL, 0.62 mmol). Stirring is continued at rt and after 1h the reaction mixture is diluted with EtOAc. The organic layer is washed with saturated aqueous $NaHCO_3$ solurion and brine, dried and concentrated. The remaining crude product is purified by flash chromatography (SiO_2; DCM/MeOH, gradient 0-10 % MeOH) to give the title compound as a white solid.

Example 351, 352 and **353** are also prepared in analogy to **Example 350**.

Example 354: {3-[1-(4-Chlorobenzyl)-5-(6-chloro-1H-indol-3yl)-4-phenyl-1H-imidazol-2-yl]-propyl}-(2-methoxy-ethyl)-methylamine

A solution of **Example 351** (40 mg, 0.07 mmol) in THF (3 mL) is treated with LAH (2M solution in THF; 36 µL) at 0°C. The reaction is allowed to warm to rt and stirred for 3 h. It is then quenched by addition of EtOAc and H_2O. The organic layer is separated and washed with brine , dried and concentrated. Silica gel flash chromatography of the crude product affords the title compound as a yellow solid.

Example 355 is also prepared in analogy to **Example 354**.

Intermediate 356.1: 6-Chloro-3-[3-(4-chlorobenzyl)-5-phenyl-2-(triisopropylsilanyl-1H-pyrrol-3-yl)-3H-imidazol-4-yl]-6-chloro-1-(toluene-4-sulfonyl)-1H-indole

The title compound is synthesized by coupling of **Intermediate 356.2** and 2-(triisopropylsilanyl-1H-pyrrol-3-yl) boronic acid analogously to the preparation of **Example 341** as a colorless solid; ES-MS: M+H = 792.7; ^{1}HNMR ($CDCl_3$) δ 8.02 (s, 1H), 7.61 (d, 2H), 7.47 (d, 2H), 7.40 (s, 1H), 7.19 (dd, 4H), 7.09-7.04 (m, 4H), 7.00 (d, 1H), 6.91 (s, 1H), 6.59 (s, 1H), 5.01 (s, 2H), 2.39 (s, 3H), 1.37-1.31 (m, 3H), 1.03 (d, 18H).

Intermediate 356.2: 3-[2-Bromo-3-(4-chlorobenzyl)-5-phenyl-3H-imidazol-4-yl]-6-chloro-1-(toluene-4-sulfonyl)-1H-indole

NBS (728 mg, 4.1 mmol) is added to a solution of **Intermediate 356.3** (1.9 g, 3.4 mmol) in THF (100 mL) at 0°C. The reaction mixture is allowed to reach rt and stirred for 4 h. The product is isolated by aqueous workup and purified bysilica gel flash chromatography to give the title compound. ES-MS: M-H = 649.7: $_{E}t_{Ret}$ = 6.71 min.

Intermediate 356.3: 6-Chloro-3-[3-(4-chlorobenzyl)-5-phenyl-3H-imidazol-4-yl]-1-(toluene-4-sulfonyl)-1H-indole

50% of NaH in mineral oil (284 mg, 5.9 mmol) is added to a solution of **Example 1** (1.65 g, 3.9 mmol) in THF (40 mL) at 0°C. The reaction mixture is allowed to warm to rt and stirred for 15 min. TsCl (902 mg, 4.7 mmol) is added and stirring continued for 1 h. The reaction is quenched by addition of EtOAc and H_2O. The organic layer is separated, washed with brine, dried and concentrated. The crude product is purified by tituration with EtOAc /hexanes to give the title compound as a white solid. ES-MS: M+H = 573.7: $_{E}t_{Ret}$ = 5.33 min.

Intermediate 357.1: 6-Chloro-3-3-(4-chloro-benzyl)-2-methyl-5-phenyl-3H-imidazol-4-yl]-1H-indole-2-carboxylic acid (which is also a compound of the formula I according to the invention)

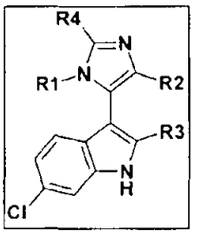
A solution of **Intermediate 357.2** (36 mg, 0.07 mmol) in EtOH (5 mL) is treated with powdered KOH (7 mg, 0.11 mmol) and heated with stirring to 90 °C for 16h. After completion of the reaction it is allowed to cool to rt and neutralized by careful addition of 1 N HCl in EtOH. It is concentrated and the remaining crude product taken up in EtOAc. The organic layer is repeatedly washed with H_2O, dried and concentrated to give the title as a white solid. ES-MS: M-H = 474.0: $_{E}t_{Ret}$ = 4.45 min

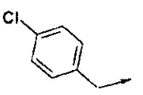
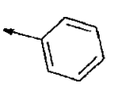
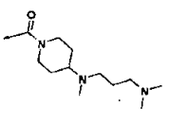
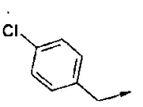
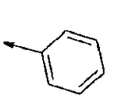
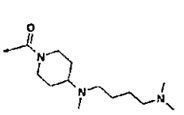
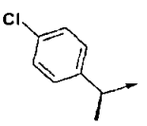
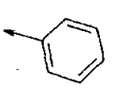
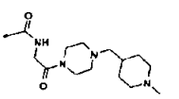
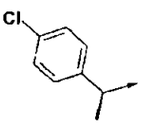
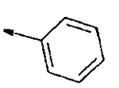
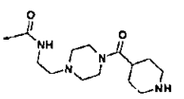
Intermediate 357.2: 6-Chloro-3-3-(4-chloro-benzyl)-2-methyl-5-phenyl-3H-imidazol-4-yl]-1H-indole-2-carboxylic acid ethyl ester (which is also a compound of the formula I according to the invention)

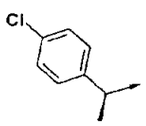
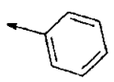
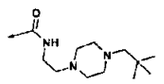
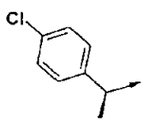
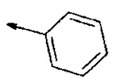
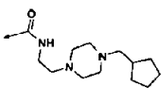
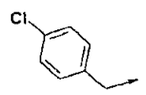
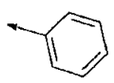
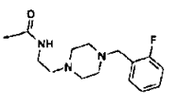
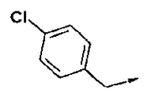
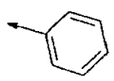
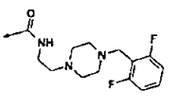
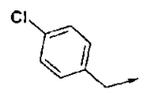
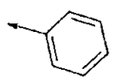
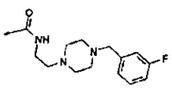
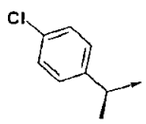
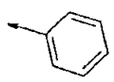
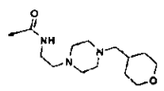
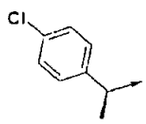
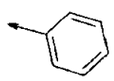
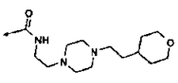
A mixture of **Example 145** (125 mg, 0.19 mmol), trimethylboroxine (110 µL, 0.78 mmol), $Pd(PPh_3)_4$ (23 mg, 0.02 mmol), K_3PO_4 (170 mg, 0.78 mmol), H_2O (3 mL) and dioxane (3 mL) is placed in a sealed tube under argon atmosphere and heated to 80 °C for 1h. After

completion the reaction mixture is quenched by addition of H_2O. EtOAc is added and the organic layer is washed with brine, dried over $MgSO_4$ and evaporated *in vacuo*. Silica gel flash chromatography of the residue affords the title compound as a colorless powder; ES-MS: M-H = 502.0: $_Et_{Ret}$ = 4.72 min.

Table 4 for further examples



Example	R^1	R^2	R^3	R^4	Analysis MS/HPLC/NMR
358				H	M+H= 642.9 $_Dt_{Ret}$ = 2.65 min
359				H	M+H= 657.0 $_Dt_{Ret}$ = 2.65 min
360				H	M+H= 711.9 $_Ct_{Ret}$ = 5.35 min
361				H	M+H= 697.8 $_Ct_{Ret}$ = 5.32 min

Example	R^1	R^2	R^3	R^4	Analysis MS/HPLC/NMR
362				H	M+H= 657.2 $_{A}t_{Ret}$ = 5.70 min
363				H	M+H= 668.9 $_{A}t_{Ret}$ = 5.72 min
364				H	M+H= 680.9 $_{D}t_{Ret}$ = 2.84 min
365				H	M+H= 698.8 $_{D}t_{Ret}$ = 2.87 min
366				H	M+H= 680.9 $_{D}t_{Ret}$ = 2.85 min
367				H	M+H= 684.8 $_{C}t_{Ret}$ = 5.54 min
368				H	M+H= 698.9 $_{C}t_{Ret}$ = 5.43 min

Intermediate 358.1: N,N,N'-Trimethyl-N'-piperidin-4-yl-propane-1,3-diamine

The title compound is synthesized by hydrogenation of **Intermediate 358.2** analogously to the preparation of **Intermediate 347.1** as a colorless solid; ES-MS: M+H = 200.2; TLC: Rf = 0.14 (DCM/MeOH/NH_3 = 70:30:1).

Intermediate 358.2: 4-[(3-Dimethylamino-propyl)-methyl-amino]-piperidine-1-carboxylic acid benzyl ester

The title compound is synthesized by reductive amination of **Intermediate 358.3** and formaldehyde analogously to the preparation of **Example 233** as a colorless oil; ES-MS: M+H = 334.3; $_Dt_{Ret}$ = 2.25 min.

Intermediate 358.3: 4-(3-Dimethylamino-propylamino)-piperidine-1-carboxylic acid benzyl ester

The title compound is synthesized by reductive amination of 4-Oxo-piperidine-1-carboxylic acid benzyl ester and N,N-dimethyl-propylamine analogously to the preparation of **Example 233** as a colorless oil; ES-MS: M+H = 320.2; $_Dt_{Ret}$ = 2.22 min.

Intermediate 359.1: N,N,N'-Trimethyl-N'-piperidin-4-yl-butane-1,4-diamine

The title compound is synthesized by hydrogenation of **Intermediate 359.2** analogously to the preparation of **Intermediate 347.1** as a colorless solid; ES-MS: M+H = 214.1; TLC: Rf = 0.05 (DCM/MeOH/NH_3 = 70:30:1).

Intermediate 359.2: 4-[(4-Dimethylamino-butyl)-methyl-amino]-piperidine-1-carboxylic acid benzyl ester

The title compound is synthesized by reductive amination of **Intermediate 359.3** and formaldehyde analogously to the preparation of **Example 233** as a colorless oil; ES-MS: M+H = 348.3; $_Dt_{Ret}$ = 2.27 min.

Intermediate 359.3: 4-(4-Dimethylamino-butylamino)-piperidine-1-carboxylic acid benzyl ester

The title compound is synthesized by reductive amination of 4-Oxo-piperidine-1-carboxylic

acid benzyl ester and N,N-dimethyl-butylamine analogously to the preparation of **Example 233** as a colorless oil; ES-MS: M+H = 334.2; $_{D}t_{Ret}$ = 2.23 min.

Intermediate 360.1: 2-Amino-1-[4-(1-methyl-piperidin-4-ylmethyl)-piperazin-1-yl]-ethanone 3HCl salt

The title compound is synthesized by deprotection of **Intermediate 360.2** analogously to the preparation of **Example 44** as a colorless oil; ES-MS: M+H = 255.2.

Intermediate 360.2: {2-[4-(1-Methyl-piperidin-4-ylmethyl)-piperazin-1-yl]-2-oxo-ethyl}-carbamic acid tert-butyl ester

The title compound is synthesized by condensation of 1-Pyridin-3-ylmethyl-piperazine and N-Boc-glycine analogously to the preparation of **Example 2** as a colorless solid; ES-MS: M+H = 355.2.

Intermediate 361.1: 4-(4-{2-[(6-Chloro-3-{3-[(S)-1-(4-chloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carbonyl)-amino]-ethyl}-piperazine-1-carbonyl)-piperidine-1-carboxylic acid tert-butyl ester

Intermediate 361.1 is also prepared in analogy to **Example 293**. ES-MS: M+H = 797.9; $_{C}t_{Ret}$ = 6.10 min.

Intermediate 362.1: 2-[4-(2,2-Dimethyl-propyl)-piperazin-1-yl]-ethylamine

The title compound is synthesized by reduction of **Intermediate 362.2** analogously to the preparation of **Intermediate 149.1** as a colorless oil; ES-MS: M+H = 200.2: TLC: Rf = 0.30 (DCM/MeOH/NH_3 = 40:10:1).

Intermediate 362.2: [4-(2,2-Dimethyl-propyl)-piperazin-1-yl]-acetonitrile

The title compound is synthesized by coupling of **Intermediate 362.3** and bromoacetonitrile analogously to the preparation of **Intermediate 149.2** as a colorless oil; ES-MS: M+H = 196.2: TLC: Rf = 0.93 (DCM/MeOH/NH_3 = 40:10:1).

Intermediate 362.3: 1-(2,2-Dimethyl-propyl)-piperazine 2HCl salt

The title compound is synthesized by deprotection of **Intermediate 362.4** analogously to the preparation of **Intermediate 193.1** as a colorless oil; ES-MS: M+H =157.2: TLC: Rf = 0.60 (DCM/MeOH/NH_3 = 40:10:1).

Intermediate 362.4: 4-(2,2-Dimethyl-propyl)-piperazine-1-carboxylic acid tert-butyl ester

The title compound is synthesized by reductive amination of 1-Boc-piperazine and Pivalaldehyde analogously to the preparation of **Example 233** as a colorless oil; ES-MS: M+H = 257.3; TLC: Rf = 0.82 (DCM/EtOAc = 4:1).

Intermediate 363.1: 2-(4-Cyclopentylmethyl-piperazin-1-yl)-ethylamine

The title compound is synthesized by reduction of **Intermediate 363.2** analogously to the preparation of **Intermediate 149.1** as a colorless oil; ES-MS: M+H = 212.2: TLC: Rf = 0.17 (DCM/MeOH/NH_3 = 40:10:1).

Intermediate 363.2: (4-Cyclopentylmethyl-piperazin-1-yl)-acetonitrile

The title compound is synthesized by coupling of **Intermediate 363.3** and bromoacetonitrile analogously to the preparation of **Intermediate 149.2** as a colorless oil; ES-MS: M+H = 208.2: TLC: Rf = 0.70 (DCM/MeOH/NH_3 = 80:10:1).

Intermediate 363.3: 1-Cyclopentylmethyl-piperazine 2HCl salt

The title compound is synthesized by deprotection of **Intermediate 363.4** analogously to the preparation of **Intermediate 193.1** as a colorless oil; ES-MS: M+H =169.2: TLC: Rf = 0.16 (DCM/MeOH/NH_3 = 80:10:1).

Intermediate 362.4: 4-Cyclopentylmethyl-piperazine-1-carboxylic acid tert-butyl ester

The title compound is synthesized by reductive amination of 1-Boc-piperazine and Cyclopentane-carboaldehyde analogously to the preparation of **Example 233** as a colorless oil; ES-MS: M+H = 269.2; TLC: Rf = 0.45 (DCM/EtOAc = 1:1).

Example 364: 6-Chloro-3-[3-(4-chloro-benzyl)-5-phenyl-3H-imidazol-4-yl]-1H-indole-2-carboxylic acid {2-[4-(2-fluoro-benzyl)-piperazin-1-yl]-ethyl}-amide

The title compound is synthesized by reductive amination of **Example 44** and 2-Fluorobenzaldehyde analogously to the preparation of **Example 233** as a colorless solid.

Example 365 and **366** are also prepared in analogy to **Example 364**.

Table 5 – Mdm2 and Mdm4 inhibitory activity of representative compounds of the present invention

compound	IC_{50} (μM) of p53-Hdm2 inhibition Fluorescence polarisation assay	IC_{50} (μM) of p53-Hdm4 inhibition (TR-FRET) Assay
42	0.30	10.4
101	0.015	1.32
135	7.2	68.3
142	0.64	43.4
148	0.11	55.3
271	0.30	54.9
328	0.19	63.7

Example 369: Tablets comprising compounds of the formula I

Tablets, comprising, as active ingredient, 100 mg of any one of the compounds of formula I of Examples 1 to 146 are prepared with the following composition, following standard procedures:

Composition

Active Ingredient	100 mg
crystalline lactose	240 mg
Avicel	80 mg
PVPPXL	20 mg
Aerosil	2 mg
magnesium stearate	5 mg

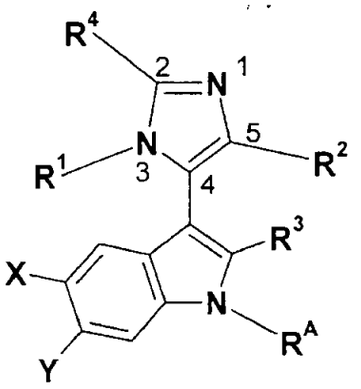
---

447 mg

Manufacture: The active ingredient is mixed with the carrier materials and compressed by means of a tabletting machine (Korsch EKO, Stempeldurchmesser 10 mm).
Avicel® is microcrystalline cellulose (FMC, Philadelphia, USA). PVPPXL is polyvinylpolypyrrolidone, cross-linked (BASF, Germany). Aerosil® is silicium dioxide (Degussa, Germany).

Claims:

1. A compound of the formula I,



(I)

wherein

R^1 is unsubstituted or substituted alkyl, unsubstituted or substituted alkenyl or unsubstituted or substituted alkinyl, unsubstituted or substituted aryl or unsubstituted or substituted heterocyclyl;

R^2 is unsubstituted or substituted alkyl, unsubstituted or substituted alkenyl, unsubstituted or substituted alkinyl, unsubstituted or substituted aryl or unsubstituted or substituted heterocyclyl;

R^3 is hydrogen, halogen, unsubstituted or substituted alkyl, unsubstituted or substituted alkenyl, unsubstituted or substituted alkinyl, unsubstituted or substituted aryl, carboxy, cyano, esterified carboxy, unsubstituted or substituted heterocyclyl-carbonyl (heterocyclyl-C)=O)-), unsubstituted or substituted carbamoyl or unsubstituted or substituted heterocyclyl;

R^4 is hydrogen, halogen, unsubstituted or substituted alkyl, unsubstituted or substituted alkenyl, unsubstituted or substituted alkinyl, unsubstituted or substituted aryl, carboxy, cyano, esterified carboxy, unsubstituted or substituted heterocyclyl-carbonyl (heterocyclyl-C)=O)-), unsubstituted or substituted carbamoyl or unsubstituted or substituted heterocyclyl;

R^A is hydrogen or unsubstituted or substituted alkyl or acyl;

X is hydrogen, C_1-C_7-alkyl, halo-C_1-C_7-alkyl, C_1-C_7-alkoxy, halo or cyano; and

Y is C_1-C_7-alkyl, halo-C_1-C_7-alkyl, C_1-C_7-alkoxy, halo or cyano;

and/or a tautomer, an N-oxide and/or a salt thereof.

2. A compound of the formula I according to claim 1, wherein

R^1 is unsubstituted or substituted alkyl, unsubstituted or substituted alkenyl or unsubstituted or substituted alkinyl;

R^2 is unsubstituted or substituted aryl;

R^3 is hydrogen, unsubstituted or substituted alkyl, carboxy, cyano, esterified carboxy, unsubstituted or substituted heterocyclyl-carbonyl (heterocyclyl-C)=O)-), unsubstituted or substituted carbamoyl, unsubstituted or substituted heterocyclyl or cyano,

R^4 is hydrogen, unsubstituted or substituted alkyl, halo or unsubstituted or substituted heterocyclyl,

R^A is hydrogen or unsubstituted or substituted alkyl or acyl;

X is hydrogen, C_1-C_7-alkyl, halo-C_1-C_7-alkyl, C_1-C_7-alkoxy, halo or cyano; and

Y is C_1-C_7-alkyl, halo-C_1-C_7-alkyl, C_1-C_7-alkoxy, halo or cyano;

and/or a tautomer, an N-oxide and/or a salt thereof.

3. A compound of the formula I according to claim 1 or to claim 2, wherein for the substituents R^1, R^2, R^3, R^4, R^A, X and Y

in unsubstituted or substituted alkyl, alkyl preferably has up to 20, more preferably up to 12 carbon atoms and is unsubstituted or substituted by one or more substitutents independently selected from the group consisting of C_1-C_7-alkyl, hydroxyl-C_1-C_7-alkyl, C_1-C_7-alkoxy-C_1-C_7-alkyl, N-mono- or N,N-di-[C_1-C_7-alkyl, phenyl, C_1-C_7-alkanoyl and/or phenyl-C_1-C_7-alkyl]-amino-C_1-C_7-alkyl, halo-C_1-C_7-alkyl, hydroxy, C_1-C_7-alkoxy, C_1-C_7-alkoxy-C_1-C_7-alkoxy, (C_1-C_7-alkoxy)-C_1-C_7-alkoxy-C_1-C_7-alkoxy, halo-C_1-C_7-alkoxy, halo, phenoxy, naphthyloxy, phenyl- or naphthyl-C_1-C_7-alkoxy; amino-C_1-C_7-alkoxy, C_1-C_7-alkanoyloxy, benzoyloxy, naphthoyloxy, oxo which is not at the binding carbon atom, amino, amino-C_1-C_7-alkyl, N-mono- or N,N-di-[C_1-C_7-alkyl, phenyl, C_1-C_7-alkanoyl and/or phenyl-C_1-C_7-alkyl]-amino, N-(heterocyclyl-C_1-C_7-alkyl)- or N-(heterocyclyl-C_1-C_7-alkyl-)-N-(C_1-C_7-alkyl)-amino wherein heterocyclyl preferably has 3 to 14 ring atoms, respectively, of which 1 to 4 are a heteroatom independently selected from N, S, S(=O), $S(=O)_2$ and O and is saturated, formyl (CHO), carboxy, C_1-C_7-alkoxy-carbonyl, phenyl- or naphthyl-C_1-C_7-alkoxycarbonyl, C_2-C_7-alkanoyl, benzoyl, naphthoyl, carbamoyl, N-mono- or N,N-di-substituted carbamoyl wherein the substitutents are selected from lower alkyl and hydroxy-lower alkyl; amidino, guanidino, ureido, mercapto, C_1-C_7-alkylthio, phenyl- or naphthylthio, phenyl- or naphthyl-C_1-C_7-

alkylthio, C_1-C_7-alkyl-phenylthio, C_1-C_7-alkyl-naphthylthio, halogen-C_1-C_7-alkylmercapto, sulfonamido, benzosulfonamido, azido, azido-C_1-C_7-alkyl, especially azidomethyl, nitro, cyano; unsubstituted or substituted heterocyclyl which is mono- to tricyclic heterocyclyl that is unsaturated or saturated, has 3 to 14 ring atoms of which 1 to 4 are a heteroatom independently selected from N, S, S(=O), $S(=O)_2$ and O, preferably N, and is unsubstituted or substituted with one or more, preferably up to three, moieties independently selected from the group consisting of C_1-C_7-alkyl, hydroxy-C_1-C_7-alkyl, hydroxy, oxo, amino or N-mono- or N,N-di-(C_1-C_7-alkyl, {amino or mono- or di-(C_1-C_7-alkyl)-amino}-C_1-C_7-alkyl, C_1-C_7-alkanoyl and/or C_1-C_7-alkoxycarbonyl)-amino, C_1-C_7-alkanoyl, C_1-C_7-alkylsulfonyl and saturated heterocyclyl with 3 to 14 ring atoms and 1 to 4 heteroatoms independently selected from N, S, S(=O), $S(=O)_2$ and O, preferably N, wherein said saturated heterocyclyl is unsubstituted or substituted by one or more, especially up to three, moieties independently selected from C_1-C_7-alkyl, hydroxy-C_1-C_7-alkyl, C_1-C_7-alkoxy-C_1-C_7-alkyl, oxo, amino, mono- or di-(C_1-C_7-alkyl)-amino), C_1-C_7-alkanoyl and C_1-C_7-alkoxycarbonyl; naphthyl or phenyl each of which is unsubstituted or substituted by one or more moieties independently selected from C_1-C_7-alkyl, halo-C_1-C_7-alkyl, hydroxyl, C_1-C_7-alkoxy, hydroxy-C_1-C_7-alkoxy, C_1-C_7-alkoxy-C_1-C_7-alkoxy, (C_1-C_7-alkoxy-C_1-C_7-alkoxy)-C_1-C_7-alkoxy, [amino, mono- or di-(C_1-C_7-alkyl)amino]-C_1-C_7-alkoxy, amino, mono- or di-[(C_1-C_7-alkyl, C_1-C_7-alkanoyl, C_1-C_7-alkoxycarbonyl, hydroxy-C_1-C_7-alkyl, C_1-C_7-alkoxy-C_1-C_7alkyl and/or (amino, mono- or di-(C_1-C_7-alkyl)-amino)-C_1-C_7-alkyl]-amino, halo and saturated heterocyclyl, saturated heterocyclyl-C_1-C_7-alkyl or saturated heterocyclyl-C_1-C_7-alkoxy wherein saturated heterocyclyl, respectively, has 3 to 14 ring atoms of which 1 to 4 are a heteroatom independently selected from N, S, S(=O), $S(=O)_2$ and O and is unsubstituted or substituted with one or more, especially up to three, moieties independently selected from C_1-C_7-alkyl, hydroxyl-C_1-C_7-alkyl, C_1-C_7-alkoxy-C_1-C_7-alkyl, hydroxyl, oxo, amino, mono- or di-(C_1-C_7-alkyl)-amino), C_1-C_7-alkanoyl and C_1-C_7-alkoxycarbonyl, nitro or cyano; and C_3-C_8-cycloalkyl, that is unsubstituted or substituted by one or more, especially up to three, substitutents independently selected from the substitutents for substituted aryl below;

where each phenyl or naphthyl (also in phenoxy or naphthoxy) mentioned above as substituent or part of a substituent of substituted alkyl (or also of substituted aryl, heterocyclyl etc. mentioned herein) is itself unsubstituted or substituted by one or more, e.g. up to three, preferably 1 or 2, substituents independently selected from C_1-C_7-alkyl, halo-C_1-C_7-alkyl, hydroxyl, C_1-C_7-alkoxy, C_1-C_7-alkoxy-C_1-C_7-alkoxy, halo, especially fluoro, chloro, bromo or

iodo, halo-C_1-C_7-alkyl, such as trifluoromethyl, azido, amino, N-mono- or N,N-di-(C_1-C_7-alkyl, phenyl, naphthyl, C_1-C_7-alkanoyl, phenyl-C_1-C_7-alkyl and/or naphthyl-C_1-C_7-alkyl)-amino, carboxy, C_1-C_7-alkoxycarbonyl carbamoyl, sulfamoyl, nitro and cyano;

unsubstituted or substituted alkenyl is C_2-C_{20}-alkenyl which is linear or branched and includes one or more double bonds, where the substituents are one or more substituents independently selected from those mentioned for substituted alkyl;

unsubstituted or substituted alkynyl is C_2-C_{20}-alkynyl which is linear or branched and includes one or more triple bonds, where the substituents are one or more substituents independently selected from those mentioned for substituted alkyl;

in unsubstituted or substituted aryl, aryl preferably has 6 to 18 carbon atoms and is a mono-, di- or polycyclic unsaturated carbocyclic moiety with conjugated double bonds in the ring, , which is unsubstituted or substituted by one or more substitutents independently selected from the group consisting of C_1-C_7-alkyl, C_2-C_7-alkenyl; C_2-C_7-alkinyl; C_6-C_{18}-aryl-C_1-C_7-alkyl in which aryl is unsubstituted or substituted by C_1-C_7-alkyl, by pyrrolidinyl, by pyrazolidinyl, by imidazolidinyl, by piperidinyl, by azepanyl, by piperazinyl, by amino, by N-mono- and/or N,N-di-C_1-C_7-alkylamino, by halo, by hydroxyl, by C_1-C_7-alkoxy, and/or by halo-C_1-C_7-alkyl; (pyrrolidinyl, pyridazolidinyl, imidazolidinyl, piperidinyl, azepanyl, piperazinyl; morpholino, thiomorpholino, pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, oxazolyl or thiazolyl)-C_1-C_7-alkyl wherein pyrrolidinyl, pyrazolidinyl, imidazolidinyl, piperidinyl, azepanyl, piperazinyl, pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, oxazolyl or thiazolyl are unsubstituted or substituted by C_1-C_7-alkyl, by pyrrolidinyl, by pyrazolidinyl, by imidazolidinyl, by azepanyl, by piperazinyl, by amino, by N-mono- and/or N,N-di-C_1-C_7-alkylamino, by halo, by C_1-C_7-alkoxy, and/or by halo-C_1-C_7-alkyl; (pyrrolidinyl, pyrazolidinyl, imidazolidinyl, piperidinyl, azepanyl, piperazinyl, pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, oxazolyl or thiazolyl)-oxy-C_1-C_7-alkyl wherein pyrrolidinyl, pyrazolidinyl, imidazolidinyl, piperidinyl, azepanyl, piperazinyl, pyridinyl; pyrimidinyl, pyrazinyl, pyridazinyl, oxazolyl and thiazolyl are unsubstituted or substituted by C_1-C_7-alkyl, by pyrrolidinyl, by pyrazolidinyl, by imidazolidinyl, by piperidinyl, by azepanyl, by piperazinyl, by amino, by N-mono- and/or N,N-di-C_1-C_7-alkylamino, by halo, by C_1-C_7-alkoxy, and/or by halo-C_1-C_7-alkyl; (pyrrolidin, pyrazolidinyl, imidazolidinyl, piperidin, azepan, piperazin, pyridin, pyrimidin, pyrazin, pyridazin, oxazoly or thiazol)-carbonyl-C_1-C_7-alkyl wherein pyrrolidin, pyrazolidin, imidazolidin, piperidin, azepan, piperazin, pyridin, pyrimidin,

pyridazin, oxazol or pyridazin are unsubstituted or substituted by C_1-C_7-alkyl, by pyrrolidinyl, by pyrazolidinyl, by imidazolidinyl, by azepanyl, by piperazinyl, by amino, by N-mono- and/or N,N-di-C_1-C_7-alkylamino, by halo, by C_1-C_7-alkoxy, and/or by halo-C_1-C_7-alkyl; halo-C_1-C_7-alkyl, hydroxy-C_1-C_7-alkyl; C_1-C_7-alkoxy-C_1-C_7-alkyl; C_1-C_7-alkoxy-C_1-C_7-alkoxy-C_1-C_7-alkyl; phenyloxy- or naphthyloxy-C_1-C_7-alkyl; phenyl-C_1-C_7-alkoxy- or naphthyl-C_1-C_7-alkoxy-C_1-C_7-alkyl; amino-C_1-C_7-alkyl; N-mono- or N,N-di-(C_1-C_7-alkyl, C_1-C_7-alkoxy-C_1-C_7-alkyl and/or (mono- or di-(C_1-C_7-alkyl)-amino)-C_1-C_7-alkyl)-amino-C_1-C_7-alkyl; C_1-C_7-alkoxy-C_1-C_7-alkyl-amino-C_1-C_7-alkyl; mono- or di-[C_6-C_{18}-aryl-C_1-C_7-alkyl in which aryl is unsubstituted or substituted by C_1-C_7-alkyl, by pyrrolidinyl, by pyrazolidinyl, by imidazolidinyl, by piperidinyl, by azepanyl, by piperazinyl, by amino, by N-mono- and/or N,N-di-C_1-C_7-alkylamino, by halo, by hydroxyl, by C_1-C_7-alkoxy, and/or by halo-C_1-C_7-alkyl; naphthyl- or phenyl-C_1-C_7-alkyl]-amino-C_1-C_7-alkyl; C_1-C_7-alkanoylamino-C_1-C_7-alkyl; carboxy-C_1-C_7-alkyl; benzoyl- or naphthoyl-amino-C_1-C_7-alkyl; C_1-C_7-alkylsulfonylamino-C_1-C_7-alkyl; phenyl- or naphthylsulfonylamino-C_1-C_7-alkyl wherein phenyl or naphthyl is unsubstituted or substituted by one or more C_1-C_7-alkyl moieties; phenyl- or naphthyl-C_1-C_7-alkylsulfonylamino-C_1-C_7-alkyl; halo; hydroxy; C_1-C_7-alkoxy; C_6-C_{18}-aryl-C_1-C_7-alkoxy in which aryl is unsubstituted or substituted by C_1-C_7-alkyl, by C_1-C_7-alkoxy, by pyrrolidinyl, by pyrazolidinyl, by imidazolidinyl, by piperidinyl, by azepanyl, by piperazinyl, by amino, by N-mono- and/or N,N-di-C_1-C_7-alkylamino, by halo, by hydroxyl, by C_1-C_7-alkoxy, and/or by halo-C_1-C_7-alkyl; halo-C_1-C_7-alkoxy; hydroxy-C_1-C_7-alkoxy; C_1-C_7-alkoxy-C_1-C_7-alkoxy; (C_1-C_7-alkoxy-C_1-C_7-alkoxy)-C_1-C_7-alkoxy; [amino, mono- or di-(C_1-C_7-alkyl)amino]-C_1-C_7-alkoxy, N-C_1-C_7-alkanoylamino-C_1-C_7-alkoxy; N-unsubstituted-, N-mono- or N,N-di-(C_1-C_7-alkyl)carbamoyl-C_1-C_7-alkoxy; phenyl- or naphthyloxy; phenyl- or naphthyl-C_1-C_7-alkyloxy; (pyrrolidinyl, pyrazolidinyl, imidazolidinyl, piperidinyl, azepanyl, piperazinyl, pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, oxazolyl or thiazolyl)-C_1-C_7-alkoxy wherein pyrrolidinyl, pyrazolidinyl, imidazolidinyl, piperidinyl, azepanyl, piperazinyl, pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, oxazolyl and thiazolyl are unsubstituted or substituted by C_1-C_7-alkyl, by pyrrolidinyl, by pyrazolidinyl, by imidazolidinyl, by piperidinyl, by azepanyl, by piperazinyl, by amino, by N-mono- and/or N,N-di-C_1-C_7-alkylamino, by halo, by C_1-C_7-alkoxy, and/or by halo-C_1-C_7-alkyl; (pyrrolidinyl, pyrazolidinyl, imidazolidinyl, piperidinyl, azepanyl, piperazinyl, pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, oxazolyl or thiazolyl)-oxy-C_1-C_7-alkoxy wherein pyrrolidinyl, pyrazolidinyl, imidazolidinyl, piperidinyl, azepanyl, piperazinyl, pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, oxazolyl and thiazolyl are unsubstituted or substituted by C_1-C_7-alkyl, by pyrrolidinyl, by pyrazolidinyl, by imidazolidinyl, by piperidinyl, by azepanyl, by piperazinyl, by amino, by N-mono- and/or N,N-di-C_1-C_7-

alkylamino, by halo, by C_1-C_7-alkoxy, and/or by halo-C_1-C_7-alkyl; C_1-C_7-alkanoyloxy; benzoyl- or naphthoyloxy; C_1-C_7-alkylthio; halo-C_1-C_7-alkylthio; C_1-C_7-alkoxy-C_1-C_7-alkylthio; phenyl- or naphthylthio; phenyl- or naphthyl-C_1-C_7-alkylthio; C_1-C_7-alkanoylthio; benzoyl- or naphthaylthio; nitro; amino; mono- or di-[(C_1-C_7-alkyl, C_1-C_7-alkanoyl, C_1-C_7-alkoxy-carbonyl, hydroxy-C_1-C_7-alkyl, C_1-C_7-alkoxy-C_1-C_7alkyl and/or (amino, mono- or di-(C_1-C_7-alkyl)-amino)-C_1-C_7-alkyl]-amino; mono- or di-(naphthyl- or phenyl-C_1-C_7-alkyl)-amino; C_1-C_7-alkanoylamino; unsubstituted or amino-, N-mono- or N,N-di-(C_1-C_7-alkyl and/or phenyl- or naphthyl-C_1-C_7alkyl)amino-substituted benzoyl- or naphthoylamino; C_1-C_7-alkoxycarbonylamino; (phenyl or naphthyl)-C_1-C_7-alkoxycarbonylamino; C_1-C_7-alkylsulfonylamino; phenyl- or naphthylsulfonylamino wherein phenyl or naphthyl is unsubstituted or substituted by one or more C_1-C_7-alkyl moieties; phenyl- or naphthyl-C_1-C_7-alkylsulfonylamino; C_1-C_7-alkanoyl; C_1-C_7-alkoxy-C_1-C_7-alkanoyl; carboxyl; C_1-C_7-alkoxy-carbonyl; phenoxy- or naphthoxycarbonyl; phenyl- or naphthyl-C_1-C_7-alkoxycarbonyl; C_1-C_{10}- especially C_1-C_4-alkylendioxy, such as methylendioxy or 1,2-ethylendioxy; carbamoyl; N-mono- or N,N-di-[C_1-C_7-alkyl, naphthyl-C_1-C_7-alkyl, phenyl-C_1-C_7-alkyl, N'-mono- or N',N'-di-(C_1-C_7-alkyl)amino-C_1-C_7-alkyl, pyrrolidinyl-C_1-C_7-alkyl, pyrazolidinyl-C_1-C_7-alkyl, imidazolidinyl-C_1-C_7-alkyl, piperidinyl-C_1-C_7-alkyl, azepanyl-C_1-C_7-alkyl, piperazinyl- or N-(C_1-C_7-alkyl)piperazinyl-C_1-C_7-alkyl, mono-C_1-C_7-alkoxy-C_1-C_7-alkyl, (N'-mono- or N',N'-di-(C_1-C_7-alkyl)-amino); phenyl, pyridinyl, oxazolyl or thiazolyl each of which is unsubstituted or substituted by C_1-C_7-alkoxy, by halo, by pyrrolidino, by pyrazolidino, by imidazolidino, by piperidino, by azepan-1-yl, by piperazino, by hydroxyl-C_1-C_7-alkylamino, by hydroxyl-C_1-C_7-alkyl, by amino or by N-mono- or N,N-di-(C_1-C_7-alkyl)amino; pyrrolidinyl, pyrazolidinyl, imidazolidinyl, piperidinyl, azepanyl, piperazinyl, pyrimidinyl, pyrazinyl and/or pyridazinyl]-amino-carbonyl, such as N- mono- or N,N-di-(C_1-C_7-alkyl)-aminocarbonyl; N-C_1-C_7-alkoxy-C_1-C_7-alkylcarbamoyl; pyrrolidin-1-carbonyl; amino-N-pyrrolidin-1-carbonyl; N-mono- or N,N-di(C_1-C_7-alkyl)amino-pyrrolidin-1-carbonyl; imidazolidin-1-carbonyl; piperidin-1-carbonylmorpholin-4-carbonyl; thiomorpholin-4-carbonyl; S-oxothiomorpholin-4-carbonyl; S,S-dioxothiomorpholin-4-carbonyl; piperazin-1-carbonyl; N-C_1-C_7-alkyl-piperazin-1-carbonyl; N-C_1-C_7-alkoxycarbonyl-piperazin-1-carbonyl; N-mono- or N,N-di-(C_1-C_7-alkyl)-amino-substituted or unsubstituted pyrrolidinyl-C_1-C_7-alkyl; cyano; C_1-C_7-alkenylene or –alkinylene; C_1-C_7-alkylsulfonyl; phenyl- or naphthylsulfonyl wherein phenyl or naphthyl is unsubstituted or substituted by one or more, especially one to three, C_1-C_7-alkyl moieties; phenyl- or naphthyl-C_1-C_7-alkylsulfonyl; sulfamoyl; N-mono or N,N-di-(C_1-C_7-alkyl, phenyl-, naphthyl-, phenyl-C_1-C_7-alkyl-, pyrrolidinyl-C_1-C_7-alkyl, pyrazolidinyl-C_1-C_7-alkyl, imidazolyl-C_1-C_7-alkyl, piperidinyl-C_1-C_7-alkyl, azepanyl-C_1-C_7-alkyl, piperazinyl-C_1-C_7-alkyl,

N-C_1-C_7-alkylpiperazinyl-C_1-C_7-alkyl, naphthyl-C_1-C_7-alkyl, phenyl which is unsubstituted or substituted by C_1-C_7-alkoxy, by halo, especially fluoro, by pyrrolidino, by pyrazolidino, by imidazolidino, by azepan-1-yl, by piperidino, by piperazino, by hydroxyl-C_1-C_7-alkyl or by N-mono- or N,N-di-(C_1-C_7-alkyl)-C_1-C_7-alkyl; pyrrolidinyl, pyrazolidinyl, imidazolidinyl, piperidinyl, azepanyl, piperazinyl, pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, oxazolyl and/or thiazolyl)-aminosulfonyl, pyrazolyl, pyrazolidinyl, pyrrolyl, pyrrolidinyl, pyridyl that is unsubstituted or substituted by C_1-C_7-alkoxy and/or by halo-C_1-C_7-alkyl, pyrrolidinyl, pyrazolidinyl, imidazolidinyl, piperidinyl, azepanyl, piperazinyl, morpholinyl, thiomorpholinyl, S-oxo-thiomorpholinyl, S,S-dioxothiomorpholinyl, piperazinyl, N-C_1-C_7-alkyl-piperazinyl, 4-(phenyl-C_1-C_7-alkyl)-piperazinyl, 4-(naphthyl-C_1-C_7-alkyl)-piperazinyl, 4-(C_1-C_7-alkoxycarbonyl)-piperazinyl, 4-(phenyl-C_1-C_7-alkoxycarbonyl)-piperazinyl, 4-(naphthyl-C_1-C_7-alkoxycarbonyl)-piperazinyl, oxazolyl and thiazolyl;

unsubstituted or substituted heterocyclyl is a heterocyclic radical that is unsaturated (then also called heteroaryl), saturated or partially saturated and is a monocyclic or bicyclic or tricyclic ring; has 3 to 24 ring atoms; wherein one to fourcarbon ring atoms are replaced by a heteroatom selected from the group consisting of nitrogen, oxygen, sulfur S(=O) or $S(=O)_2$, the bonding ring having 4 to 12ring atoms; which heterocyclyl is unsubstituted or substituted by one or moresubstituents independently selected from the group consisting of the substituents defined above for substituted alkyl or for substituted aryl;

unsubstituted or substituted cycloalkyl is C_3-C_8-cycloalkyl and is unsubstituted or substituted by one or more substitutents independently selected from the substitutents for substituted aryl above;

esterified carboxy is unsubstituted or substituted alkyloxy-carbonyl, unsubstituted or substituted aryloxy-carbonyl, unsubstituted or substituted cycloalkyloxy-carbonyl or unsubstituted or substituted heterocyclyloxy-carbonyl, wherein alkyl, aryl, cycloalkyl and heterocyclyl and their substituted forms are as defined above;

in unsubstituted or substituted heterocyclyl-carbonyl, heterocyclyl is preferably a moiety chosen from heterocyclyl as defined above and is unsubstituted or substituted by one or more substitutents independently selected from those for substituted alkyl and substituted aryl and from oxo;

in unsubstituted or substituted carbamoyl, the N-substituents are selected from one or two substituents independently selected from unsubstituted or substituted C_1-C_7-alkyl as defined above, unsubstituted or substituted aryl as defined above, unsubstituted or substituted cycloalkyl as defined above and from unsubstituted or substituted heterocyclyl as defined above, where preferably either only one carbamoyl N-substituent is present or one N-substituent is C_1-C_7-alkyl, the other is selected from the group of substituents just mentioned;

acyl is unsubstituted or substituted aryl-carbonyl or –sulfonyl, unsubstituted or substituted heterocyclylcarbonyl or -sulfonyl, unsubstituted or substituted cycloalkylcarbonyl or -sulfonyl, formyl or unsubstituted or substituted alkylcarbonyl or -sulfonyl, unsubstituted or substituted alkyloxycarbonyl or –oxysulfonyl, unsubstituted or substituted aryl-oxycarbonyl or -oxysulfonyl, unsubstituted or substituted heterocyclyloxycarbonyl or -oxysulfonyl, unsubstituted or substituted cycloalkyloxycarbonyl or -oxysulfonyl or N-mono- or N,N-di-(unsubstituted or substituted aryl, unsubstituted or substituted heterocyclyl, unsubstituted or substituted cycloalkyl or unsubstituted or substituted alkyl)-aminocarbonyl; wherein unsubstituted or substituted aryl, unsubstituted or substituted heterocyclyl, unsubstituted or substituted cycloalkyl and unsubstituted or substituted alkyl are as described above;

and/or a tautomer, an N-oxide and/or a salt thereof.

4. A compound of the formula I according to claim 1 or to claim 2, wherein
R^1 is C_1-C_7-alkyl that is linear or branched and is unsubstituted or substituted by one or more, especially up to three, moieties independently selected from the group consisting of C_1-C_7-alkyl, especially methyl, of hydroxyl, of hydroxyl-C_1-C_7-alkyl, especially hydroxymethyl, of C_1-C_7-alkoxy-C_7-C_7-alkyl, especially 2-methoxy-ethoxy or methoxyethoxy or ethoxy-methoxy, of C_6-C_{14}-aryl, especially phenyl, wherein aryl is unsubstituted or substituted by one or more, especially up to three, moieties independently selected from the group consisting of C_1-C_7-alkyl, especially methyl, halo-C_1-C_7-alkyl, especially trifluoromethyl, hydroxyl, C_1-C_7-alkoxy, C_1-C_7-alkoxy-C_1-C_7-alkoxy, especially 2-methoxyethoxy or 3-methoxypropoxy, [amino, mono- or di-(C_1-C_7-alkyl)-amino]-C_1-C_7-alkoxy, amino, mono- or di-[C_1-C_7-alkyl, hydroxy-C_1-C_7-alkyl, C_1-C_7-alkoxy-C_1-C_7-alkyl, amino-C_1-C_7-alkyl, amino and/or mono- or di-(C_1-C_7-alkyl)-amino-C_1-C_7-alkyl]-amino, halo, especially fluoro, chloro or bromo, and saturated heterocyclyl-C_1-C_7-alkoxy wherein saturated heterocyclyl has 3 to 14 ring atoms of

which 1 to 4 are a heteroatom independently selected from N, S, S(=O), $S(=O)_2$ and O and is unsubstituted or substituted with C_1-C_7-alkyl, especially pyrrolidinyl-, piperidinyl-, piperazinyl- or N-(C_1-C_7-alkyl)-piperazinyl-C_1-C_7-alkoxy, and of mono- or bicyclic C_3-C_{14}-heterocyclyl with 3 to 14 ring atoms of which 1 to 4 are a heteroatom independently selected from N, S, S(=O), $S(=O)_2$ and O and is unsubstituted or substituted with C_1-C_7-alkyl, especially corresponding heteroaryl, more especially indolyl, isoindolyl, indazolyl, quinolinyl, isoquinolinyl, phthalazinyl, quinoxalinyl, quinazolinyl, cinnolinyl, benzofuranyl, isobenzofuranyl, chromenyl, isochromenyl, benzothiophenyl, thiochromenyl or isothiochromenyl,

R^2 is C_6-C_{14}-aryl (especially phenyl) that is unsubstituted or substituted by one or more, especially up to three, moieties independently selected from the group consisting of C_1-C_7-alkyl-phenyl, especially methyl, hydroxyl, and halo, especially fluoro or chloro,

R^3 is hydrogen or preferably

C_1-C_7-alkyl that is unsubsituted by one or more, especially up to three, moieties independently selected from the group consisting of hydroxyl, amino and heterocyclyl-C_1-C_7-alkylamino wherein heterocyclyl has 3 to 14 ring atoms of which 1 to 4 are a heteroatom independently selected from N, S, S(=O), $S(=O)_2$ and O, and is saturated, especially (morpholinyl, thiomorpholiny, S-oxothiomorpholinyl or S,S-dioxothiomorpholinyl)-C_1-C_7-alkylamino,

cyano, carboxy, C_1-C_7-alkoxycarbonyl or C_6-C_{14}-aryl-C_1-C_7-alkoxycarbonyl;

heterocyclyl-carbonyl (heterocyclyl-C(=O)) wherein heterocyclyl is unsaturated or preferably saturated, has 3 to 14 ring atoms of which 1 to 4 are a heteroatom independently selected from N, S, S(=O), $S(=O)_2$ and O, preferably N, such as pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, thiomorpholinyl, S-oxothiomorpholinyl or S,S-dioxothiomorpholinyl, and is unsubstituted or substituted with one or more, especially one to three, moieties independently selected from the group consisting of C_1-C_7-alkyl, hydroxy-C_1-C_7-alkyl, hydroxy, oxo, amino or N-mono- or N,N-di-(C_1-C_7-alkyl, {amino or mono- or di-C_1-C_7-alkylamino}-C_1-C_7-alkyl, C_1-C_7-alkanoyl and/or C_1-C_7-alkoxycarbonyl)-amino, C_1-C_7-alkanoyl, C_1-C_7-alkylsulfonyl and saturated heterocyclyl with 3 to 14 ring atoms and 1 to 4 heteroatoms independently selected from N, S, S(=O), $S(=O)_2$ and O, preferably N , e.g. pyrrolidinyl, imidazolidinyl, piperidinyl, piperazinyl, morpholinyl, thiomorpholinyl, S-oxo-thiomorpholinyl or S,S-dioxothiomorpholinyl, wherein said saturated heterocyclyl is unsubstituted or substituted by one or more,

especially up to three, moieties independently selected from C_1-C_7-alkyl, hydroxy-C_1-C_7-alkyl C_1-C_7-alkoxy-C_1-C_7-alkyl, oxo, amino and mono- or di-(C_1-C_7-alkyl)-amino),

carbamoyl, N-mono- or N,N-di-[C_1-C_7-alkyl, hydroxy-C_1-C_7-alkyl, C_1-C_7-alkoxy-C_1-C_7-alkyl, amino-C_1-C_7-alkyl, mono- or di-(C_1-C_7-alkyl)-amino-C_1-C_7-alkyl, C_6-C_{14}-aryl wherein aryl is unsubstituted or substituted by one or more, especially up to three, moieties independently selected from the group consisting of C_1-C_7-alkyl, C_1-C_7-alkoxy, saturated heterocyclyl with 3 to 14 ring atoms and 1 to 4 heteroatoms independently selected from N, S, S(=O), $S(=O)_2$ and O, preferably N , e.g. pyrrolidinyl, imidazolidinyl, piperidinyl, piperazinyl, azepanyl, morpholinyl, thiomorpholinyl, S-oxo-thiomorpholinyl or S,S-dioxothiomorpholinyl, wherein said saturated heterocyclyl is unsubstituted or substituted with one or more, especially up to three, moieties independently selected from C_1-C_7-alkyl, hydroxy-C_1-C_7-alkyl, hydroxy, oxo, and C_1-C_7-alkoxycarbonyl, C_6-C_{14}-aryl-C_1-C_7-alkyl, and saturated heterocyclyl or (saturated heterocyclyl)-C_1-C_7-alkyl wherein saturated heterocyclyl in both cases has 3 to 14 ring atoms and 1 to 4 heteroatoms independently selected from N, S, S(=O), $S(=O)_2$ and O, preferably N , e.g. pyrrolidinyl, imidazolidinyl, piperidinyl, piperazinyl, azepanyl, morpholinyl, thiomorpholinyl, S-oxo-thiomorpholinyl, S,S-dioxothiomorpholinyl, indolyl or isoindolyl or (pyrrolidinyl, imidazolidinyl, piperidinyl, piperazinyl, azepanyl, morpholinyl, thiomorpholinyl, S-oxo-thiomorpholinyl, S,S-dioxothiomorpholinyl, indolyl or isoindolyl)-C_1-C_7-alkyl, wherein said saturated heterocyclyl is unsubstituted or substituted with one or more, especially up to three, moieties independently selected from C_1-C_7-alkyl, hydroxy-C_1-C_7-alkyl, C_1-C_7-alkoxy-C_1-C_7-alkyl, oxo, C_1-C_7-alkanoyl and C_1-C_7-alkoxycarbonyl]-carbamoyl,

heteroaryl with 3 to 14 ring atoms and 1 to 5 ring heteroatoms independently selected from the group consisting of N, S, S(=O), $S(=O)_2$ and O, especially N, S and O, such as triazolyl or especially tetrazolyl,

or cyano,

R^4 is hydrogen, C_1-C_7-alkyl, halo or heteroaryl with 3 to 14 ring atoms and 1 to 5 heteroatoms independently selected from the group consisting of N, S, S(=O), $S(=O)_2$ and O, especially N, such as pyridyl,

R^A is hydrogen or C_1-C_7-alkyl, preferably hydrogen;

X is hydrogen, C_1-C_7-alkyl, halo or cyano, especially hydrogen or fluoro, and

Y is C_1-C_7-alkyl, halo or cyano, especially methyl, fluoro, chloro, bromo or cyano,

and/or a tautomer, an N-oxide and/or a pharmaceutically acceptable salt thereof.

5. A compound of the formula I according to claim 1 or to claim 2, wherein

R^1 is C_1-C_7-alkyl, especially 3,3-dimethylbutyl, C_1-C_7-alkylbenzyl, especially methyl-benzyl, more especially 4-methylbenzyl, (halo-C_1-C_7-alkyl)-benzyl, especially trifluoromethylbenzyl, more especially 4-trifluoromethylbenzyl, hydroxy-halo-benzyl, especially chloro-hydroxy-benzyl, more especially 4-chloro-2-hydroxybenzyl, halobenzyl, especially bromobenzyl, more especially 4-bromobenzyl, chlorobenzyl, more especially 4-chlorobenzyl, fluorobenzyl, more especially 4-fluorobenzyl, dichlorobenzyl, more especially 3,4- or 2,4-dichlorobenzyl, chloro-fluorobenzyl, more especially 4-chloro-3-fluorobenzyl, 3-chloro-4-fluorobenzyl or 4-chloro-2-fluorobenzyl, (R,S)- or preferably (R)- or (S)-1-(halo-phenyl)-1-(C_1-C_7-alkyl or hydroxy)-C_1-C_7-alkyl, especially (R,S)- or preferably (R)- or (S)-1-(fluorophenyl, chlorophenyl or bromo-phenyl)-1-(methyl or hydroxy)-methyl, more especially (R,S)- or preferably (R)- or (S)-1-(4-fluorophenyl, 4-chlorophenyl or 4-bromophenyl)-1-(methyl or hydroxy)-methyl, (R,S)- or preferably (R)- or (S)-1-(halo-phenyl)-1-[(hydroxy or C_1-C_7-alkoxy)-C_1-C_7-alkyl]-C_1-C_7-alkyl, especially (R,S)- or preferably (R)- or (S)-1-(chlorophenyl)-1-(hydroxymethyl or methoxymethyl)-methyl, more especially (R,S)- or preferably (R)- or (S)-1-(4-chlorophenyl)- 1-(hydroxymethyl or methoxymethyl)-methyl, C_1-C_7-alkyl-halo-benzyl, especially methyl-halo-benzyl, more especially 4-chloro-2-methyl-benzyl, hydroxy-halo-benzyl, especially hydroxy-chloro-benzyl, more especially 4-chloro-2-hydroxybenzyl, C_1-C_7-alkoxy-halo-benzyl, especially methoxy-chloro-benzyl, such as 4-chloro-2-methoxybenzyl, (hydroxy-C_1-C_7-alkoxy or C_1-C_7-alkoxy-C_1-C_7-alkoxy)-halo-benzyl, especially (2-hydroxyethoxy, 3-hydroxypropoxy or 2-methoxy-ethoxy)-chloro-benzyl, more especially 4-chloro-2-(2-hydroxyethoxy, 3-hydroxy-propoxy or 2-methoxy-ethoxy)- benzyl, [amino, N-mono- or N,N-di-(C_1-C_7-alkylamino)-C_1-C_7-alkoxy]-halo-benzyl, especially [2-(N,N-dimethylamino)-ethoxy]-chloro-benzyl, more especially 2-[2-(N,N-dimethylamino)-ethoxy]-4-chloro-benzyl, (hydroxy-C_1-C_7-alkyl-amino)-halo-benzyl, especially [(2-hydroxymethyl- or 3-hydroxypropyl)-amino]-chloro-benzyl, more especially 2-[(2-hydroxymethyl- or 3-hydroxypropyl)-amino]-4-chloro-benzyl, (C_1-C_7-alkoxy-C_1-C_7-alkyl-amino)-halo-benzyl, especially [(2-methoxymethyl- or 3-methoxypropyl)-amino]-chloro-benzyl, more especially 2-[(2-methoxymethyl- or 3-methoxypropyl)-amino]-4-chloro-benzyl, [{amino, N-mono- or N,N-di-(C_1-C_7-alkyl)-amino}-C_1-C_7-alkylamino]-halo-benzyl, especially [(2-dimethylaminoethyl-amino]-chloro-benzyl, more especially 2-(2-dimethylaminoethyl-amino)-4-chloro-benzyl, (pyrrolidinyl-, piperidinyl-, piperazinyl- or N-(C_1-C_7-alkyl)-piperazinyl-C_1-C_7-alkoxy)-halo-benzyl, especially (pyrrolidino-, piperidino-, piperazino- or 4-(C_1-C_7-alkyl)-piperazin-1-yl-C_1-C_7-alkoxy)-halo-benzyl, more especially 4-chloro-2-[2-(pyrrolidino-, piperidino-, piperazino- or 4-(C_1-C_7-alkyl)-piperazin-1-yl)-ethoxy]-benzyl,

indolyl-C_1-C_7-alkyl, especially indolylmethyl, more especially indol-6-ylmethyl, benzofuranyl-C_1-C_7-alkyl, especially benzofuranylmethyl, more especially benzofuran-6-ylmethyl, or benzothiophenyl-C_1-C_7-alkyl, especially benzothiophenylmethyl, more especially benzothiophen-6-ylmethyl;

R^2 is phenyl, C_1-C_7-alkyl-phenyl, especially methylphenyl, more especially 2-methylphenyl, hydroxyphenyl, especially 3-hydroxyphenyl, or halophenyl, especially phenyl or fluoro-, chloro- or fluoro-chloro-phenyl, more especially phenyl, 2-fluoropheny, 3-fluorophenyl or 3-chloro-2-fluorophenyl,

R^3 is hydrogen or preferably hydroxyl-C_1-C_7-alkyl, especially hydroxymethyl, amino-C_1-C_7-alkyl, especially 2-aminoethyl, (morpholinyl, thiomorpholiny, S-oxothiomorpholinyl or S,S-dioxothiomorpholinyl)-C_1-C_7-alkylamino-C_1-C_7-alkyl, especially N-(2-morpholinoethyl)-amino-methyl,

cyano, carboxy, C_1-C_7-alkoxycarbonyl, especially methoxycarbonyl or ethoxycarbonyl,

azetidin-carbonyl, especially acetidin-1-ylcarbonyl, pyrrolidin-carbonyl, especially pyrrolidin-1-carbonyl, achiral or (R,S)- or preferably (R)- or (S)-[amino or N'-mono- or N',N'-di-(C_1-C_7-alkyl and/or {amino or mono- or di-C_1-C_7-alkylamino}-C_1-C_7-alkyl)-amino]-pyrrolidin-carbonyl, especially (R,S)- or preferably (R)- or (S)-3-(dimethylamino)-pyrrolidin-1-carbonyl, (R,S)- or preferably (R)- or (S)-3-(diethylamino)-pyrrolidin-1-carbonyl, (R,S)- or preferably (R)- or (S)-3-[N-2-(dimethylamino)-ethyl-amino]-pyrrolidin-1-carbonyl, (R,S)- or preferably (R)- or (S)-3-[N-3-(dimethylamino)-propyl-amino]-pyrrolidin-1-carbonyl, (R,S)- or preferably (R)- or (S)-3-[N-2-(dimethylamino)-ethyl-N-methyl-amino]-pyrrolidin-1-carbonyl, or (R,S)- or preferably (R)- or (S)-3-[N-3-(dimethylamino)-propyl-N-methyl-amino]-pyrrolidin-1-carbonyl or (R,S)-, (R,S)- or preferably (R)- or (S)-pyrrolidinyl-pyrrolidin-carbonyl, especially (R,S)- or preferably (R)- or (S)-3-(pyrrolidin-1-yl)-pyrrolidin-carbonyl, (R,S)- or preferably (R)- or (S)-[(amino, mono- or di-(C_1-C_7-alkyl)-amino)-piperidinyl]-pyrrolidincarbonyl, especially (R,S)- or preferably (R)- or (S)-3-(4-dimethylamino-piperidin-1-yl)-pyrrolidin-1-carbonyl, (R,S)- or preferably (R)- or (S)-[hydroxy-C_1-C_7-alkyl, hydroxy, amino or mono- or di-(C_1-C_7-alkyl, C_1-C_7-alkanoyl, C_1-C_7-alkoxycarbonyl)-amino]-pyrrolidin-carbonyl, especially (R,S)- or preferably (R)- or (S)-3-hydroxy-pyrrolidin-1-carbonyl, especially (R,S)- or preferably (R)- or (S)-3-hydroxymethyl-pyrrolidin-1-carbonyl, (R,S)- or preferably (R)- or (S)-3-amino-pyrrolidin-1-carbonyl, (R,S)- or preferably (R)- or (S)-3-ethylamino-pyrrolidin-1-carbonyl, (R,S)- or preferably (R)- or (S)-3-tert-butoxycarbonylamino-pyrrolidin-1-carbonyl, (R,S)- or preferably (R)- or (S)-3-(N-methyl-N-acetyl-amino)-pyrrolidin-1-carbonyl, (R,S)- or preferably (R)- or (S)-(piperazinyl, C_1-C_7-

alkylpiperazinyl, (hydroxy-C_1-C_7-alkyl)-piperazinyl morpholinyl, thiomorpholinyl, S-oxo-thiomorpholinyl or S,S-dioxo-thiomorpholinyl)-pyrrolidin-carbonyl, especially (R,S)- or preferably (R)- or (S)-3-(4-methylpiperazino)-pyrrolidin-1-carbonyl, (R,S)- or preferably (R)- or (S)-3-(4-(2-hydroxyethyl)-piperazino)-pyrrolidin-1-carbonyl, (R,S)- or preferably (R)- or (S)-3-morpholino-pyrrolidin-1-carbonyl or (R,S)- or preferably (R)- or (S)-3-dioxothiomorpholino-pyrrolidin-1-carbonyl,

piperidinyl-carbonyl, especially piperidin-1-carbonyl (piperidin-1-yl-C(=O)-), (hydroxy, hydroxy-C_1-C_7-alkyl, amino or mono- or di-(C_1-C_7-alkyl)amino)-piperidin-carbonyl, especially 4-hydroxymethyl-piperidin-1- carbonyl or 4-dimethylamino-piperidin-1-carbonyl, oxoimidazolidinyl-piperidincarbonyl, especially 4-(2-oxo-imidazolidin-1-yl)-piperidin-1-carbonyl, (phenyl-oxoimidazolidinyl)-piperidincarbonyl, especially 4-(3-phenyl-2-oxo-imidazolidin-1-yl)-piperidin-1-carbonyl, pyrrolidinyl- or oxopyrrolidinyl-piperidincarbonyl, especially 4-(pyrrolidin-1-yl)-piperidin-1 -carbonyl or 4-(2-oxo-pyrrolidin-1-yl-)-piperidin-1 -carbonyl, piperazinyl- or N-(C_1-C_7-alkyl)-piperazinyl-piperidin-carbonyl, especially 4-(4-methyl-piperazin-1-yl)-piperidin-1-carbonyl, (morpholinyl, thiomorpholinyl, S-oxo-thiomorpholinyl or S,S-dioxo-thiomorpholinyl)-piperidin-carbonyl, especially 4-morpholino-piperidin-1-carbonyl, (oxo-benzoimidazolidinyl)-piperidin-carbonyl, especially (2-oxo-1,3-benzoimidazolidin-1-yl)-piperidin-carbonyl, piperazin-carbonyl, especially piperazin-1-carbonyl, (C_1-C_7-alkyl or hydroxyl-C_1-C_7-alkyl)-piperazin-carbonyl, especially 4-methyl-, 4-(2-hydroxyethyl)- or 4-(3-hydroxypropyl)-piperazin-1-carbonyl, oxopiperazin-carbonyl, especially 2-oxo-piperazin-4-carbonyl, C_1-C_7-alkanoyl-piperazin-carbonyl, especially 1-acetyl-piperazin-4-carbonyl, C_1-C_7-alkylsulfonyl-piperazin-carbonyl, especially 4-methanesulfonyl-piperazin-1- carbonyl,

morpholin-carbonyl (morpholinyl-C(=O)-), especially morpholin-1-carbonyl, (thiomorpholin, S-oxothiomorpholin or S,S-dioxothiomorpholin)-carbonyl, especially S,S-dioxothiomorpholin-1-carbonyl,

carbamoyl (synonymous: amino-carbonyl, -C(=O)-NH_2),

N-mono- or N,N-di-(C_1-C_7-alkyl)-carbamoyl, especially N-methyl-, N,N-dimethyl-, N-ethyl-or N-tert-butyl-carbamoyl,

N-[(hydroxy- or C_1-C_7-alkoxy)-C_1-C_7-alkyl]-carbamoyl, especially N-(2-hydroxyethyl)-carbamoyl, N-(3-hydroxypropyl)-carbamoyl, N-(2-methoxyethyl)-carbamoyl or N-(3-methoxypropyl)-carbamoyl, N-[(amino, mono- or di-(C_1-C_7-alkyl)-amino)-C_1-C_7-alkyl]-carbamoyl, especially N-(2-amino-ethyl)-carbamoyl, N-(2-(methylamino)-ethyl-carbamoyl, 2-(N,N-di-(methyl)-amino)-ethyl-carbamoyl, 3-(N,N-di-(methyl)-amino)-propyl-carbamoyl, N-[2-(N,N-di-(methyl)-amino)-ethyl]-N-methyl-carbamoyl, N-[3-(N,N-di-(methyl)-amino)-propyl]-N-

methyl-carbamoyl, 2-(N,N-di-(ethyl)-amino)-ethyl-carbamoyl, 3-(N,N-di-(ethyl)-amino)-propyl-carbamoyl, N-[2-(N,N-di-(ethyl)-amino)-ethyl]-N-methyl-carbamoyl, N-[3-(N,N-di-(ethyl)-amino)-propyl]-N-methyl-carbamoyl, N-phenyl-carbamoyl, N-(C_1-C_7-alkoxy-phenyl)-carbamoyl, especially N-(methoxyphenyl)-carbamoyl, [(pyrrolidinyl, piperidinyl, piperazinyl or 1-(C_1-C_7-alkyl)-piperazinyl)-phenyl]-carbamoyl, especially N-[3-(piperazin-4-yl or 1-methyl-piperazin-4-yl)-phenyl]-carbamoyl, N-(phenyl-C_1-C_7-alkyl)-carbamoyl, especially N-benzyl-carbamoyl, N-(oxoimidazolidinyl-C_1-C_7-alkyl)-carbamoyl, especially N-[2-(2-oxoimidazol-1-yl)-ethyl]-carbamoyl, N-(pyrrolidinyl-C_1-C_7-alkyl)-carbamoyl, especially N-(pyrrolidinomethyl)-carbamoyl, N-(2-pyrrolidino-ethyl)-carbamoyl or N-(3-pyrrolidino-propyl)-carbamoyl, N-(oxopyrrolidinyl-C_1-C_7-alkyl)-carbamoyl, especially N-(2-oxo-pyrrolidinomethyl)-carbamoyl, N-[2-(2-oxopyrrolidino)-ethyl]-carbamoyl or N-[3-(2-oxopyrrolidino)-propyl]-carbamoyl,

N-Piperidinyl-carbamoyl, especially N-piperidin-4-yl-carbamoyl, N-[(C_1-C_7-alkyl)-piperidinyl]-carbamoyl, especially N-(1-methyl-piperidin-4-yl)-carbamoyl, N-[(hydroxyl-C_1-C_7-alkyl)-piperidinyl]-carbamoyl, especially N-[1-(2-hydroxyethyl)-piperidin-4-yl]-carbamoyl, N-[N-(C_1-C_7-alkoxycarbonyl)-piperidinyl]-carbamoyl, especially N-[1-(tert-butoxycarbonyl) -piperidin-4-yl]-carbamoyl, N-(piperidinyl-C_1-C_7-alkyl)-carbamoyl, especially N-(piperidin-1-yl-methyl)-, N-[2-(piperidin-1-yl-)-ethyl]- or N-[3-(piperidin-1-yl)-propyl]-carbamoyl, N-(azepan-C_1-C_7-alkyl)-carbamoyl, especially N-(azepan-1-yl-methyl)-, N-[2-(piperidin-1-yl-)-ethyl]- or N-[3-(piperidin-1-yl)-propyl]-carbamoyl, N-(piperazinyl-C_1-C_7-alkyl)-carbamoyl, especially N-(piperazin-1-yl-methyl)-, N-[2-(piperazin-1-yl-)-ethyl]- or N-[3-(piperazin-1-yl)-propyl]-carbamoyl, N-(oxopiperazinyl-C_1-C_7-alkyl)-carbamoyl, especially N-[(2-oxo-piperazin-4-yl-)-methyl]-, N-[2-(2-oxo-piperazin-4-yl-)-ethyl]- or N-[3-(2-oxo-piperazin-4-yl)-propyl]-carbamoyl, N-((C_1-C_7-alkyl)-piperazinyl-C_1-C_7-alkyl)-carbamoyl, especially N-[(1-methyl-piperazin-4-yl-)-methyl]-, N-[2-(1-methyl-piperazin-4-yl-)-ethyl]- or N-[3-(1-methyl-piperazin-1-yl)-propyl]-carbamoyl, N-(1-(hydroxyl-C_1-C_7-alkyl)-piperazinyl-C_1-C_7-alkyl)-carbamoyl, especially N-[(1-(2-hydroxyethyl)-piperazin-4-yl-)-methyl]-, N-[2-(1-(2-hydroxyethyl)-piperazin-4-yl-)-ethyl]- or N-[3-(1-(2-hydroxyethyl)-piperazin-1-yl)-propyl]-carbamoyl, N-(1-(C_1-C_7-alkanoyl)-piperazinyl-C_1-C_7-alkyl)-carbamoyl, especially N-[(1-acetyl-piperazin-4-yl-)-methyl]-, N-[2-(1-acetyl-piperazin-4-yl-)-ethyl]- or N-[3-(1-acetyl-piperazin-1-yl)-propyl]-carbamoyl, N-(1-(C_1-C_7-alkoxycarbonyl)-piperazinyl-C_1-C_7-alkyl)-carbamoyl, especially N-[(1-(tert-butoxycarbonyl)-piperazin-4-yl-)-methyl]-, N-[2-(1-(tert-butoxycarbonyl)-piperazin-4-yl-)-ethyl]- or N-[3-(1-(tert-butoxycarbonyl)-piperazin-1-yl)-propyl]-carbamoyl, N-[(morpholinyl, thiomorpholinyl, S-oxo-thiomorpholinyl or S,S-dioxo-thiomorpholinyl)-C_1-C_7-alkyl]-carbamoyl, especially N-morpholinomethyl-, N-(2-morpholino-ethyl)-, N-(3-morpholinopropyl)-carbamoyl, N-(S,S-dioxothiomorpholino)-methyl-, N-[2-(S,S-

dioxothiomorpholino)-ethyl]- or N-[3-(S,S-dioxothiomorpholino)-propyl]-carbamoyl, N-[dioxo-1H, 3H-isoindolyl)-C_1-C_7-alkyl)-carbamoyl, especially N-(1,7-dioxo-1H, 7H-isoindolin-2-yl-methyl)-, N-[2-(1,7-dioxo-1H, 7H-isoindolin-2-yl)-ethyl]- or N-[3-(1,7-dioxo-1H, 7H-isoindolin-2-yl)-propyl]-carbamoyl,
triazolyl or tetrazolyl, especially tetrazol-5-yl,
or cyano,

R^4 is hydrogen, C_1-C_7-alkyl, especially methyl, halo, especially bromo or chloro, or pyridyl, especially pyridin-3-, -4- or –2-yl,
R^A is hydrogen or C_1-C_7-alkyl, preferably hydrogen;
X is hydrogen, C_1-C_7-alkyl, halo or cyano, especially hydrogen or fluoro, and
Y is C_1-C_7-alkyl, halo or cyano, especially methyl, fluoro, chloro, bromo or cyano,

and/or a tautomer, an N-oxide and/or a pharmaceutically acceptable salt thereof.

6. A compound of the formula I according to claim 1 or to claim 2, wherein
R^1 is halobenzyl, especially bromobenzyl, more especially 4-bromobenzyl, chlorobenzyl, more especially 4-chlorobenzyl, or fluorobenzyl, more especially 4-fluorobenzyl,
R^2 is phenyl,
R^3 is hydroxyl-C_1-C_7-alkyl, especially hydroxymethyl, carboxy, achiral or (R,S)- or preferably (R)- or (S)-[amino or N'-mono- or N',N'-di-(C_1-C_7-alkyl and/or {amino or mono- or di-C_1-C_7-alkylamino}-C_1-C_7-alkyl)-amino]-pyrrolidin-carbonyl, especially (R,S)- or preferably (R)- or (S)-3-[N-2-(dimethylamino)-ethyl-N-methyl-amino]-pyrrolidin-1-carbonyl, amino or mono- or di-(C_1-C_7-alkyl)amino-piperidin-carbonyl, especially 4-dimethylamino-piperidin-1-carbonyl, carbamoyl, N-C_1-C_7-alkylcarbamoyl, especially N-methyl- or N-ethylcarbamoyl, N-((C_1-C_7-alkyl)-piperazinyl-C_1-C_7-alkyl)-carbamoyl, especially N-[(1-methyl-piperazin-4-yl-)-methyl]-, N-[2-(1-methyl-piperazin-4-yl-)-ethyl]- or N-[3-(1-methyl-piperazin-1-yl)-propyl]-carbamoyl, or N-[(morpholinyl or thiomorpholinyl)-C_1-C_7-alkyl]-carbamoyl, especially N-morpholinomethyl-, N-(2-morpholinoethyl)-, N-(3-morpholinopropyl)-carbamoyl,

R^4 is hydrogen or C_1-C_7-alkyl, especially methyl, or halo, especially bromo or chloro, more preferably hydrogen,
R^A is hydrogen;
X is halo or fluoro, and

Y is halo or cyano, especially chloro or cyano;

and/or a tautomer, an N-oxide and/or a pharmaceutically acceptable salt thereof,.

7. A compound of the formula I according to claim 1 or to claim 2, selected from the group of compounds with the following names:
6-chloro-3-[3-(4-chloro-benzyl)-5-phenyl-3H-imidazol-4-yl]-1H-indole;
6-chloro-3-[3-(4-chloro-benzyl)-5-phenyl-3H-imidazol-4-yl]-1H-indole-2-carboxylic acid (2-morpholin-4-yl-ethyl)-amide;
6-chloro-3-[3-(4-chloro-benzyl)-5-phenyl-3H-imidazol-4-yl]-1H-indole-2-carboxylic acid;
6-chloro-3-[3-(4-chloro-benzyl)-5-phenyl-3H-imidazol-4-yl]-1H-indole-2-carboxylic acid ethyl ester;
6-chloro-3-[3-(4-chloro-benzyl)-5-phenyl-3H-imidazol-4-yl]-1H-indole-2-carboxylic acid [2-(1,3-dioxo-1,3-dihydro-isoindol-2-yl)-ethyl]-amide;
4-[2-({6-chloro-3-[3-(4-chloro-benzyl)-5-phenyl-3H-imidazol-4-yl]-1H-indole-2-carbonyl}-amino)-ethyl]-piperazine-1-carboxylic acid tert-butyl ester;
4-[3-({6-chloro-3-[3-(4-chloro-benzyl)-5-phenyl-3H-imidazol-4-yl]-1H-indole-2-carbonyl}-amino)-propyl]-piperazine-1-carboxylic acid tert-butyl ester;
4-({6-chloro-3-[3-(4-chloro-benzyl)-5-phenyl-3H-imidazol-4-yl]-1H-indole-2-carbonyl}-amino)-piperidine-1-carboxylic acid tert-butyl ester;
6-chloro-3-[3-(4-chloro-benzyl)-5-phenyl-3H-imidazol-4-yl]-1H-indole-2-carboxylic acid [2-(tert-butyl-dimethyl-silanyloxy)-ethyl]-amide;
6-chloro-3-[3-(4-chloro-benzyl)-5-phenyl-3H-imidazol-4-yl]-1H-indole-2-carboxylic acid [3-(tert-butyl-dimethyl-silanyloxy)-propyl]-amide;
((S)-1-{6-chloro-3-[3-(4-chloro-benzyl)-5-phenyl-3H-imidazol-4-yl]-1H-indole-2-carbonyl}-pyrrolidin-3-yl)-carbamic acid tert-butyl ester;
6-chloro-3-[3-(4-chloro-benzyl)-5-phenyl-3H-imidazol-4-yl]-5-fluoro-1H-indole-2-carboxylic acid;
6-chloro-3-[3-(4-chloro-benzyl)-5-phenyl-3H-imidazol-4-yl]-5-fluoro-1H-indole-2-carboxylic acid methyl ester;
((R)-1-{6-chloro-3-[3-(4-chloro-benzyl)-5-phenyl-3H-imidazol-4-yl]-1H-indole-2-carbonyl}-pyrrolidin-3-yl)-carbamic acid tert-butyl ester;
3-[3-(4-bromo-benzyl)-5-phenyl-3H-imidazol-4-yl]-6-chloro-1H-indole-2-carboxylic acid;

3-[3-(4-bromo-benzyl)-5-phenyl-3H-imidazol-4-yl]-6-chloro-1H-indole-2-carboxylic acid; ethyl ester

3-[3-(2-tert-butoxy-4-chloro-benzyl)-5-phenyl-3H-imidazol-4-yl]-6-chloro-5-fluoro-1H-indole;

3-[3-(4-chloro-benzyl)-5-phenyl-3H-imidazol-4-yl]-6-cyano-1H-indole-2-carboxylic acid;

3-[3-(4-chloro-benzyl)-5-phenyl-3H-imidazol-4-yl]-6-cyano-1H-indole-2-carboxylic acid methyl ester;

6-chloro-3-{3-[(S)-1-(4-chloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carboxylic acid;

6-chloro-3-{3-[(S)-1-(4-chloro-phenyl)-ethyl]-5-phenyl-3H-imidazol-4-yl}-1H-indole-2-carboxylic acid ethyl ester;

6-chloro-3-[3-(3,3-dimethyl-butyl)-5-phenyl-3H-imidazol-4-yl]-1H-indole-2-carboxylic acid amide;

6-chloro-3-[3-(3,3-dimethyl-butyl)-5-phenyl-3H-imidazol-4-yl]-1H-indole-2-carboxylic acid ethyl ester;

6-chloro-3-[3-(3,3-dimethyl-butyl)-5-phenyl-3H-imidazol-4-yl]-1H-indole-2-carboxylic acid amide;

6-chloro-3-[3-(4-chloro-benzyl)-5-phenyl-3H-imidazol-4-yl]-2-(1H-tetrazol-5-yl)-1H-indole;

6-chloro-3-[3-(4-chloro-benzyl)-5-phenyl-3H-imidazol-4-yl]-1H-indole-2-carbonitrile;

{6-chloro-3-[3-(4-chloro-benzyl)-5-phenyl-3H-imidazol-4-yl]-1H-indol-2-yl}-methanol;

{6-chloro-3-[3-(4-chloro-benzyl)-5-phenyl-3H-imidazol-4-yl]-1H-indol-2-ylmethyl}-(2-morpholin-4-yl-ethyl)-amine;

3-[1-(4-chloro-benzyl)-5-(6-chloro-5-fluoro-1H-indol-3-yl)-1H-imidazol-4-yl]-phenol;

6-chloro-3-[3-(4-chloro-benzyl)-5-(3-methoxy-phenyl)-3H-imidazol-4-yl]-5-fluoro-1H-indole;

{6-chloro-3-[3-(4-chloro-benzyl)-5-(3-hydroxy-phenyl)-3H-imidazol-4-yl]-1H-indol-2-yl}-((S)-3-dimethylamino-pyrrolidin-1-yl)-methanone;

{6-chloro-3-[3-(4-chloro-benzyl)-5-(3-methoxy-phenyl)-3H-imidazol-4-yl]-1H-indol-2-yl}-((S)-3-dimethylamino-pyrrolidin-1-yl)-methanone;

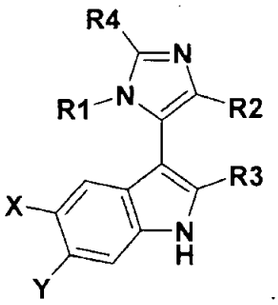
6-chloro-3-[3-(4-chloro-benzyl)-2-methyl-5-phenyl-3H-imidazol-4-yl]-1H-indole;

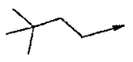
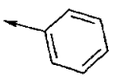
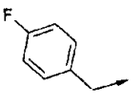
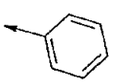
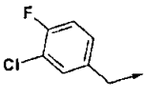
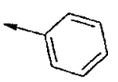
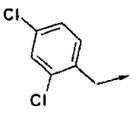
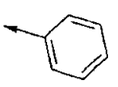
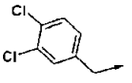
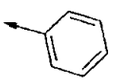
6-bromo-3-[2-chloro-3-(4-chloro-benzyl)-5-phenyl-3H-imidazol-4-yl]-1H-indole-2-carboxylic acid ethyl ester and

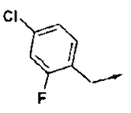
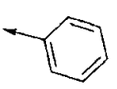
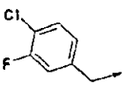
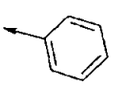
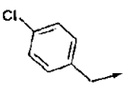
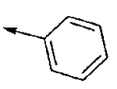
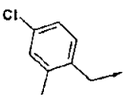
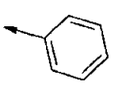
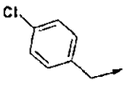
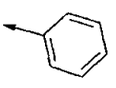
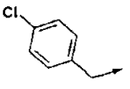
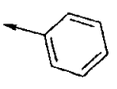
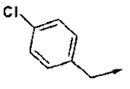
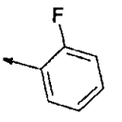
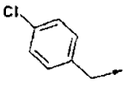
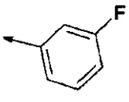
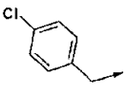
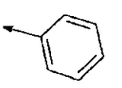
6-Chloro-3-[2-chloro-3-(4-chloro-benzyl)-5-phenyl-3H-imidazol-4-yl]-1H-indole-2-carboxylic acid ethyl ester,

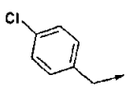
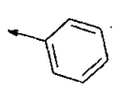
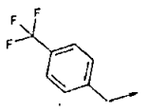
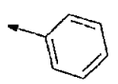
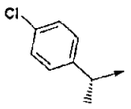
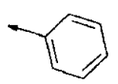
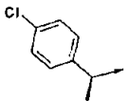
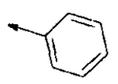
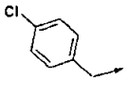
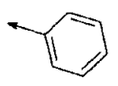
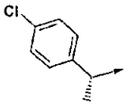
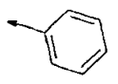
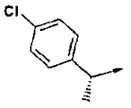
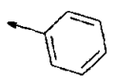
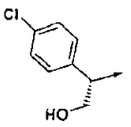
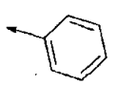
and/or a tautomer, an N-oxide and/or a pharmaceutically acceptable salt thereof.

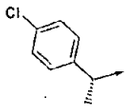
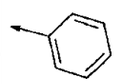
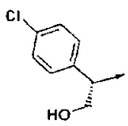
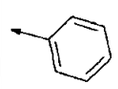
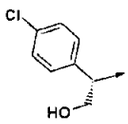
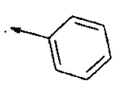
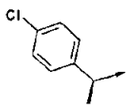
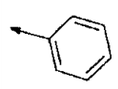
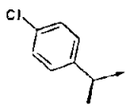
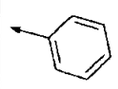
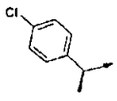
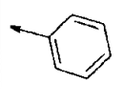
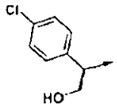
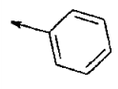
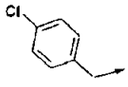
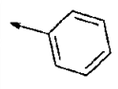
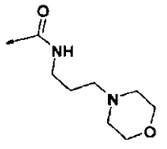
8. A compound of the formula I according to claim 1 or to claim 2, selected from the group of compounds given in the following tables and by the following formula

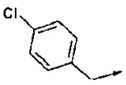
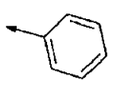
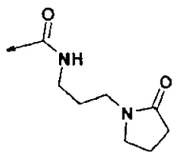
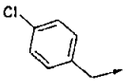
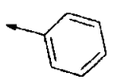
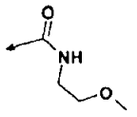
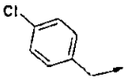
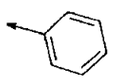
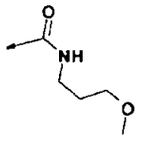
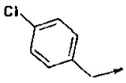
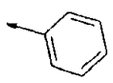
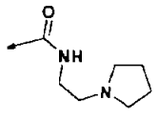
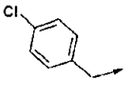
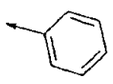
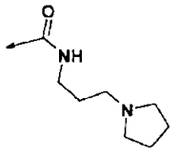
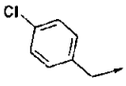
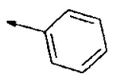
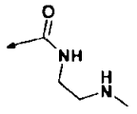
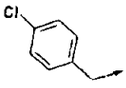
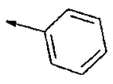
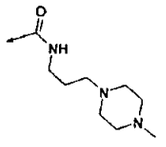


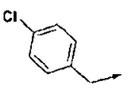
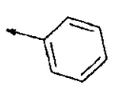
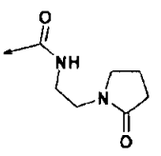
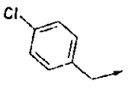
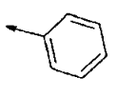
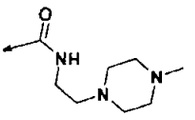
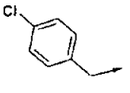
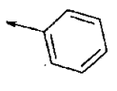
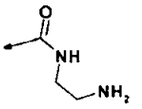
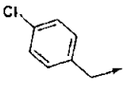
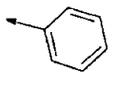
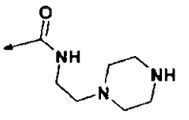
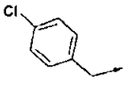
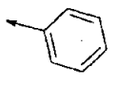
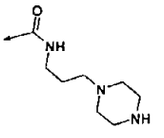
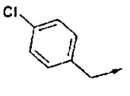
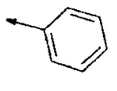
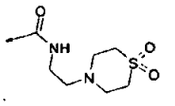
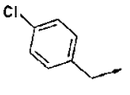
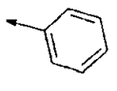
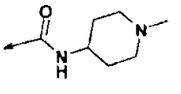
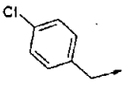
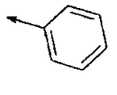
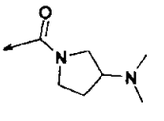
Compound	X and Y	R^1	R^2	R^3	R^4
AA	X=H Y=Cl			H	H
AB	X=H Y=Cl			H	H
AC	X=H Y=Cl			H	H
AD	X=H Y=Cl			H	H
AE	X=H Y=Cl			H	H

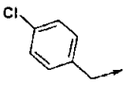
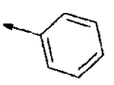
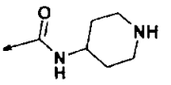
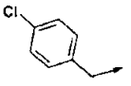
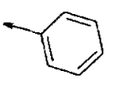
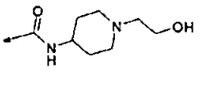
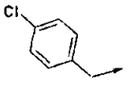
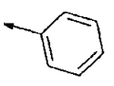
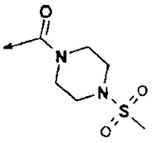
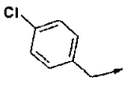
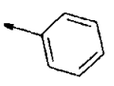
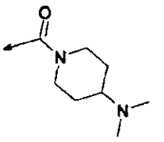
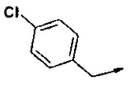
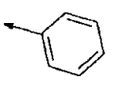
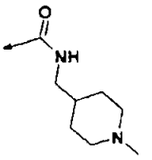
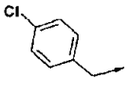
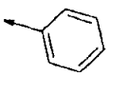
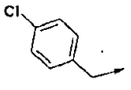
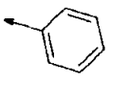
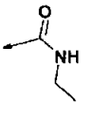
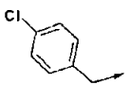
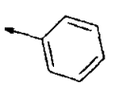
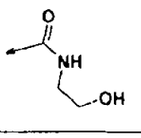
Compound	X and Y	R^1	R^2	R^3	R^4
AF	X=H Y=Cl			H	H
AG	X=H Y=Cl			H	H
AH	X=F Y=Cl			H	H
AI	X=H Y=Cl			H	H
AJ	X=H Y=Br			H	H
AK	X=H Y=Me			H	H
AL	X=H Y=Cl			H	H
AM	X=H Y=Cl			H	H
AO	X=H Y=CN			H	H

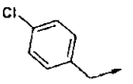
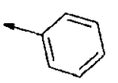
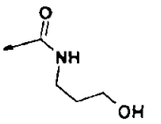
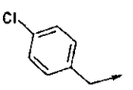
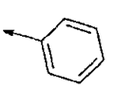
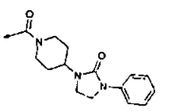
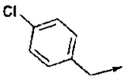
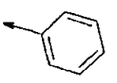
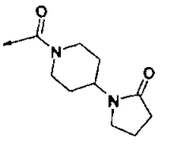
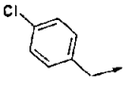
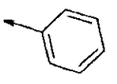
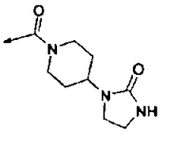
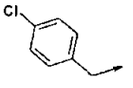
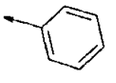
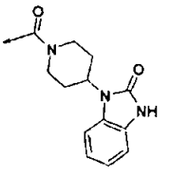
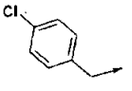
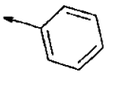
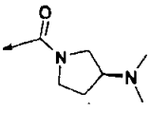
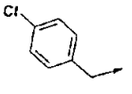
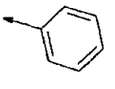
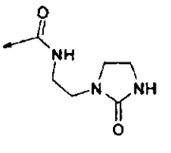
Compound	X and Y	R^1	R^2	R^3	R^4
AP	X=F Y=F			H	H
AQ	X=H Y=Cl			H	H
AR	X=H Y=Cl			H	H
AS	X=H Y=Cl			H	H
AT	X=H Y=Cl			H	H
AU	X=F Y=Cl			H	H
AV	X=F Y=F			H	H
AX	X=H Y=Cl			H	H

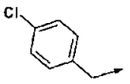
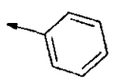
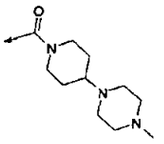
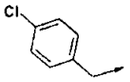
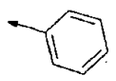
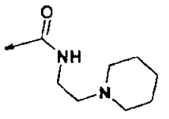
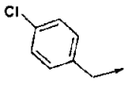
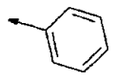
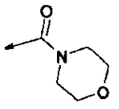
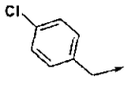
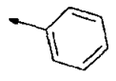
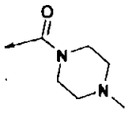
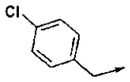
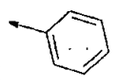
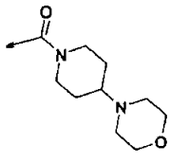
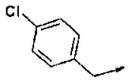
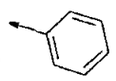
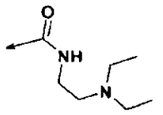
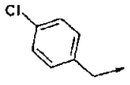
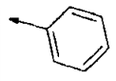
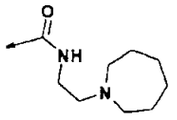
Compound	X and Y	R^1	R^2	R^3	R^4
AY	X=H Y=CN			H	H
AZ	X=F Y=Cl			H	H
BA	X=H Y=CN			H	H
BB	X=F Y=Cl			H	H
BC	X=H Y=CN			H	H
BD	X=F Y=F			H	H
BE	X=F Y=Cl			H	H
BF	X=H Y=Cl				H

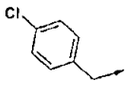
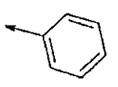
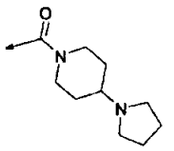
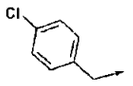
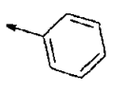
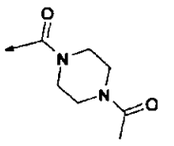
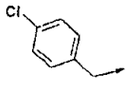
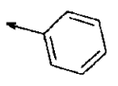
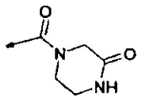
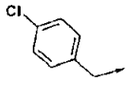
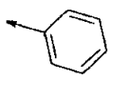
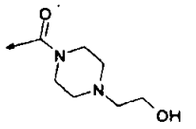
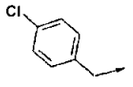
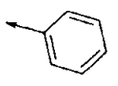
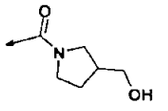
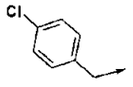
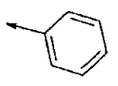
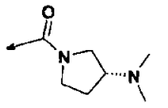
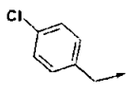
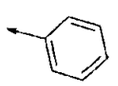
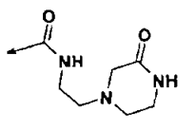
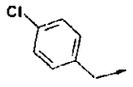
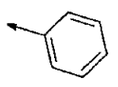
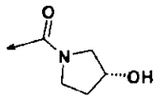
Compound	X and Y	R^1	R^2	R^3	R^4
BG	X=H Y=Cl				H
BH	X=H Y=Cl				H
BI	X=H Y=Cl				H
BJ	X=H Y=Cl				H
BK	X=H Y=Cl				H
BL	X=H Y=Cl				H
BM	X=H Y=Cl				H

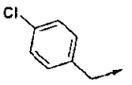
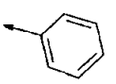
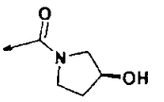
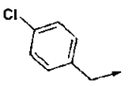
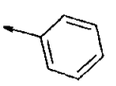
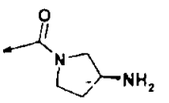
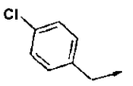
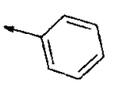
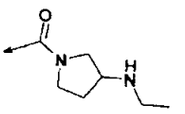
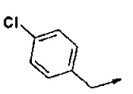
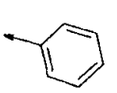
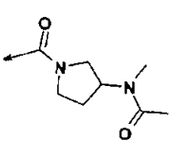
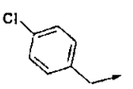
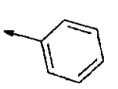
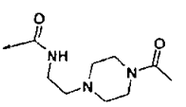
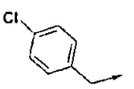
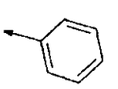
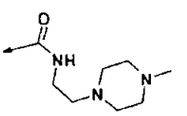
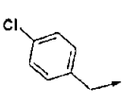
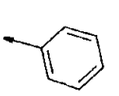
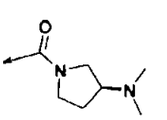
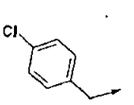
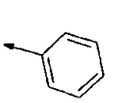
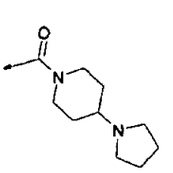
Compound	X and Y	R^1	R^2	R^3	R^4
BN	X=H Y=Cl				H
BO	X=H Y=Cl				H
BP	X=H Y=Cl				H
BQ	X=H Y=Cl				H
BR	X=H Y=Cl				H
BS	X=H Y=Cl				H
BT	X=H Y=Cl				H
BU	X=H Y=Cl				H

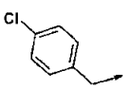
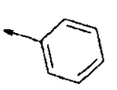
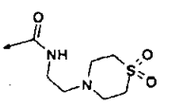
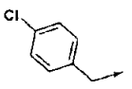
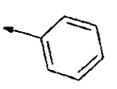
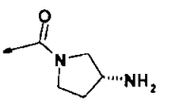
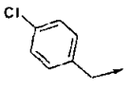
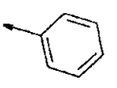
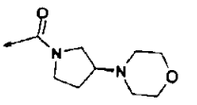
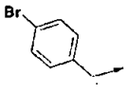
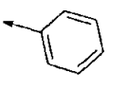
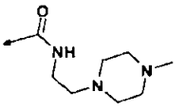
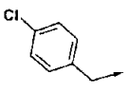
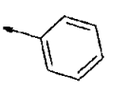
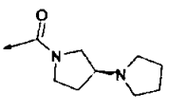
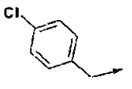
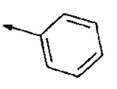
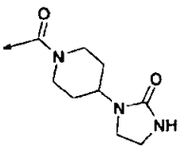
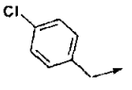
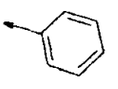
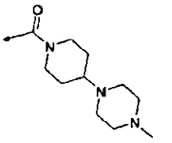
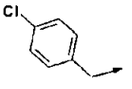
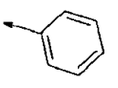
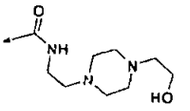
Compound	X and Y	R^1	R^2	R^3	R^4
BV	X=H Y=Cl				H
BX	X=H Y=Cl				H
BY	X=H Y=Cl				H
BZ	X=H Y=Cl				H
CA	X=H Y=Cl				H
CB	X=H Y=Cl				H
CC	X=H Y=Cl				H
CD	X=H Y=Cl				H

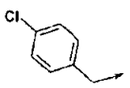
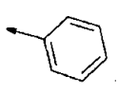
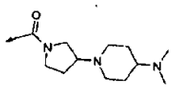
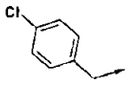
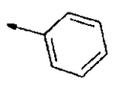
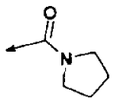
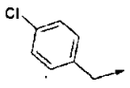
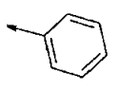
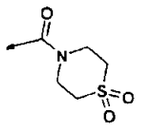
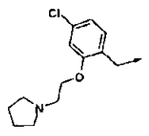
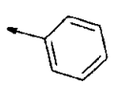
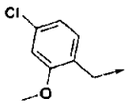
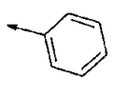
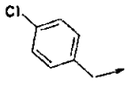
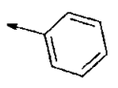
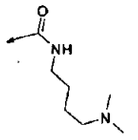
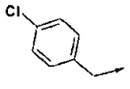
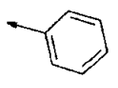
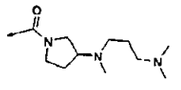
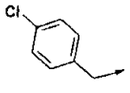
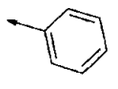
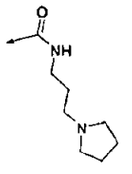
Compound	X and Y	R^1	R^2	R^3	R^4
CE	X=H Y=Cl				H
CF	X=H Y=Cl				H
CG	X=H Y=Cl				H
CH	X=H Y=Cl				H
CI	X=H Y=Cl				H
CJ	X=H Y=Cl				H
CK	X=H Y=Cl				H

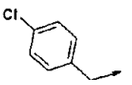
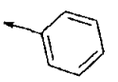
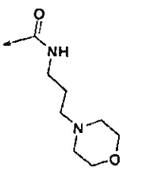
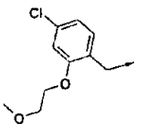
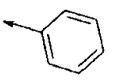
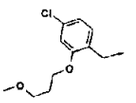
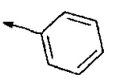
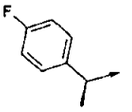
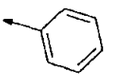
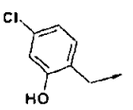
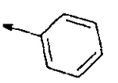
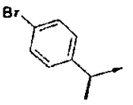
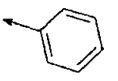
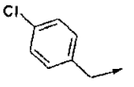
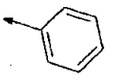
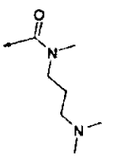
Compound	X and Y	R^1	R^2	R^3	R^4
CL	X=H Y=Ci				H
CM	X=H Y=Cl				H
CN	X=H Y=Cl				H
CO	X=H Y=Cl				H
CP	X=H Y=Cl				H
CQ	X=H Y=Cl				H
CR	X=H Y=Cl				H

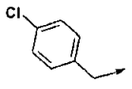
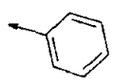
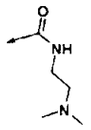
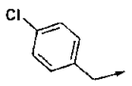
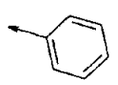
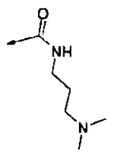
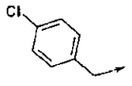
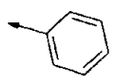
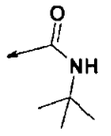
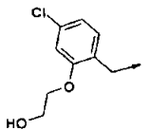
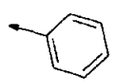
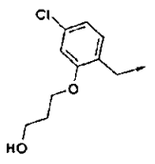
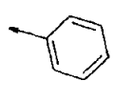
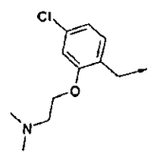
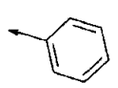
Compound	X and Y	R^1	R^2	R^3	R^4
CS	X=H Y=Cl				H
CT	X=H Y=Cl				H
CU	X=H Y=Cl				H
CV	X=H Y=Cl				H
CW	X=H Y=Cl				H
CX	X=H Y=Cl				H
CY	X=H Y=Cl				H
CZ	X=H Y=Cl				H

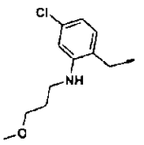
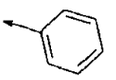
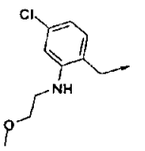
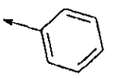
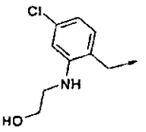
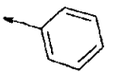
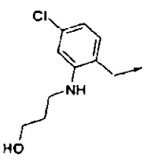
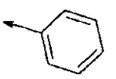
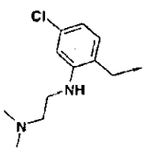
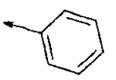
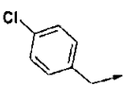
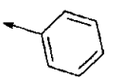
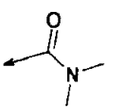
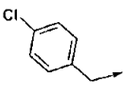
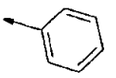
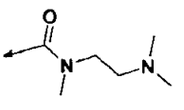
Compound	X and Y	R^1	R^2	R^3	R^4
DA	X=H Y=Cl				H
DB	X=H Y=Cl				H
DC	X=H Y=Cl				H
DD	X=H Y=Cl				H
DE	X=H Y=Cl				H
DF	X=F Y=Cl				H
DG	X=F Y=Cl				H
DH	X=F Y=Cl				H

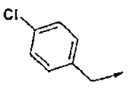
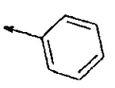
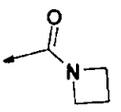
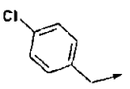
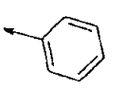
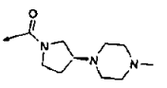
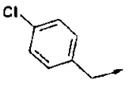
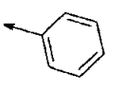
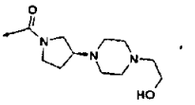
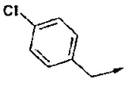
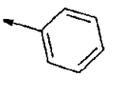
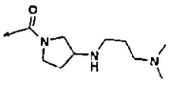
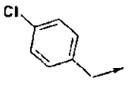
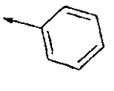
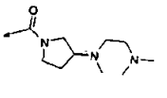
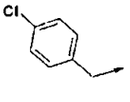
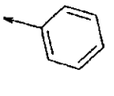
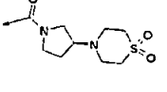
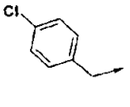
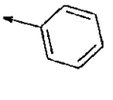
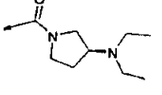
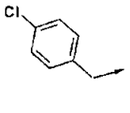
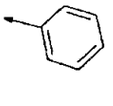
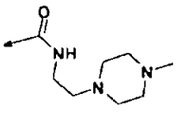
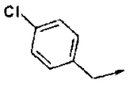
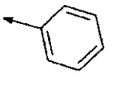
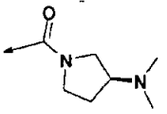
Compound	X and Y	R^1	R^2	R^3	R^4
DI	X=F Y=Cl				H
DJ	X=H Y=Cl				H
DK	X=H Y=Cl				H
DL	X=H Y=Cl				H
DM	X=H Y=Cl				H
DN	X=F Y=Cl				H
DO	X=F Y=Cl				H
DP	X=H Y=Cl				H

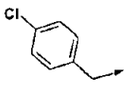
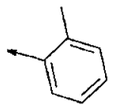
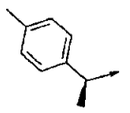
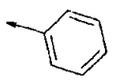
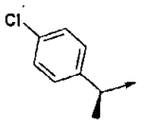
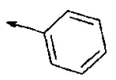
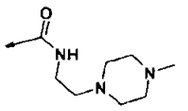
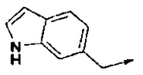
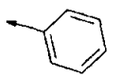
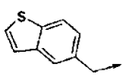
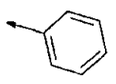
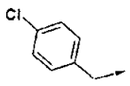
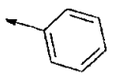
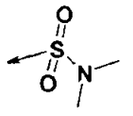
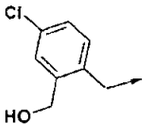
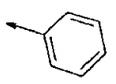
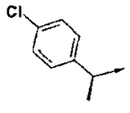
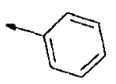
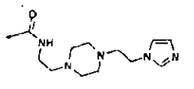
Compound	X and Y	R^1	R^2	R^3	R^4
DQ	X=H Y=Cl				H
DR	X=H Y=Cl				H
DS	X=H Y=Cl				H
DT	X=F Y=Cl			H	H
DU	X=F Y=Cl			H	H
DV	X=H Y=Cl				H
DW	X=H Y=Cl				H
DX	X=F Y=Cl				H

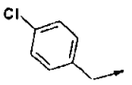
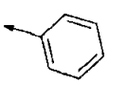
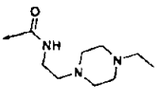
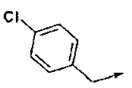
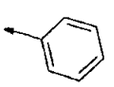
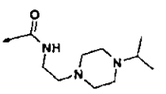
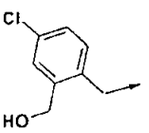
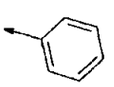
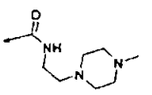
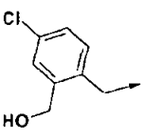
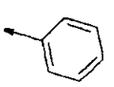
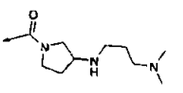
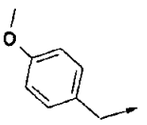
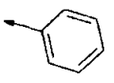
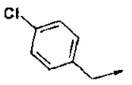
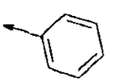
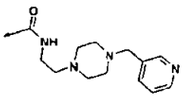
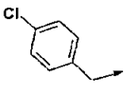
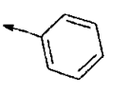
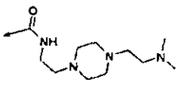
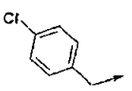
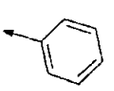
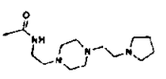
Compound	X and Y	R^1	R^2	R^3	R^4
DY	X=F Y=Cl				H
DZ	X=F Y=Cl			H	H
EA	X=F Y=Cl			H	H
EB	X=F Y=Cl			H	H
EC	X=F Y=Cl			H	H
ED	X=F Y=Cl			H	H
EF	X=H Y=Cl				H

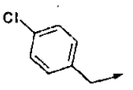
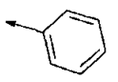
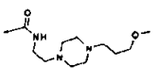
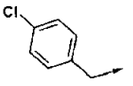
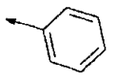
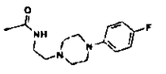
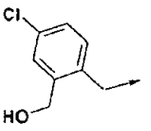
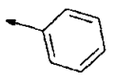
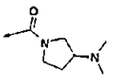
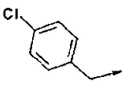
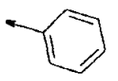
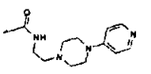
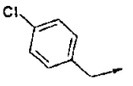
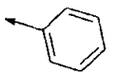
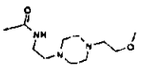
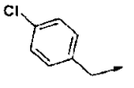
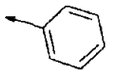
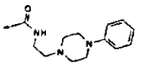
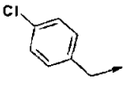
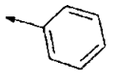
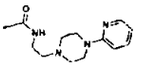
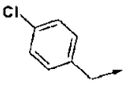
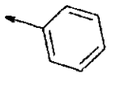
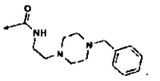
Compound	X and Y	R^1	R^2	R^3	R^4
EG	X=H Y=Cl				H
EH	X=H Y=Cl				H
EI	X=H Y=Cl				H
EJ	X=F Y=Cl			H	H
EK	X=F Y=Cl			H	H
EL	X=F Y=Cl			H	H

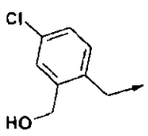
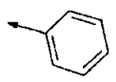
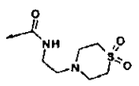
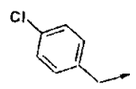
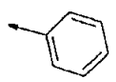
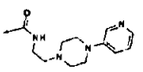
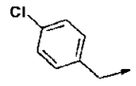
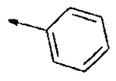
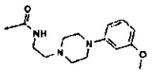
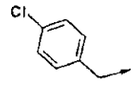
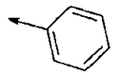
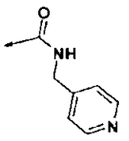
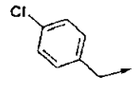
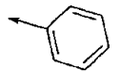
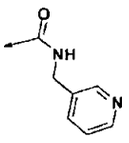
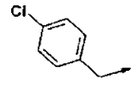
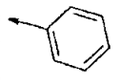
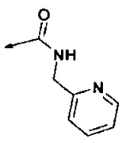
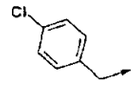
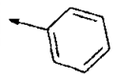
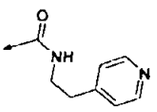
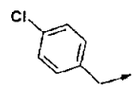
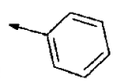
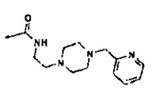
Compound	X and Y	R^1	R^2	R^3	R^4
EM	X=F Y=Cl			H	H
EN	X=F Y=Cl			H	H
EO	X=F Y=Cl			H	H
EP	X=F Y=Cl			H	H
EQ	X=F Y=Cl			H	H
ER	X=H Y=Cl				H
ES	X=H Y=Cl				H

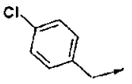
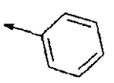
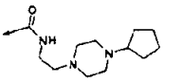
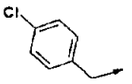
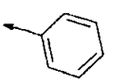
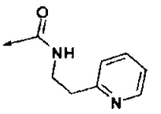
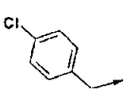
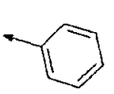
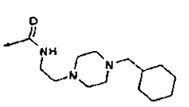
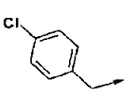
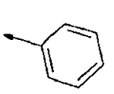
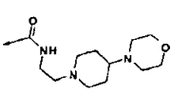
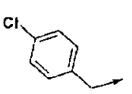
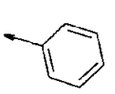
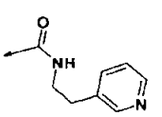
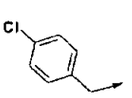
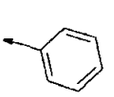
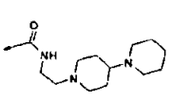
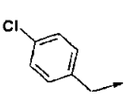
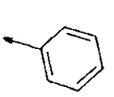
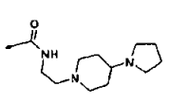
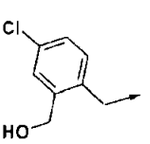
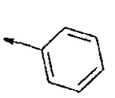
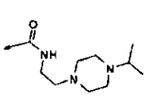
Compound	X and Y	R^1	R^2	R^3	R^4
ET	X=H Y=Cl				H
EU	X=H Y=Cl				H
EV	X=H Y=Cl				H
EW	X=H Y=Cl				H
EX	X=H Y=Cl				H
EY	X=H Y=Cl				H
EZ	X=H Y=Cl				H
FA	X=H Y=CN				H
FB	X=H Y=CN				H

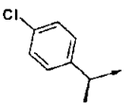
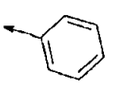
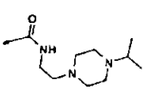
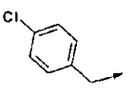
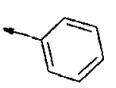
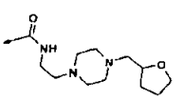
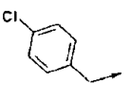
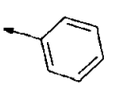
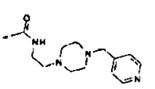
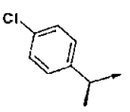
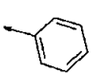
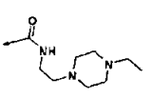
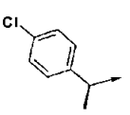
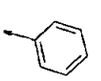
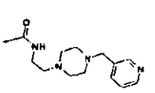
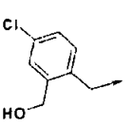
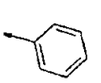
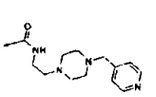
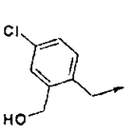
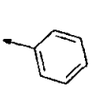
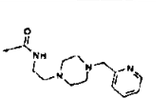
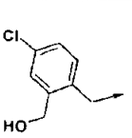
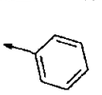
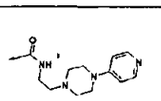
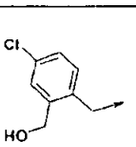
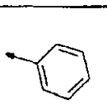
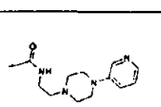
Compound	X and Y	R^1	R^2	R^3	R^4
FC	X=F Y=Cl			H	H
FD	X=F Y=Cl			H	H
FE	X=H Y=Cl				H
FF	X=F Y=Cl			H	H
FG	X=F Y=Cl			H	H
FH	X=H Y=Cl				H
FI	X=F Y=Cl			H	H
FJ	X=H Y=Cl				H

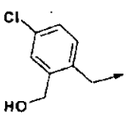
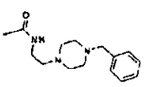
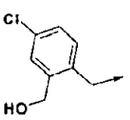
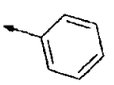
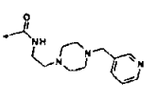
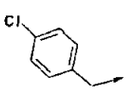
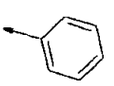
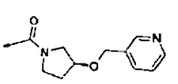
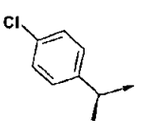
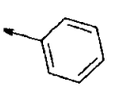
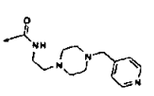
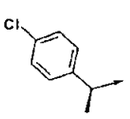
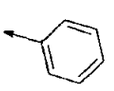
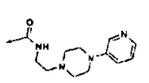
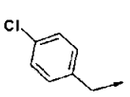
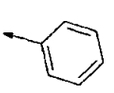
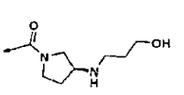
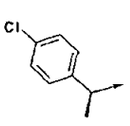
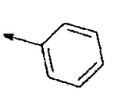
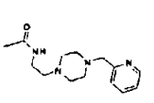
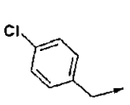
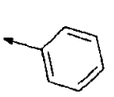
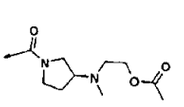
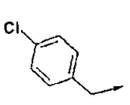
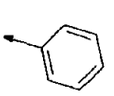
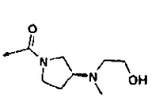
Compound	X and Y	R^1	R^2	R^3	R^4
FK	X=H Y=Cl				H
FL	X=H Y=Cl				H
FM	X=H Y=Cl				H
FN	X=H Y=Cl				H
FO	X=F Y=Cl			H	H
FP	X=H Y=Cl				H
FQ	X=H Y=Cl				H
FR	X=H Y=Cl				H

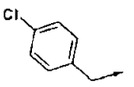
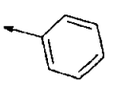
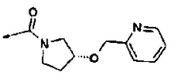
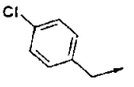
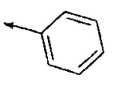
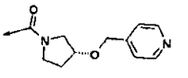
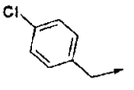
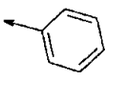
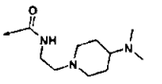
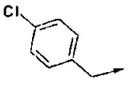
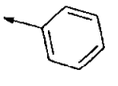
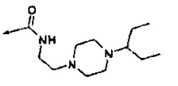
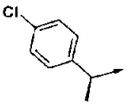
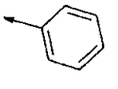
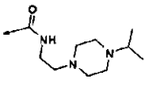
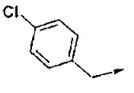
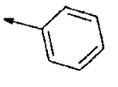
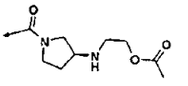
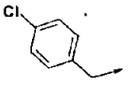
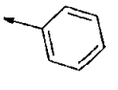
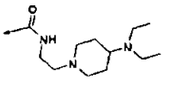
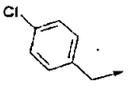
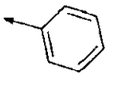
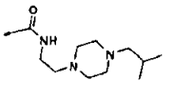
Compound	X and Y	R^1	R^2	R^3	R^4
FS	X=H Y=Cl				H
FT	X=H Y=Cl				H
FU	X=H Y=Cl				H
FV	X=H Y=Cl				H
FW	X=H Y=Cl				H
FX	X=H Y=Cl				H
FY	X=H Y=Cl				H
FZ	X=H Y=Cl				H

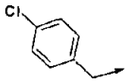
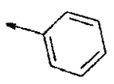
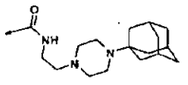
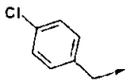
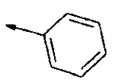
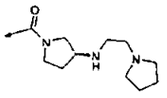
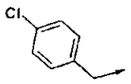
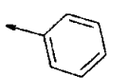
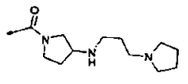
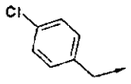
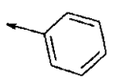
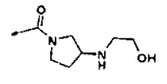
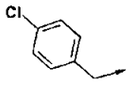
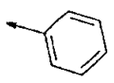
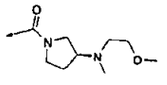
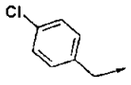
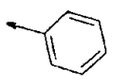
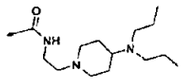
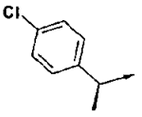
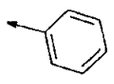
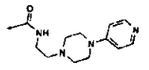
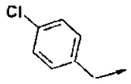
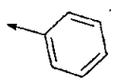
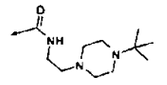
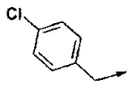
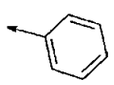
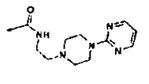
Compound	X and Y	R^1	R^2	R^3	R^4
GA	X=H Y=Cl				H
GB	X=H Y=Cl				H
GC	X=H Y=Cl				H
GD	X=H Y=Cl				H
GE	X=H Y=Cl				H
GF	X=H Y=Cl				H
GG	X=H Y=Cl				H
GH	X=H Y=Cl				H

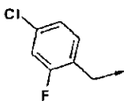
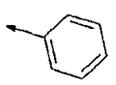
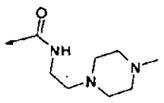
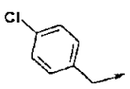
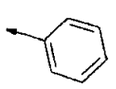
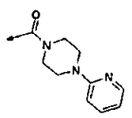
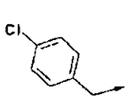
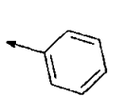
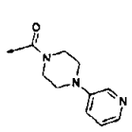
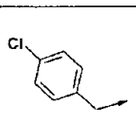
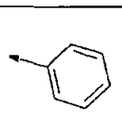
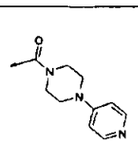
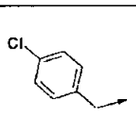
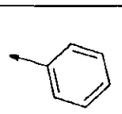
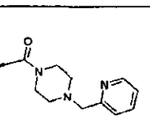
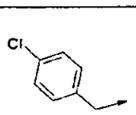
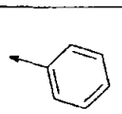
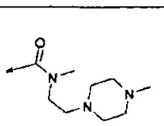
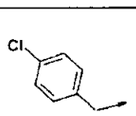
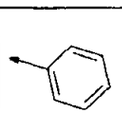
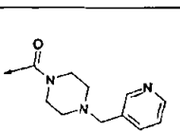
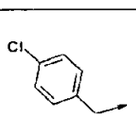
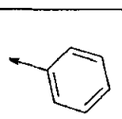
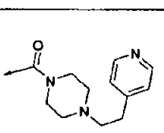
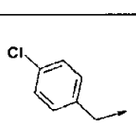
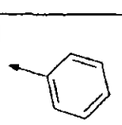
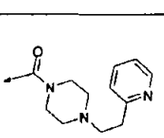
Compound	X and Y	R^1	R^2	R^3	R^4
GI	X=H Y=Cl				H
GJ	X=H Y=Cl				H
GK	X=H Y=Cl				H
GL	X=H Y=Cl				H
GM	X=H Y=Cl				H
GN	X=H Y=Cl				H
GO	X=H Y=Cl				H
GP	X=H Y=Cl				H

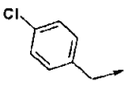
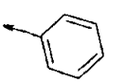
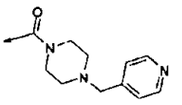
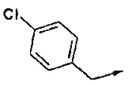
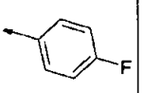
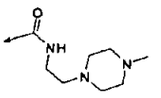
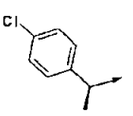
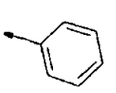
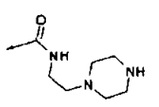
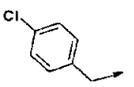
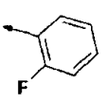
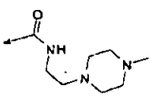
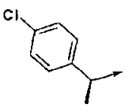
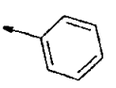
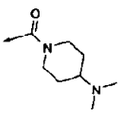
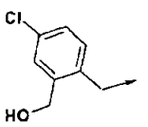
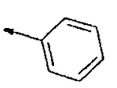
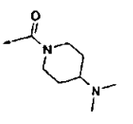
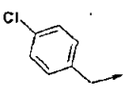
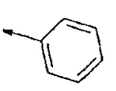
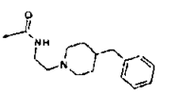
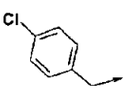
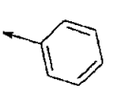
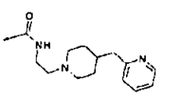
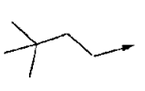
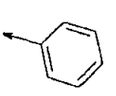
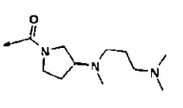
Compound	X and Y	R^1	R^2	R^3	R^4
GQ	X=H Y=Cl				H
GR	X=H Y=Cl				H
GS	X=H Y=Cl				H
GT	X=H Y=Cl				H
GU	X=H Y=Cl				H
GV	X=H Y=Cl				H
GW	X=H Y=Cl				H
GX	X=H Y=Cl				H
GY	X=H Y=Cl				H

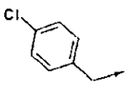
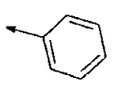
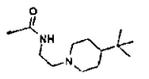
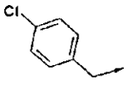
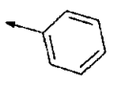
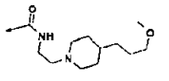
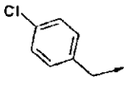
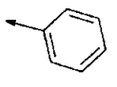
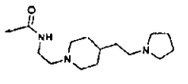
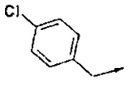
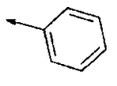
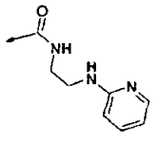
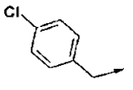
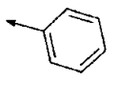
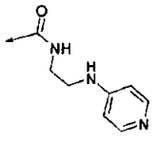
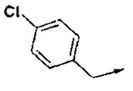
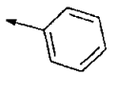
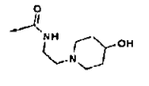
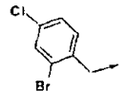
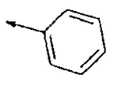
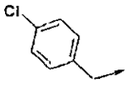
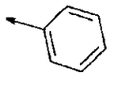
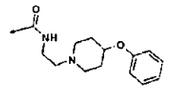
Compound	X and Y	R^1	R^2	R^3	R^4
GZ	X=H Y=Cl				H
HA	X=H Y=Cl				H
HB	X=H Y=Cl				H
HC	X=H Y=Cl				H
HD	X=H Y=Cl				H
HE	X=H Y=Cl				H
HF	X=H Y=Cl				H
HG	X=H Y=Cl				H
HH	X=H				H

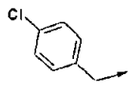
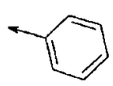
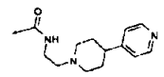
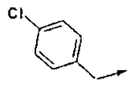
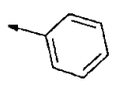
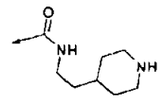
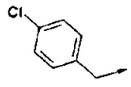
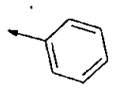
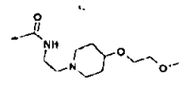
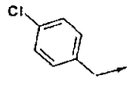
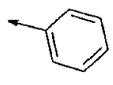
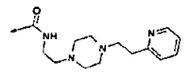
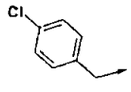
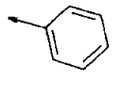
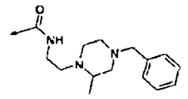
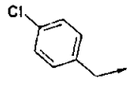
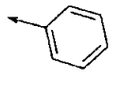
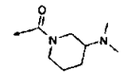
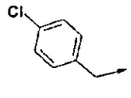
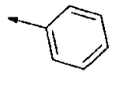
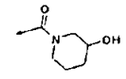
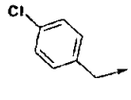
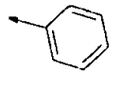
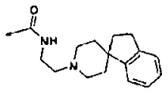
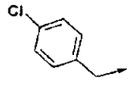
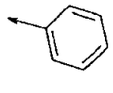
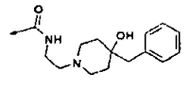
Compound	X and Y	R^1	R^2	R^3	R^4
	Y=Cl				
HI	X=H Y=Cl				H
HJ	X=H Y=Cl				H
HK	X=H Y=Cl				H
HL	X=H Y=Cl				H
HM	X=H Y=Cl				H
HN	X=H Y=Cl				H
HO	X=H Y=Cl				H
HP	X=H Y=Cl				H

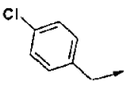
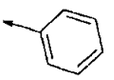
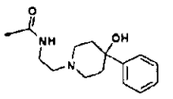
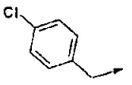
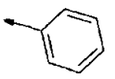
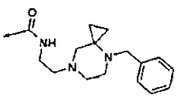
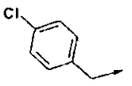
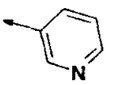
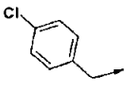
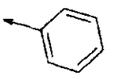
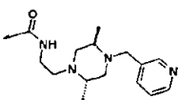
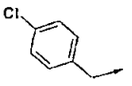
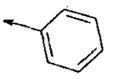
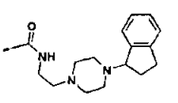
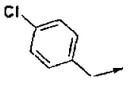
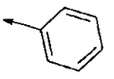
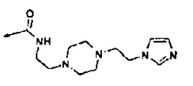
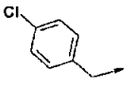
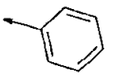
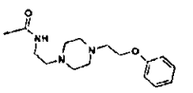
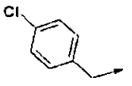
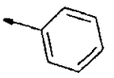
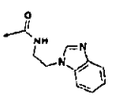
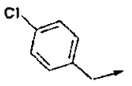
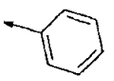
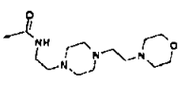
Compound	X and Y	R^1	R^2	R^3	R^4
HQ	X=H Y=Cl				H
HR	X=H Y=Cl				H
HS	X=H Y=Cl				H
HT	X=H Y=Cl				H
HU	X=H Y=Cl				H
HV	X=H Y=Cl				H
HW	X=H Y=Cl				H
HX	X=H Y=Cl				H
HY	X=H Y=Cl				H

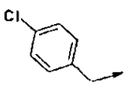
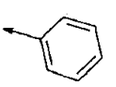
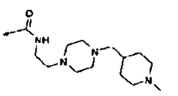
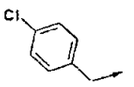
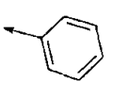
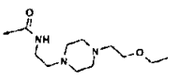
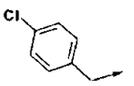
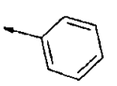
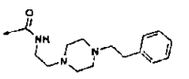
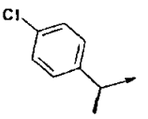
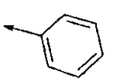
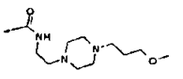
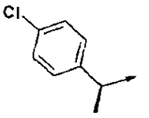
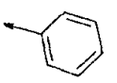
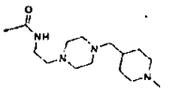
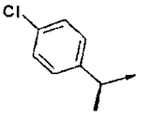
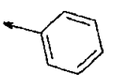
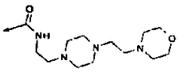
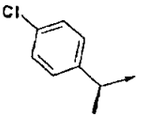
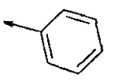
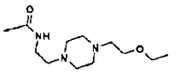
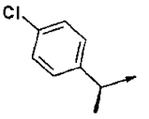
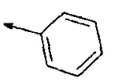
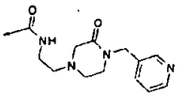
Compound	X and Y	R^1	R^2	R^3	R^4
HZ	X=H Y=Cl				H
IA	X=H Y=Cl				H
IB	X=H Y=Cl				H
IC	X=H Y=Cl				H
ID	X=H Y=Cl				H
IE	X=H Y=Cl				H
IF	X=H Y=Cl				H
IG	X=H Y=Cl				H
IH	X=H Y=Cl				H

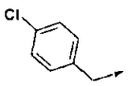
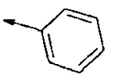
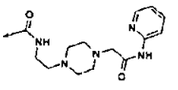
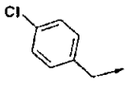
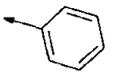
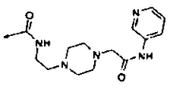
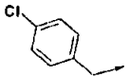
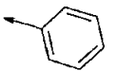
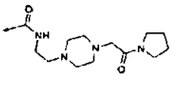
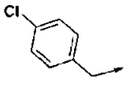
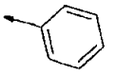
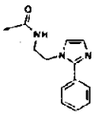
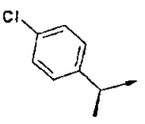
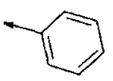
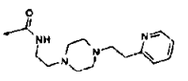
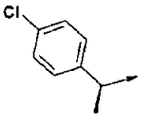
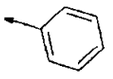
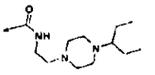
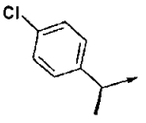
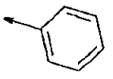
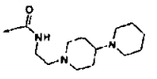
Compound	X and Y	R^1	R^2	R^3	R^4
II	X=H Y=Cl				H
IJ	X=H Y=Cl				H
IK	X=H Y=Cl				H
IL	X=H Y=Cl				H
IM	X=H Y=Cl				H
IN	X=H Y=Cl				H
IO	X=H Y=Cl				H
IP	X=H Y=Cl				H
IQ	X=H				H

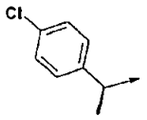
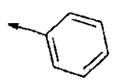
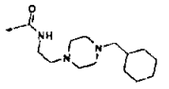
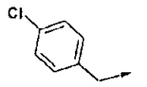
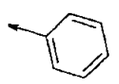
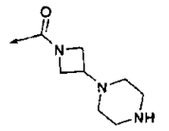
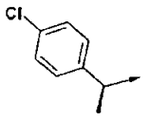
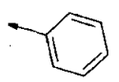
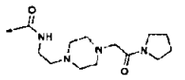
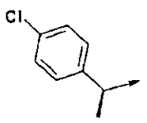
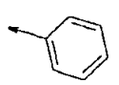
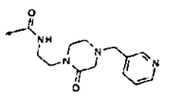
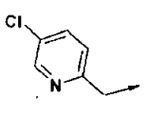
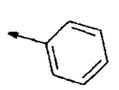
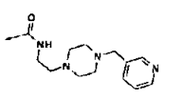
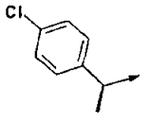
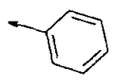
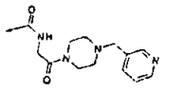
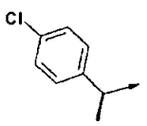
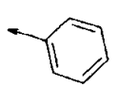
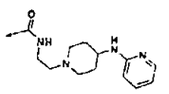
Compound	X and Y	R^1	R^2	R^3	R^4
	Y=Cl				
IR	X=H Y=Cl				H
IS	X=H Y=Cl				H
IT	X=H Y=Cl				H
IU	X=H Y=Cl				H
IV	X=H Y=Cl				H
IW	X=H Y=Cl				H
IX	X=F Y=Cl			H	H
IY	X=H Y=Cl				H

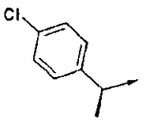
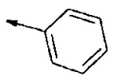
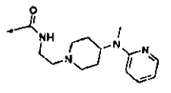
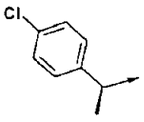
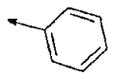
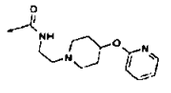
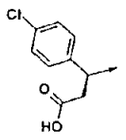
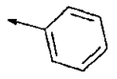
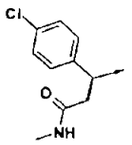
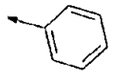
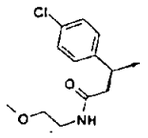
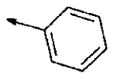
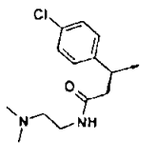
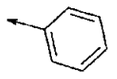
Compound	X and Y	R^1	R^2	R^3	R^4
IZ	X=H Y=Cl				H
JA	X=H Y=Cl				H
JB	X=H Y=Cl				H
JC	X=H Y=Cl				H
JD	X=H Y=Cl				H
JE	X=H Y=Cl				H
JF	X=H Y=Cl				H
JG	X=H Y=Cl				H
JH	X=H Y=Cl				H

Compound	X and Y	R^1	R^2	R^3	R^4
JI	X=H Y=Cl				H
JJ	X=H Y=Cl				H
JK	X=F Y=Cl			H	H
JL	X=H Y=Cl				H
JM	X=H Y=Cl				H
JN	X=H Y=Cl				H
JO	X=H Y=Cl				H
JP	X=H Y=Cl				H
JQ	X=H Y=Cl				H

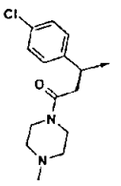
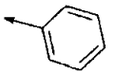
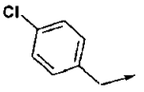
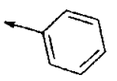
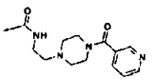
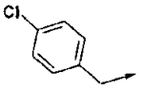
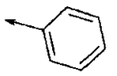
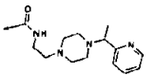
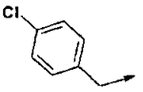
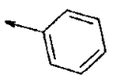
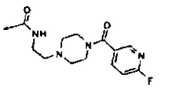
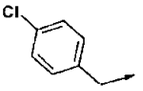
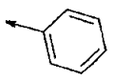
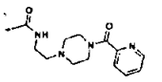
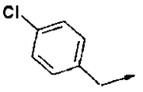
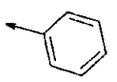
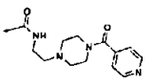
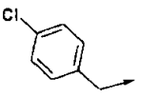
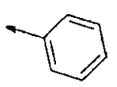
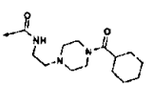
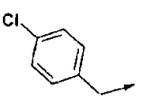
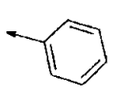
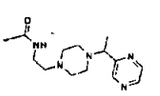
Compound	X and Y	R^1	R^2	R^3	R^4
JR	X=H Y=Cl				H
JS	X=H Y=Cl				H
JT	X=H Y=Cl				H
JU	X=H Y=Cl				H
JV	X=H Y=Cl				H
JW	X=H Y=Cl				H
JX	X=H Y=Cl				H
JY	X=H Y=Cl				H

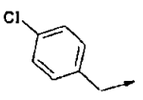
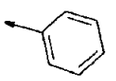
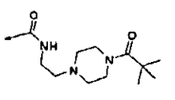
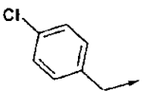
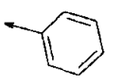
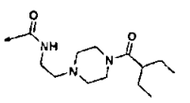
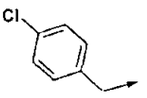
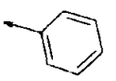
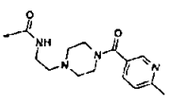
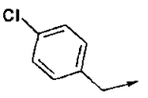
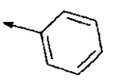
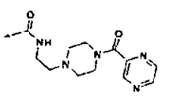
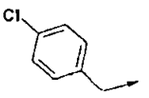
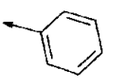
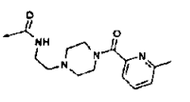
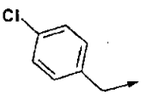
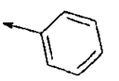
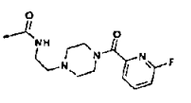
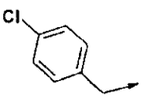
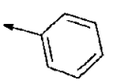
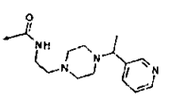
Compound	X and Y	R^1	R^2	R^3	R^4
JZ	X=H Y=Cl				H
KA	X=H Y=Cl				H
KB	X=H Y=Cl				H
KC	X=H Y=Cl				H
KD	X=H Y=Cl				H
KE	X=H Y=Cl				H
KF	X=H Y=Cl				H

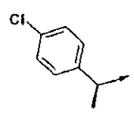
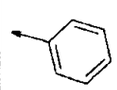
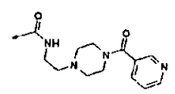
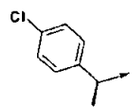
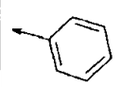
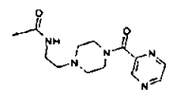
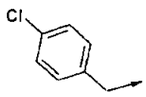
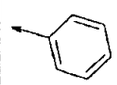
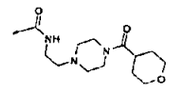
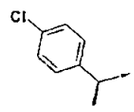
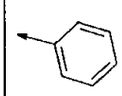
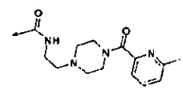
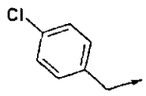
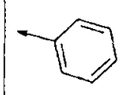
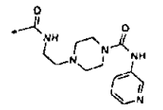
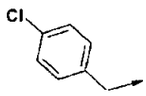
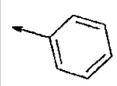
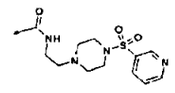
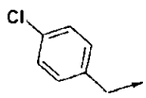
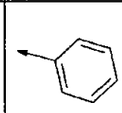
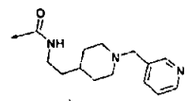
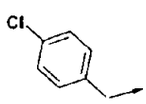
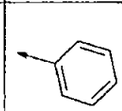
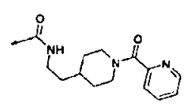
Compound	X and Y	R^1	R^2	R^3	R^4
KG	X=H Y=Cl				H
KH	X=H Y=Cl				H
KI	X=H Y=Cl				H
KJ	X=H Y=Cl				H
KK	X=H Y=Cl				H
KL	X=H Y=Cl				H
KM	X=H Y=Cl				H

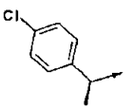
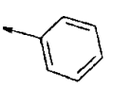
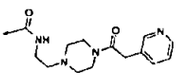
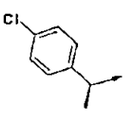
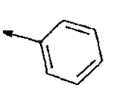
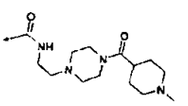
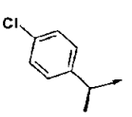
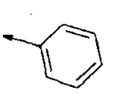
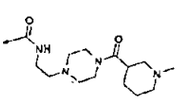
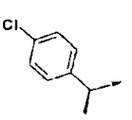
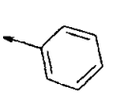
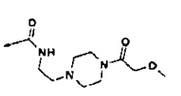
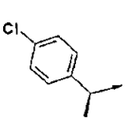
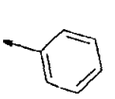
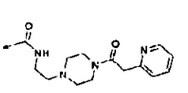
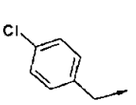
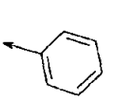
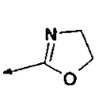
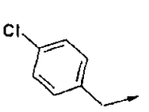
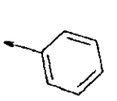
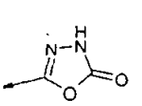
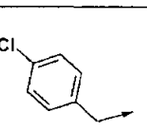
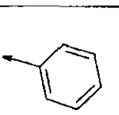
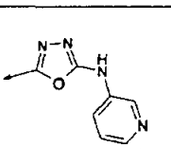
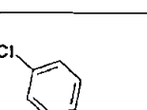
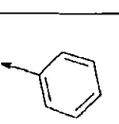
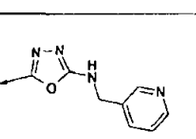
Compound	X and Y	R^1	R^2	R^3	R^4
KN	X=H Y=Cl				H
KO	X=H Y=Cl				H
KP	X=F Y=Cl			H	H
KQ	X=F Y=Cl			H	H
KR	X=F Y=Cl			H	H
KS	X=F Y=Cl			H	H

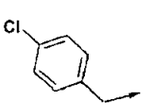
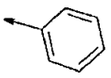
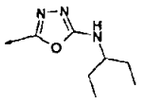
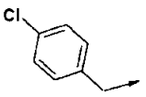
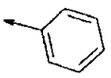
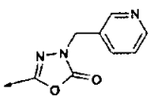
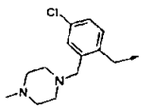
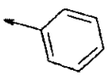
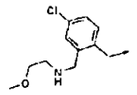
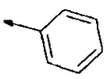
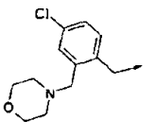
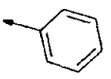
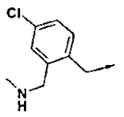
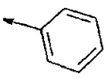
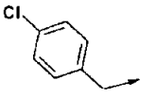
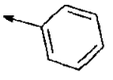
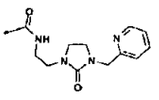
264

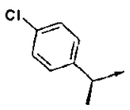
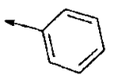
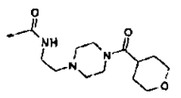
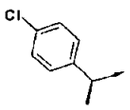
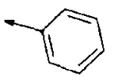
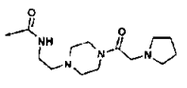
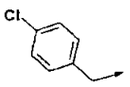
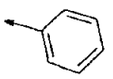
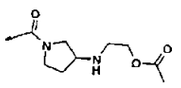
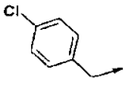
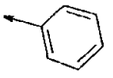
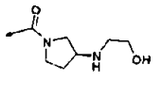
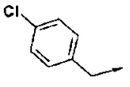
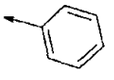
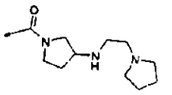
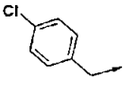
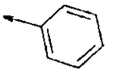
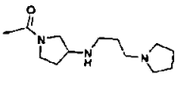
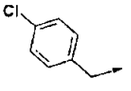
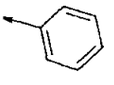
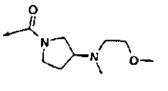
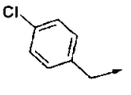
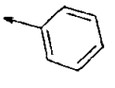
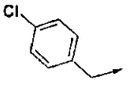
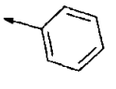
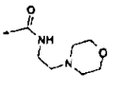
Compound	X and Y	R^1	R^2	R^3	R^4
KT	X=F Y=Cl			H	H
KU	X=H Y=Cl				H
KV	X=H Y=Cl				H
KW	X=H Y=Cl				H
KX	X=H Y=Cl				H
KY	X=H Y=Cl				H
KZ	X=H Y=Cl				H
LA	X=H Y=Cl				H

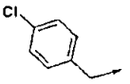
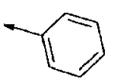
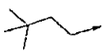
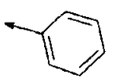
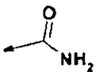
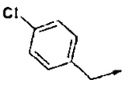
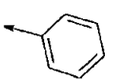
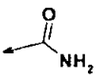
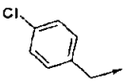
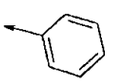
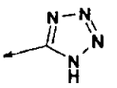
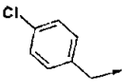
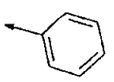
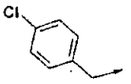
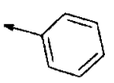
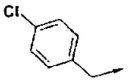
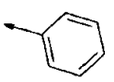
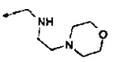
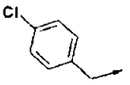
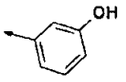
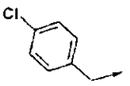
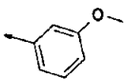
Compound	X and Y	R^1	R^2	R^3	R^4
LB	X=H Y=Cl				H
LC	X=H Y=Cl				H
LD	X=H Y=Cl				H
LE	X=H Y=Cl				H
LF	X=H Y=Cl				H
LG	X=H Y=Cl				H
LH	X=H Y=Cl				H

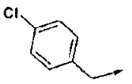
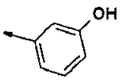
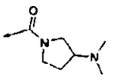
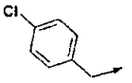
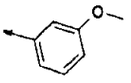
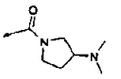
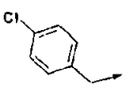
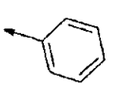
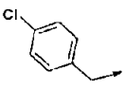
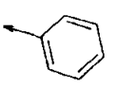
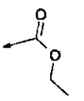
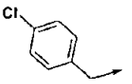
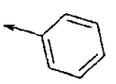
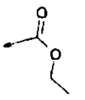
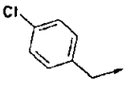
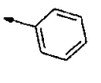
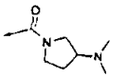
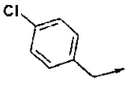
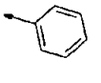
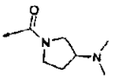
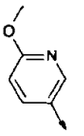
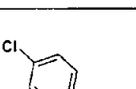
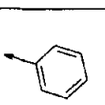
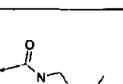
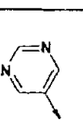
Compound	X and Y	R^1	R^2	R^3	R^4
LI	X=H Y=Cl				H
LJ	X=H Y=Cl				H
LK	X=H Y=Cl				H
LL	X=H Y=Cl				H
LM	X=H Y=Cl				H
LN	X=H Y=Cl				H
LO	X=H Y=Cl				H
LP	X=H Y=Cl				H

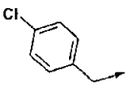
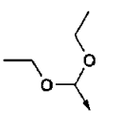
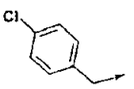
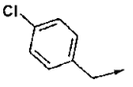
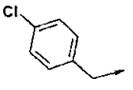
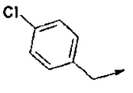
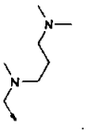
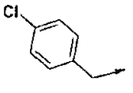
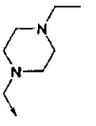
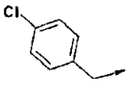
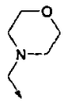
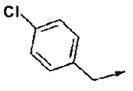
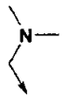
Compound	X and Y	R^1	R^2	R^3	R^4
LQ	X=H Y=Cl				H
LR	X=H Y=Cl				H
LS	X=H Y=Cl				H
LT	X=H Y=Cl				H
LU	X=H Y=Cl				H
LV	X=H Y=Cl				H
LW	X=H Y=Cl				H
LX	X=H Y=Cl				H
LY	X=H				H

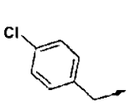
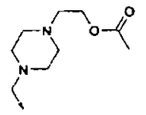
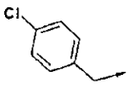
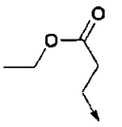
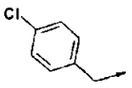
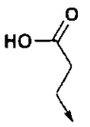
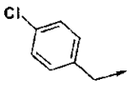
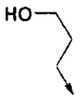
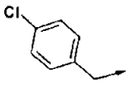
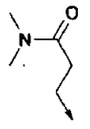
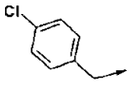
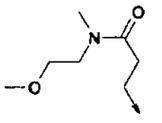
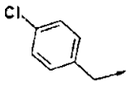
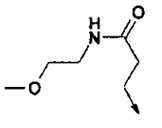
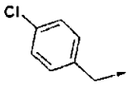
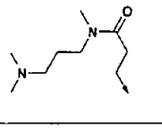
Compound	X and Y	R^1	R^2	R^3	R^4
	Y=Cl				
LZ	X=H Y=Cl				H
MA	X=H Y=Cl				H
MB	X=F Y=Cl			H	H
MC	X=F Y=Cl			H	H
MD	X=F Y=Cl			H	H
ME	X=F Y=Cl			H	H
MF	X=H Y=Cl				H

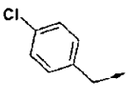
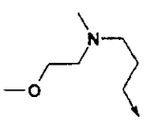
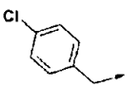
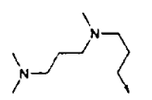
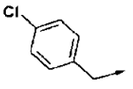
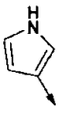
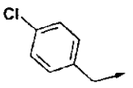
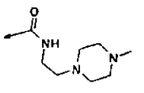
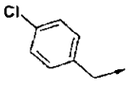
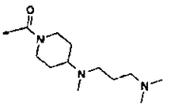
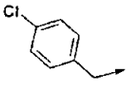
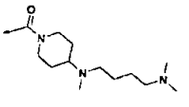
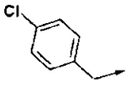
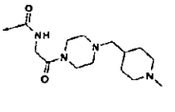
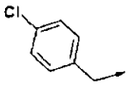
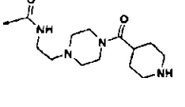
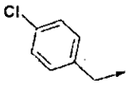
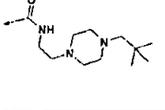
Compound	X and Y	R^1	R^2	R^3	R^4
MG	X=H Y=Cl				H
MH	X=H Y=Cl				H
MI	X=H Y=Cl				H
MJ	X=H Y=Cl				H
MK	X=H Y=Cl				H
ML	X=H Y=Cl				H
MM	X=H Y=Cl				H
MN	X=H Y=Cl			H	H
MO	X=H Y=Cl				H

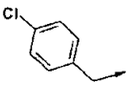
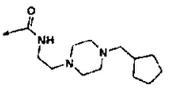
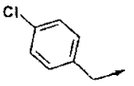
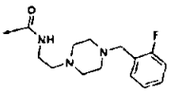
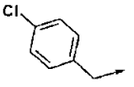
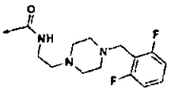
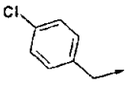
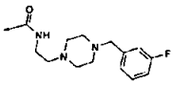
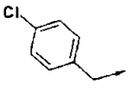
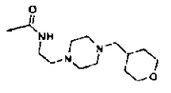
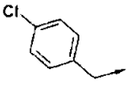
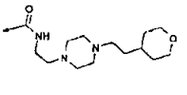
Compound	X and Y	R^1	R^2	R^3	R^4
MP	X=H Y=Cl				H
MQ	X=H Y=Cl				H
MR	X=H Y=Cl				H
MS	X=H Y=Cl				H
MT	X=H Y=Cl				H
MU	X=H Y=Cl				H
MV	X=H Y=Cl				H
MW	X=F Y=Cl			H	H
MX	X=F Y=Cl			H	H

Compound	X and Y	R^1	R^2	R^3	R^4
MY	X=H Y=Cl				H
MZ	X=H Y=Cl				H
NA	X=H Y=Cl			H	Me
NB	X=H Y=Cl				Br
NC	X=H Y=Cl				Cl
ND	X=H Y=Cl				
NE	X=H Y=Cl				
NF	X=H Y=Cl				

Compound	X and Y	R^1	R^2	R^3	R^4
NG	X=H Y=Cl			H	
NH	X=H Y=Cl			H	
NI	X=H Y=Cl			H	
NJ	X=H Y=Cl			H	
NK	X=H Y=Cl			H	
NL	X=H Y=Cl			H	
NM	X=H Y=Cl			H	
NN	X=H Y=Cl			H	

Compound	X and Y	R^1	R^2	R^3	R^4
NO	X=H Y=Cl			H	
NP	X=H Y=Cl			H	
NQ	X=H Y=Cl			H	
NR	X=H Y=Cl			H	
NS	X=H Y=Cl			H	
NT	X=H Y=Cl			H	
NU	X=H Y=Cl			H	
NV	X=H Y=Cl			H	

Compound	X and Y	R^1	R^2	R^3	R^4
NW	X=H Y=Cl			H	
NX	X=H Y=Cl			H	
NY	X=H Y=Cl			H	
NZ	X=H Y=Cl				Me
OA	X=H Y=Cl				H
OB	X=H Y=Cl				H
OC	X=H Y=Cl				H
OD	X=H Y=Cl				H
OE	X=H Y=Cl				H

Compound	X and Y	R^1	R^2	R^3	R^4
OF	X=H Y=Cl				H
OG	X=H Y=Cl				H
OH	X=H Y=Cl				H
OI	X=H Y=Cl				H
OJ	X=H Y=Cl				H
OK	X=H Y=Cl				H

and/or a tautomer, an N-oxide and/or a pharmaceutically acceptable salt thereof.

9. A pharmaceutical composition comprising a compound of the formula I, and/or a tautomer, an N-oxide and/or a pharmaceutically acceptable salt thereof, according to any one of claims 1 to 8 and at least one pharmaceutically acceptable carrier material.

10. A pharmaceutical composition according to claim 9 for use in the treatment of a disorder or disease which is mediated by the activity of MDM2 and/or MDM4, or variants thereof.

11. A compound of the formula I, and/or a tautomer, an N-oxide and/or a pharmaceutically acceptable salt thereof, according to any one of claims 1 to 8 for use as a medicament.

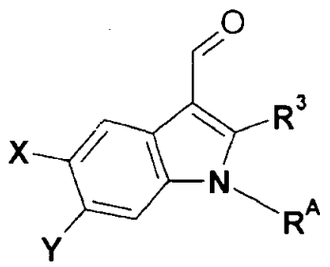
12. Use of a compound of the formula I, and/or a tautomer, an N-oxide and/or a pharmaceutically acceptable salt thereof, according to any one of claims 1 to 8 for the preparation of a pharmaceutical composition for the treatment of a disorder or disease which is mediated by the activity of MDM2 and/or MDM4, or variants thereof.

13. A compound of the formula I, and/or an N-oxide, a tautomer and/or a pharmaceutically acceptable salt thereof, according to any one of claims 1 to 8 for the treatment of a disorder or disease which is mediated by the activity of MDM2 and/or MDM4, or variants thereof.

14. A method of treatment comprising administering a compound of the formula I, and/or a tautomer, an N-oxide and/or a pharmaceutically acceptable salt thereof, according to any one of claims 1 to 8 to a person in need of such treatment in an effective amount for the prophylactic and/or therapeutic treatment of a disease or disorder which is mediated by the activity of MDM2 and/or MDM4, or variants thereof.

15. A method for the manufacture of a compound of the formula I, comprising

a) for the manufacture of a compound of the formula I wherein R^4 is hydrogen and R^1, R^2, R^3, R^A, X and Y are as defined for a compound of the formula I in any one of claims 1 to 8, reacting a formylindole derivative of the formula II

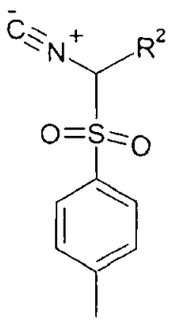


(II)

wherein R^3, R^A, X and Y are as defined for a compound of the formula I in any one of claims 1 to 8, with an amino compound of the formula III,

R^1-NH_2 (III)

wherein R^1 is as defined for a compound of the formula I in any one of claims 1 to 8, in the presence of a tosyl-methyl isocyanide of the formula IV,

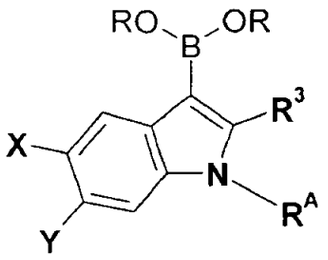


(IV)

wherein $R^2$is as defined for a compound of the formula I in any one of claims 1 to 8;

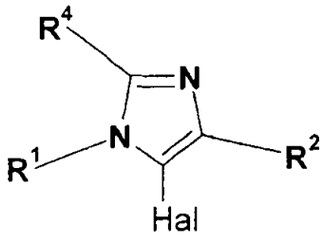
or

b) coupling an indole-boronic acid of the formula V,



(V)

wherein R^3, R^A, X and Y are as defined for a compound of the formula I in any one of claims 1 to 8, and each R is aryl, alkenyl or especially alkyl, or wherein the two R form a bridge, especially R is H, lower alkyl or R and R together form 1,1,2,2-tetramethyl-1,2-ethylene, with a halo-imidazole of the formula VI,



(VI)

wherein R^1, R^2 and R^4 are as defined for a compound of the formula I in any one of claims 1 to 8 and Hal is halo, especially bromo or more especially iodo,

where in the reaction functional groups in the starting materials can be present in protected form and in the obtainable compounds of the formula I carrying one or more protect-

ting groups such protecting groups are removed;

and, if desired, a compound of the formula I obtainable according to the reaction given above is converted into a different compound of the formula I, an obtainable salt of a compound of the formula I is converted into a different salt thereof, an obtainable free compound of the formula I is converted into a salt thereof, and/or an obtainable isomer of a compound of the formula I is separated from one or more different obtainable isomers of the formula I.

3-IMIDAZOLIL-INDOLES PARA EL TRATAMIENTO DE ENFERMEDADES PROLIFERATIVAS

La presente invención se refiere a compuestos de 3-heterociclil-indolilo capaces de inhibir la interacción entre p53, o variantes de la misma, y MDM2 y/o MDM4, o variantes de los mismos, respectivamente, en especial el enlace con MDM2 y/o MDM4, o variantes de los mismos, a un proceso para la preparación de estos compuestos, a las preparaciones farmacéuticas que comprenden tales compuestos, a usos y métodos de uso para estos compuestos en el tratamiento (incluyendo terapia y/o profilaxis), y/o materia objeto relacionada, como se especifica más adelante. MDM2 se refiere a todos los genes y/o proteínas codificadas del mismo, con los nombres MDM2, Mdm2, HDM2, Hdm2. MDM4 se refiere a todos los genes y/o proteínas codificadas del mismo con los nombres MDM4, Mdm4, HDM4, Hdm4, MDMX, MdmX, HDMX, HdmX.

La proteína p53 se conoce como una proteína supresora de tumor, la cual ayuda a controlar la integridad celular, y previene la proliferación de las células permanentemente dañadas, mediante el inicio del paro de crecimiento o apoptosis (muerte celular controlada). p53 media sus efectos en que es un factor de transcripción capaz de regular un número de genes que regulan el ciclo celular y la apoptosis. Por consiguiente, p53 es un inhibidor del ciclo celular importante. Estas actividades son estrechamente controladas por MDM2, un regulador negativo importante del

supresor de tumor p53. "MDM2" (originalmente a partir del oncogén "[di]minuto doble de murino") se refiere tanto al nombre del gen como a la proteína codificada por ese gen. La proteína MDM2 funciona como una ligasa de ubiquitina E3 que reconoce el dominio de trans-activación (TAD) N-terminal del supresor de tumor p53, y por consiguiente, media la degradación de p53 dependiente de ubiquitina, así como funciona como un inhibidor de la activación de transcripción de p53.

El oncogén de ratón original, que codifica para la proteína MDM2, fue originalmente clonado a partir de una línea celular de ratón transformada. Posteriormente se identificó el homólogo humano de esta proteína, y algunas veces también es denominada como HDM2 (por "[di]minuta doble humana 2"). Apoyando adicionalmente el papel de MDM2 como un oncogén, se ha demostrado que varios tipos de tumores humanos y enfermedades proliferativas tienen mayores niveles de MDM2, incluyendo, entre otras cosas, sarcomas de tejido blando, cáncer de hueso, por ejemplo, osteosarcomas, tumores de mama, cáncer de vejiga, síndrome de Li-Fraumeni, tumor de cerebro, rabdomiosarcoma y carcinoma adrenocortical, y similares. Otra proteína perteneciente a la familia MDM2 es la MDM4, también conocida como MDMX.

Por consiguiente, se puede encontrar una mala regulación de la proporción de MDM2/p53, por ejemplo, debido a mutaciones o a defectos moleculares en las células afectadas, en muchas enfermedades proliferativas. MDM2, en vista de sus efectos

mencionados, es capaz de inhibir la actividad de la proteína supresora de tumor p53, y por consiguiente, conduce a la pérdida de la actividad supresora de tumor de p53, y a la inhibición de los mecanismos reguladores que impiden la proliferación incontrolada de las células. Como una consecuencia, puede tener lugar una proliferación incontrolada, que conduce a tumores, leucemias, u otras enfermedades proliferativas.

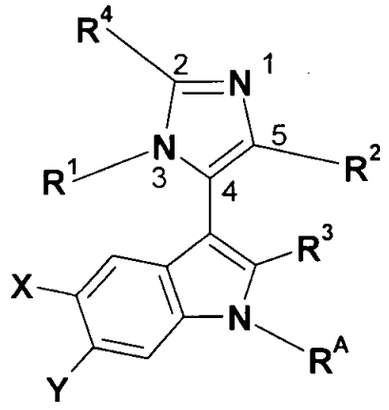
Por consiguiente, existe una necesidad de nuevos fármacos que sean capaces de interferir con la interacción entre p53 y mdm2, o en especial las variantes oncogénicas del mismo, y que, por consiguiente, permitan que p53 ejerza su efecto benéfico contra el crecimiento tumoral incontrolado, permitiéndole, por ejemplo, acumularse, detener el ciclo celular, y/o provocar la apoptosis de las células afectadas.

Breve Descripción de la Invención

Ahora se ha encontrado que una clase novedosa de 3-heterociclil-indoles muestra una potente inhibición de la interacción de MDM2/p53 (incluyendo este término la interacción de MDM2/p53 y/o la interacción de MDM4/p53 en la presente), y los compuestos correspondientes, por consiguiente, representan un tipo novedoso de compuestos que son útiles en el tratamiento de un número de trastornos, tales como enfermedades proliferativas. La invención se refiere, por consiguiente, a estos compuestos, así como a las otras modalidades de la invención indicadas anteriormente y más adelante.

Descripción Detallada de la Invención

En una primera modalidad preferida, la invención se refiere a un compuesto de la fórmula I:



(I)

en donde:

R^1 es alquilo insustituido o sustituido, alquenilo insustituido o sustituido o alquinilo insustituido o sustituido, arilo insustituido o sustituido o heterociclilo insustituido o sustituido;

R^2 es alquilo insustituido o sustituido, alquenilo insustituido o sustituido, alquinilo insustituido o sustituido, arilo insustituido o sustituido o heterociclilo insustituido o sustituido;

R^3 es hidrógeno, halógeno, alquilo insustituido o sustituido, alquenilo insustituido o sustituido, alquinilo insustituido o sustituido, arilo insustituido o sustituido, carboxilo, ciano, carboxilo esterificado, heterociclil-carbonilo insustituido o sustituido (heterociclil-C)=O)-), carbamoílo insustituido o sustituido o heterociclilo insustituido o sustituido;

R^4 es hidrógeno, halógeno, alquilo insustituido o sustituido, alquenilo insustituido o sustituido, alquinilo insustituido o sustituido,

arilo insustituido o sustituido, carboxilo, ciano, carboxilo esterificado, heterociclil-carbonilo insustituido o sustituido (heterociclil-C)=O)-), carbamoílo insustituido o sustituido o heterociclilo insustituido o sustituido;

R^A es hidrógeno o alquilo insustituido o sustituido o acilo;

X es hidrógeno, alquilo de 1 a 7 átomos de carbono, halo-alquilo de 1 a 7 átomos de carbono, alcoxilo de 1 a 7 átomos de carbono, halógeno o ciano; e

Y es alquilo de 1 a 7 átomos de carbono, halo-alquilo de 1 a 7 átomos de carbono, alcoxilo de 1 a 7 átomos de carbono, halógeno o ciano;

y/o un tautómero, un N-óxido, y/o una sal (de preferencia farmacéuticamente aceptable) del mismo.

Los términos generales utilizados anteriormente en la presente y más adelante en la presente, de preferencia tienen, dentro del contexto de esta divulgación, los siguientes significados, a menos que se indique de otra manera, en donde los términos más generales en dondequiera que se utilicen, pueden ser reemplazados, independientemente unos de otros, por definiciones más específicas, o siguen definiendo, por consiguiente, las modalidades más preferidas de la invención:

El prefijo "inferior" o "de 1 a 7 átomos de carbono" denota un radical que tiene hasta e incluyendo un máximo de 7, en especial hasta e incluyendo un máximo de 4 átomos de carbono, siendo los radicales en cuestión lineales o ramificados con ramificación

individual o múltiple.

Por ejemplo, alquilo inferior (o alquilo de 1 a 7 átomos de carbono) es de preferencia alquilo con desde e incluyendo 1 hasta e incluyendo 7, de preferencia desde e incluyendo 1 hasta e incluyendo 4, y es lineal o ramificado; de preferencia, alquilo inferior es butilo, tal como butilo normal, butilo secundario, isobutilo, butilo terciario, propilo, tal como propilo normal o isopropilo, etilo o de preferencia metilo.

La numeración de las posiciones de sustituyentes en el imidazol central, dada en la presente divulgación (por ejemplo, en los Ejemplos) usualmente (aunque en casos excepcionales esto puede diferir) se proporciona en la fórmula I anterior, mediante los números pequeños 1, 2, 3, 4 y 5.

Halógeno (o halo) es en especial flúor, cloro, bromo, o yodo, en especial flúor, cloro o bromo.

"Alquilo inferior-sulfonilo" representa alquilo-$S(=O)_2$- (algunas veces también referido como alcano inferior-sulfonilo).

Los compuestos de la fórmula I pueden tener diferentes formas isoméricas. Por ejemplo, cualquier átomo de carbono asimétrico puede estar presente en la configuración (R), (S), o (R,S), de preferencia en la configuración (R) o (S). Los sustituyentes en un doble enlace, o en especial en un anillo, pueden estar presentes en la forma *cis*- (=Z-) o *trans* (=E-). Los compuestos, por lo tanto, pueden estar presentes como mezclas de isómeros o de preferencia como los isómeros puros, de preferencia como los diaestereómeros

puros o los enantiómeros puros.

Cuando se utiliza la forma plural (por ejemplo, los compuestos, sales), ésta incluye al singular (por ejemplo, un solo compuesto, una sola sal). "Un compuesto" no excluye que esté presente (por ejemplo, en una formulación farmacéutica) más de un compuesto de la fórmula I (o una sal del mismo), representando el "un", meramente al artículo indefinido. "Un", por consiguiente, se puede leer de preferencia como "uno o más", y con menos preferencia de una manera alternativa como "uno".

En alquilo insustituido o sustituido, alquilo (también en alcoxilo o similares) de preferencia tiene hasta 20, más preferiblemente hasta 12 átomos de carbono, es lineal o ramificado, y es más preferiblemente alquilo de 1 a 7 átomos de carbono, en especial alquilo de 1 a 4 átomos de carbono. Alquilo sustituido es de preferencia alquilo de 1 a 20 átomos de carbono, más preferiblemente alquilo de 1 a 7 átomos de carbono, en especial alquilo de 1 a 4 átomos de carbono, que puede ser lineal o ramificado una o más veces (en el entendido de que el número de átomos de carbono lo permita), por ejemplo, metilo, etilo, propilo, butilo normal, butilo secundario, isobutilo, butilo terciario, 2,2-dimetil-propilo, 1,2,2-trimetil-propilo, 1-etil-propilo, y que está sustituido por uno o más, de preferencia hasta tres, sustituyentes seleccionados independientemente a partir del grupo que consiste en alquilo de 1 a 7 átomos de carbono, hidroxi-alquilo de 1 a 7 átomos de carbono, alcoxilo de 1 a 7 átomos de carbono-alquilo de 1 a 7

átomos de carbono, N-mono- o N,N-di-[alquilo de 1 a 7 átomos de carbono, fenilo, alcanoílo de 1 a 7 átomos de carbono y/o fenil-alquilo de 1 a 7 átomos de carbono]-amino-alquilo de 1 a 7 átomos de carbono (tal como –metilo), halo-alquilo de 1 a 7 átomos de carbono, tal como trifluoro-metilo, hidroxilo, alcoxilo de 1 a 7 átomos de carbono, alcoxilo de 1 a 7 átomos de carbono-alcoxilo de 1 a 7 átomos de carbono, (alcoxilo de 1 a 7 átomos de carbono)-alcoxilo de 1 a 7 átomos de carbono-alcoxilo de 1 a 7 átomos de carbono, halo-alcoxilo de 1 a 7 átomos de carbono, halógeno, en especial flúor, cloro o bromo o yodo, fenoxilo, naftiloxilo, fenil- o naftil-alcoxilo de 1 a 7 átomos de carbono; amino-alcoxilo de 1 a 7 átomos de carbono, alcanoiloxilo de 1 a 7 átomos de carbono, benzoiloxilo, naftoiloxilo, oxo (de preferencia no en el átomo de carbono de enlace), amino, amino-alquilo de 1 a 7 átomos de carbono, en especial amino-metilo, N-mono- o N,N-di-[alquilo de 1 a 7 átomos de carbono, fenilo, alcanoílo de 1 a 7 átomos de carbono y/o fenil-alquilo de 1 a 7 átomos de carbono]-amino, N-(heterociclil-alquilo de 1 a 7 átomos de carbono)- o N-(heterociclil-alquilo de 1 a 7 átomos de carbono-)-N-(alquilo de 1 a 7 átomos de carbono)-amino, en donde el heterociclilo de preferencia tiene de 3 a 14 átomos del anillo, respectivamente, de los cuales de 1 a 4 son un heteroátomo independientemente seleccionado a partir de N, S, S(=O), $S(=O)_2$ y O, y está saturado, en especial (pirrolidinilo, pirazolidinilo, imidazolidinilo, piperidinilo, azepanilo, piperazinilo, morfolinilo, tiomorfolinilo, S-oxo-tiomorfolinilo o S,S-dioxo-tiomorfolinil)-alquilo

de 1 a 7 átomos de carbono-amino, formilo (CHO), carboxilo, alcoxilo de 1 a 7 átomos de carbono-carbonilo, fenil- o naftil-alcoxilo de 1 a 7 átomos de carbono-carbonilo, tal como benciloxi-carbonilo; alcanoílo de 2 a 7 átomos de carbono, tal como acetilo, benzoílo, naftoílo, carbamoílo, carbamoílo N-mono- o N,N-disustituido, en donde los sustituyentes se seleccionan a partir de alquilo inferior e hidroxi-alquilo inferior; amidino, guanidino, ureido, mercapto, tioalquilo de 1 a 7 átomos de carbono, tiofenilo o tionaftilo, fenil- o naftil-tioalquilo de 1 a 7 átomos de carbono, alquilo de 1 a 7 átomos de carbono-tiofenilo, alquilo de 1 a 7 átomos de carbono-tionaftilo, halo-alquilo de 1 a 7 átomos de carbono-mercapto, sulfonamido, benzo-sulfonamido, azido, azido-alquilo de 1 a 7 átomos de carbono, en especial azido-metilo, nitro, ciano; heterociclilo insustituido o sustituido como se describe más adelante, en especial heterociclilo mono- a tri-cíclico que está insaturado o saturado, tiene de 3 a 14 átomos del anillo, de los cuales de 1 a 4 son un heteroátomo independientemente seleccionado a partir de N, S, S(=O), $S(=O)_2$ y O, de preferencia N, tal como pirrolidinilo, pirazidinilo, imidazolidinilo, piperidinilo, azepanilo, piperazinilo, morfolinilo, tiomorfolinilo, S-oxo-tiomorfolinilo, S,S-dioxo-tiomorfolinilo, indolilo, isoindolilo, indazolilo, quinolinilo, isoquinolinilo, ftalazinilo, quinoxalinilo, quinazolinilo, cinolinilo, benzo-furanilo, isobenzo-furanilo, cromenilo, isocromenilo, benzo-tiofenilo, tiocromenilo o isotiocromenilo, y está insustituido o sustituido como se describe más adelante para heterociclilo sustituido, en especial con una o

más, de preferencia hasta tres, fracciones independientemente seleccionadas a partir del grupo que consiste en alquilo de 1 a 7 átomos de carbono, hidroxi-alquilo de 1 a 7 átomos de carbono, hidroxilo, oxo, amino o N-mono- o N,N-di-(alquilo de 1 a 7 átomos de carbono, {amino o mono- o di-(alquilo de 1 a 7 átomos de carbono)-amino}-alquilo de 1 a 7 átomos de carbono, alcanoílo de 1 a 7 átomos de carbono y/o alcoxilo de 1 a 7 átomos de carbono-carbonil)-amino, alcanoílo de 1 a 7 átomos de carbono, alquilo de 1 a 7 átomos de carbono-sulfonilo y heterociclilo saturado con 3 a 14 átomos del anillo y con 1 a 4 heteroátomos independientemente seleccionados a partir de N, S, S(=O), $S(=O)_2$ y O, de preferencia N, por ejemplo, pirrolidinilo, pirazolidinilo, imidazolidinilo, tetrahidrofuranilo, piperidinilo, azepanilo, piperazinilo, morfolinilo, tiomorfolinilo, S-oxo-tiomorfolinilo o S,S-dioxo-tiomorfolinilo, en donde este heterociclilo saturado está insustituido o sustituido por una o más, en especial hasta tres, fracciones independientemente seleccionadas a partir de alquilo de 1 a 7 átomos de carbono, hidroxi-alquilo de 1 a 7 átomos de carbono, alcoxilo de 1 a 7 átomos de carbono-alquilo de 1 a 7 átomos de carbono, oxo, amino, mono- o di-(alquilo de 1 a 7 átomos de carbono)-amino), alcanoílo de 1 a 7 átomos de carbono y alcoxilo de 1 a 7 átomos de carbono-carbonilo; arilo insustituido o sustituido como se define más adelante, en especial naftilo o fenilo, cada uno de los cuales está insustituido o sustituido por una o más, en especial hasta tres, fracciones independientemente seleccionadas a partir de alquilo de 1 a 7

átomos de carbono, halo-alquilo de 1 a 7 átomos de carbono, hidroxilo, alcoxilo de 1 a 7 átomos de carbono, hidroxi-alcoxilo de 1 a 7 átomos de carbono, alcoxilo de 1 a 7 átomos de carbono-alcoxilo de 1 a 7 átomos de carbono, (alcoxilo de 1 a 7 átomos de carbono-alcoxilo de 1 a 7 átomos de carbono)-alcoxilo de 1 a 7 átomos de carbono, [amino, mono- o di-(alquilo de 1 a 7 átomos de carbono)-amino]-alcoxilo de 1 a 7 átomos de carbono, amino, mono- o di-[(alquilo de 1 a 7 átomos de carbono, alcanoílo de 1 a 7 átomos de carbono, alcoxilo de 1 a 7 átomos de carbono-carbonilo, hidroxi-alquilo de 1 a 7 átomos de carbono, alcoxilo de 1 a 7 átomos de carbono-alquilo de 1 a 7 átomos de carbono y/o (amino, mono- o di-(alquilo de 1 a 7 átomos de carbono)-amino)-alquilo de 1 a 7 átomos de carbono]-amino, halógeno y heterociclilo saturado, heterociclilo saturado-alquilo de 1 a 7 átomos de carbono o heterociclilo saturado-alcoxilo de 1 a 7 átomos de carbono, en donde el heterociclilo saturado, respectivamente, de preferencia tiene de 3 a 14 átomos del anillo, de los cuales de 1 a 4 son un heteroátomo independientemente seleccionado a partir de N, S, S(=O), $S(=O)_2$ y O, y está insustituido o sustituido con una o más, en especial hasta tres, fracciones independientemente seleccionadas a partir de alquilo de 1 a 7 átomos de carbono, hidroxi-alquilo de 1 a 7 átomos de carbono, alcoxilo de 1 a 7 átomos de carbono-alquilo de 1 a 7 átomos de carbono, hidroxilo, oxo, amino, mono- o di-(alquilo de 1 a 7 átomos de carbono)-amino), alcanoílo de 1 a 7 átomos de carbono y alcoxilo de 1 a 7 átomos de carbono-carbonilo, en especial

pirrolidinilo, pirazolidinilo, imidazolidinilo, piperidinilo, azepanilo, piperazinilo, [N-(alquilo de 1 a 7 átomos de carbono)-piperazinilo o pirrolidinil-, pirazolidinil-, imidazolidinil-, piperidinil-, azepanil-, piperazinil- o N-(alquilo de 1 a 7 átomos de carbono)-piperazinil]-alquilo de 1 a 7 átomos de carbono o [N-(alquilo de 1 a 7 átomos de carbono)-piperazinilo o pirrolidinil-, pirazolidinil-, imidazolidinil-, piperidinil-, azepanil-, piperazinil- o N-(alquilo de 1 a 7 átomos de carbono)-piperazinil]-alcoxilo de 1 a 7 átomos de carbono, nitro o ciano; y cicloalquilo insustituido o sustituido, en especial cicloalquilo de 3 a 8 átomos de carbono, que está insustituido o sustituido por uno o más, en especial hasta tres, sustituyentes seleccionados independientemente a partir de los sustituyentes para arilo sustituido más adelante;

en donde cada fenilo o naftilo (también en fenoxilo o naftoxilo) mencionado anteriormente como sustituyente o parte de un sustituyente de alquilo sustituido (o también de arilo sustituido, heterociclilo etc. mencionados en la presente) está él mismo insustituido o sustituido por uno o más, por ejemplo, hasta tres, de preferencia 1 ó 2 sustituyentes seleccionados independientemente a partir de alquilo de 1 a 7 átomos de carbono, halo-alquilo de 1 a 7 átomos de carbono, hidroxilo, alcoxilo de 1 a 7 átomos de carbono, alcoxilo de 1 a 7 átomos de carbono-alcoxilo de 1 a 7 átomos de carbono, halógeno, en especial flúor, cloro, bromo o yodo, halo-alquilo de 1 a 7 átomos de carbono, tal como trifluoro-metilo, azido, amino, N-mono- o N,N-di-(alquilo de 1 a 7 átomos de carbono, fenilo,

naftilo, alcanoílo de 1 a 7 átomos de carbono, fenil-alquilo de 1 a 7 átomos de carbono y/o naftil-alquilo de 1 a 7 átomos de carbono)-amino, carboxilo, alcoxilo de 1 a 7 átomos de cárbono-carbonilo carbamoílo, sulfamoílo, nitro y ciano.

Alquenilo insustituido o sustituido es de preferencia alquenilo de 2 a 20 átomos de carbono, más preferiblemente alquenilo de 2 12 átomos de carbono, todavía más preferiblemente alquenilo de 2 a 7 átomos de carbono, el cual es lineal o ramificado e incluye uno o más dobles enlaces. Los sustituyentes son de preferencia uno o más, en especial hasta tres, sustituyentes seleccionados independientemente a partir de aquéllos mencionados para alquilo sustituido, de preferencia con la condición de que los sustituyentes con hidrógeno activo (tal como amino o hidroxilo) también pueden estar presentes en una forma tautomérica (como compuestos ceto o imino) o se excluyen de los sustituyentes en donde la estabilidad es demasiado baja.

Alquinilo insustituido o sustituido es de preferencia alquinilo de 2 a 20 átomos de carbono, más preferiblemente alquinilo de 3 a 12 átomos de carbono, todavía más preferiblemente alquinilo de 3 a 7 átomos de carbono, el cual es lineal o ramificado e incluye uno o más triples enlaces. Los sustituyentes son de preferencia uno o más, en especial hasta tres, sustituyentes seleccionados independientemente a partir de aquéllos mencionados para alquilo sustituido, de preferencia con la condición de que los sustituyentes con hidrógeno activo (tal como amino o hidroxilo) también pueden

estar presentes en una forma tautomérica (como compuestos ceto o imino) o se excluyen de los sustituyentes en donde la estabilidad es demasiado baja.

En arilo insustituido o sustituido, arilo de preferencia tiene de 6 a 18, más preferiblemente de 8 a 14 átomos de carbono y es una fracción carbocíclica insaturada mono-, di-, o poli-cíclica (de preferencia hasta tri-cíclica, más preferiblemente hasta bi-cíclica) con dobles enlaces conjugados en el anillo, en especial fenilo, naftilo, bifenilenilo, indacenilo, acenaftilenilo, fluorenilo, fenalenilo, fenantrenilo o antracenilo. Se prefieren en especial naftilo y de preferencia fenilo. Arilo está insustituido o (en el caso de arilo sustituido) sustituido por uno o más, por ejemplo, uno a tres sustituyentes de preferencia independientemente seleccionados a partir del grupo que consiste en alquilo de 1 a 7 átomos de carbono, tal como metilo, etilo, propilo normal, isopropilo, butilo normal, isobutilo, butilo secundario o butilo terciario; alquenilo de 2 a 7 átomos de carbono; alquinilo de 2 a 7 átomos de carbono; arilo de 6 a 18 átomos de carbono-alquilo de 1 a 7 átomos de carbono, en donde arilo es de preferencia fenilo, naftilo, bifenilenilo, indacenilo, acenaftilenilo, fluorenilo, fenalenilo, fenantrenilo o antracenilo, y está insustituido o sustituido por alquilo de 1 a 7 átomos de carbono, tal como metilo o etilo, por pirrolidinilo, en especial pirrolidino, por pirazolidinilo, en especial pirazolidino, por imidazolidinilo, en especial imidazolidino, por piperidinilo, en especial piperidin-1-ilo, por azepanilo, en especial azepan-1-ilo, piperazinilo, en especial

piperazino, por amino, por N-mono- y/o N,N-di-alquilo de 1 a 7 átomos de carbono-amino, por halógeno, por hidroxilo, por alcoxilo de 1 a 7 átomos de carbono, tal como metoxilo, y/o por halo-alquilo de 1 a 7 átomos de carbono, tal como trifluoro-metilo; (pirrolidinilo (en especial pirrolidino), piridazolidinilo, en especial piridazolidino, imidazolidinilo (en especial imidazolidino), piperidinilo (en especial piperidino), azepanilo (en especial azepan-1-ilo), piperazinilo (en especial piperazino), morfolino, tiomorfolino, piridinilo, pirimidinilo, pirazinilo, piridazinilo, oxazolilo o tiazolil)-alquilo de 1 a 7 átomos de carbono, en donde pirrolidinilo, pirazolidinilo, imidazolidinilo, piperidinilo, azepanilo, piperazinilo, piridinilo, pirimidinilo, pirazinilo, piridazinilo, oxazolilo o tiazolilo están insustituidos o sustituidos por alquilo de 1 a 7 átomos de carbono, tal como metilo o etilo, por pirrolidinilo, en especial pirrolidino, por pirazolidinilo, en especial pirazolidino, por imidazolidinilo, en especial imidazolidino, por azepanilo, en especial azepan-1-ilo, por piperazinilo, en especial piperazino, por amino, por N-mono- y/o N,N-di-alquilo de 1 a 7 átomos de carbono-amino, por halógeno, por alcoxilo de 1 a 7 átomos de carbono, tal como metoxilo, y/o por halo-alquilo de 1 a 7 átomos de carbono, tal como trifluoro-metilo, por ejemplo pirrolidino-alquilo de 1 a 7 átomos de carbono, pirazolidino-alquilo de 1 a 7 átomos de carbono, imidazolidino-alquilo de 1 a 7 átomos de carbono, piperidino-alquilo de 1 a 7 átomos de carbono, azepan-1-il-alquilo de 1 a 7 átomos de carbono, piperazino-alquilo de 1 a 7 átomos de carbono, morfolino-alquilo de 1 a 7 átomos de carbono,

tiomorfolino-alquilo de 1 a 7 átomos de carbono, N-alquilo de 1 a 7 átomos de carbono-piperazino-alquilo de 1 a 7 átomos de carbono, o N-mono- o N,N-di-(alquilo de 1 a 7 átomos de carbono)-amino-sustituido o insustituido pirrolidino-alquilo de 1 a 7 átomos de carbono; (pirrolidinilo (en especial pirrolidino), pirazolidinilo, (en especial pirazolidino), imidazolidinilo (en especial imidazolidino) piperidinilo (en especial piperidino), azepanilo (en especial azepan-1-ilo), piperazinilo (en especial piperazino), piridinilo, pirimidinilo, pirazinilo, piridazinilo, oxazolilo o tiazolil)-oxi-alquilo de 1 a 7 átomos de carbono, en donde pirrolidinilo, pirazolidinilo, imidazolidinilo, piperidinilo, azepanilo, piperazinilo, piridinilo, pirimidinilo, pirazinilo, piridazinilo, oxazolilo y tiazolilo están insustituidos o sustituidos por alquilo de 1 a 7 átomos de carbono, tal como metilo o etilo, por pirrolidinilo, en especial pirrolidino, por pirazolidinilo, en especial pirazolidino, por imidazolidinilo, en especial imidazolidino, por piperidinilo, en especial piperidino, por azepanilo, en especial azepan-1-ilo, por piperazinilo, en especial piperazino, por amino, por N-mono- y/o N,N-di-alquilo de 1 a 7 átomos de carbono-amino, por halógeno, por alcoxilo de 1 a 7 átomos de carbono, tal como metoxilo, y/o por halo-alquilo de 1 a 7 átomos de carbono, tal como trifluoro-metilo; (pirrolidina (en especial pirrolidino), pirazolidinilo (en especial pirazolidino), imidazolidinilo (en especial imidazolidino), piperidina (en especial piperidino), azepano (en especial azepan-1-ilo), piperazina (en especial piperazino), piridina, pirimidina, pirazina, piridazina, oxazol o tiazol)-carbonil-alquilo de 1 a 7 átomos de

carbono, en donde pirrolidina, pirazolidina, imidazolidina, piperidina, azepano, piperazina, piridina, pirimidina, piridazina, oxazol o piridazina están insustituidos o sustituidos por alquilo de 1 a 7 átomos de carbono, tal como metilo o etilo, por pirrolidinilo, en especial pirrolidino, por pirazolidinilo, en especial pirazolidino, por imidazolidinilo, en especial imidazolidino, por azepanilo, en especial azepan-1-ilo, por piperazinilo, en especial piperazino, por amino, por N-mono- y/o N,N-di-alquilo de 1 a 7 átomos de carbono-amino, por halógeno, por alcoxilo de 1 a 7 átomos de carbono, tal como metoxilo, y/o por halo-alquilo de 1 a 7 átomos de carbono, tal como trifluoro-metilo; halo-alquilo de 1 a 7 átomos de carbono, tal como trifluoro-metilo; hidroxi-alquilo de 1 a 7 átomos de carbono, tal como hidroxi-metilo; alcoxilo de 1 a 7 átomos de carbono-alquilo de 1 a 7 átomos de carbono, tal como 3-metoxi-propilo o 2-metoxi-etilo; alcoxilo de 1 a 7 átomos de carbono-alcoxilo de 1 a 7 átomos de carbono-alquilo de 1 a 7 átomos de carbono; feniloxi- o naftiloxi-alquilo de 1 a 7 átomos de carbono; fenil-alcoxilo de 1 a 7 átomos de carbono- o naftil-alcoxilo de 1 a 7 átomos de carbono-alquilo de 1 a 7 átomos de carbono; amino-alquilo de 1 a 7 átomos de carbono, tal como amino-metilo; N-mono- o N,N-di-(alquilo de 1 a 7 átomos de carbono, alcoxilo de 1 a 7 átomos de carbono-alquilo de 1 a 7 átomos de carbono y/o (mono- o di-(alquilo de 1 a 7 átomos de carbono)-amino)-alquilo de 1 a 7 átomos de carbono)-amino-alquilo de 1 a 7 átomos de carbono; alcoxilo de 1 a 7 átomos de carbono-alquilo de 1 a 7 átomos de carbono-amino-alquilo de 1 a 7 átomos de

carbono; mono- o di-[arilo de 6 a 18 átomos de carbono-alquilo de 1 a 7 átomos de carbono, en donde arilo es de preferencia fenilo, naftilo, bifenilenilo, indacenilo, acenaftilenilo, fluorenilo, fenalenilo, fenantrenilo o antracenilo, y está insustituido o sustituido por alquilo de 1 a 7 átomos de carbono, tal como metilo o etilo, por pirrolidinilo, en especial pirrolidino, por pirazolidinilo, en especial pirazolidino, por imidazolidinilo, en especial imidazolidino, por piperidinilo, en especial piperidino, por azepanilo, en especial azepan-1-ilo, por piperazinilo, en especial piperazino, por amino, por N-mono- y/o N,N-di-alquilo de 1 a 7 átomos de carbono-amino, por halógeno, por hidroxilo, por alcoxilo de 1 a 7 átomos de carbono, tal como metoxilo, y/o por halo-alquilo de 1 a 7 átomos de carbono, tal como trifluoro-metilo; naftil- o fenil-alquilo de 1 a 7 átomos de carbono]-amino-alquilo de 1 a 7 átomos de carbono; alcanoílo de 1 a 7 átomos de carbono-amino-alquilo de 1 a 7 átomos de carbono; carboxi-alquilo de 1 a 7 átomos de carbono; benzoil- o naftoil-amino-alquilo de 1 a 7 átomos de carbono; alquilo de 1 a 7 átomos de carbono-sulfonil-amino-alquilo de 1 a 7 átomos de carbono; fenil- o naftil-sulfonil-amino-alquilo de 1 a 7 átomos de carbono, en donde fenilo o naftilo está insustituido o sustituido por una o más, en especial una a tres, fracciones de alquilo de 1 a 7 átomos de carbono; fenil- o naftil-alquilo de 1 a 7 átomos de carbono-sulfonil-amino-alquilo de 1 a 7 átomos de carbono; halógeno, en especial fluoro (preferido), cloro (preferido) o bromo; hidroxilo; alcoxilo de 1 a 7 átomos de carbono; arilo de 6 a 18 átomos de carbono-alcoxilo de 1 a 7 átomos de

carbono, en donde arilo es de preferencia fenilo, naftilo, bifenilenilo, indacenilo, acenaftilenilo, fluorenilo, fenalenilo, fenantrenilo o antracenilo y está insustituido o sustituido por alquilo de 1 a 7 átomos de carbono, tal como metilo o etilo, por alcoxilo de 1 a 7 átomos de carbono, por pirrolidinilo, en especial pirrolidino, por pirazolidinilo, en especial parazolidino, por imidazolidinilo, en especial imidazolidino, piperidinilo, en especial piperidino, por azepanilo, en especial azepan-1-ilo, por piperazinilo, en especial piperazino, por amino, por N-mono- y/o N,N-di-alquilo de 1 a 7 átomos de carbono-amino, por halógeno, por hidroxilo, por alcoxilo de 1 a 7 átomos de carbono, tal como metoxilo, y/o por halo-alquilo de 1 a 7 átomos de carbono, tal como trifluoro-metilo; tal como fenil-alcoxilo de 1 a 7 átomos de carbono, en donde fenilo está insustituido o sustituido por alcoxilo de 1 a 7 átomos de carbono y/o halógeno; halo-alcoxilo de 1 a 7 átomos de carbono, tal como trifluoro-metoxilo; hidroxi-alcoxilo de 1 a 7 átomos de carbono; alcoxilo de 1 a 7 átomos de carbono-alcoxilo de 1 a 7 átomos de carbono, tal como 2-(metoxi)-etoxilo; (alcoxilo de 1 a 7 átomos de carbono-alcoxilo de 1 a 7 átomos de carbono)-alcoxilo de 1 a 7 átomos de carbono; [amino, mono- o di-(alquilo de 1 a 7 átomos de carbono)-amino]-alcoxilo de 1 a 7 átomos de carbono, N-alcanoílo de 1 a 7 átomos de carbono-amino-alcoxilo de 1 a 7 átomos de carbono; N-insustituido-, N-mono- o N,N-di-(alquilo de 1 a 7 átomos de carbono)-carbamoil-alcoxilo de 1 a 7 átomos de carbono; fenil- o naftiloxilo; fenil- o naftil-alquiloxilo de 1 a 7 átomos de carbono; (pirrolidinilo (en

especial pirrolidino), pirazolidinilo (en especial pirazolidino), imidazolidinilo (en especial imidazolidino), piperidinilo (en especial piperidino), azepanilo (en especial azepan-1-ilo), piperazinilo (en especial piperazino), piridinilo, pirimidinilo, pirazinilo, piridazinilo, oxazolilo o tiazolil)-alcoxilo de 1 a 7 átomos de carbono, en donde pirrolidinilo, pirazolidinilo, imidazolidinilo, piperidinilo, azepanilo, piperazinilo, piridinilo, pirimidinilo, pirazinilo, piridazinilo, oxazolilo y tiazolilo están insustituidos o sustituidos por alquilo de 1 a 7 átomos de carbono, tal como metilo o etilo, por pirrolidinilo, en especial pirrolidino, por pirazolidinilo, en especial pirazolidino, por imidazolidinilo, en especial imidazolidino, por piperidinilo, en especial piperidino, por azepanilo, en especial azepan-1-ilo, por piperazinilo, en especial piperazino, por amino, por N-mono- y/o N,N-di-alquilo de 1 a 7 átomos de carbono-amino, por halógeno, por alcoxilo de 1 a 7 átomos de carbono, tal como metoxilo, y/o por halo-alquilo de 1 a 7 átomos de carbono, tal como trifluoro-metilo; (pirrolidinilo (en especial pirrolidino), pirazolidinilo (en especial pirazolidino), imidazolidinilo (en especial imidazolidino), piperidinilo (en especial piperidino), azepanilo (en especial azepan-1-ilo), piperazinilo (en especial piperazino), piridinilo, pirimidinilo, pirazinilo, piridazinilo, oxazolilo o tiazolil)-oxi-alcoxilo de 1 a 7 átomos de carbono, en donde pirrolidinilo, pirazolidinilo, imidazolidinilo, piperidinilo, azepanilo, piperazinilo, piridinilo, pirimidinilo, pirazinilo, piridazinilo, oxazolilo y tiazolilo están insustituidos o sustituidos por alquilo de 1 a 7 átomos de carbono, tal

como metilo o etilo, por pirrolidinilo, en especial pirrolidino, por pirazolidinilo, en especial pirazolidino, por imidazolidinilo,. en especial imidazolidino, por piperidinilo, en especial piperidino, por azepanilo, en especial azepan-1-ilo, por piperazinilo, en especial piperazino, por amino, por N-mono- y/o N,N-di-alquilo de 1 a 7 átomos de carbono-amino, por halógeno, por alcoxilo de 1 a 7 átomos de carbono, tal como metoxilo, y/o por halo-alquilo de 1 a 7 átomos de carbono, tal como trifluoro-metilo; alcanoiloxilo de 1 a 7 átomos de carbono; benzoil- o naftoiloxilo; tioalquilo de 1 a 7 átomos de carbono; halo-tioalquilo de 1 a 7 átomos de carbono, tal como trifluoro-tiometilo; alcoxilo de 1 a 7 átomos de carbono-tioalquilo de 1 a 7 átomos de carbono; tiofenilo o tionaftilo; fenil- o naftil-tioalquilo de 1 a 7 átomos de carbono; tioalcanoílo de 1 a 7 átomos de carbono; tiobenzoílo o tionaftoílo; nitro; amino; mono- o di-[(alquilo de 1 a 7 átomos de carbono, alcanoílo de 1 a 7 átomos de carbono, alcoxilo de 1 a 7 átomos de carbono-carbonilo, hidroxi-alquilo de 1 a 7 átomos de carbono, alcoxilo de 1 a 7 átomos de carbono-alquilo de 1 a 7 átomos de carbono y/o (amino, mono- o di-(alquilo de 1 a 7 átomos de carbono)-amino)-alquilo de 1 a 7 átomos de carbono]-amino; mono- o di-(naftil- o fenil-alquilo de 1 a 7 átomos de carbono)-amino; alcanoílo de 1 a 7 átomos de carbono-amino; benzoil- o naftoil-amino insustituido o sustituido por amino-, N-mono- o N,N-di-(alquilo de 1 a 7 átomos de carbono y/o fenil- o naftil-alquilo de 1 a 7 átomos de carbono)-amino; alcoxilo de 1 a 7 átomos de carbono-carbonil-amino; (fenil o naftil)-alcoxilo de 1 a 7 átomos de

carbono-carbonil-amino; alquilo de 1 a 7 átomos de carbono-sulfonil-amino (= alquilo de 1 a 7 átomos de carbono-$S(=O)_2$-NH-); fenil- o naftil-sulfonil-amino, en donde fenilo o naftilo está insustituido o sustituido por una o más, en especial una a tres, fracciones de alquilo de 1 a 7 átomos de carbono; fenil- o naftil-alquilo de 1 a 7 átomos de carbono-sulfonil-amino; alcanoílo de 1 a 7 átomos de carbono; alcoxilo de 1 a 7 átomos de carbono-alcanoílo de 1 a 7 átomos de carbono; carboxilo (-COOH); alcoxilo de 1 a 7 átomos de carbono-carbonilo; fenoxi- o naftoxi-carbonilo; fenil- o naftil-alcoxilo de 1 a 7 átomos de carbono-carbonilo; alquilendioxilo de 1 a 10 átomos de carbono, en especial de 1 a 4 átomos de carbono, tal como metilendioxilo o 1,2-etilendioxilo; carbamoílo; N-mono- o N,N-di-[alquilo de 1 a 7 átomos de carbono, naftil-alquilo de 1 a 7 átomos de carbono, fenil-alquilo de 1 a 7 átomos de carbono, N'-mono- o N',N'-di-(alquilo de 1 a 7 átomos de carbono)-amino-alquilo de 1 a 7 átomos de carbono, pirrolidinilo (en especial pirrolidino)-alquilo de 1 a 7 átomos de carbono, pirazolidinilo (en especial pirazolidino)-alquilo de 1 a 7 átomos de carbono, imidazolidinilo (en especial imidazolidino)-alquilo de 1 a 7 átomos de carbono, piperidinilo (en especial piperidino)-alquilo de 1 a 7 átomos de carbono, azepanilo (en especial azepan-1-il)-alquilo de 1 a 7 átomos de carbono, piperazinil- o N-(alquilo de 1 a 7 átomos de carbono)-piperazinilo (en especial piperazino o 4-alquilo de 1 a 7 átomos de carbono-piperazino)-alquilo de 1 a 7 átomos de carbono, mono-alcoxilo de 1 a 7 átomos de carbono-alquilo de 1 a 7 átomos de carbono, (N'-mono-

o N',N'-di-(alquilo de 1 a 7 átomos de carbono)-amino); fenilo, piridinilo, oxazolilo o tiazolilo, cada uno de los cuales está insustituido o sustituido por alcoxilo de 1 a 7 átomos de carbono, por halógeno, en especial flúor, por pirrolidino, por pirazolidino, por imidazolidino, por piperidino, por azepan-1-ilo, por piperazino, por hidroxi-alquilo de 1 a 7 átomos de carbono-amino, por hidroxi-alquilo de 1 a 7 átomos de carbono, por amino o por N-mono- o N,N-di-(alquilo de 1 a 7 átomos de carbono)-amino; pirrolidinilo, pirazolidinilo, imidazolidinilo, piperidinilo, azepanilo, piperazinilo, pirimidinilo, pirazinilo y/o piridazinil]-amino-carbonilo, tal como N-mono- o N,N-di-(alquilo de 1 a 7 átomos de carbono)-amino-carbonilo; N-alcoxilo de 1 a 7 átomos de carbono-alquilo de 1 a 7 átomos de carbono-carbamoílo; pirrolidin-1-carbonilo; amino-N-pirrolidin-1-carbonilo; N-mono- o N,N-di-(alquilo de 1 a 7 átomos de carbono)-amino-pirrolidin-1-carbonilo; imidazolidin-1-carbonilo; piperidin-1-carbonil-morfolin-4-carbonilo; tiomorfolin-4-carbonilo; S-oxo-tiomorfolin-4-carbonilo; S,S-dioxo-tiomorfolin-4-carbonilo; piperazin-1-carbonilo; N-alquilo de 1 a 7 átomos de carbono-piperazin-1-carbonilo; N-alcoxilo de 1 a 7 átomos de carbono-carbonil-piperazin-1-carbonilo; pirrolidinil-alquilo de 1 a 7 átomos de carbono sustituido por N-mono- o N,N-di-(alquilo de 1 a 7 átomos de carbono)-amino o insustituido; ciano; alquenileno de 1 a 7 átomos de carbono, o -alquinileno; alquilo de 1 a 7 átomos de carbono-sulfonilo; fenil- o naftil-sulfonilo, en donde fenilo o naftilo está insustituido o sustituido por una o más, en especial una a tres, fracciones de

alquilo de 1 a 7 átomos de carbono; fenil- o naftil-alquilo de 1 a 7 átomos de carbono-sulfonilo; sulfamoílo; N-mono- o N,N-di-(alquilo de 1 a 7 átomos de carbono, fenil-, naftil-, fenil-alquilo de 1 a 7 átomos de carbono-, pirrolidinilo (en especial pirrolidino)-alquilo de 1 a 7 átomos de carbono, pirazolidinilo (en especial pirazolidino)-alquilo de 1 a 7 átomos de carbono, imidazolilo (en especial imidazol-1-il))-alquilo de 1 a 7 átomos de carbono, piperidinilo (en especial piperidino)-alquilo de 1 a 7 átomos de carbono, azepanilo (en especial azepan-1-il))-alquilo de 1 a 7 átomos de carbono, piperazinilo (en especial piperazino)-alquilo de 1 a 7 átomos de carbono, N-alquilo de 1 a 7 átomos de carbono-piperazinilo (en especial 4-alquilo de 1 a 7 átomos de carbono-piperazino)-alquilo de 1 a 7 átomos de carbono, naftil-alquilo de 1 a 7 átomos de carbono, fenilo que está insustituido o sustituido por alcoxilo de 1 a 7 átomos de carbono, por halógeno, en especial flúor, por pirrolidino, por pirazolidino, por imidazolidino, por azepan-1-ilo, por piperidino, por piperazino, por hidroxi-alquilo de 1 a 7 átomos de carbono o por N-mono- o N,N-di-(alquilo de 1 a 7 átomos de carbono)-alquilo de 1 a 7 átomos de carbono; pirrolidinilo (en especial pirrolidino), pirazolidinilo (en especial pirazolidino), imidazolidinilo (en especial imidazolidino), piperidinilo (en especial piperidino), azepanilo (en especial azepan-1-ilo), piperazinilo (en especial piperazino), piridinilo, pirimidinilo, pirazinilo, piridazinilo, oxazolilo y/o tiazolil)-amino-sulfonilo, pirazolilo, pirazolidinilo, pirrolilo, pirrolidinilo, piridilo que está insustituido o sustituido por alcoxilo de 1 a 7 átomos de

carbono, tal como metoxilo, y/o por halo-alquilo de 1 a 7 átomos de carbono, tal como trifluoro-metilo, pirrolidinilo, pirazolidinilo, imidazolidinilo, piperidinilo, azepanilo, piperazinilo, morfolinilo, tiomorfolinilo, S-oxo-tiomorfolinilo, S,S-dioxo-tiomorfolinilo, piperazinilo, N-alquilo de 1 a 7 átomos de carbono-piperazinilo, 4-(fenil-alquilo de 1 a 7 átomos de carbono)-piperazinilo, 4-(naftil-alquilo de 1 a 7 átomos de carbono)-piperazinilo, 4-(alcoxilo de 1 a 7 átomos de carbono-carbonil)-piperazinilo, 4-(fenil-alcoxilo de 1 a 7 átomos de carbono-carbonil)-piperazinilo, 4-(naftil-alcoxilo de 1 a 7 átomos de carbono-carbonil)-piperazinilo, oxazolilo y tiazolilo.

De una manera especialmente preferible, arilo es fenilo o naftilo, cada uno de los cuales está insustituido o sustituido como justamente se describió, más preferiblemente por uno o más, por ejemplo, hasta tres, sustituyentes seleccionados independientemente a partir del grupo que consiste en alquilo de 1 a 7 átomos de carbono, hidroxi-alquilo de 1 a 7 átomos de carbono, tal como hidroxi-metilo, alcoxilo de 1 a 7 átomos de carbono-alquilo de 1 a 7 átomos de carbono, tal como metoxi-metilo, halo-alquilo, tal como trifluoro-metilo, amino- o mono- o di-(alquilo de 1 a 7 átomos de carbono)-amino-alquilo de 1 a 7 átomos de carbono, halógeno, hidroxilo, alcoxilo de 1 a 7 átomos de carbono, amino, mono- o di-(alquilo de 1 a 7 átomos de carbono y/o hidroxi-alquilo de 1 a 7 átomos de carbono)-amino, benzoílo de 1 a 7 átomos de carbono-amino, amino-benzoil-amino, alcoxilo de 1 a 7 átomos de carbono-carbonil-amino, (fenil o naftil)-alcoxilo de 1 a 7 átomos de carbono-

carbonil-amino, carbamoílo, N-mono- o N,N-di-(alquilo de 1 a 7 átomos de carbono y/o fenil-alquilo de 1 a 7 átomos de carbono)-amino-carbonilo, fenil-amino-carbonilo, halofenil-amino-carbonilo, N-[N'-mono- o N',N'-di-(alquilo de 1 a 7 átomos de carbono)-amino-alquilo de 1 a 7 átomos de carbono]-amino-carbonilo, sulfamoílo (= amino-sulfonilo) o N-mono- o N,N-di-(alquilo de 1 a 7 átomos de carbono y/o fenil-alquilo de 1 a 7 átomos de carbono)-amino-sulfonilo.

Heterociclilo insustituido o sustituido es de preferencia un radical heterocíclico que está insaturado (= que lleva el número más alto posible de dobles enlaces conjugados en el(los) anillo(s), y entonces también denominado como hetero-arilo), saturado (entonces también denominado como heterociclilo saturado en la presente) o parcialmente saturado y es mono- o poli-cíclico, de preferencia un anillo monocíclico o bicíclico o tricíclico; y tiene de 3 a 24, más preferiblemente de 4 a 16, más preferiblemente de 4 a 10 átomos del anillo; en donde uno o más, de preferencia uno a cuatro, en especial uno a tres átomos de carbono del anillo son reemplazados por un heteroátomo independientemente seleccionado a partir del grupo que consiste en nitrógeno, oxígeno y azufre (incluyendo S(=O) o $S(=O)_2$), teniendo el anillo de enlace de preferencia de 4 a 12, en especial de 5 a 7 átomos del anillo; cuyo radical heterocíclico (heterociclilo) está insustituido o sustituido por uno o más, en especial 1 a 3 sustituyentes seleccionados independientemente a partir del grupo que consiste en los

sustituyentes definidos anteriormente para alquilo sustituido o para arilo sustituido; y en donde el heterociclilo es en especial un radical de heterociclilo seleccionado a partir del grupo que consiste en oxiranilo, azirinilo, aziridinilo, 1,2-oxatiolanilo, tienilo (= tiofenilo), furanilo, tetrahidro-furilo, piranilo, tiopiranilo, tiantrenilo, isobenzo-furanilo, benzo-furanilo, cromenilo, 2H-pirrolilo, pirrolilo, pirrolinilo, pirrolidinilo, imidazolilo, imidazolidinilo, bencimidazolilo, pirazolilo, pirazinilo, pirazolidinilo, tiazolilo, isotiazolilo, ditiazolilo, oxazolilo, isoxazolilo, piridilo, pirazinilo, pirimidinilo, piperidinilo, piperazinilo, piridazinilo, morfolinilo, tiomorfolinilo, (S-oxo o S,S-dioxo)-tiomorfolinilo, indolizinilo, azepanilo, diazepanilo, en especial 1,4-diazepanilo, isoindolilo, 3H-indolilo, indolilo, isoindolilo, indazolilo, bencimidazolilo, cumarilo, triazolilo, tetrazolilo, purinilo, 4H-quinolizinilo, isoquinolilo, isoquinolilo, tetrahidro-quinolilo, tetrahidro-isoquinolilo, decahidro-quinolilo, octahidro-isoquinolilo, benzo-furanilo, isobenzo-furanilo, dibenzo-furanilo, benzo-tiofenilo, dibenzo-tiofenilo, ftalazinilo, naftiridinilo, quinoxalilo (= quinoxalinilo), quinazolinilo, quinazolinilo, cinolinilo, pteridinilo, carbazolilo, beta-carbolinilo, fenantridinilo, acridinilo, perimidinilo, fenantrolinilo, furazanilo, fenazinilo, fenotiazinilo, fenoxazinilo, cromenilo, isocromenilo, cromanilo, benzo-[1,3]-dioxol-5-ilo, 2,3-dihidro-benzo-[1,4]-dioxin-6-ilo, tiocromenilo e isotiocromenilo, estando cada uno de estos radicales insustituido o sustituido por uno o más, de preferencia hasta tres, sustituyentes seleccionados a partir de aquéllos mencionados anteriormente para alquilo sustituido

y para arilo y a partir de oxo, en especial sustituyentes seleccionados independientemente a partir del grupo que consiste en alquilo de 1 a 7 átomos de carbono, hidroxi-alquilo de 1 a 7 átomos de carbono, hidroxilo, alcoxilo de 1 a 7 átomos de carbono, hidroxi-alcoxilo de 1 a 7 átomos de carbono, alcoxilo de 1 a 7 átomos de carbono-alcoxilo de 1 a 7 átomos de carbono, (alcoxilo de 1 a 7 átomos de carbono-alcoxilo de 1 a 7 átomos de carbono)-alcoxilo de 1 a 7 átomos de carbono, (amino-mono- o di-(alquilo de 1 a 7 átomos de carbono)-amino)-alcoxilo de 1 a 7 átomos de carbono, oxo, amino, N-mono- o N,N-di-(alquilo de 1 a 7 átomos de carbono, {amino o mono- o di-(alquilo de 1 a 7 átomos de carbono)-amino}-alquilo de 1 a 7 átomos de carbono, alcanoílo de 1 a 7 átomos de carbono y/o alcoxilo de 1 a 7 átomos de carbono-carbonil)-amino, alcanoílo de 1 a 7 átomos de carbono, alquilo de 1 a 7 átomos de carbono-sulfonilo y heterociclilo saturado con 3 a 14 átomos del anillo y con 1 a 4 heteroátomos independientemente seleccionados a partir de N, S, S(=O), $S(=O)_2$ y O, de preferencia N, por ejemplo, pirrolidinilo, imidazolidinilo, piperidinilo, piperazinilo, morfolinilo, tiomorfolinilo, S-oxo-tiomorfolinilo o S,S-dioxo-tiomorfolinilo, en donde este heterociclilo saturado está insustituido o sustituido por una o más, en especial hasta tres, fracciones independientemente seleccionadas a partir de alquilo de 1 a 7 átomos de carbono, hidroxi-alquilo de 1 a 7 átomos de carbono-alcoxilo de 1 a 7 átomos de carbono-alquilo de 1 a 7 átomos de carbono, oxo, amino y mono- o di-(alquilo de 1 a 7 átomos de carbono)-amino).

Cicloalquilo insustituido o sustituido es de preferencia cicloalquilo de 3 a 8 átomos de carbono, y está insustituido o sustituido por uno o más, en especial hasta tres, sustituyentes seleccionados independientemente a partir de los sustituyentes para arilo sustituido anteriores.

Carboxilo es –COOH.

Carboxilo esterificado es de preferencia alquiloxi-carbonilo insustituido o sustituido (= alquil-O-C(=O)-), ariloxi-carbonilo insustituido o sustituido (= ariloxi-C(=O)-), cicloalquiloxi-carbonilo insustituido o sustituido (= cicloalquil-O-C(=O)-) o heterociclíloxi-carbonilo insustituido o sustituido (= heterociclil-O-C(=O)-), en donde alquilo, arilo, cicloalquilo y heterociclilo y sus formas sustituidas son como se definen anteriormente. Más preferiblemente, carboxilo esterificado es alcoxilo de 1 a 7 átomos de carbono-carbonilo o arilo de 6 a 14 átomos de carbono-alcoxilo de 1 a 7 átomos de carbono-carbonilo.

En heterociclil-carbonilo insustituido o sustituido (heterociclil-C)=O)-), heterociclilo es de preferencia una fracción seleccionada a partir de heterociclilo como se define anteriormente, y está insustituido o sustituido por uno o más, en especial hasta tres, sustituyentes seleccionados independientemente a partir de aquéllos para alquilo sustituido y arilo sustituido, y a partir de oxo, en especial a partir del grupo que consiste en alquilo de 1 a 7 átomos de carbono, hidroxi-alquilo de 1 a 7 átomos de carbono, hidroxilo, alcoxilo de 1 a 7 átomos de carbono, hidroxi-alcoxilo de 1 a 7 átomos

de carbono, alcoxilo de 1 a 7 átomos de carbono-alcoxilo de 1 a 7 átomos de carbono, (alcoxilo de 1 a 7 átomos de carbono-alcoxilo de 1 a 7 átomos de carbono)-alcoxilo de 1 a 7 átomos de carbono, (amino-mono- o di-(alquilo de 1 a 7 átomos de carbono)-amino)-alcoxilo de 1 a 7 átomos de carbono, oxo, amino, N-mono- o N,N-di-(alquilo de 1 a 7 átomos de carbono, {amino o mono- o di-(alquilo de 1 a 7 átomos de carbono)-amino}-alquilo de 1 a 7 átomos de carbono, alcanoílo de 1 a 7 átomos de carbono y/o alcoxilo de 1 a 7 átomos de carbono-carbonil)-amino, alcanoílo de 1 a 7 átomos de carbono, alquilo de 1 a 7 átomos de carbono-sulfonilo y heterociclilo saturado con 3 a 14 átomos del anillo y con 1 a 4 heteroátomos independientemente seleccionados a partir de N, S, S(=O), $S(=O)_2$ y O, de preferencia N, por ejemplo, pirrolidinilo, imidazolidinilo, piperidinilo, piperazinilo, morfolinilo, tiomorfolinilo, S-oxo-tiomorfolinilo o S,S-dioxo-tiomorfolinilo, en donde este heterociclilo saturado está insustituido o sustituido por una o más, en especial hasta tres, fracciones independientemente seleccionadas a partir de alquilo de 1 a 7 átomos de carbono, hidroxi-alquilo de 1 a 7 átomos de carbono-alcoxilo de 1 a 7 átomos de carbono-alquilo de 1 a 7 átomos de carbono, oxo, amino y mono- o di-(alquilo de 1 a 7 átomos de carbono)-amino). De preferencia heterociclilo en heterociclil-carbonilo está insaturado o de preferencia saturado, tiene de 3 a 14 átomos del anillo, de los cuales de 1 a 4 son un heteroátomo independientemente seleccionado a partir de N, S, S(=O), $S(=O)_2$ y O, de preferencia N, y se selecciona más preferiblemente a partir del

grupo que consiste en pirrolidinilo, piperidinilo, piperazinilo, morfolinilo, tiomorfolinilo, S-oxo-tiomorfolinilo o S,S-dioxo-tiomorfolinilo, y está insustituido o sustituido como se describe anteriormente para arilo sustituido, alquilo sustituido, y a partir de oxo, más especialmente a partir de los sustituyentes mencionados como preferidos después de "en especial" en la oración anterior.

En carbamoílo insustituido o sustituido (= carbamoílo insustituido o N-sustituido), los sustituyentes (N-) (en el átomo de nitrógeno del grupo carbamoílo $-C(=O)-NH_2$) se seleccionan de preferencia a partir de uno o dos (significando que se reemplazan uno o dos de los átomos de hidrógeno en el nitrógeno) sustituyentes seleccionados independientemente a partir de alquilo de 1 a 7 átomos de carbono insustituido o sustituido (como se define anteriormente), arilo insustituido o sustituido (como se define anteriormente), cicloalquilo insustituido o sustituido (como se define anteriormente) y a partir de heterociclilo insustituido o sustituido (como se define anteriormente), en donde de preferencia solamente está presente un sustituyente-N de carbamoílo, o bien, un sustituyente-N es alquilo de 1 a 7 átomos de carbono, y el otro se selecciona a partir del grupo de sustituyentes justamente mencionados. Más preferiblemente, carbamoílo sustituido es N-mono- o N,N-di-[alquilo de 1 a 7 átomos de carbono, hidroxi-alquilo de 1 a 7 átomos de carbono, alcoxilo de 1 a 7 átomos de carbono-alquilo de 1 a 7 átomos de carbono, amino-alquilo de 1 a 7 átomos de carbono, mono- o di-(alquilo de 1 a 7 átomos de carbono)-amino-

alquilo de 1 a 7 átomos de carbono, arilo de 6 a 14 átomos de carbono, en donde arilo está insustituido o sustituido por una o más, en especial hasta tres, fracciones independientemente seleccionadas a partir del grupo que consiste en alquilo de 1 a 7 átomos de carbono, alcoxilo de 1 a 7 átomos de carbono, heterociclilo saturado con 3 a 14 átomos del anillo y con 1 a 4 heteroátomos independientemente seleccionados a partir de N, S, S(=O), $S(=O)_2$ y O, de preferencia N, por ejemplo, pirrolidinilo, imidazolidinilo, piperidinilo, piperazinilo, azepanilo, morfolinilo, tiomorfolinilo, S-oxo-tiomorfolinilo o S,S-dioxo-tiomorfolinilo, en donde este heterociclilo saturado está insustituido o sustituido con una o más, en especial hasta tres, fracciones independientemente seleccionadas a partir de alquilo de 1 a 7 átomos de carbono, hidroxi-alquilo de 1 a 7 átomos de carbono, hidroxilo, oxo, y alcoxilo de 1 a 7 átomos de carbono-carbonilo, arilo de 6 a 14 átomos de carbono-alquilo de 1 a 7 átomos de carbono, y heterociclilo saturado o (heterociclilo saturado)-alquilo de 1 a 7 átomos de carbono, en donde heterociclilo saturado en ambos casos tiene de 3 a 14 átomos del anillo y de 1 a 4 heteroátomos independientemente seleccionados a partir de N, S, S(=O), $S(=O)_2$ y O, de preferencia N, por ejemplo, pirrolidinilo, imidazolidinilo, piperidinilo, piperazinilo, azepanilo, morfolinilo, tiomorfolinilo, S-oxo-tiomorfolinilo, S,S-dioxo-tiomorfolinilo, indolilo o isoindolilo o (pirrolidinilo, imidazolidinilo, piperidinilo, piperazinilo, azepanilo, morfolinilo, tiomorfolinilo, S-oxo-tiomorfolinilo, S,S-dioxo-tiomorfolinilo, indolilo o isoindolil)-alquilo de 1 a 7 átomos de

carbono, en donde este heterociclilo saturado está insustituido o sustituido con una o más, en especial hasta tres, fracciones independientemente seleccionadas a partir de alquilo de 1 a 7 átomos de carbono, hidroxi-alquilo de 1 a 7 átomos de carbono, alcoxilo de 1 a 7 átomos de carbono-alquilo de 1 a 7 átomos de carbono, oxo, alcanoílo de 1 a 7 átomos de carbono y alcoxilo de 1 a 7 átomos de carbono-carbonil]-carbamoílo.

En el caso de R^4, alquilo insustituido o sustituido, halógeno y heterociclilo insustituido o sustituido son de preferencia como se definen anteriormente; más preferiblemente, R^4 es alquilo de 1 a 7 átomos de carbono, halógeno, en especial cloro o bromo, pirrolilo, imidazolilo, piridilo o pirazinilo.

En el caso de R^A, alquilo insustituido o sustituido es de preferencia como se define anteriormente, más preferiblemente es alquilo de 1 a 7 átomos de carbono,

En el caso de Y, se prefieren alquilo de 1 a 7 átomos de carbono, halógeno o ciano, más preferiblemente metilo, flúor, cloro, bromo o ciano; en especial cloro o bromo.

Acilo es de preferencia aril-carbonilo insustituido o sustituido (= aril-CO-; = aroil) o –sulfonilo (= aril-$S(O)_2$-), heterociclil-carbonilo o -sulfonilo insustituido o sustituido, cicloalquil-carbonilo o -sulfonilo insustituido o sustituido, formilo o alquil-carbonilo o -sulfonilo insustituido o sustituido, alquil-oxicarbonilo u -oxisulfonilo insustituido o sustituido, aril-oxi-carbonilo u -oxisulfonilo insustituido o sustituido, heterociclil-oxicarbonilo u -oxisulfonilo insustituido o

sustituido, cicloalquiloxi-carbonilo u -oxisulfonilo insustituido o sustituido o N-mono- o N,N-di-(arilo insustituido o sustituido, heterociclilo insustituido o sustituido, cicloalquilo insustituido o sustituido o alquilo insustituido o sustituido)-amino-carbonilo; en donde arilo insustituido o sustituido, heterociclilo insustituido o sustituido, cicloalquilo insustituido o sustituido y alquilo insustituido o sustituido son de preferencia como se describen anteriormente. Se prefiere alcanoílo de 1 a 7 átomos de carbono, tal como acetilo, benzoílo o naftoílo insustituido o sustituido por mono-, di- o tri-(halo y/o alquilo de 1 a 7 átomos de carbono), cicloalquilo de 3 a 8 átomos de carbono-carbonilo, pirrolidin-carbonilo, en especial pirrolidino-carbonilo, pirazolidin-carbonilo, imidazolidin-carbonilo, piperidin-carbonilo, piperazin-carbonilo, 4-alquilo de 1 a 7 átomos de carbono-piperazin-1-ilo, alquilo de 1 a 7 átomos de carbono-sulfonilo, tal como metil-sulfonilo (= metan-sulfonilo), (fenil- o naftil)-alquilo de 1 a 7 átomos de carbono-sulfonilo, tal como fenil-metan-sulfonilo, o (fenil o naftil)-sulfonilo (insustituido, o sustituido por [alquilo de 1 a 7 átomos de carbono-, fenil-, halo-alquilo inferior-, halógeno, oxo-alquilo de 1 a 7 átomos de carbono-alquiloxilo de 1 a 7 átomos de carbono-, fenil-alcoxilo de 1 a 7 átomos de carbono-, halo-alquiloxilo de 1 a 7 átomos de carbono-, fenoxi-, alcanoílo de 1 a 7 átomos de carbono-amino-, ciano-, alcanoílo de 1 a 7 átomos de carbono- y/o alquilo de 1 a 7 átomos de carbono-sulfonilo]), tal como fenil-sulfonilo (= bencen-sulfonilo), naftalen-1-sulfonilo, naftalen-2-sulfonilo o toluen-4-sulfonilo, carbamoílo, N-mono- o N,N-di-(alquilo

de 1 a 7 átomos de carbono, fenilo o naftilo (insustituido o sustituido por halógeno), fenil-alquilo de 1 a 7 átomos de carbono, naftil-alquilo de 1 a 7 átomos de carbono o cicloalquilo de 3 a 8 átomos de carbono)-amino-carbonilo, tal como N-etil-carbamoílo, o (alquilo de 1 a 7 átomos de carbono, fenilo, naftilo, fenil-alquilo de 1 a 7 átomos de carbono y/o naftil-alquilo de 1 a 7 átomos de carbono)-oxi-carbonilo, por ejemplo, alcoxilo de 1 a 7 átomos de carbono-carbonilo, tal como metoxi-carbonilo. Se prefiere alcanoílo de 1 a 7 átomos de carbono, alcoxilo de 1 a 7 átomos de carbono-carbonilo o (arilo de 6 a 14 átomos de carbono, tal como fenil o naftil)-alcoxilo de 1 a 7 átomos de carbono-carbonilo.

En dondequiera que se mencione un compuesto o compuestos de la fórmula I, esto también pretende incluir adicionalmente los N-óxidos de estos compuestos y/o tautómeros de los mismos.

El término "y/o un N-óxido del mismo, un tautómero del mismo y/o una sal (de preferencia farmacéuticamente aceptable) del mismo", en especial significa que un compuesto de la fórmula I puede estar presente como tal o en mezcla con su N-óxido, como tautómero (por ejemplo, debido un tautomerismo de ceto-enol, lactama-lactima, amida-ácido imídico o enamina-imina), o en mezcla (por ejemplo, causada por reacción de equivalencia) con su tautómero, o como una sal del compuesto de la fórmula I y/o cualquiera de estas formas o las mezclas de dos o más de tales formas.

Los compuestos de la fórmula I también se pueden modificar

adjuntando las funcionalidades apropiadas para mejorar las propiedades biológicas selectivas. Las modificaciones de esta clase se conocen en la técnica, e incluyen aquéllas que aumentan la penetración en un sistema biológico dado (por ejemplo, sangre, sistema linfático, sistema nervioso central, testículos), aquéllas que aumentan la biodisponibilidad, que aumentan la solubilidad para permitir la administración parenteral (por ejemplo, inyección, infusión), que alteran el metabolismo y/o que alteran la velocidad de secreción. Los ejemplos de este tipo de modificaciones incluyen, pero no se limitan a, esterificación, por ejemplo, con polietilenglicoles, derivación con pivaloiloxilo o sustituyentes de ácidos grasos, conversión hasta carbamatos, hidroxilación de anillos aromáticos y sustitución de heteroátomos en anillos aromáticos. En dondequiera que se mencionen los compuestos de la fórmula I, y/o N-óxidos, tautómeros y/o sales (de preferencia farmacéuticamente aceptables) de los mismos, esto comprende las fórmulas modificadas, mientras que, de preferencia, se pretende indicar las moléculas de la fórmula I, sus N-óxidos, sus tautómeros y/o sus sales.

En vista de la estrecha relación entre los compuestos novedosos de la fórmula I en forma libre y aquéllos en la forma de sus sales, incluyendo las sales que se pueden utilizar como intermediarios, por ejemplo en la purificación o identificación de los compuestos novedosos, cualquier referencia a los compuestos o a un compuesto de la fórmula I anteriormente en la presente y

posteriormente en la presente, se debe entender para referirse al compuesto en forma libre y/o también a una o más sales del mismo, como sea apropiado y conveniente, así como a uno o más solvatos, por ejemplo, hidratos.

Las sales se forman, por ejemplo, como las sales de adición de ácido, de preferencia con ácidos orgánicos o inorgánicos, a partir de los compuestos de la fórmula I, con un átomo de nitrógeno básico, en especial las sales farmacéuticamente aceptables. Los ácidos inorgánicos adecuados son, por ejemplo, los ácidos de halógeno, tales como ácido clorhídrico, ácido sulfúrico, o ácido fosfórico. Los ácidos orgánicos adecuados son, por ejemplo, los ácidos carboxílicos, fosfónicos, sulfónicos o sulfámicos, por ejemplo ácido acético, ácido propiónico, ácido octanoico, ácido decanoico, ácido dodecanoico, ácido glicólico, ácido láctico, ácido fumárico, ácido succínico, ácido malónico, ácido adípico, ácido pimélico, ácido subérico, ácido azelaico, ácido málico, ácido tartárico, ácido cítrico, aminoácidos, tales como ácido glutámico o ácido aspártico, ácido maleico, ácido hidroxi-maleico, ácido metil-maleico, ácido ciclohexan-carboxílico, ácido adamantan-carboxílico, ácido benzoico, ácido salicílico, ácido 4-amino-salicílico, ácido ftálico, ácido fenil-acético, ácido mandélico, ácido cinámico, ácido metan- o etan-sulfónico, ácido 2-hidroxi-etan-sulfónico, ácido etan-1,2-disulfónico, ácido bencen-sulfónico, ácido 4-toluen-sulfónico, ácido 2-naftalen-sulfónico, ácido 1,5-naftalen-disulfónico, ácido 2- o 3-metil-bencen-sulfónico, ácido metil-sulfúrico, ácido etil-sulfúrico, ácido dodecil-

sulfúrico, ácido N-ciclohexil-sulfámico, ácido N-metil-, N-etil- o N-propil-sulfámico, u otros ácidos protónicos orgánicos, tales como ácido ascórbico.

Para propósitos de aislamiento o purificación, también es posible utilizar sales farmacéuticamente inaceptables, por ejemplo picratos o percloratos. Para uso terapéutico, solamente se emplean las sales farmacéuticamente aceptables o los compuestos libres (donde sea aplicable, en la forma de preparaciones farmacéuticas), y por consiguiente, éstas son las preferidas.

p53 se refiere a la proteína humana misma, como es descrita por Matlashewski y colaboradores, en EMBO J. 3, 3257-62 (1984) (denominada también como p53 de tipo silvestre en la presente, o a cualquier variante (por ejemplo, un mutante, fragmento, o isoforma, debido a una supresión, inserción y/o intercambio de uno o más, por ejemplo de 1 a 200, de los aminoácidos) de la misma, que todavía es capaz de retener de preferencia cuando menos el 1 por ciento, más preferiblemente cuando menos el 5 por ciento, todavía más preferiblemente cuando menos el 10 por ciento, el 20 por ciento, el 30 por ciento, el 40 por ciento, el 50 por ciento o más del 50 por ciento de la actividad de p53 en la supresión del crecimiento, por ejemplo, en el ensayo de supresión del crecimiento descrito en Pietenpol y colaboradores, Proc. Nat. Acad. Sci. EUA 91, 1998-2002 (1994) y, si se compara con la secuencia correspondiente de p53 de tipo silvestre, muestra una identidad de cuando menos el 20 por ciento, más preferiblemente cuando menos el 25 por ciento con la

secuencia completa, por ejemplo, una identidad de cuando menos el 90 por ciento con una secuencia parcial de la misma.

Como ya se indicó anteriormente, MDM2 (en especial cuando se menciona como MDM2 o variantes del mismo) en términos generales, se refiere a todos los genes y/o proteínas codificadas del mismo con los nombres MDM2, Mdm2, HDM2, Hdm2, o una variante de las mismas. MDM4 (en especial cuando se menciona como MDM4 o variantes del mismo) se refiere a todos los genes y/o proteínas codificadas del mismo con los nombres MDM4, Mdm4, HDM4, Hdm4, MDMX, MdmX, HDMX, HdmX, o una variante de las mismas.

MDM2 específicamente se refiere a MDM2 como se describe en EMBO J. 10, 1565-9, Fakharzadeh y colaboradores, 1991; una variante de la misma se refiere a una variante de la misma que todavía se enlace con p53 en el sistema de ensayo descrito más adelante (por ejemplo, una isoforma, fragmento, mutante, u oncogén debido a una supresión, inserción, y/o intercambio de uno o más, por ejemplo, 1 a 430, de los aminoácidos), correspondientes a las proteínas de longitud completa, como se describen originalmente, de preferencia cuando menos con el 0.5 por ciento, más preferiblemente cuando menos con el 5 por ciento, el 10 por ciento, el 20 por ciento, el 30 por ciento, el 40 por ciento o en especial el 50 por ciento o más de la afinidad de MDM2 con p53, y tienen una identidad de secuencia de cuando menos el 20 por ciento, más preferiblemente cuando menos el 25 por ciento, con MDM2 o con HDM2, como se describen originalmente, o como se menciona más adelante de una manera

específica. En donde no se mencione de otra manera, MDM2 en términos generales se refiere a MDM2, Mdm2, HDM2 o Hdm2, o variantes de los mismos, respectivamente, como justamente se definió.

MDM4 específicamente se refiere a MDM4 como se describe en Genomics 43, 34-42, Shvarts y colaboradores, 1997; una variante de la misma se refiere a una variante de la misma que todavía se enlaza con p53 en el sistema de ensayo descrito más adelante (por ejemplo, una isoforma, fragmento, mutante, u oncogén, debido a una supresión, inserción y/o intercambio de uno o más, por ejemplo, de 1 a 430, de los aminoácidos), correspondientes a las proteínas de longitud completa, como fueron originalmente descritas, de preferencia cuando menos con el 0.5 por ciento, más preferiblemente cuando menos con el 5 por ciento, el 10 por ciento, el 20 por ciento, el 30 por ciento, el 40 por ciento o en especial el 50 por ciento o más de la afinidad de MDM4 con p53, y tienen una identidad de secuencia de cuando menos el 20 por ciento, más preferiblemente cuando menos el 25 por ciento, con MDM4, con MDMX, con HDM4 o con HDM2, como se describieron originalmente, o como se menciona más adelante de una manera específica. En donde no se mencione de otra manera, MDM4 en términos generales se refiere a MDM4, Mdm4, HDM4, Hdm4, MDMX, MdmX, HDMX o HdmX, o variantes de las mismas, respectivamente, como justamente se definió.

El porcentaje de identidad de secuencia, denominado también con frecuencia como homología, entre una proteína y una variante de

la misma, se determina de preferencia mediante un programa de computación comúnmente empleado para este propósito, tal como el programa Gap (Wisconsin Sequence Analysis Package, Versión 8 para Unix, Genetics Computer Group, University Rescada Park, Madison Wisconsin, EUA, el cual utiliza el algoritmo de Smith y Waterman (Adv. Appl. Math. 2: 482-489 (1981), en especial utilizando una búsqueda de huecos de afinidad, con una multa de abertura de hueco de 12, y una multa de extensión de hueco de 1.

"Variantes de las mismas", en donde se mencionan, significan uno o más variantes.

Un proto-oncogén es un gen normal que puede llegar a ser un oncogén, ya sea después de la mutación o de una mayor expresión. Los proto-oncogenes codifican proteínas que ayudan a regular el crecimiento y la diferenciación celular. Los proto-oncogenes con frecuencia están involucrados en la transducción de señales y en la ejecución de las señales mitogénicas, usualmente a través de sus productos de proteína. Después de la activación, un proto-oncogén (o su producto) llega a ser un agente inductor de tumor, un oncogén.

De una manera muy inesperada, ahora se ha encontrado que los compuestos de la fórmula I tienen propiedades farmacológicas convenientes, y alteran la interacción de enlace (también referida en la presente como la interacción de p53/MDM2 y de p53/MDM4, o como la interacción de p53/MDM2 exclusivamente) entre p53 por un lado, y MDM2 y/o MDM4 o variantes de las mismas (en especial oncogénicas) que todavía sean capaces de enlazarse con p53, por

otro lado.

La eficacia de los compuestos de la fórmula I, y de las sales de los mismos, como moduladores que afecten la interacción, se puede demostrar como se ilustra en la Publicación Internacional Número WO 98/01467 (la cual, en especial con respecto a los ensayos, se incluye en la presente como referencia), o de preferencia como sigue:

Ensayo de polarización de fluorescencia

Se mide la inhibición de la interacción de p53-Hdm2 mediante polarización de fluorescencia. La polarización de fluorescencia mide el movimiento giratorio de las moléculas en una suspensión homogénea. Para este ensayo, se combina la proteína Hdm2 (aminoácidos 2-185) con un péptido derivado de p53 marcado con Cy5 optimizado para el enlace de Hdm2 (*J. Med. Chem.* 2000, *43*, 3205-3208). Después de la excitación de la luz fluorescente de Cy5 con la luz linealmente polarizada, el péptido gira más rápido y emite luz, la cual se polariza perpendicularmente. Si el péptido se enlaza con Hdm2, la rotación se hará más lenta, y el componente perpendicular disminuirá. La alteración de la formación del complejo de péptido Hdm2 debido a una molécula inhibidora que se enlaza con el sitio de enlace de p53 de Hdm2, da como resultado una rotación más rápida del péptido. La lectura del ensayo de polarización radiométrico se calcula a partir de los componentes paralelos y perpendiculares de la luz de fluorescencia con respecto a la polarización de la luz de excitación.

La prueba se lleva a cabo mediante la combinación de 7 microlitros de los compuestos diluidos en sulfóxido de dimetilo (DMSO) (concentración final del 10 por ciento) con 31.5 microlitros de Hdm2(2-188) (concentración final de 3nM) en regulador de reacción (suero regulado con fosfato, 0.1 por ciento de CHAPS, DTT 1 mM (ditioeritritol)). La solución se deja pre-incubar durante 5 minutos a temperatura ambiente, seguida por la adición de 31.5 microlitros de péptido en regulador de reacción (concentración final de 1nM), y 5 minutos adicionales de incubación. Se distribuye un volumen final de 20 microlitros (por triplicado) en placas negras de 384 pozos de pequeño volumen (Greiner Bio-ona GmbH, Frickenhausen, Alemania). Para la medición de las muestras, se utiliza un lector de microplacas de múltiples modos Analyst AD (Molecular Devices Corporation, Sunnyvale, CA, EUA) con las siguientes posiciones: Espejo dicroico de 650 nanómetros, Excitación de 630 nanómetros, Emisión de 695 nanómetros. Los valores brutos se expresan como un porcentaje del control de sulfóxido de dimetilo, en donde primero se sustrae el fondo (regulador de reacción con péptido pero no con Hdm2) a partir de los valores brutos. Los valores IC_{50} se calculan mediante el ajuste de la curva utilizando XLfit. Si no se especifican, los reactivos se adquirieron en Sigma Chemical Co.

Los compuestos descritos en la presente invención de preferencia exhiben una inhibición de la interacción de p53-Hdm2 a las IC_{50}s en el intervalo de 0.0003 a 25 μM, de preferencia de 0.0003 a 10 μM.

Ensayo de Transferencia de Energía de Fluorescencia Resuelta en el Tiempo (TR-FRET)

La inhibición de la interacción de p53-Hdm4 se mide mediante transferencia de energía de fluorescencia resuelta en el tiempo (TR-FRET). La transferencia de energía de fluorescencia (o la transferencia de energía de resonancia de Foerster) describe una transferencia de energía entre las moléculas fluorescentes donadoras y aceptoras. Para este ensayo, se utiliza la proteína MDM4 (aminoácidos 2-185), marcada con una fracción de biotina C-terminal, en combinación con una estreptavidina marcada de Europio (Perkin Elmer, Inc., Waltham, MA, EUA) que sirve como el fluoróforo donador. El péptido marcado con Cy5, derivado de p53, Cy5-TFSDLWKLL (p53 aa18-26) es el aceptor de energía. Después de la excitación de la molécula donadora a 340 nanómetros, la interacción de enlace entre MDM4 y el péptido p53, induce la transferencia de energía y una mejor respuesta a la longitud de onda de emisión del aceptor de 665 nanómetros. La alteración de la formación del complejo de p53-MDM4 debido a una molécula inhibidora que se enlaza con el sitio de enlace de p53 de MDM4, da como resultado una mayor emisión del donador a 615 nanómetros. L lectura del ensayo radiométrico FRET se calcula a partir de los datos brutos de las dos distintas señales de fluorescencia medidas en el modo resuelto en el tiempo (índice de conteo de 655 nanómetros/índice de conteo de 615 nanómetros x 1000).

La prueba se lleva a cabo en placas de microtitulación

blancas de 1536 pozos (Greiner Bio-ona GmbH, Frickenhausen, Alemania) en un volumen total de 3.1 microlitros, mediante la combinación de 100 nanolitros de los compuestos diluidos en sulfóxido de dimetilo al 90 por ciento/H_2O al 10 por ciento (concentración final de sulfóxido de dimetilo del 3.2 por ciento) con 2 microlitros de estreptavidina marcada con Europio (concentración final de 2.5 nM) en regulador de reacción (suero regulado con fosfato, NaCl 125 mM, Novexin al 0.001 por ciento (consiste en polímeros de carbohidrato (polímeros Novexin), diseñados para aumentar la solubilidad y la estabilidad de las proteínas; Novexin Ltd., Cambridgeshire, Reino Unido), Gelatina al 0.01 por ciento, Pluronic al 0.2 por ciento (copolímero de bloques de óxido de etileno y óxido de propileno, BASF, Ludwigshafen, Alemania), DTT 1 mM), seguido por la adición de 0.5 microlitros de MDM4-Bio diluido en regulador de ensayo (concentración final de 10nM). La solución se deja pre-incubar durante 15 minutos a temperatura ambiente, seguido por la adición de 0.5 microlitros de péptido Cy5-p53 en regulador de ensayo (concentración final de 20nM). Se incuba a temperatura ambiente durante 10 minutos antes de leer la placa. Para la medición de las muestras, se utiliza un lector de microplacas de múltiples modos Analyst GT (Molecular Devices) con las siguientes posiciones: Espejo dicroico de 380 nanómetros, Excitación de 330 nanómetros, Emisión de Donador de 615 nanómetros, y Emisión del Aceptor de 665 nanómetros. Los valores IC_{50} se calculan mediante ajuste de la curva, utilizando XLfit. Si no se especifican,

los reactivos se adquieren en Sigma Chemical Co, St. Louis, MO, EUA.

La presente invención también se refiere a aspectos novedosos de los ensayos anteriormente descritos.

Los compuestos descritos en la presente invención de preferencia exhiben una inhibición de la interacción de p53-Hdm4 a IC_{50}s de 0.005 a 100 μM, por ejemplo, de 10 nM a 50 μM.

Las inhibiciones de p53-Hdm2 y p53-Hdm4 mediante los compuestos representativos en la presente invención, se exhiben en la Tabla 5 más adelante en la presente.

Considerando su efecto inhibidor sobre la interacción de p53/MDM2 y/o p53/MDM4, los compuestos de la fórmula (I) en forma libre o de sal farmacéuticamente aceptable, son útiles en el tratamiento de condiciones que sean mediadas por la actividad (incluyendo la actividad normal, o en especial la sobre-actividad) de MDM2 y/o MDM4, o variantes de los mismos, respectivamente, como se describen, tales como condiciones proliferativas y/o inflamatorias, por ejemplo, mediante la activación de la interacción de P53/MDM2, y/o que respondan (significando en especial de una manera terapéuticamente benéfica) a la inhibición de la interacción de p53/MDM2, más especialmente una enfermedad o trastorno como se menciona más adelante en la presente.

El "tratamiento" de acuerdo con la invención, puede ser terapéutico, por ejemplo, sintomático, paliativo y/o curativo, y/o profiláctico. Se prefiere el tratamiento de animales de sangre

caliente, en especial seres humanos.

Se prefiere un compuesto de la fórmula I para utilizarse, o el uso del mismo en el tratamiento de una enfermedad o trastorno que responda al tratamiento con un compuesto de la fórmula I, en especial seleccionado a partir de una enfermedad que se base en la mala regulación del ciclo celular, o en especial apoptosis, por ejemplo, enfermedades que involucren al sistema inmune, por ejemplo, enfermedades autoinmunes o enfermedades inmunes resultantes debido a trasplante (tal como artritis reumatoide, enfermedad del injerto contra el huésped, lupus eritematoso sistémico, síndrome de Sjögren, esclerosis múltiple, tiroiditis de Hashimoto, polimiositis), condiciones inflamatorias crónicas, tales como asma, osteoartritis, ateroesclerosis, Morbus Crohn o condiciones inflamatorias o alérgicas de la piel, por ejemplo soriasis, dermatitis por contacto, dermatitis atópica, alopecia areata, eritema multiforme, dermatitis herpetiforme, esclerodermia, vitiligo, angiitis por hipersensibilidad, urticaria, penfigoide buloso, penfigo, epidermólisis bulosa acquisita, u otras condiciones inflamatorias o alérgicas de la piel, trastornos hiperproliferativos, (por ejemplo, síndrome de Li-Fraumeni, cáncer o enfermedades tumorales, tales como tumores benignos o malignos, sarcomas, tales como rabdomiosarcoma, cáncer de huesos, por ejemplo, osteosarcomas, carcinoma del cerebro, por ejemplo, tumor cerebral del tejido blando, tumores de riñón, hígado, glándula adrenal, vejiga, mama, estómago, tumores gástricos, de ovarios, colon, recto, próstata, páncreas,

pulmón, vagina o tiroides, glioblastomas, mieloma múltiple, cáncer gastrointestinal, en especial carcinoma de colon o adenoma colo-rectal, un tumor de cuello y cabeza, melanoma, hiperplasia de próstata, una neoplasia, una neoplasia de carácter epitelial, un carcinoma mamario, una leucemia, tal como carcinoma adrenocortical de linfomas de células-B o de células-T, incluyendo metástasis en otros órganos, respectivamente), infecciones virales (por ejemplo, herpes, papiloma, VIH, hepatitis viral) u otras enfermedades, por ejemplo aquéllas en donde la interacción de p53/MDM2 y/o p53/MDM4 esté mal regulada y/o que respondan a la inhibición de la interacción de p53/MDM2 y/o de p53/MDM4.

La invención se refiere en especial al uso de un compuesto de la fórmula I (o una formulación farmacéutica, la cual comprende un compuesto de la fórmula I) en el tratamiento de una o más de las enfermedades mencionadas anteriormente y más adelante, en donde las enfermedades responden (de una manera benéfica, por ejemplo, mediante la remoción parcial o completa de uno o más de sus sintomas hasta llevar a cabo la cura o la remisión) a una inhibición de la interacción de p53/MDM2, en especial en donde MDM2 o MDM4 y/o la muestra variante (por ejemplo, en el contexto de otros mecanismos reguladores, debido a una sobre-expresión, a mutación o similares) tiene una actividad inadecuadamente alta o más alta que la actividad normal.

En dondequiera que se mencione el término "uso" o "usado", o en especial uso, esto pretende incluir un compuesto de la fórmula I

para utilizarse en el tratamiento profiláctico y/o terapéutico de una enfermedad de un animal de sangre caliente, en especial un ser humano, de preferencia de una o más enfermedades mencionadas anteriormente o más adelante, un método de uso o un método de tratamiento, el cual comprende administrar un compuesto de la fórmula I a una persona que necesite dicho tratamiento en una cantidad efectiva para el tratamiento profiláctico y/o terapéutico de una enfermedad como se menciona anteriormente y más adelante, la preparación o un método para la preparación de una formulación farmacéutica/preparación para utilizarse en el tratamiento profiláctico y terapéutico de una enfermedad o trastorno mencionado anteriormente y más adelante, en especial que involucre combinar un compuesto de la fórmula I (como ingrediente terapéuticamente activo) con cuando menos un material portador farmacéuticamente aceptable, de preferencia incluyendo dejarlo listo para utilizarse en este tratamiento (por ejemplo, agregar un inserto de instrucciones (por ejemplo, un folleto del paquete o similar), formulación, preparación apropiada, adaptación para usos específicos, adaptación a la medida, y similares), y/o el uso de un compuesto de la fórmula I para esta preparación, y/o todos los demas usos profilácticos o terapéuticos mencionados anteriormente en la presente o más adelante. La invención también puede relacionarse con el uso de un compuesto de la fórmula I para inducir la desaceleración del ciclo celular o de preferencia el paro y/o apoptosis en las células que contengan p53 o variantes del mismo que sean todavía funcionales,

para sensibilizar a las células a uno o más agentes farmacéuticamente activos adicionales, tales como inductores de apoptosis y/o de la desaceleración o paro del ciclo celular, y con la quimioprotección de las células normales a través de la inducción de la desaceleración o paro del ciclo celular antes del tratamiento con uno o más agentes quimioterapéuticos diferentes, al uso para hacer a las células normales resistentes a los agentes quimioterapéuticos y/o tratamientos, y/o al uso en la protección de las células de los efectos secundarios tóxicos de los agentes o tratamientos quimioterapéuticos, tales como los efectos secundarios que dan como resultado mucositis, estomatitis, xerostomia, trastornos gastrointestinales y/o alopecia.

Todos estos aspectos son las modalidades preferidas de la presente invención.

También se presentan experimentos que pueden demostrar la actividad anti-tumoral de los compuestos de la fórmula (I) *in vivo*.

Por ejemplo, se pueden utilizar ratones nu/nu atímicos Harlan hembras (Indianápolis, Indiana, EUA) con tumores de osteosarcoma humano SJSA-1 trasplantado subcutáneamente, para determinar la actividad anti-tumoral de los inhibidores de la interacción de p53/MDM2. En el día 0, con los animales bajo narcosis con peroral Forene® (1-cloro-2,2,2-trifluoro-etil-difluoro-metil-éter, Abbot, Wiesbaden, Alemania), se inyectan 3x106 células bajo la piel del flanco izquierdo de los animales. Cuando los tumores alcanzan un volumen de 100 milímetros cúbicos, los ratones se dividen

aleatoriamente en grupos de 6 a 8 animales, y comienza el tratamiento. El tratamiento se lleva a cabo durante un período de 2 a 3 semanas con administración peroral, intravenosa o intraperitoneal una vez al día (o con menos frecuencia) de un compuesto de la fórmula (I) en un vehículo adecuado en dosis definidas. Los tumores se miden dos veces a la semana con un calibre, y se calcula el volumen de los tumores.

Como una alternativa a la línea celular SJSA-1, también se pueden utilizar otras líneas celulares de la misma manera, por ejemplo,

- la línea celular de carcinoma de colon HCT116 (ATCC No. CCL-247);
- la línea celular de carcinoma de próstata LNCaP clon FGC (ATCC No. CRL-1740);
- la línea celular de carcinoma de colon RKO (ATCC No. CRL-2577);
- la línea celular de fibrosarcoma HT1080 (ATCC No. CCL-121);
- la línea celular de melanoma maligno A375 (ATCC No. CRL-1619),
- la línea celular de carcinoma pulmonar de células grandes NCI-H460 (ATCC No. HTB-177).

Un compuesto de la fórmula (I) también se puede utilizar con ventaja en combinación con otros compuestos antiproliferativos. Estos compuestos antiproliferativos incluyen, pero no se limitan a,

inhibidores de aromatasa; anti-estrógenos; inhibidores de topoisomerasa I; inhibidores de topoisomerasa II; compuestos activos en microtúbulos; compuestos alquilantes; inhibidores de desacetilasa de histona; compuestos que inducen los procesos de diferenciación celular; inhibidores de ciclo-oxigenasa; inhibidores de MMP; inhibidores de mTOR, tales como RAD001; anti-metabolitos anti-neoplásicos; compuestos de platina; compuestos que dirigen/reducen una actividad de cinasa de proteína o de lípido y otros compuestos anti-angiogénicos; compuestos que dirigen, reducen, o inhiben la actividad de una fosfátasa de proteína o de lípido; agonistas de gonadorelina; anti-andrógenos; inhibidores de amino-peptidasa de metionina; bisfosfonatos; modificadores de la respuesta biológica; anticuerpos anti-proliferativos, tales como HCD122; inhibidores de heparanasa; inhibidores de las isoformas oncogénicas Ras; inhibidores de telomerasa; inhibidores de proteasoma; compuestos utilizados en el tratamiento de malignidades hematológicas, tales como FLUDARABINA; compuestos que dirigen, reducen, o inhiben la actividad de Flt-3, tales como PKC412; inhibidores de Hsp90, tales como 17-AAG (17-alil-amino-geldanamicina, NSC330507), 17-DMAG (17-dimetil-amino-etil-amino-17-demetoxi-geldanamicina, NSC707545), IPI-504, CNF1010, CNF2024, CNF1010 de Conform Therapeutics, y AUY922; temozolomida (TEMODAL®); inhibidores de proteína de huso de cinesina, tales como SB715992 o SB743921 de GlaxoSmithKline, o pentamidina/clorpromazina de CombinatoRx; inhibidores de PI3K,

tales como BEZ235; inhibidores de RAF, tales como RAF265; inhibidores de MEK, tales como ARRY142886 de Array PioPharma, AZD6244 de AstraZeneca, PD181461 de Pfizer, leucovorina, Aglutinantes EDG, compuestos contra la leucemia, inhibidores de reductasa de ribonucleótido, inhibidores de descarboxilasa de S-adenosil-metionina, anticuerpos anti-proliferativos, u otros compuestos quimioterapéuticos. Además, de una manera alternativa o en adición, se pueden utilizar en combinación con otros planteamientos de tratamiento de tumores, incluyendo cirugía, radiación ionizante, terapia fotodinámica, implantes, por ejemplo, con corticosteroides, hormonas, o se pueden utilizar como radiosensibilizantes. También, en el tratamiento anti-inflamatorio y/o anti-proliferativo, se incluye la combinación con fármacos anti-inflamatorios. También es posible la combinación con sustancias de fármaco anti-histamínicas, fármacos broncodilatadores, fármacos anti-inflamatorios no esteroideos (NSAID) o antagonistas de los receptores de quimiocina.

El término "inhibidor de aromatasa", como se utiliza en la presente, se refiere a un compuesto que inhibe la producción de estrógeno, es decir, la conversión de los sustratos androstenodiona y testosterona hasta estrona y estradiol, respectivamente. El término incluye, pero no se limita a, esteroides, en especial atamestano, exemestano y formestano, y, en particular, no esteroides, en especial amino-glutetimida, rogletimida, pirido-glutetimida, trilostano, testolactona, quetoconazol, vorozol, fadrozol, anastrozol y letrozol.

El exemestano se puede administrar, por ejemplo, en la forma como se comercia, por ejemplo, bajo la marca comercial registrada AROMASIN. El formestano se puede administrar, por ejemplo, en la forma como se comercia, por ejemplo, bajo la marca comercial registrada LENTARON. El fadrozol se puede administrar, por ejemplo, en la forma como se comercia, por ejemplo, bajo la marca comercial registrada AFEMA. El anastrozol se puede administrar, por ejemplo, en la forma como se comercia, por ejemplo, bajo la marca comercial registrada ARIMIDEX. El letrozol se puede administrar, por ejemplo, en la forma como se comercia, por ejemplo, bajo la marca comercial registrada FEMARA o FEMAR. La amino-glutetimida se puede administrar, por ejemplo, en la forma como se comercia, por ejemplo, bajo la marca comercial registrada ORIMETEN. Una combinación de la invención que comprenda un agente quimioterapéutico que sea un inhibidor de aromatasa, es en particular útil para el tratamiento de los tumores positivos para el receptor de hormonas, por ejemplo, tumores de mama.

El término "anti-estrógeno", como se utiliza en la presente, se refiere a un compuesto que antagoniza el efecto de los estrógenos al nivel del receptor de estrógeno. El término incluye, pero no se limita a, tamoxifeno, fulvestrant, raloxifeno y clorhidrato de raloxifeno. El tamoxifeno se puede administrar, por ejemplo, en la forma como se comercia, por ejemplo, bajo la marca comercial registrada NOLVADEX. El clorhidrato de raloxifeno se puede administrar, por ejemplo, en la forma como se comercia, por ejemplo,

bajo la marca comercial registrada EVISTA. El fulvestrant se puede formular como se da a conocer en la Patente de los Estados Unidos de Norteamérica Número 4,659,516 o se puede administrar, por ejemplo, en la forma como se comercia, por ejemplo, bajo la marca comercial registrada FASLODEX. Una combinación de la invención que comprenda un agente quimioterapéutico que sea un anti-estrógeno es en particular útil para el tratamiento de los tumores positivos para el receptor de estrógeno, por ejemplo, tumores de mama.

El término "anti-andrógeno", como se utiliza en la presente, se refiere a cualquier sustancia que sea capaz de inhibir los efectos biológicos de las hormonas androgénicas e incluye, pero no se limita a, bicalutamida (CASODEX), que se puede formular, por ejemplo, como se da a conocer en la Patente de los Estados Unidos de Norteamérica Número 4,636,505.

El término "agonista de gonadorelina", como se utiliza en la presente, incluye, pero no se limita a, abarelix, goserelina y acetato de goserelina. La goserelina se da a conocer en la Patente de los Estados Unidos de Norteamérica Número US 4,100,274, y se puede administrar, por ejemplo, en la forma como se comercia, por ejemplo, bajo la marca comercial registrada ZOLADEX. El abarelix se puede formular, por ejemplo, como se da a conocer en la Patente de los Estados Unidos de Norteamérica Número US 5,843,901.

El término "inhibidor de topoisomerasa I", como se utiliza en la presente, incluye, pero no se limita a, topotecano, gimatecano,

irinotecano, camptotecina y sus análogos, 9-nitro-camptotecina y el conjugado de camptotecina macromolecular PNU-166148 (el compuesto A1 de la Publicación Internacional Número WO99/17804). El irinotecano se puede administrar, por ejemplo, en la forma como se comercia, por ejemplo, bajo la marca comercial registrada CAMPTOSAR. El topotecano se puede administrar, por ejemplo, en la forma como se comercia, por ejemplo, bajo la marca comercial registrada HYCAMTIN.

El término "inhibidor de topoisomerasa II", como se utiliza en la presente, incluye, pero no se limita a, las antraciclinas, tales como doxorrubicina (incluyendo la formulación liposomal, por ejemplo, CAELYX), daunorrubicina, epirrubicina, idarrubicina y nemorrubicina, las antraquinonas mitoxantrona y losoxantrona, y las podofilotoxinas etoposida y teniposida. La etoposida se puede administrar, por ejemplo, en la forma como se comercia, por ejemplo, bajo la marca comercial registrada ETOPOPHOS. La teniposida se puede administrar, por ejemplo, en la forma como se comercia, por ejemplo, bajo la marca comercial registrada VM 26-BRISTOL. La doxorrubicina se puede administrar, por ejemplo, en la forma como se comercia, por ejemplo, bajo la marca comercial registrada ADRIBLASTIN o ADRIAMYCIN. La epirrubicina se puede administrar, por ejemplo, en la forma como se comercia, por ejemplo, bajo la marca comercial registrada FARMORUBICIN. La idarrubicina se puede administrar, por ejemplo, en la forma como se comercia, por ejemplo, bajo la marca comercial registrada ZAVEDOS. La mitoxantrona se puede

administrar, por ejemplo, en la forma como se comercia, por ejemplo, bajo la marca comercial registrada NOVANTRON.

El término "compuesto activo en microtúbulos" se refiere a los compuestos estabilizantes de microtúbulos y desestabilizantes de microtúbulos, y a los inhibidores de la polimerización de microtubulina, incluyendo, pero no limitándose a, taxanos, por ejemplo, paclitaxel y docetaxel, alcaloides vinca, por ejemplo, vinblastina, en especial sulfato de vinblastina, vincristina, en especial sulfato de vincristina, y vinorelbina, discodermolidas, colquicina y epotilonas y derivados de las mismas, por ejemplo, epotilona B o D o derivados de las mismas. El paclitaxel se puede administrar, por ejemplo, en la forma como se comercia, por ejemplo, TAXOL. El docetaxel se puede administrar, por ejemplo, en la forma como se comercia, por ejemplo, bajo la marca comercial registrada TAXOTERE. El sulfato de vinblastina se puede administrar, por ejemplo, en la forma como se comercia, por ejemplo, bajo la marca comercial registrada VINBLASTIN R.P. El sulfato de vincristina se puede administrar, por ejemplo, en la forma como se comercia, por ejemplo, bajo la marca comercial registrada FARMISTIN. La discodermolida se puede obtener, por ejemplo, como se da a conocer en la Patente de los Estados Unidos de Norteamérica Número US 5,010,099. También se incluyen los derivados de epotilona que se dan a conocer en las Patentes Números WO 98/10121, US 6,194,181, WO 98/25929, WO 98/08849, WO 99/43653, WO 98/22461 y WO 00/31247. Se prefieren en especial Epotilona A y/o B.

El término "compuesto alquilante", como se utiliza en la presente, incluye, pero no se limita a, ciclofosfamida, ifosfamida, melfalano o nitrosourea (BCNU o Gliadel). La ciclofosfamida se puede administrar, por ejemplo, en la formá como se comercia, por ejemplo, bajo la marca comercial registrada CICLOSTIN. La ifosfamida se puede administrar, por ejemplo, en la forma como se comercia, por ejemplo, bajo la marca comercial registrada HOLOXAN.

El término "inhibidores de desacetilasa de histona" o "inhibidores de HDAC", se refiere a compuestos que inhiben el desacetilasa de histona y que poseen una actividad antiproliferativa. Esto incluye compuestos tales como LDH589 dados a conocer en la Publicación Internacional Número WO 02/22577, en especial N-hidroxi-3-[4-[[(2-hidroxi-etil)[2-(1H-indol-3-il)-etil]-amino]-metil]-fenil]-2E-2-propenamida, N-hidroxi-3-[4-[[[2-(2-metil-1*H*-indol-3-il)-etil]-amino]-metil]-fenil]-2*E*-2-propenamida y las sales farmacéuticamente aceptables de las mismas. Además, incluye en especial ácido hidroxámico de suberoilanilida (SAHA).

El término "anti-metabolito anti-neoplásico" incluye, pero no se limita a, 5-fluoro-uracilo o 5-FU, capecitabina, gemcitabina, compuestos desmetilantes de ADN, tales como 5-azacitidina y decitabina, metotrexato y edatrexato, y antagonistas de ácido fólico, tales como pemetrexed. La capecitabina se puede administrar, por ejemplo, en la forma como se comercia, por ejemplo, bajo la marca comercial registrada XELODA. La gemcitabina se puede administrar,

por ejemplo, en la forma como se comercia, por ejemplo, bajo la marca comercial registrada GEMZAR..

El término "compuesto de platino", como se utiliza en la presente, incluye, pero no se limita a, carboplatina, cisplatina, cisplatino y oxaliplatina. La carboplatina se puede administrar, por ejemplo, en la forma como se comercia, por ejemplo, bajo la marca comercial registrada CARBOPLAT. La oxaliplatina se puede administrar, por ejemplo, en la forma como se comercia, por ejemplo, bajo la marca comercial registrada ELOXATIN.

El término "compuestos que dirigen/reducen una actividad de cinasa de proteína o de lípido"; o una "actividad de fosfatasa de proteína o de lípido"; o "compuestos anti-angiogénicos adicionales", como se utiliza en la presente, incluye, pero no se limita a, inhibidores de cinasa de proteína tirosina y/o de cinasa de serina y/o treonina, o inhibidores de cinasa de lípido, por ejemplo,

a) compuestos que dirigen, reducen, o inhiben la actividad de los receptores del factor de crecimiento derivado de plaquetas (PDGFR), tales como compuestos que dirigen, reducen, o inhiben la actividad de PDGFR, en especial compuestos que inhiben al receptor del factor de crecimiento derivado de plaquetas, por ejemplo, un derivado de N-fenil-2-pirimidin-amina, por ejemplo, imatinib, SU101, SU6668 y GFB-111;

b) compuestos que dirigen, reducen, o inhiben la actividad de los receptores del factor de crecimiento de fibroblastos (FGFR);

c) compuestos que dirigen, reducen, o inhiben la actividad del receptor del factor de crecimiento tipo insulina I (IGF-IR), tales como compuestos que dirigen, reducen, o inhiben la actividad de IGF-IR, en especial compuestos que inhiben la actividad de cinasa del receptor de IGF-I, tales como los compuestos dados a conocer en la Publicación Internacional Número WO 02/092599, o anticuerpos que se dirigen hacia el dominio extracelular del receptor de IGF-I o sus factores de crecimiento;

d) compuestos que dirigen, reducen, o inhiben la actividad de la familia de cinasa de tirosina receptora Trk, o los inhibidores de efrina B4;

e) compuestos que dirigen, reducen, o inhiben la actividad de la familia de cinasa de tirosina receptora Axl;

f) compuestos que dirigen, reducen, o inhiben la actividad de la cinasa de tirosina receptora Ret;

g) compuestos que dirigen, reducen, o inhiben la actividad de la cinasa de tirosina receptora Kit/SCFR, es decir, las cinasas de tirosina receptoras C-kit - (parte de la familia de PDGFR), tales como los compuestos que dirigen, reducen, o inhiben la actividad de la familia de cinasa de tirosina receptora c-Kit, en especial los compuestos que inhiben el receptor c-Kit, por ejemplo, imatinib;

h) compuestos que dirigen, reducen, o inhiben la actividad de los miembros de la familia c-Abl, sus productos de fusión genética (por ejemplo, cinasa BCR-Abl) y mutantes, tales

como los compuestos que dirigen, reducen, o inhiben la actividad de los miembros de la familia c-Abl y sus productos de fusión genética, por ejemplo, un derivado de N-fenil-2-pirimidin-amina, por ejemplo, imatinib o nilotinib (AMN107); PD180970; AG957; NSC 680410; PD173955 de ParkeDavis; o dasatinib (BMS-354825);

i) compuestos que dirigen, reducen, o inhiben la actividad de los miembros de la cinasa C de proteina (PKC) y de la familia de cinasas de serina/treonina Raf, los miembros de la familia MEK, SRC, JAK, FAK, PDK1, PKB/Akt, y Ras/MAPK, y/o los miembros de la familia de cinasa dependiente de ciclina (CDK), y son en especial los derivados de estaurosporina que se dan a conocer en la Patente de los Estados Unidos de Norteamérica Número US 5,093,330, por ejemplo, midostaurina; los ejemplos de compuestos adicionales incluyen, por ejemplo, UCN-01, safingol, BAY 43-9006, Briostatina 1, Perifosina; Ilmofosina; RO 318220 y RO 320432; GO 6976; Isis 3521; LY333531/LY379196; los compuestos de isoquinolina, tales como los que se dan a conocer en la Publicación Internacional Número WO 00/09495; FTIs; BEZ235 (un inhibidor de P13K) o AT7519 (inhibidor de CDK);

j) compuestos que dirigen, reducen, o inhiben la actividad de los inhibidores de cinasa de proteína tirosina, tales como compuestos que dirigen, reducen, o inhiben la actividad de los inhibidores de cinasa de proteína tirosina, incluyendo mesilato de Imatinib (GLEEVEC) o tirfostina. Una tirfostina es de preferencia un compuesto de bajo peso molecular (Mr < 1500), o una sal

farmacéuticamente aceptable del mismo, en especial un compuesto seleccionado a partir de la clase de benciliden-malonitrilo o la clase de compuestos de S-aril-bencen-malonitrilo o del bisustrato de quinolina, más especialmente cualquier compuesto seleccionado a partir del grupo que consiste en Tirfostina A23/RG-50810; AG 99; Tirfostina AG 213; Tirfostina AG 1748; Tirfostina AG 490; Tirfostina B44; enantiómero (+) de Tirfostina B44; Tirfostina AG 555; AG 494; Tirfostina AG 556, AG957, y adafostina (adamantil-éster del ácido 4-{[(2,5-dihidroxifenil)metil]amino}-benzoico; NSC 680410, adafostina);

k) compuestos que dirigen, reducen, o inhiben la actividad de la familia de cinasas de tirosina receptoras del factor de crecimiento epidérmico (EGFR, ErbB2, ErbB3, ErbB4 como homo- o hetero-dímeros) y sus mutantes, tales como compuestos que dirigen, reducen, o inhiben la actividad de la familia de receptores del factor de crecimiento epidérmico, son en especial los compuestos, proteínas o anticuerpos que inhiben a los miembros de la familia de cinasa de tirosina receptora del factor de crecimiento epidérmico, por ejemplo, el receptor de EGF, ErbB2, ErbB3 y ErbB4, o que se enlazan con el factor de crecimiento epidérmico o con los ligandos relacionados con el factor de crecimiento epidérmico, y son en particular los compuestos, proteínas, o anticuerpos monoclonales genérica y específicamente dados a conocer en la Publicación Internacional Número WO 97/02266, por ejemplo, el compuesto del Ejemplo 39, o en las Patentes Números EP 0 564 409, WO 99/03854, EP 0520722, EP 0 566 226, EP 0 787 722, EP 0 837 063, US

5,747,498, WO 98/10767, WO 97/30034, WO 97/49688, WO 97/38983 y, en especial, en la Publicación Internacional Número WO 96/30347 (por ejemplo, el compuesto conocido como CP 358774), en la Publicación Internacional Número WO 96/33980 (por ejemplo, el compuesto ZD 1839) y en la Publicación Internacional Número WO 95/03283 (por ejemplo, el compuesto ZM105180); por ejemplo, trastuzumab (Herceptin^{MR}), cetuximab (Erbitux^{MR}), Iressa, Tarceva, OSI-774, CI-1033, EKB-569, GW-2016, E1.1, E2.4, E2.5, E6.2, E6.4, E2.11, E6.3 o E7.6.3, y derivados de 7H-pirrolo-[2,3-d]-pirimidina que se dan a conocer en la Publicación Internacional Número WO 03/013541; y

l) compuestos que dirigen, reducen, o inhiben la actividad del receptor c-Met, tales como compuestos que dirigen, reducen, o inhiben la actividad de c-Met, en especial compuestos que inhiben la actividad de cinasa del receptor c-Met, o anticuerpos que se dirigen al dominio extracelular de c-Met o que se enlazan con el HGF.

Otros compuestos anti-angiogénicos incluyen los compuestos que tienen otro mecanismo para su actividad, por ejemplo, no relacionados con la inhibición de cinasa de proteína o de lipido, por ejemplo, talidomida (THALOMID) y TNP-470.

Los compuestos que dirigen, reducen, o inhiben la actividad de una fosfatasa de proteína o de lípido son, por ejemplo, inhibidores de fosfatasa 1, fosfatasa 2A, o CDC25, por ejemplo, ácido ocadaico o un derivado del mismo.

Los compuestos que inducen los procesos de diferenciación celular son por ejemplo, ácido retinoico, α- γ- ó δ-tocoferol o α- γ- ó δ-tocotrienol.

El término inhibidor de ciclo-oxigenasa, como se utiliza en la presente, incluye, pero no se limita a, por ejemplo, inhibidores de Cox-2, ácido 2-aril-amino-fenil-acético sustituido por 5-alquilo y sus derivados, tales como celecoxib (CELEBREX), rofecoxib (VIOXX), etoricoxib, valdecoxib o un ácido 5-alquil-2-aril-amino-fenil-acético, por ejemplo, ácido 5-metil-2-(2'-cloro-6'-fluoro-anilino)-fenil-acético, lumiracoxib.

El término "bisfosfonatos", como se utiliza en la presente, incluye, pero no se limita a, ácido etridónico, clodrónico, tiludrónico, pamidrónico, alendrónico, ibandrónico, risedrónico, y zoledrónico. El "ácido etridónico" se puede administrar, por ejemplo, en la forma como se comercia, por ejemplo, bajo la marca comercial registrada DIDRONEL. El "ácido clodrónico" se puede administrar, por ejemplo, en la forma como se comercia, por ejemplo, bajo la marca comercial registrada BONEFOS. El "ácido tiludrónico" se puede administrar, por ejemplo, en la forma como se comercia, por ejemplo, bajo la marca comercial registrada SKELID. El "ácido pamidrónico" se puede administrar, por ejemplo, en la forma como se comercia, por ejemplo, bajo la marca comercial registrada AREDIA^{MR}. El "ácido alendrónico" se puede administrar, por ejemplo, en la forma como se comercia, por ejemplo, bajo la marca comercial registrada FOSAMAX. El "ácido ibandrónico" se puede administrar, por ejemplo, en la forma como se

comercia, por ejemplo, bajo la marca comercial registrada BONDRANAT. El "ácido risedrónico" se puede administrar, por ejemplo, en la forma como se comercia, por ejemplo, bajo la marca comercial registrada ACTONEL. El "ácido zoledrónico" se puede administrar, por ejemplo, en la forma como se comercia, por ejemplo, bajo la marca comercial registrada ZOMETA.

El término "inhibidor de mTORs" se refiere a compuestos que inhiben el objetivo de mamífero de rapamicina (mTOR) y que poseen una actividad antiproliferativa, tal como sirolimus (Rapamune®), everolimus (Certican^{MR}), CCI-779 y ABT578.

El término "inhibidor de heparanasa", como se utiliza en la presente, se refiere a compuestos que dirigen, reducen, o inhiben la degradación del sulfato de heparina. El término incluye, pero no se limita a, PI-88.

El término "modificador de la respuesta biológica", como se utiliza en la presente, se refiere a una linfocina o interferones, por ejemplo, interferón γ.

El término "inhibidor de las isoformas oncogénicas Ras", por ejemplo, H-Ras, K-Ras, o N-Ras, como se utiliza en la presente, se refiere a compuestos que dirigen, reducen, o inhiben la actividad oncogénica de Ras, por ejemplo, un "inhibidor de transferasa de farnesilo" por ejemplo, L-744832, DK8G557 o R115777 (Zarnestra).

El término "inhibidor de telomerasa", como se utiliza en la presente, se refiere a compuestos que dirigen, reducen, o inhiben la actividad de la telomerasa. Los compuestos que dirigen, reducen, o

inhiben la actividad de la telomerasa son en especial los compuestos que inhiben el receptor de telomerasa, por ejemplo, telomestatina.

El término "inhibidor de amino-peptidasa de metionina", como se utiliza en la presente, se refiere a compuestos que dirigen, reducen, o inhiben la actividad de la amino-peptidasa de metionina. Los compuestos que dirigen, reducen, o inhiben la actividad de la amino-peptidasa de metionina son, por ejemplo, bengamida o un derivado de la misma.

El término "inhibidor de proteasoma", como se utiliza en la presente, se refiere a compuestos que dirigen, reducen, o inhiben la actividad del proteasoma. Los compuestos que dirigen, reducen, o inhiben la actividad del proteasoma incluyen, por ejemplo, Bortezomid (Velcade^{MR}) y MLN 341.

El término "inhibidor de metaloproteinasa de matriz" o (inhibidor de "MMP") como se utiliza en la presente, incluye, pero no se limita a, inhibidores peptidomiméticos y no peptidomiméticos de colágeno, derivados de tetraciclina, por ejemplo, el inhibidor peptidomimético de hidroxamato batimastato, y su análogo oralmente biodisponible marimastato (BB-2516), prinomastato (AG3340), metastato (NSC 683551) BMS-279251, BAY 12-9566, TAA211, MMI270B o AAJ996.

El término "compuestos utilizados en el tratamiento de malignidades hematológicas", como se utiliza en la presente, incluye, pero no se limita a, inhibidores de cinasa de tirosina tipo FMS, por ejemplo, los compuestos que dirigen, reducen, o inhiben la actividad

de los receptores de cinasa de tirosina tipo FMS (FIt-3R); interferón, 1-b-D-arabino-furansil-citosina (ara-c) y bisulfano; y los inhibidores de ALK, por ejemplo, los compuestos que dirigen, reducen, o inhiben la cinasa de linfoma anaplásico.

Los compuestos que dirigen, reducen, o inhiben la actividad de los receptores de cinasa de tirosina tipo FMS (FIt-3R) son en especial los compuestos, proteínas o anticuerpos que inhiben a los miembros de la familia de cinasa receptora FIt-3R, por ejemplo, PKC412, TKI258, midostaurina, un derivado de estaurosporina, SU11248 y MLN518.

El término "inhibidores de HSP90", como se utiliza en la presente, incluye, pero no se limita a, los compuestos que dirigen, reducen, o inhiben la actividad de ATPasa intrínseca de HSP90; que degrada, dirige, reduce, o inhibe las proteínas cliente de HSP90 por medio de la senda de proteasoma de ubiquitina. Los compuestos que dirigen, reducen, o inhiben la actividad de ATPasa intrínseca de HSP90 son en especial los compuestos, proteínas o anticuerpos que inhiben la actividad de ATPasa de HSP90, por ejemplo, 17-alil-amino-17-demetoxi-geldanamicina (17AAG), un derivado de geldanamicina; otros compuestos relacionados con geldanamicina; radicicol e inhibidores de HDAC. Un inhibidor de HSP90 de ejemplo es AUY922.

El término "anticuerpos anti-proliferativos", como se utiliza en la presente, incluye, pero no se limita a, trastuzumab (Herceptin^{MR}), Trastuzumab-DM1, erbitux, bevacizumab (Avastin^{MR}), rituximab

(Rituxan®), PRO64553 (anti-CD40), anticuerpo 2C4 y anticuerpo HCD122 (anti-CD40). Anticuerpos significan, por ejemplo, los anticuerpos monoclonales intactos, anticuerpos policlonales, anticuerpos multiespecíficos formados a partir de cuando menos 2 anticuerpos intactos, y fragmentos de anticuerpos, siempre que éstos exhiban la actividad biológica deseada.

Para el tratamiento de leucemia mieloide aguda (AML), los compuestos de la fórmula (I) se pueden utilizar en combinación con terapias para leucemia convencionales, en especial en combinación con las terapias utilizadas para el tratamiento de leucemia mieloide aguda. En particular, los compuestos de la fórmula (I) se pueden administrar en combinación con, por ejemplo, inhibidores de farnesil-transferasa y/u otros fármacos útiles para el tratamiento de leucemia mieloide aguda, tales como Daunorrubicina, Adriamicina, Ara-C, VP-16, Teniposida, Mitoxantrona, Idarrubicina, Carboplatino, y PKC412.

El término "compuestos antileucémicos" incluye, por ejemplo, Ara-C, un análogo de pirimidina, el cual es el derivado de 2'-alfa-hidroxi-ribosa (arabinosida) de desoxicitidina. También se incluye el análogo de purina de la hipoxantina, 6-mercapto-purina (6-MP) y fosfato de fludarabina.

Los compuestos que dirigen, reducen, o inhiben la actividad de los inhibidores de la desacetilasa de histona (HDAC), tales como butirato de sodio y ácido hidroxámico de suberoilanilida (SAHA), inhiben la actividad de las enzimas conocidas como desacetilasas de histona. Los inhibidores de desacetilasa de histona específicos

incluyen MS275, SAHA, FK228 (anteriormente FR901228), Tricostatina A y los compuestos que se dan a conocer en la Patente de los Estados Unidos de Norteamérica Número US 6,552,065, en particular, *N*-hidroxi-3-[4-[[[2-(2-metil-1*H*-indol-3-il)-etil]-amino]-metil]-fenil]-2*E*-2-propenamida, o una sal farmacéuticamente aceptable de la misma, y *N*-hidroxi-3-[4-[(2-hidroxi-etil)-{2-(1*H*-indol-3-il)-etil]-amino]-metil]-fenil]-2*E*-2-propenamida, o una sal farmacéuticamente aceptable de la misma, en especial la sal de lactato.

Antagonistas del receptor de somatostatina, como se utiliza en la presente, se refiere a compuestos que dirigen, tratan, o inhiben el receptor de somatostatina, tales como octreotida, y SOM230 (pasireotida).

Los planteamientos que dañan las células tumorales se refieren a planteamientos tales como radiación ionizante. El término "radiación ionizante" referido anteriormente y más adelante en la presente, significa la radiación ionizante que se presenta como rayos electromagnéticos (tales como rayos-X y rayos gamma), o bien partículas (tales como partículas alfa y beta). La radiación ionizante se proporciona en, pero no limitándose a, terapia de radiación y se conoce en este campo. Véase Hellman, Principles of Radiación Therapy, Cancer, en *Principles and Practice of Oncology*, Devita y colaboradores, Editores, 4a. Edición, Volumen 1, páginas 248-275 (1993).

El término "Aglutinantes EDG", como se utiliza en la presente,

se refiere a una clase de inmunosupresores que modulan la recirculación de los linfocitos, tales como FTY720.

El término "inhibidores de reductasa de ribonucleótido" se refiere a los análogos de nucleósido de pirimidina o purina incluyendo, pero no limitándose a, fludarabina y/o citosina-arabinosida (ara-C), 6-tioguanina, 5-fluoro-uracilo, cladribina, 6-mercapto-purina (en especial en combinación con ara-C contra la leucemia linfocítica aguda), y/o pentostatina. Los inhibidores de reductasa de ribonucleótido son en especial hidroxiurea o los derivados de 2-hidroxi-1H-isoindol-1,3-diona, tales como PL-1, PL-2, PL-3, PL-4, PL-5, PL-6, PL-7 o PL-8 mencionados en Nandy y colaboradores, *Acta Oncologica*, Volumen 33, Número 8, páginas 953-961 (1994).

El término "inhibidores de descarboxilasa de S-adenosil-metionina", como se utiliza en la presente, incluye, pero no se limita a, los compuestos que se dan a conocer en la Patente de los Estados Unidos de Norteamérica Número US 5,461,076.

También se incluyen en particular los compuestos, proteínas, o anticuerpos monoclonales del factor de crecimiento endotelial vascular que se dan a conocer en la Publicación Internacional Número WO 98/35958, por ejemplo, 1-(4-cloro-anilino)-4-(4-piridil-metil)-ftalazina o una sal farmacéuticamente aceptable de la misma, por ejemplo, el succinato, o en las Patentes Números WO 00/09495, WO 00/27820, WO 00/59509, WO 98/11223, WO 00/27819 y EP 0 769 947; aquéllos descritos por Prewett y colaboradores, *Cancer*

Res, Volumen 59, páginas 5209-5218 (1999); Yuan y colaboradores, *Proc Natl Acad Sci EUA*, Volumen 93, páginas 14765-14770 (1996); Zhu y colaboradores, *Cancer Res*, Volumen 58, páginas 3209-3214 (1998); y Mordenti y colaboradores, *Toxicol Pathol*, Volumen 27, Número 1, páginas 14-21 (1999); en las Publicaciones Internacionales Números WO 00/37502 y WO 94/10202; ANGIOSTATINA, descrita por O'Reilly y colaboradores, *Cell*, Volumen 79, páginas 315-328 (1994); ENDOSTATINA, descrita por O'Reilly y colaboradores, *Cell*, Volumen 88, páginas 277-285 (1997); amidas del ácido antranílico; ZD4190; ZD6474; SU5416; SU6668; bevacizumab; o anticuerpos contra el factor de crecimiento endotelial vascular o anticuerpos contra el receptor del factor de crecimiento endotelial vascular, por ejemplo, rhuMAb y RHUFab, aptámero del factor de crecimiento endotelial vascular, por ejemplo, Macugon; inhibidores de FLT-4, inhibidores de FLT-3, anticuerpo IgG1 de VEGFR-2 Angiozima (RPI 4610) y Bevacizumab (Avastin^{MR}).

Terapia fotodinámica, como se utiliza en la presente, se refiere a la terapia que utiliza ciertos productos químicos conocidos como compuestos fotosensibilizantes para tratar o prevenir cánceres. Los ejemplos de terapia fotodinámica incluyen el tratamiento con compuestos, tales como, por ejemplo, VISUDYNE y porfímero-sodio.

Esteroides angiostáticos, como se utilizan en la presente, se refieren a los compuestos que bloquean o inhiben la angiogénesis, tales como, por ejemplo, anecortave, triamcinolona, hidrocortisona, 11-α-epihidrocotisol, cortexolona, 17α-hidroxi-progesterona,

corticosterona, desoxi-corticosterona, testosterona, estrona y dexametasona.

Los implantes que contienen corticosteroides se refieren a compuestos, tales como, por ejemplo, fluocinolona, dexametasona.

"Otros compuestos quimioterapéuticos" incluyen, pero no se limitan a, alcaloides de plantas, los compuestos y antagonistas hormonales; modificadores de la respuesta biológica, de preferencia linfocinas o interferones; oligonucleótidos anti-sentido o derivados de oligonucleótidos; ARNsh o ARNsi; o compuestos varios, o compuestos con un mecanismo de acción diferente o desconocido.

La estructura de los compuestos activos identificados por números de código, nombres genéricos o comerciales, se puede tomar de la edición actual del compendio estándar "The Merck Index" o de las bases de datos, por ejemplo, Patents International (por ejemplo, IMS World Publications).

Ninguna de las citas de referencias hechas en la presente divulgación debe entenderse como una admisión de que las referencias citadas sean técnica anterior que afectaría negativamente la patentabilidad de la presente invención.

Modalidades preferidas de la invención

En las siguientes modalidades preferidas de la invención, los términos más generales, individualmente o algunos o todos, pueden ser reemplazados con los términos específicos mencionados anteriormente o más adelante para definir las modalidades más preferidas de la invención.

Una modalidad preferida de la invención se refiere a un compuesto de la fórmula I, en donde:

R^1 es alquilo insustituido o sustituido, alquenilo insustituido o sustituido o alquinilo insustituido o sustituido;

R^2 es arilo insustituido o sustituido;

R^3 es hidrógeno, alquilo insustituido o sustituido, carboxilo, ciano, carboxilo esterificado, heterociclil-carbonilo insustituido o sustituido (heterociclil-C)=O)-), carbamoílo insustituido o sustituido, heterociclilo insustituido o sustituido o ciano,

R^4 es hidrógeno, alquilo insustituido o sustituido, halógeno o heterociclilo insustituido o sustituido,

R^A es hidrógeno o alquilo insustituido o sustituido o acilo;

X es hidrógeno, alquilo de 1 a 7 átomos de carbono, halo-alquilo de 1 a 7 átomos de carbono, alcoxilo de 1 a 7 átomos de carbono, halógeno o ciano; y

Y es alquilo de 1 a 7 átomos de carbono, halo-alquilo de 1 a 7 átomos de carbono, alcoxilo de 1 a 7 átomos de carbono, halógeno o ciano;

y/o un tautómero, un N-óxido, y/o una sal del mismo.

Se prefiere en especial un compuesto de la fórmula I, en donde:

R^1 es alquilo de 1 a 7 átomos de carbono que es lineal o ramificado y está insustituido o sustituido por una o más, en especial hasta tres, fracciones independientemente seleccionadas a partir del grupo que consiste en alquilo de 1 a 7 átomos de carbono, en

especial metilo, de hidroxilo, de hidroxi-alquilo de 1 a 7 átomos de carbono, en especial hidroxi-metilo, de alcoxilo de 1 a 7 átomos de carbono-alquilo de 1 a 7 átomos de carbono, en especial 2-metoxi-etoxilo o metoxi-etoxilo o etoxi-metoxilo, de arilo de 6 a 14 átomos de carbono, en especial fenilo, en donde arilo está insustituido o sustituido por una o más, en especial hasta tres, fracciones independientemente seleccionadas a partir del grupo que consiste en alquilo de 1 a 7 átomos de carbono, en especial metilo, halo-alquilo de 1 a 7 átomos de carbono, en especial trifluoro-metilo, hidroxilo, alcoxilo de 1 a 7 átomos de carbono, alcoxilo de 1 a 7 átomos de carbono-alcoxilo de 1 a 7 átomos de carbono, en especial 2-metoxi-etoxilo ó 3-metoxi-propoxilo, [amino, mono- o di-(alquilo de 1 a 7 átomos de carbono)-amino]-alcoxilo de 1 a 7 átomos de carbono, amino, mono- o di-[alquilo de 1 a 7 átomos de carbono, hidroxi-alquilo de 1 a 7 átomos de carbono, alcoxilo de 1 a 7 átomos de carbono-alquilo de 1 a 7 átomos de carbono, amino-alquilo de 1 a 7 átomos de carbono, amino y/o mono- o di-(alquilo de 1 a 7 átomos de carbono)-amino-alquilo de 1 a 7 átomos de carbono]-amino, halógeno, en especial flúor, cloro o bromo, y heterociclilo saturado-alcoxilo de 1 a 7 átomos de carbono, en donde heterociclilo saturado tiene de 3 a 14 átomos del anillo, de los cuales de 1 a 4 son un heteroátomo independientemente seleccionado a partir de N, S, S(=O), $S(=O)_2$ y O, y está insustituido o sustituido con alquilo de 1 a 7 átomos de carbono, en especial pirrolidinil-, piperidinil-, piperazinil- o N-(alquilo de 1 a 7 átomos de carbono)-piperazinil-alcoxilo de 1 a 7

átomos de carbono, y de heterociclilo de 3 a 14 átomos de carbono mono- o bi-cíclico con 3 a 14 átomos del anillo, de los cuales de 1 a 4 son un heteroátomo independientemente seleccionado a partir de N, S, S(=O), $S(=O)_2$ y O, y está insustituido o sustituido con alquilo de 1 a 7 átomos de carbono, en especial el hetero-arilo correspondiente, más especialmente indolilo, isoindolilo, indazolilo, quinolinilo, isoquinolinilo, ftalazinilo, quinoxalinilo, quinazolinilo, cinolinilo, benzo-furanilo, isobenzo-furanilo, cromenilo, isocromenilo, benzo-tiofenilo, tiocromenilo o isotiocromenilo,

R^2 es arilo de 6 a 14 átomos de carbono (en especial fenilo) que está insustituido o sustituido por una o más, en especial hasta tres, fracciones independientemente seleccionadas a partir del grupo que consiste en alquilo de 1 a 7 átomos de carbono-fenilo, en especial metilo, hidroxilo, y halógeno, en especial flúor o cloro,

R^3 es hidrógeno o de preferencia:

alquilo de 1 a 7 átomos de carbono que está insustituido por una o más, en especial hasta tres, fracciones independientemente seleccionadas a partir del grupo que consiste en hidroxilo, amino y heterociclil-alquilo de 1 a 7 átomos de carbono-amino, en donde el heterociclilo tiene de 3 a 14 átomos del anillo, de los cuales de 1 a 4 son un heteroátomo independientemente seleccionado a partir de N, S, S(=O), $S(=O)_2$ y O, y está saturado, en especial (morfolinilo, tiomorfolinilo, S-oxo-tiomorfolinilo o S,S-dioxo-tiomorfolinil)-alquilo de 1 a 7 átomos de carbono-amino,

ciano, carboxilo, alcoxilo de 1 a 7 átomos de carbono-

carbonilo o arilo de 6 a 14 átomos de carbono-alcoxilo de 1 a 7 átomos de carbono-carbonilo;

heterociclil-carbonilo (heterociclil-C(=O)) en donde el heterociclilo está insaturado o de preferencia saturado, tiene de 3 a 14 átomos del anillo, de los cuales de 1 a 4 son un heteroátomo independientemente seleccionado a partir de N, S, S(=O), $S(=O)_2$ y O, de preferencia N, tal como pirrolidinilo, piperidinilo, piperazinilo, morfolinilo, tiomorfolinilo, S-oxo-tiomorfolinilo o S,S-dioxo-tiomorfolinilo, y está insustituido o sustituido con una o más, en especial una a tres, fracciones independientemente seleccionadas a partir del grupo que consiste en alquilo de 1 a 7 átomos de carbono, hidroxi-alquilo de 1 a 7 átomos de carbono, hidroxilo, oxo, amino o N-mono- o N,N-di-(alquilo de 1 a 7 átomos de carbono, {amino o mono- o di-alquilo de 1 a 7 átomos de carbono-amino}-alquilo de 1 a 7 átomos de carbono, alcanoílo de 1 a 7 átomos de carbono y/o alcoxilo de 1 a 7 átomos de carbono-carbonil)-amino, alcanoílo de 1 a 7 átomos de carbono, alquilo de 1 a 7 átomos de carbono-sulfonilo y heterociclilo saturado con 3 a 14 átomos del anillo y con 1 a 4 heteroátomos independientemente seleccionados a partir de N, S, S(=O), $S(=O)_2$ y O, de preferencia N, por ejemplo, pirrolidinilo, imidazolidinilo, piperidinilo, piperazinilo, morfolinilo, tiomorfolinilo, S-oxo-tiomorfolinilo o S,S-dioxo-tiomorfolinilo, en donde este heterociclilo saturado está insustituido o sustituido por una o más, en especial hasta tres, fracciones independientemente seleccionadas a partir de alquilo de 1 a 7 átomos de carbono, hidroxi-alquilo de 1 a 7

átomos de carbono-alcoxilo de 1 a 7 átomos de carbono-alquilo de 1 a 7 átomos de carbono, oxo, amino y mono- o di-(alquilo de 1 a 7 átomos de carbono)-amino),

carbamoílo, N-mono- o N,N-di-[alquilo de 1 a 7 átomos de carbono, hidroxi-alquilo de 1 a 7 átomos de carbono, alcoxilo de 1 a 7 átomos de carbono-alquilo de 1 a 7 átomos de carbono, amino-alquilo de 1 a 7 átomos de carbono, mono- o di-(alquilo de 1 a 7 átomos de carbono)-amino-alquilo de 1 a 7 átomos de carbono, arilo de 6 a 14 átomos de carbono, en donde arilo está insustituido o sustituido por una o más, en especial hasta tres, fracciones independientemente seleccionadas a partir del grupo que consiste en alquilo de 1 a 7 átomos de carbono, alcoxilo de 1 a 7 átomos de carbono, heterociclilo saturado con 3 a 14 átomos del anillo y con 1 a 4 heteroátomos independientemente seleccionados a partir de N, S, S(=O), $S(=O)_2$ y O, de preferencia N, por ejemplo, pirrolidinilo, imidazolidinilo, piperidinilo, piperazinilo, azepanilo, morfolinilo, tiomorfolinilo, S-oxo-tiomorfolinilo o S,S-dioxo-tiomorfolinilo, en donde este heterociclilo saturado está insustituido o sustituido con una o más, en especial hasta tres, fracciones independientemente seleccionadas a partir de alquilo de 1 a 7 átomos de carbono, hidroxi-alquilo de 1 a 7 átomos de carbono, hidroxilo, oxo, y alcoxilo de 1 a 7 átomos de carbono-carbonilo, arilo de 6 a 14 átomos de carbono-alquilo de 1 a 7 átomos de carbono, y heterociclilo saturado o (heterociclilo saturado)-alquilo de 1 a 7 átomos de carbono, en donde heterociclilo saturado en ambos casos tiene de 3 a 14 átomos

del anillo y de 1 a 4 heteroátomos independientemente seleccionados a partir de N, S, S(=O), $S(=O)_2$ y O, de preferencia N, por ejemplo, pirrolidinilo, imidazolidinilo, piperidinilo, piperazinilo, azepanilo, morfolinilo, tiomorfolinilo, S-oxo-tiomorfolinilo, S,S-dioxo-tiomorfolinilo, indolilo o isoindolilo o (pirrolidinilo, imidazolidinilo, piperidinilo, piperazinilo, azepanilo, morfolinilo, tiomorfolinilo, S-oxo-tiomorfolinilo, S,S-dioxo-tiomorfolinilo, indolilo o isoindolil)-alquilo de 1 a 7 átomos de carbono, en donde este heterociclilo saturado está insustituido o sustituido con una o más, en especial hasta tres, fracciones independientemente seleccionadas a partir de alquilo de 1 a 7 átomos de carbono, hidroxi-alquilo de 1 a 7 átomos de carbono, alcoxilo de 1 a 7 átomos de carbono-alquilo de 1 a 7 átomos de carbono, oxo, alcanoílo de 1 a 7 átomos de carbono y alcoxilo de 1 a 7 átomos de carbono-carbonil]-carbamoílo,

hetero-arilo con 3 a 14 átomos del anillo y con 1 a 5 heteroátomos del anillo independientemente seleccionados a partir del grupo que consiste en N, S, S(=O), $S(=O)_2$ y O, en especial N, S y O, tal como triazolilo o en especial tetrazolilo,

o ciano,

R^4 es hidrógeno, alquilo de 1 a 7 átomos de carbono, halógeno o hetero-arilo con 3 a 14 átomos del anillo y con 1 a 5 heteroátomos independientemente seleccionados a partir del grupo que consiste en N, S, S(=O), $S(=O)_2$ y O, en especial N, tal como piridilo,

R^A es hidrógeno o alquilo de 1 a 7 átomos de carbono, de

preferencia hidrógeno;

X es hidrógeno, alquilo de 1 a 7 átomos de carbono, halógeno o ciano, en especial hidrógeno o flúor, y

Y es alquilo de 1 a 7 átomos de carbono, halógeno o ciano; en especial metilo, flúor, cloro, bromo o ciano,

y/o un tautómero, un N-óxido y/o una sal farmacéuticamente aceptable del mismo.

Se prefiere altamente un compuesto de la fórmula I, en donde:

R^1 es alquilo de 1 a 7 átomos de carbono, en especial 3,3-dimetil-butilo, alquilo de 1 a 7 átomos de carbono-bencilo, en especial metil-bencilo, más especialmente 4-metil-bencilo, (halo-alquilo de 1 a 7 átomos de carbono)-bencilo, en especial trifluoro-metil-bencilo, más especialmente 4-trifluoro-metil-bencilo, hidroxi-halo-bencilo, en especial cloro-hidroxi-bencilo, más especialmente 4-cloro-2-hidroxi-bencilo, halo-bencilo, en especial bromo-bencilo, más especialmente 4-bromo-bencilo, cloro-bencilo, más especialmente 4-cloro-bencilo, fluoro-bencilo, más especialmente 4-fluoro-bencilo, dicloro-bencilo, más especialmente 3,4- ó 2,4-dicloro-bencilo, cloro-fluoro-bencilo, más especialmente 4-cloro-3-fluoro-bencilo, 3-cloro-4-fluoro-bencilo o 4-cloro-2-fluoro-bencilo, (R,S)- o de preferencia (R)- o (S)-1-(halo-fenil)-1-(alquilo de 1 a 7 átomos de carbono o hidroxi)-alquilo de 1 a 7 átomos de carbono, en especial (R,S)- o de preferencia (R)- o (S)-1-(fluoro-fenilo, cloro-fenilo o bromo-fenil)-1-(metil o hidroxi)-metilo, más especialmente (R,S)- o de preferencia (R)- o (S)-1-(4-fluoro-fenilo, 4-cloro-fenil o 4-bromo-fenil)-1-(metil o

hidroxi)-metilo, (R,S)- o de preferencia (R)- o (S)-1-(halo-fenil)-1-[(hidroxilo o alcoxilo de 1 a 7 átomos de carbono)-alquilo de 1 a 7 átomos de carbono]-alquilo de 1 a 7 átomos de carbono, en especial (R,S)- o de preferencia (R)- o (S)-1-(cloro-fenil)-1-(hidroxi-metil o metoxi-metil)-metilo, más especialmente (R,S)- o de preferencia (R)- o (S)-1-(4-cloro-fenil)- 1-(hidroxi-metil o metoxi-metil)-metilo, alquilo de 1 a 7 átomos de carbono-halo-bencilo, en especial metil-halo-bencilo, más especialmente 4-cloro-2-metil-bencilo, hidroxi-halo-bencilo, en especial hidroxi-cloro-bencilo, más especialmente 4-cloro-2-hidroxi-bencilo, alcoxilo de 1 a 7 átomos de carbono-halo-bencilo, en especial metoxi-cloro-bencilo, tal como 4-cloro-2-metoxi-bencilo, (hidroxi-alcoxilo de 1 a 7 átomos de carbono, o alcoxilo de 1 a 7 átomos de carbono-alcoxilo de 1 a 7 átomos de carbono)-halo-bencilo, en especial (2-hidroxi-etoxilo, 3-hidroxi-propoxilo o 2-metoxi-etoxi)-cloro-bencilo, más especialmente 4-cloro-2-(2-hidroxi-etoxilo, 3-hidroxi-propoxi o 2-metoxi-etoxi)-bencilo, [amino, N-mono- o N,N-di-(alquilo de 1 a 7 átomos de carbono-amino)-alcoxilo de 1 a 7 átomos de carbono]-halo-bencilo, en especial [2-(N,N-dimetil-amino)-etoxi]-cloro-bencilo, más especialmente 2-[2-(N,N-dimetil-amino)-etoxi]-4-cloro-bencilo, (hidroxi-alquilo de 1 a 7 átomos de carbono-amino)-halo-bencilo, en especial [(2-hidroxi-metil- ó 3-hidroxi-propil)-amino]-cloro-bencilo, más especialmente 2-[(2-hidroxi-metil- ó 3-hidroxi-propil)-amino]-4-cloro-bencilo, (alcoxilo de 1 a 7 átomos de carbono-alquilo de 1 a 7 átomos de carbono-amino)-halo-bencilo, en especial [(2-metoxi-metil- ó 3-metoxi-propil)-amino]-cloro-bencilo,

más especialmente 2-[(2-metoxi-metil- ó 3-metoxi-propil)-amino]-4-cloro-bencilo, [{amino, N-mono- o N,N-di-(alquilo de 1 a 7 átomos de carbono)-amino}-alquilo de 1 a 7 átomos de carbono-amino]-halo-bencilo, en especial [(2-dimetil-amino-etil-amino]-cloro-bencilo, más especialmente 2-(2-dimetil-amino-etil-amino)-4-cloro-bencilo, (pirrolidinil-, piperidinil-, piperazinil- o N-(alquilo de 1 a 7 átomos de carbono)-piperazinil-alcoxilo de 1 a 7 átomos de carbono)-halo-bencilo, en especial (pirrolidino-, piperidino-, piperazino- o 4-(alquilo de 1 a 7 átomos de carbono)-piperazin-1-il-alcoxilo de 1 a 7 átomos de carbono)-halo-bencilo, más especialmente 4-cloro-2-[2-(pirrolidino-, piperidino-, piperazino- o 4-(alquilo de 1 a 7 átomos de carbono)-piperazin-1-il)-etoxi]-bencilo, indolil-alquilo de 1 a 7 átomos de carbono, en especial indolil-metilo, más especialmente indol-6-il-metilo, benzo-furanil-alquilo de 1 a 7 átomos de carbono, en especial benzo-furanil-metilo, más especialmente benzo-furan-6-il-metilo, o benzo-tiofenil-alquilo de 1 a 7 átomos de carbono, en especial benzo-tiofenil-metilo, más especialmente benzo-tiofen-6-il-metilo;

R^2 es fenilo, alquilo de 1 a 7 átomos de carbono-fenilo, en especial metil-fenilo, más especialmente 2-metil-fenilo, hidroxi-fenilo, en especial 3-hidroxi-fenilo, o halofenilo, en especial fenilo o fluoro-, cloro- o fluoro-cloro-fenilo, más especialmente fenilo, 2-fluoro-fenilo, 3-fluoro-fenilo o 3-cloro-2-fluoro-fenilo,

R^3 es hidrógeno o de preferencia hidroxi-alquilo de 1 a 7 átomos de carbono, en especial hidroxi-metilo, amino-alquilo de 1 a 7 átomos de carbono, en especial 2-amino-etilo, (morfolinilo,

tiomorfolinilo, S-oxo-tiomorfolinilo o S,S-dioxo-tiomorfolinil)-alquilo de 1 a 7 átomos de carbono-amino-alquilo de 1 a 7 átomos de carbono, en especial N-(2-morfolino-etil)-amino-metilo,

ciano, carboxilo, alcoxilo de 1 a 7 átomos de carbono-carbonilo, en especial metoxi-carbonilo o etoxi-carbonilo,

azetidin-carbonilo, en especial azetidin-1-il-carbonilo, pirrolidin-carbonilo, en especial pirrolidin-1-carbonilo, (R,S)- o de preferencia (R)- o (S)-[amino o N'-mono- o N',N'-di-(alquilo de 1 a 7 átomos de carbono y/o {amino o mono- o di-alquilo de 1 a 7 átomos de carbono-amino}-alquilo de 1 a 7 átomos de carbono)-amino]-pirrolidin-carbonilo, en especial (R,S)- o de preferencia (R)- o (S)-3-(dimetil-amino)-pirrolidin-1-carbonilo o aquiral, (R,S)- o de preferencia (R)- o (S)-3-(dietil-amino)-pirrolidin-1-carbonilo, (R,S)- o de preferencia (R)- o (S)-3-[N-2-(dimetil-amino)-etil-amino]-pirrolidin-1-carbonilo, (R,S)- o de preferencia (R)- o (S)-3-[N-3-(dimetil-amino)-propil-amino]-pirrolidin-1-carbonilo, (R,S)- o de preferencia (R)- o (S)-3-[N-2-(dimetil-amino)-etil-N-metil-amino]-pirrolidin-1-carbonilo, o (R,S)- o de preferencia (R)- o (S)-3-[N-3-(dimetil-amino)-propil-N-metil-amino]-pirrolidin-1-carbonilo o (R,S)-, (R,S)- o de preferencia (R)- o (S)-pirrolidinil-pirrolidin-carbonilo, en especial (R,S)- o de preferencia (R)- o (S)-3-(pirrolidin-1-il)-pirrolidin-carbonilo, (R,S)- o de preferencia (R)- o (S)-[(amino, mono- o di-(alquilo de 1 a 7 átomos de carbono)-amino)-piperidinil]-pirrolidin-carbonilo, en especial (R,S)- o de preferencia (R)- o (S)-3-(4-dimetil-amino-piperidin-1-il)-pirrolidin-1-carbonilo, (R,S)- o de preferencia (R)- o

(S)-[hidroxi-alquilo de 1 a 7 átomos de carbono, hidroxilo, amino o mono- o di-(alquilo de 1 a 7 átomos de carbono, alcanoílo de 1 a 7 átomos de carbono, alcoxilo de 1 a 7 átomos de carbono-carbonil)-amino]-pirrolidin-carbonilo, en especial (R,S)- o de preferencia (R)- o (S)-3-hidroxi-pirrolidin-1-carbonilo, en especial (R,S)- o de preferencia (R)- o (S)-3-hidroxi-metil-pirrolidin-1-carbonilo, (R,S)- o de preferencia (R)- o (S)-3-amino-pirrolidin-1-carbonilo, (R,S)- o de preferencia (R)- o (S)-3-etil-amino-pirrolidin-1-carbonilo, (R,S)- o de preferencia (R)- o (S)-3-terbutoxi-carbonil-amino-pirrolidin-1-carbonilo, (R,S)- o de preferencia (R)- o (S)-3-(N-metil-N-acetil-amino)-pirrolidin-1-carbonilo, (R,S)- o de preferencia (R)- o (S)-(piperazinilo, alquilo de 1 a 7 átomos de carbono-piperazinilo, (hidroxi-alquilo de 1 a 7 átomos de carbono)-piperazinilo, morfolinilo, tiomorfolinilo, S-oxo-tiomorfolinilo o S,S-dioxo-tiomorfolinil)-pirrolidin-carbonilo, en especial (R,S)- o de preferencia (R)- o (S)-3-(4-metil-piperazino)-pirrolidin-1-carbonilo, (R,S)- o de preferencia (R)- o (S)-3-(4-(2-hidroxi-etil)-piperazino)-pirrolidin-1-carbonilo, (R,S)- o de preferencia (R)- o (S)-3-morfolino-pirrolidin-1-carbonilo o (R,S)- o de preferencia (R)- o (S)-3-dioxo-tiomorfolino-pirrolidin-1-carbonilo,

piperidinil-carbonilo, en especial piperidin-1-carbonilo (piperidin-1-il-C(=O)-), (hidroxilo, hidroxi-alquilo de 1 a 7 átomos de carbono, amino o mono- o di-(alquilo de 1 a 7 átomos de carbono)-amino)-piperidin-carbonilo, en especial 4-hidroxi-metil-piperidin-1-carbonilo o 4-dimetil-amino-piperidin-1-carbonilo, oxoimidazolidinil-

piperidin-carbonilo, en especial 4-(2-oxo-imidazolidin-1-il)-piperidin-1-carbonilo, (fenil-oxoimidazolidinil)-piperidin-carbonilo, en especial 4-(3-fenil-2-oxo-imidazolidin-1-il)-piperidin-1-carbonilo, pirrolidinil- u oxo-pirrolidinil-piperidin-carbonilo, en especial 4-(pirrolidin-1-il)-piperidin-1-carbonilo o 4-(2-oxo-pirrolidin-1-il)-piperidin-1-carbonilo, piperazinil- o N-(alquilo de 1 a 7 átomos de carbono)-piperazinil-piperidin-carbonilo, en especial 4-(4-metil-piperazin-1-il)-piperidin-1-carbonilo, (morfolinilo, tiomorfolinilo, S-oxo-tiomorfolinilo o S,S-dioxo-tiomorfolinil)-piperidin-carbonilo, en especial 4-morfolino-piperidin-1-carbonilo, (oxo-benzo-imidazolidinil)-piperidin-carbonilo, en especial (2-oxo-1,3-benzo-imidazolidin-1-il)-piperidin-carbonilo, piperazin-carbonilo, en especial piperazin-1-carbonilo, (alquilo de 1 a 7 átomos de carbono o hidroxi-alquilo de 1 a 7 átomos de carbono)-piperazin-carbonilo, en especial 4-metil-, 4-(2-hidroxi-etil)- o 4-(3-hidroxi-propil)-piperazin-1-carbonilo, oxopiperazin-carbonilo, en especial 2-oxo-piperazin-4-carbonilo, alcanoílo de 1 a 7 átomos de carbono-piperazin-carbonilo, en especial 1-acetil-piperazin-4-carbonilo, alquilo de 1 a 7 átomos de carbono-sulfonil-piperazin-carbonilo, en especial 4-metan-sulfonil-piperazin-1- carbonilo,

morfolin-carbonilo (morfolinil-C(=O)-), en especial morfolin-1-carbonilo, (tiomorfolin, S-oxo-tiomorfolin o S,S-dioxo-tiomorfolin)-carbonilo, en especial S,S-dioxo-tiomorfolin-1-carbonilo,

carbamoílo (sinónimo: amino-carbonilo, -C(=O)-NH_2),

N-mono- o N,N-di-(alquilo de 1 a 7 átomos de carbono)-carbamoílo, en especial N-metil-, N,N-dimetil-, N-etil- o N-terbutil-

carbamoílo,

N-[(hidroxi- o alcoxilo de 1 a 7 átomos de carbono)-alquilo de 1 a 7 átomos de carbono]-carbamoílo, en especial N-(2-hidroxi-etil)-carbamoílo, N-(3-hidroxi-propil)-carbamoílo, N-(2-metoxi-etil)-carbamoílo o N-(3-metoxi-propil)-carbamoílo, N-[(amino, mono- o di-(alquilo de 1 a 7 átomos de carbono)-amino)-alquilo de 1 a 7 átomos de carbono]-carbamoílo, en especial N-(2-amino-etil)-carbamoílo, N-(2-(metil-amino)-etil-carbamoílo, 2-(N,N-di-(metil)-amino)-etil-carbamoílo, 3-(N,N-di-(metil)-amino)-propil-carbamoílo, N-[2-(N,N-di-(metil)-amino)-etil]-N-metil-carbamoílo, N-[3-(N,N-di-(metil)-amino)-propil]-N-metil-carbamoílo, 2-(N,N-di-(etil)-amino)-etil-carbamoílo, 3-(N,N-di-(etil)-amino)-propil-carbamoílo, N-[2-(N,N-di-(etil)-amino)-etil]-N-metil-carbamoílo, N-[3-(N,N-di-(etil)-amino)-propil]-N-metil-carbamoílo, N-fenil-carbamoílo, N-(alcoxilo de 1 a 7 átomos de carbono-fenil)-carbamoílo, en especial N-(metoxi-fenil)-carbamoílo, [(pirrolidinilo, piperidinilo, piperazinilo o 1-(alquilo de 1 a 7 átomos de carbono)-piperazinil)-fenil]-carbamoílo, en especial N-[3-(piperazin-4-ilo o 1-metil-piperazin-4-il)-fenil]-carbamoílo, N-(fenil-alquilo de 1 a 7 átomos de carbono)-carbamoílo, en especial N-bencil-carbamoílo, N-(oxoimidazolidinil-alquilo de 1 a 7 átomos de carbono)-carbamoílo, en especial N-[2-(2-oxoimidazol-1-il)-etil]-carbamoílo, N-(pirrolidinil-alquilo de 1 a 7 átomos de carbono)-carbamoílo, en especial N-(pirrolidino-metil)-carbamoílo, N-(2-pirrolidino-etil)-carbamoílo o N-(3-pirrolidino-propil)-carbamoílo, N-(oxo-pirrolidinil-alquilo de 1 a 7 átomos de carbono)-carbamoílo, en

especial N-(2-oxo-pirrolidino-metil)-carbamoílo, N-[2-(2-oxo-pirrolidino)-etil]-carbamoílo o N-[3-(2-oxo-pirrolidino)-propil]-carbamoílo,

N-piperidinil-carbamoílo, en especial N-piperidin-4-il-carbamoílo, N-[(alquilo de 1 a 7 átomos de carbono)-piperidinil]-carbamoílo, en especial N-(1-metil-piperidin-4-il)-carbamoílo, N-[(hidroxi-alquilo de 1 a 7 átomos de carbono)-piperidinil]-carbamoílo, en especial N-[1-(2-hidroxi-etil)-piperidin-4-il]-carbamoílo, N-[N-(alcoxilo de 1 a 7 átomos de carbono-carbonil)-piperidinil]-carbamoílo, en especial N-[1-(terbutoxi-carbonil)-piperidin-4-il]-carbamoílo, N-(piperidinil-alquilo de 1 a 7 átomos de carbono)-carbamoílo, en especial N-(piperidin-1-il-metil)-, N-[2-(piperidin-1-il)-etil]- o N-[3-(piperidin-1-il)-propil]-carbamoílo, N-(azepan-alquilo de 1 a 7 átomos de carbono)-carbamoílo, en especial N-(azepan-1-il-metil)-, N-[2-(piperidin-1-il)-etil]- o N-[3-(piperidin-1-il)-propil]-carbamoílo, N-(piperazinil-alquilo de 1 a 7 átomos de carbono)-carbamoílo, en especial N-(piperazin-1-il-metil)-, N-[2-(piperazin-1-il)-etil]- o N-[3-(piperazin-1-il)-propil]-carbamoílo, N-(oxopiperazinil-alquilo de 1 a 7 átomos de carbono)-carbamoilo, en especial N-[(2-oxo-piperazin-4-il)-metil]-, N-[2-(2-oxo-piperazin-4-il)-etil]- o N-[3-(2-oxo-piperazin-4-il)-propil]-carbamoílo, N-((alquilo de 1 a 7 átomos de carbono)-piperazinil-alquilo de 1 a 7 átomos de carbono)-carbamoílo, en especial N-[(1-metil-piperazin-4-il)-metil]-, N-[2-(1-metil-piperazin-4-il)-etil]- o N-[3-(1-metil-piperazin-1-il)-propil]-carbamoílo, N-(1-(hidroxi-alquilo de 1 a 7 átomos de carbono)-piperazinil-alquilo de 1 a 7 átomos de carbono)-carbamoílo, en especial N-[(1-(2-hidroxi-

etil)-piperazin-4-il)-metil]-, N-[2-(1-(2-hidroxi-etil)-piperazin-4-il)-etil]- o N-[3-(1-(2-hidroxi-etil)-piperazin-1-il)-propil]-carbamoílo, N-(1-(alcanoílo de 1 a 7 átomos de carbono)-piperazinil-alquilo de 1 a 7 átomos de carbono)-carbamoílo, en especial N-[(1-acetil-piperazin-4-il)-metil]-, N-[2-(1-acetil-piperazin-4-il)-etil]- o N-[3-(1-acetil-piperazin-1-il)-propil]-carbamoílo, N-(1-(alcoxilo de 1 a 7 átomos de carbono-carbonil)-piperazinil-alquilo de 1 a 7 átomos de carbono)-carbamoílo, en especial N-[(1-(terbutoxi-carbonil)-piperazin-4-il)-metil]-, N-[2-(1-(terbutoxi-carbonil)-piperazin-4-il)-etil]- o N-[3-(1-(terbutoxi-carbonil)-piperazin-1-il)-propil]-carbamoílo, N-[(morfolinilo, tiomorfolinilo, S-oxo-tiomorfolinilo o S,S-dioxo-tiomorfolinil)-alquilo de 1 a 7 átomos de carbono]-carbamoílo, en especial N-morfolino-metil-, N-(2-morfolino-etil)-, N-(3-morfolino-propil)-carbamoílo, N-(S,S-dioxo-tiomorfolino)-metil-, N-[2-(S,S-dioxo-tiomorfolino)-etil]- o N-[3-(S,S-dioxo-tiomorfolino)-propil]-carbamoílo, N-[dioxo-1H, 3H-isoindolil)-alquilo de 1 a 7 átomos de carbono)-carbamoílo, en especial N-(1,7-dioxo-1H, 7H-isoindolin-2-il-metil)-, N-[2-(1,7-dioxo-1H, 7H-isoindolin-2-il)-etil]- o N-[3-(1,7-dioxo-1H, 7H-isoindolin-2-il)-propil]-carbamoílo,

triazolilo o tetrazolilo, en especial tetrazol-5-ilo,

o ciano,

R^4 es hidrógeno, alquilo de 1 a 7 átomos de carbono, en especial metilo, halógeno, en especial bromo o cloro, o piridilo, en especial piridin-3-, -4- ó -2-ilo,

R^A es hidrógeno o alquilo de 1 a 7 átomos de carbono, de

preferencia hidrógeno;

X es hidrógeno, alquilo de 1 a 7 átomos de carbono, halógeno o ciano, en especial hidrógeno o flúor, e

Y es alquilo de 1 a 7 átomos de carbono, halógeno o ciano, en especial metilo, flúor, cloro, bromo o ciano,

y/o un tautómero, un N-óxido y/o una sal farmacéuticamente aceptable del mismo.

Todavía se prefiere más altamente un compuesto de la fórmula I, en donde:

R^1 es halo-bencilo, en especial bromo-bencilo, más especialmente 4-bromo-bencilo, cloro-bencilo, más especialmente 4-cloro-bencilo, o fluoro-bencilo, más especialmente 4-fluoro-bencilo,

R^2 es fenilo,

R^3 es hidroxi-alquilo de 1 a 7 átomos de carbono, en especial hidroxi-metilo, carboxilo, (R,S)- o de preferencia (R)- o (S)-[amino o N'-mono- o N',N'-di-(alquilo de 1 a 7 átomos de carbono y/o {amino o mono- o di-alquilo de 1 a 7 átomos de carbono-amino}-alquilo de 1 a 7 átomos de carbono)-amino]-pirrolidin-carbonilo o aquiral, en especial (R,S)- o de preferencia (R)- o (S)-3-[N-2-(dimetil-amino)-etil-N-metil-amino]-pirrolidin-1-carbonilo, amino o mono- o di-(alquilo de 1 a 7 átomos de carbono)-amino-piperidin-carbonilo, en especial 4-dimetil-amino-piperidin-1-carbonilo, carbamoílo, N-alquilo de 1 a 7 átomos de carbono-carbamoílo, en especial N-metil- o N-etil-carbamoílo, N-((alquilo de 1 a 7 átomos de carbono)-piperazinil-alquilo de 1 a 7 átomos de carbono)-carbamoílo, en especial N-[(1-

metil-piperazin-4-il)-metil]-, N-[2-(1-metil-piperazin-4-il)-etil]- o N-[3-(1-metil-piperazin-1-il)-propil]-carbamoílo, o N-[(morfolinil o tiomorfolinil)-alquilo de 1 a 7 átomos de carbono]-carbamoílo, en especial N-morfolino-metil-, N-(2-morfolino-etil)-, N-(3-morfolino-propil)-carbamoílo,

R^4 es hidrógeno o alquilo de 1 a 7 átomos de carbono, en especial metilo, o halógeno, en especial bromo o cloro, más preferiblemente hidrógeno,

R^A es hidrógeno;

X es halógeno o flúor, e

Y es halógeno o ciano, en especial cloro o ciano;

y/o un tautómero, un N-óxido y/o una sal farmacéuticamente aceptable del mismo.

También son muy preferidas las modalidades de la invención representadas en las reivindicaciones, las cuales, por consiguiente, se incorporan como referencia en la presente.

La invención también se refiere de preferencia a un método de manufactura o el uso de cualquiera o más de los compuestos de la fórmula I, y/o tautómeros de los mismos, N-óxidos de los mismos y/o sales (de preferencia farmacéuticamente aceptables) de los mismos mencionados como preferidos en la presente, así como a una composición farmacéutica, la cual comprende los comprende.

La invención se refiere en especial a un compuesto de la fórmula I seleccionado a partir del grupo de compuestos como se mencionan más adelante en los Ejemplos por sus nombres o

fórmulas, de preferencia los isómeros mostrados como fórmulas, respectivamente, y/o un tautómero de los mismos, un N-óxido de los mismos, y/o una sal farmacéuticamente aceptable de los mismos, o su uso de acuerdo con la invención, así como a una composición farmacéutica, la cual los comprende.

Formulaciones farmacéuticas, usos y métodos

Los compuestos anteriormente mencionados, los cuales se pueden utilizar en combinación con un compuesto de la fórmula I, se pueden preparar y administrar como se describe en la técnica, tal como en los documentos citados anteriormente.

"Combinación" significa ya sea una combinación fija en una forma unitaria de dosificación, o bien un kit de partes para la administración combinada, en donde un compuesto de la fórmula I y un componente de combinación, se pueden administrar independientemente al mismo tiempo o por separado dentro de intervalos de tiempo que permitan que los componentes de combinación muestren un efecto cooperativo, por ejemplo sinérgico.

La invención también proporciona una preparación farmacéutica, la cual comprende un compuesto de la fórmula I como se define en la presente, y/o un N-óxido o un tautómero del mismo, y/o una sal farmacéuticamente aceptable de este compuesto, o un hidrato o solvato del mismo (todos referidos con frecuencia como "un compuesto de la fórmula I" meramente en la presente), y cuando menos un vehículo farmacéuticamente aceptable.

Un compuesto de la fórmula I se puede administrar solo o en

combinación con uno o más compuestos terapéuticos diferentes, tomando la posible terapia de combinación la forma de combinaciones fijas, o la administración de un compuesto de la invención y uno o más compuestos terapéuticos diferentes (incluyendo profilácticos) de una forma escalonada, o dados independientemente unos de otros, o la administración combinada de combinaciones fijas y uno o más compuestos terapéuticos diferentes. Un compuesto de la fórmula I, además o en adición, se puede administrar en especial para la terapia de tumores en combinación con quimioterapia, radioterapia, inmunoterapia, fototerapia, intervención quirúrgica, o una combinación de las mismas. Igualmente es posible la terapia a largo plazo, así como la terapia adyuvante en el contexto de otras estrategias de tratamiento, como se describe anteriormente. Otros posibles tratamientos son la terapia para mantener el estado del paciente después de la regresión del tumor, o inclusive terapia quimiopreventiva, por ejemplo en los pacientes en riesgo.

La dosificación del ingrediente activo depende de una variedad de factores, incluyendo el tipo, la especie, la edad, el peso, el sexo y la condición médica del paciente; la severidad de la condición que se vaya a tratar; la vía de administración; la función renal y hepática del paciente; y el compuesto particular empleado. Un médico, clínico, o veterinario de una experiencia ordinaria puede determinar fácilmente y prescribir la cantidad efectiva del fármaco requerida para prevenir, contrarrestar, o detener el progreso de la

condición. La precisión óptima para alcanzar la concentración del fármaco dentro del intervalo que proporcione eficacia, requiere de un régimen basado en la cinética de la disponibilidad del fármaco para los sitios objetivo. Esto involucra una consideración de la distribución, el equilibrio, y la eliminación de un fármaco.

La dosis de un compuesto de la fórmula I o una sal farmacéuticamente aceptable del mismo para administrarse a animales de sangre caliente, por ejemplo seres humanos de un peso corporal de aproximadamente 70 kilogramos, es de preferencia de aproximadamente 3 miligramos a aproximadamente 15 gramos, más preferiblemente de aproximadamente 10 miligramos a aproximadamente 3 gramos, todavía más preferiblemente de aproximadamente 50 miligramos a 1.5 gramos por persona al día, no divididos en 1 dosis, o bien divididos de preferencia en 2 a 4, por ejemplo, 2 ó 3, dosis individuales, las cuales, por ejemplo, pueden ser del mismo tamaño. Usualmente, los niños reciben la mitad de la dosis para adultos.

Los compuestos de la fórmula I se pueden administrar por cualquier vía convencional, en particular parenteralmente, por ejemplo en la forma de soluciones o suspensiones inyectables, enteralmente, por ejemplo, oralmente, por ejemplo en la forma de tabletas o cápsulas, tópicamente, por ejemplo, en la forma de lociones, geles, ungüentos o cremas, o en una forma nasal o de supositorio. La administración tópica es, por ejemplo, a la piel. Una forma adicional de administración tópica es a los ojos. Las

composiciones farmacéuticas que comprendan un compuesto de la invención en asociación con cuando menos un vehículo o diluyente farmacéuticamente aceptable se pueden fabricar de una manera convencional mezclando con un vehículo o diluyente farmacéuticamente aceptable.

La invención se refiere también a composiciones farmacéuticas que comprenden una cantidad efectiva, en especial una cantidad efectiva en el tratamiento de uno de los trastornos anteriormente mencionados, de un compuesto de la fórmula I y/o un N-óxido o un tautómero del mismo, y/o una sal farmacéuticamente aceptable del mismo, junto con uno o más vehículos farmacéuticamente aceptables que sean adecuados para administración tópica, enteral, por ejemplo oral o rectal, o parenteral, y los cuales pueden ser inorgánicos u orgánicos, sólidos o líquidos. Para la administración oral se pueden utilizar en especial tabletas o cápsulas de gelatina que comprendan al ingrediente activo junto con diluyentes, por ejemplo lactosa, dextrosa, manitol, y/o glicerol, y/o lubricantes y/o polietilenglicol. Las tabletas también pueden comprender aglutinantes, por ejemplo silicato de magnesio y aluminio, almidones, tales como almidón de maíz, de trigo, o de arroz, gelatina, metil-celulosa, carboxi-metil-celulosa de sodio, y/o polivinil-pirrolidona, y si se desea, desintegrantes, por ejemplo almidones, ágar, ácido algínico o una sal del mismo, tal como alginato de sodio, y/o mezclas efervescentes, o adsorbentes, tintes, saborizantes, y edulcorantes. También es posible utilizar los

compuestos farmacológicamente activos de la presente invención en la forma de composiciones parenteralmente administrables o en la forma de soluciones para infusión. Las composiciones farmacéuticas se pueden esterilizar y/o pueden comprender excipientes, por ejemplo conservadores, estabilizantes, compuestos humectantes y/o emulsionantes, solubilizantes, sales para regular la presión osmótica, y/o reguladores del pH. Las presentes composiciones farmacéuticas, las cuales, si se desea, pueden comprender otras sustancias farmacológicamente activas, se preparan de una manera conocida por sí misma, por ejemplo por medio de procesos convencionales de mezcla, granulación, confitería, disolución, o liofilización, y comprenden de aproximadamente el 1 por ciento al 99 por ciento, en especial de aproximadamente el 1 por ciento a aproximadamente el 20 por ciento, de ingrediente(s) activo(s).

Adicionalmente, la presente invención proporciona un compuesto de la fórmula I, y/o un N-óxido o un tautómero del mismo, y/o una sal farmacéuticamente aceptable del mismo, para utilizarse en un método para el tratamiento del cuerpo humano o animal, en especial para el tratamiento de una enfermedad mencionada en la presente, más especialmente en un paciente que requiera dicho tratamiento.

La presente invención también se refiere al uso de un compuesto de la fórmula I y/o un N-óxido o un tautómero del mismo, y/o una sal farmacéuticamente aceptable de este compuesto, para la preparación de un medicamento para el tratamiento en especial de

una enfermedad proliferativa.

Adicionalmente, la invención se refiere a un método para el tratamiento de una enfermedad proliferativa que responda a una inhibición de la interacción de p53/MDM2, el cual comprende administrar un compuesto de la fórmula I, y/o un N-óxido o un tautómero del mismo, y/o una sal farmacéuticamente aceptable del mismo, en donde los radicales y símbolos tienen los significados definidos anteriormente, a un animal de sangre caliente que requiera dicho tratamiento, en especial en una cantidad efectiva contra esta enfermedad y/o capaz de inhibir la interacción de p53/MDM2 en el animal de sangre caliente.

Adicionalmente, la invención se refiere a una composición farmacéutica para el tratamiento de tumores sólidos o líquidos en animales de sangre caliente, incluyendo seres humanos, la cual comprende una dosis antiproliferativamente efectiva de un compuesto de la fórmula I como se describe anteriormente, o una sal farmacéuticamente aceptable de este compuesto junto con un vehiculo farmacéutico.

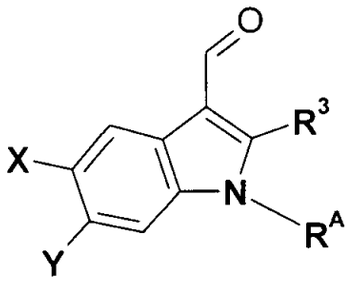
Proceso de Fabricación:

La invención se refiere también a un proceso para la fabricación de un compuesto de la fórmula I, y/o un N-óxido del mismo o un tautómero del mismo, y/o una sal del mismo.

Los compuestos de la fórmula I se pueden preparar de acuerdo con, o en analogía a, los métodos que, en principio y con otros eductos, intermediarios, y productos finales, son conocidos en

la materia, en especial y de acuerdo con la invención mediante un proceso que comprende:

a) para la fabricación de un compuesto de la fórmula I, en donde R^4 es hidrógeno y R^1, R^2, R^3, R^A, X e Y son como se definen para un compuesto de la fórmula I, hacer reaccionar un derivado de formil-indol de la fórmula II:

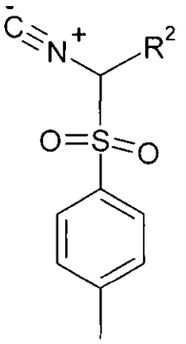


(II)

en donde R^3, R^A, X e Y son como se definen para un compuesto de la fórmula I, con un compuesto de amino de la fórmula III,

$$R^1\text{-}NH_2 \qquad \text{(III)}$$

en donde R^1 es como se define para un compuesto de la fórmula I, en la presencia de un isocianuro de tosil-metilo de la fórmula IV:

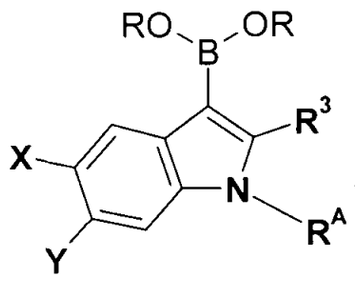


(IV)

en donde R^2 es como se define para un compuesto de la fórmula I;

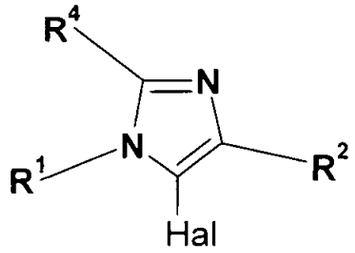
o

b) (para la síntesis de un compuesto de la fórmula I) acoplar un ácido indol-borónico de la fórmula V:



(V)

en donde R^3, R^A, X e Y son como se definen para un compuesto de la fórmula I, y cada R es arilo, alquenilo o en especial alquilo, o en donde los dos R forman un puente, en especial R es H, alquilo inferior, o R y R forman juntos 1,1,2,2-tetrametil-1,2-etileno, con un halo-imidazol de la fórmula VI:



(VI)

en donde R^1, R^2 y R^4 son como se definen para un compuesto de la fórmula I, y Hal es halógeno, en especial bromo o más especialmente yodo,

en donde, en la reacción, los grupos funcionales de los materiales de partida pueden estar presentes en una forma protegida

y en donde se puedan obtener compuestos de la fórmula I que lleven uno o más grupos protectores, se remueven estos grupos protectores;

y, si se desea, un compuesto de la fórmula I que se pueda obtener de acuerdo con la reacción dada anteriormente, se convierte en un compuesto diferente de la fórmula I, una sal que se pueda obtener de un compuesto de la fórmula I se convierte en una sal diferente del mismo, un compuesto libre de la fórmula I que se pueda obtener se convierte en una sal del mismo, y/o un isómero que se pueda obtener de un compuesto de la fórmula I se separa en uno o más isómeros diferentes que se puedan obtener de la fórmula I.

Condiciones de reacción preferidas:

En la siguiente descripción más detallada del proceso, las reacciones y conversiones opcionales, la síntesis de los materiales de partida e intermediarios y similares, R^1, R^2, R^3, R^4, R^A, X e Y tienen los significados dados para un compuesto de la fórmula I o el compuesto mencionado específicamente, mientras que otras fracciones, si están presentes, son como se definen para un compuesto de la fórmula II, III, IV, V o VI, respectivamente.

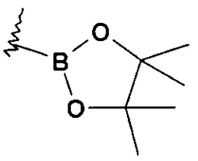
La Variante a) es una reacción de ciclación que forma el anillo de imidazol que falta en la fórmula II, y de preferencia tiene lugar a una temperatura elevada, por ejemplo, a temperaturas en el intervalo de 50°C a 130°C, por ejemplo, a aproximadamente 110°C, si se requiere en recipientes de reacción sellados, en un solvente apropiado, por ejemplo, un éter, de preferencia un éter cíclico, tal

como tetrahidrofurano. El calentamiento, por ejemplo, se puede llevar a cabo mediante un horno de microondas.

La Variante b) (la cual no solamente permite sintetizar también el compuesto de la fórmula I, en donde R^4 es hidrógeno pero también en donde tiene los significados dados para R^4 en los compuestos de la fórmula I en donde R^4 es diferente de hidrógeno).

La reacción de preferencia tiene lugar bajo condiciones de Suzuki-(Miyaura), es decir, mediante acoplamiento cruzado de organoboranos catalizado por paladio, mediante la reacción del compuesto que lleva halógeno de la fórmula II con el ácido borónico de la fórmula III, o un derivado reactivo del mismo.

Un derivado reactivo de un ácido borónico de la fórmula V es de preferencia uno en donde, en lugar de los grupos hidroxilo en el átomo de boro, está presente una fracción de arilo, alquenilo, o en especial alquilo, o en donde los grupos OH están presentes en una forma puenteada, por ejemplo, junto con el átomo de boro, formando un grupo de la fórmula (A):



(A).

La reacción de preferencia tiene lugar en una mezcla de un solvente aprótico polar, tal como dimetil-formamida (DMF) o tetrahidrofurano, y agua, en la presencia de un catalizador para el acoplamiento cruzado, en especial un catalizador de metal noble, de preferencia un catalizador de paladio, tal como un complejo de

paladio(II), por ejemplo dicloruro de bis-(trifenil-fosfina)-paladio(II), en la presencia de una base, tal como carbonato de potasio, hidróxido de sodio o carbonato de sodio, a una temperatura preferida en el intervalo de 60°C a 130°C, por ejemplo, a aproximadamente 80°C; o de acuerdo con otro método preferido, en un solvente de éter, por ejemplo, tetrahidrofurano o 1,2-dimetoxi-etano, en la presencia de un catalizador para el acoplamiento cruzado, en especial un catalizador de metal noble, de preferencia un complejo de paladio(0), por ejemplo tris-(dibenciliden-acetona)-dipaladio(0) o tetraquis-(trifenil-fosfina)-paladio(0), en la presencia de una base, tal como hidróxido de sodio, carbonato de potasio o carbonato de sodio, si se desea en la presencia de un ligando apropiado, tal como 2-diciclohexil-fosfino-2',6'-dimetoxi-bifenilo (SPhos), a una temperatura preferida en el intervalo de 60°C a 150°C, de preferencia de 70°C a 110°C; si se requiere, conducir la reacción en un recipiente sellado (por ejemplo, un reactor sellado) si se excede el punto de ebullición de la mezcla de reacción, y en especial si el calentamiento se efectúa mediante excitación de microondas. De preferencia, se excluye el oxígeno, por ejemplo, mediante la presencia de un gas inerte, tal como nitrógeno o en especial argón.

De una manera conveniente, en donde R^A en un compuesto de la fórmula V es hidrógeno, el hidrógeno es reemplazado por un grupo protector de nitrógeno, tal como terbutoxi-carbonilo, el cual, después de la reacción con el compuesto de la fórmula VI, se puede remover de acuerdo con los métodos bien conocidos, por ejemplo, como se

describe en las referencias mencionadas más adelante.

En donde sea útil o requerido, las reacciones (así como los materiales de partida o intermediarios para su formación) peden tener lugar bajo un gas inerte, tal como nitrógeno o argón.

Los grupos protectores

Si se necesita proteger a uno o más grupos funcionales diferentes, por ejemplo carboxilo, hidroxilo, amino, o mercapto, en un material de partida, por ejemplo, en cualquiera o más materiales de partida de la fórmula II o III, u otros materiales de partida, intermediarios y eductos mencionados más adelante, debido a que no deban tomar parte en la reacción o no deban alterar la reacción, éstos son los grupos que se utilizan usualmente en la síntesis de compuestos peptídicos, y también de cefalosporinas y penicilinas, así como derivados de ácidos nucleicos y azúcares. Los grupos protectores son los grupos que ya no están presentes en los compuestos finales una vez que se remueven, mientras que lo grupos que permanecen como sustituyentes no son los grupos protectores en el sentido empleado en la presente, en donde los grupos se agregan en cierta etapa intermedia y se remueven para obtener un compuesto final. Por ejemplo, si el terbutoxilo permanece en un compuesto de la fórmula I es un sustituyente, mientras que si se remueve para obtener el compuesto final de la fórmula I, es un grupo protector.

Los grupos protectores pueden ya estar presentes en los precursores y deben proteger a los grupos funcionales concernidos

contra las reacciones secundarias indeseadas, tales como acilaciones, eterificaciones, esterificaciones, oxidaciones, solvólisis, y reacciones similares. Es una característica de los grupos protectores que se prestan fácilmente, es decir, sin reacciones secundarias indeseadas, a la remoción, típicamente mediante acetólisis, protonólisis, solvólisis, reducción, fotólisis, o también mediante la actividad enzimática, por ejemplo bajo condiciones análogas a las condiciones fisiológicas, y que no están presentes en los productos finales. El especialista sabe, o puede establecer fácilmente, cuáles grupos protectores son adecuados con las reacciones mencionadas anteriormente y más adelante.

La protección de estos grupos funcionales mediante tales grupos protectores, los grupos protectores mismos, y sus reacciones de remoción se describen, por ejemplo, en los trabajos de referencia convencionales, tales como J. F. W. McOmie, "Protective Groups in Organic Chemistry", Plenum Press, Londres y Nueva York 1973, en T. W. Greene, "Protective Groups in Organic Synthesis", Tercera Edición, Wiley, Nueva York 1999, en "The Peptides"; Volumen 3 (Editores: E. Gross y J. Meienhofer), Academic Press, Londres y Nueva York 1981, en "Methoden der organischen Chemie" (*Métodos de química orgánica*), Houben Weil, 4a. Edición, Volumen 15/I, Georg Thieme Verlag, Stuttgart 1974, en H.-D. Jakubke y H. Jescheit, "Aminosäuren, Peptide, Proteine" (*Aminoácidos, péptidos, proteínas*), Verlag Chemie, Weinheim, Deerfield Beach, y Basilea 1982, y en Jochen Lehmann, "Chemie der Kohlenhydrate: Monosaccharide und

Derivate" (*Química de carbohidratos: monosacáridos y derivados*), Georg Thieme Verlag, Stuttgart 1974.

Reacciones y conversiones opcionales

Un compuesto de la fórmula I se puede convertir en un compuesto diferente de la fórmula I.

Por ejemplo, un compuesto de la fórmula I, en donde R^3 es carboxilo esterificado, en especial alcoxilo de 1 a 7 átomos de carbono-carbonilo, se puede convertir a un compuesto de la fórmula I, en donde R^3 es un carboxilo esterificado diferente, carbamoílo, heterociclil-carbonilo insustituido o sustituido (es decir, heterociclil-C)=O)-) en donde el heterociclilo está enlazado por medio de un nitrógeno (trivalente en una forma no protonada), o carbamoílo insustituido o sustituido, para la síntesis de una amida correspondiente, mediante la reacción con un compuesto de la fórmula VII:

$$R^a\text{-}NH\text{-}R^b \qquad (VII)$$

en donde cada uno de R^a y R^b, independientemente uno del otro, es alquilo de 1 a 7 átomos de carbono insustituido o sustituido, arilo insustituido o sustituido, cicloalquilo insustituido o sustituido o heterociclilo insustituido o sustituido, o R^a y R^b junto con el nitrógeno de enlace son heterociclilo que es de preferencia una fracción seleccionada a partir de heterociclilo como se define anteriormente, con un anillo de NH y que está insustituido o sustituido;

o, para la síntesis de un éster correspondiente, un alcohol de

la fórmula VIII:

$$R^c\text{-}OH \qquad (VIII)$$

en donde R^c es alquilo insustituido o sustituido, arilo insustituido o sustituido, cicloalquilo insustituido o sustituido, o heterociclilo insustituido o sustituido.

La reacción puede tener lugar ya sea hidrolizando primero el carboxilo esterificado, por ejemplo, alcoxilo de 1 a 7 átomos de carbono-carbonilo, hasta carboxilo, por ejemplo, en la presencia de un ácido o de preferencia una base, tal como un hidróxido de metal alcalino, tal como hidróxido de sodio o de potasio, en un solvente apropiado, tal como un alcohol, por ejemplo, metanol o etanol, de preferencia a una temperatura elevada, por ejemplo, en el intervalo de 50°C hasta la temperatura de reflujo de la mezcla de reacción, seguido entonces por el acoplamiento del ácido carboxílico libre de la fórmula I (el cual, por consiguiente, también que se puede obtener mediante conversión) bajo condiciones de acoplamiento apropiadas, por ejemplo, en la presencia de un agente de acoplamiento que forme un derivado reactivo del grupo carboxilo *in situ*, por ejemplo diciclohexil-carbodi-imida/1-hidroxi-benzo-triazol (DCC/HOBT); cloruro bis-(2-oxo-3-oxazolidinil)-fosfínico (BOPCl); tetrafluoro-borato de O-(1,2-dihidro-2-oxo-1-piridil)-N,N,N',N'-tetrametil-uronio (TPTU); tetrafluoro-borato de O-benzotriazol-1-il)-N,N,N',N'-tetrametil-uronio (TBTU); hexafluoro-fosfato de (benzotriazol-1-iloxi)-tripirrolidino-fosfonio (PyBOP), hexafluoro-fosfato de O-(1H-6-cloro-benzotriazol-

1-il)-1,1,3,3-tetrametil-uronio, clorhidrato de 1-(3-dimetil-amino-propil)-3-etil-carbodi-imida/hidroxi-benzotriazol, hexafluorofosfato de O-(7-azabenzotriazol-1-il)-N,N,N',N'-tetrametiluronio (HATU) o /1-hidroxi-7-azabenzo-triazol (EDC/HOBT o EDC/HOAt) o HOAt solo, o con (1-cloro-2-metil-propenil)-dimetil-amina. Para una revisión de algunos otros posibles agentes de acoplamiento, véase por ejemplo, Klauser; Bodansky, *Synthesis* (1972), 453-463. La mezcla de reacción, la cual convenientemente puede comprender un solvente apropiado, por ejemplo, dimetil-formamida o dioxano, y/o N-metil-morfolina, se mantiene de preferencia, por ejemplo, agitándose, a una temperatura de entre aproximadamente -20°C y 80°C, en especial entre 0°C y 60°C, por ejemplo, a temperatura ambiente o a aproximadamente 50°C.

De una manera alternativa, también es posible reemplazar directamente el grupo esterificante original, por ejemplo, alcoxilo de 1 a 7 átomos de carbono, mediante la reacción con un compuesto de la fórmula VII o VIII, por ejemplo, a una temperatura elevada, por ejemplo en el intervalo de 30°C hasta la temperatura de reflujo, por ejemplo, a aproximadamente 60°C, en la presencia de un solvente apropiado, tal como un alcanol inferior, por ejemplo, metanol o etanol.

En un compuesto de la fórmula I con carbamoílo R^3, esta fracción se puede convertir en ciano, por ejemplo, mediante la reacción del compuesto correspondiente de la fórmula I, en la presencia de anhídrido trifluoroacético en un solvente apropiado, por

ejemplo, dicloro-metano, por ejemplo, a una temperatura elevada en el intervalo de 30°C hasta la temperatura de reflujo de la mezcla de reacción.

En un compuesto de la fórmula I con ciano R^3 (que se puede obtener por ejemplo, de acuerdo con el párrafo anterior), el ciano se puede convertir en tetrazolilo R^3 por ejemplo, mediante la reacción con azida de sodio en un solvente apropiado, tal como 2-metoxi-etanol, de preferencia a una temperatura elevada, por ejemplo, a aproximadamente 130°C.

En un compuesto de la fórmula I, en donde R^3 es carbamoílo o heterociclil-carbonilo, en donde el heterociclilo está enlazado por medio de un átomo de nitrógeno (trivalente en una forma no protonada), el –C(=O) enlazante se puede reducir hasta un puente de metileno (-CH_2-), por ejemplo mediante la reacción con un agente reductor apropiado, tal como a hidruro, por ejemplo, hidruro de litio y aluminio, por ejemplo, en la presencia de un ácido de Lewis, tal como tricloruro de aluminio, en un solvente apropiado, por ejemplo, un éter, tal como tetrahidrofurano, de preferencia a temperatura elevada, por ejemplo, en el intervalo de 50°C hasta la temperatura de reflujo de la mezcla de reacción, por consiguiente, proporcionando alquilo insustituido o sustituido R^3.

En un compuesto de la fórmula I, en donde R^3 es carboxilo, este carboxilo también se puede reducir hasta el grupo hidroxi-metilo R^3 correspondiente, por ejemplo, mediante la reacción con hidruro de litio y aluminio, en un solvente apropiado, tal como tetrahidrofurano,

a temperaturas en el intervalo de 20 ° C hasta la temperatura de reflujo de la mezcla de reacción.

Un sustituyente de alcoxilo de 1 a 7 átomos de carbono de arilo, por ejemplo, como sustituyente de arilo R^2, se puede convertir en un sustituyente de hidroxilo correspondiente, por ejemplo, mediante la reacción con BBR_3 en un solvente apropiado, por ejemplo, dicloro-metano, por ejemplo a temperaturas de 0°C a 50°C.

Un átomo de nitrógeno del anillo dentro de un compuesto de la fórmula I, por ejemplo, en el núcleo de imidazolinil-indol, o un sustituyente heterocíclico que contiene nitrógeno (por ejemplo, hetero-arilo), se puede convertir en un N-óxido en la presencia de un agente oxidante adecuado, por ejemplo, un peróxido, tal como ácido m-cloro-perbenzoico o peróxido de hidrógeno, si es útil, en un solvente apropiado.

Se pueden deducir otros ejemplos de conversión a partir de los Ejemplos, por ejemplo, en donde una reacción a partir de un material de partida que sea al mismo tiempo también un compuesto de la fórmula I, involucra la remoción de un grupo que corresponde a un grupo protector, por ejemplo, la disociación de un éster, por ejemplo, para convertir el alcoxilo de 1 a 7 átomos de carbono-carbonilo en carboxilo, la remoción de un terbutoxi-carbonilo o metan-sulfonilo o terbutil-dimetil-sililo, o la disociación de isoindol-1,3-dion-2-ilo, enmascarando un grupo amino o hidroxilo para dar el grupo hidroxilo o amino libre, o la disociación de piperazinilo o N-alquil-piperazin-1-ilo hasta 2-(N-alquil-amino)-etilo).

También, en los pasos opcionales del proceso llevado a cabo, "si se desea", los grupos funcionales de los compuestos de partida que no deban tomar parte en la reacción, pueden estar presentes en una forma desprotegida, o se pueden proteger, por ejemplo, mediante uno o más de los grupos protectores mencionados anteriormente en la presente bajo "Los grupos protectores". Los grupos protectores se remueven entonces total o parcialmente de acuerdo con uno de los métodos descritos en ese párrafo.

Se pueden preparar sales de un compuesto de la fórmula I con un grupo formador de sales, de una manera conocida por sí misma. De esta manera, se pueden obtener sales de adición de ácido de los compuestos de la fórmula I mediante el tratamiento con un ácido o con un reactivo de intercambio de aniones adecuado, sales con bases mediante la reacción con reactivos de intercambio de cationes adecuados, o con las bases correspondientes, por ejemplo, hidróxidos de metales o similares.

Las sales normalmente se pueden convertir hasta los compuestos libres, por ejemplo, las sales de adición de ácido mediante el tratamiento con compuestos básicos adecuados, por ejemplo con carbonatos de metales alcalinos, carbonatos ácidos de metales alcalinos, o hidróxidos de metales alcalinos, típicamente carbonato de potasio o hidróxido de sodio, sales con bases mediante la reacción con los ácidos apropiados, tales como ácidos inorgánicos, por ejemplo, ácido clorhídrico o ácido sulfúrico, o ácidos orgánicos suficientemente fuertes, por ejemplo, ácidos sulfónicos.

Las mezclas estereoisoméricas, por ejemplo las mezclas de diaestereómeros, se pueden separar en sus isómeros correspondientes de una manera conocida por sí misma, por medio de métodos de separación adecuados. Por ejemplo, las mezclas diaestereoméricas se pueden separar en sus diaestereómeros individuales por medio de cristalización fraccionaria, cromatografía, distribución de solvente, y procedimientos similares. Esta separación puede tener lugar ya sea al nivel de un compuesto de partida, o bien en un compuesto de la fórmula I mismo. Los enantiómeros se pueden separar a través de la formación de sales diaestereoméricas, por ejemplo mediante la formación de sal con un ácido quiral puro en enantiómeros, o por medio de cromatografía, por ejemplo mediante HPLC, utilizando sustratos cromatográficos con ligandos quirales, o mediante cualquier otro método conocidc en este campo, por ejemplo, utilizando cristalización de emulsión.

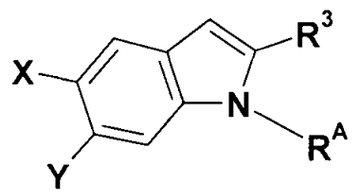
Se debe enfatizar que también pueden tener lugar reacciones análogas a las conversiones mencionadas en este capítulo al nivel de los Intermediarios apropiados (y por lo tanto, son útiles en la preparación de los materiales de partida correspondientes).

Materiales de partida:

Los materiales de partida de las fórmulas II, III, IV, V, VI, VII y VIII, así como otros materiales de partida, intermediarios o eductos mencionados en la presente, por ejemplo, más adelante, se pueden preparar de acuerdo con, o en analogía a, los métodos que son conocidos en la materia, los materiales se conocen en la técnica, y/o

están comercialmente disponibles, o mediante o en analogía al los métodos mencionados en los Ejemplos. Los materiales de partida novedosos, así como los procesos para su preparación, de la misma manera son una modalidad de la presente invención. En las modalidades preferidas, se utilizan los materiales de partida y se selecciona la reacción, de tal manera que se haga posible la obtención de los compuestos preferidos.

Por ejemplo, un derivado de formil-indol de la fórmula II se puede obtener de preferencia mediante la formilación de un derivado de indol de la fórmula IX:



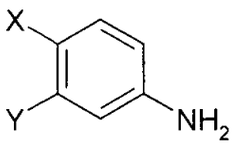
(IX)

en donde R^3, R^A, X e Y son como se definen para un compuesto de la fórmula I, mediante su reacción con una dialquil-formamida, tal como dimetil-formamida, o con N-metil-N-fenil-formamida o bajo condiciones de Vilsmeier, por ejemplo, en la presencia de oxicloruro de fósforo, en la presencia o de preferencia en ausencia de un solvente adicional, y a temperaturas, por ejemplo, en el intervalo de aproximadamente 0°C a aproximadamente 80°C, o de una manera alternativa con cianuro de hidrógeno (HCN), bajo condiciones de Gattermann, en la presencia de un catalizador de Lewis, tal como tricloruro de aluminio, y de cloruro de hidrógeno (HCl), o con cianuro de zinc, en la presencia de cloruro de hidrógeno

(HCl), o bajo condiciones de Gattermann-Koch con monóxido de carbono, cloruro de hidrógeno, y un ácido de Lewis, mediante la formilación de Rieche o similares.

Los compuestos de la fórmula IX son conocidos en la materia, se pueden preparar de acuerdo con los métodos conocidos en este campo, están comercialmente disponibles y/o se pueden preparar de acuerdo con, o en analogía a, los métodos descritos en los Ejemplos.

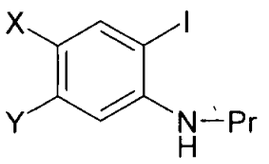
Un compuesto de la fórmula IX, en donde R^3 es carboxilo esterificado, por ejemplo, se puede obtener a partir de un compuesto de anilina de la fórmula X:



(X)

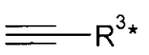
en donde X e Y son como se definen para un compuesto de la fórmula I mediante yodación, por ejemplo, con N-yodo-succinimida en la presencia de un ácido, tal como ácido acético, por ejemplo, a temperaturas en el intervalo de 0°C a 50°C, luego la introducción de un grupo protector para la función de amino, por ejemplo, mediante la reacción con cloruro de mesitilo, en la presencia de una base, tal como piridina, en un solvente apropiado, tal como dicloro-metano, por ejemplo, a temperaturas en el intervalo de 0°C a 50°C, seguida por la remoción de uno de los dos grupos metan-sulfonilo, por consiguiente, introducidos en la función de amino con carbonato de potasio en un solvente apropiado, tal como metanol/tetrahidrofurano, por ejemplo, a temperaturas en el intervalo de 0°C a 50°C, para dar

un derivado de yodo-anilina protegido de la fórmula XI:



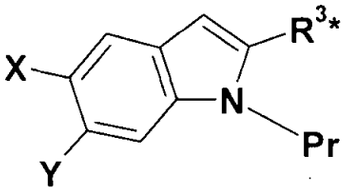
(XI)

en donde Pr es un grupo protector, en especial metan-sulfonilo, cuyo compuesto se hace reaccionar entonces con un compuesto de propiolato de la fórmula XII:



(XII)

en donde R^{3*} es carboxilo esterificado, en especial metoxi-carbonilo, bajo ciclación en la presencia de una base, tal como N-etil-di-isopropilamina, y un catalizador, por ejemplo, tetraquis-trifenil-fosfina-paladio, en un solvente apropiado, tal como dioxano, a una temperatura elevada, por ejemplo, a la temperatura de reflujo del solvente, hasta un compuesto correspondiente de la fórmula XIII:



(XIII)

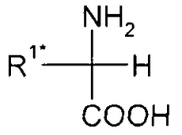
en donde X e Y son como se definen para un compuesto de la fórmula I, y R^{3*} es carboxilo esterificado, por ejemplo, metoxi-carbonilo, el cual entonces se puede desproteger bajo la remoción del grupo protector Pr, por ejemplo, con fluoruro de tetrabutil-amonio, en un solvente apropiado, tal como tetrahidrofurano, a

temperaturas, por ejemplo, en el intervalo de 0°C a 50°C, hasta el compuesto correspondiente de la fórmula IX.

Los compuestos de la fórmula X y de la fórmula XII son conocidos en la materia, se pueden preparar de acuerdo con los métodos conocidos en este campo, están comercialmente disponibles y/o se pueden preparar de acuerdo con, o en analogía a, los métodos descritos en los Ejemplos.

Los compuestos de amino de la fórmula III son conocidos en la materia, se pueden preparar de acuerdo con los métodos que son conocidos en la materia, están comercialmente disponibles y/o se pueden preparar de acuerdo con, o en analogía a, los métodos descritos en los Ejemplos.

Por ejemplo, un compuesto de la fórmula III en donde R^1 es 1-(arilo insustituido o sustituido)-1-hidroxi-metil-metilo se puede obtener a partir del derivado de glicina correspondiente de la fórmula XIV:



(XIV)

en donde R^{1*} es arilo insustituido o sustituido, el cual puede estar presente en la forma (R,S) o de preferencia (R) o (S), mediante la reducción con un reductor apropiado, por ejemplo, hidruro de litio y aluminio, en un solvente apropiado, por ejemplo, tetrahidrofurano, de preferencia a temperaturas elevadas, por ejemplo, a la temperatura de reflujo de la mezcla de reacción, hasta el compuesto

correspondiente en donde está presente un hidroxi-metilo en lugar del carboxilo en la fórmula XIV.

Los compuestos de la fórmula XIV son conocidos en la materia, se pueden preparar de acuerdo con los métodos que son conocidos en la materia, están comercialmente disponibles y/o se pueden preparar mediante, o en analogía a, los métodos descritos en los Ejemplos. Por ejemplo, se pueden preparar a partir de ácidos aril-borónicos como se describe en Tetrahedron, Volumen 53, Número 48, 1997, páginas 16463-16470(8).

Los compuestos de la fórmula III en donde R^1 es metilo sustituido, por ejemplo, se pueden preparar a partir de un cianuro de la fórmula XV:

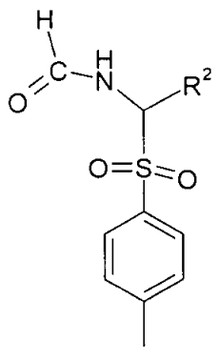
$$R^{1**}\text{-}CN \qquad (XV)$$

en donde R^{1**} es un sustituyente como se menciona para alquilo sustituido, en especial alquilo de 1 a 7 átomos de carbono, heterociclilo insustituido o sustituido como se describe anteriormente, o arilo insustituido o sustituido como se define anteriormente, mediante reducción en la presencia de un agente de hidrogenación apropiado, tal como hidruro de litio y aluminio, en un solvente apropiado, por ejemplo, tetrahidrofurano, por ejemplo, a temperaturas en el intervalo de -10°C a +50°C, por ejemplo, de aproximadamente 0°C a aproximadamente la temperatura ambiente, hasta el compuesto correspondiente de la fórmula III.

Los cianuros de la fórmula XV son conocidos en la materia, se pueden preparar de acuerdo con los métodos que son conocidos en la materia, están comercialmente disponibles y/o se pueden preparar mediante, o en analogía a, los métodos descritos en los Ejemplos.

Los isocianuros de tosil-metilo de la fórmula IV son conocidos en la materia, se pueden preparar de acuerdo con los métodos conocidos en este campo, están comercialmente disponibles y/o se pueden preparar mediante, o en analogía a, los métodos descritos en los Ejemplos.

Por ejemplo, se pueden obtener a partir de una tosamida de la fórmula XVI:



(XVI)

en donde R^2 es como se define para un compuesto de la fórmula I, mediante la reacción con un haluro de ácido inorgánico, en especial cloruro de tionilo u oxicloruro de fósforo, en un solvente apropiado, por ejemplo, dimetil-éter, dimetil-formamida o de preferencia tetrahidrofurano, de preferencia en la presencia de una amina terciaria, tal como trietil-amina, a temperaturas, por ejemplo, en el intervalo de -20°C a 30°C, por ejemplo, a aproximadamente 0°C.

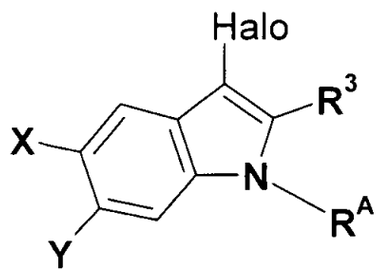
Las tosamidas de la fórmula XVI se pueden obtener, por ejemplo, a partir de aldehídos de la fórmula XVII:

R^2-CHO (XVII)

en donde R^2 es como se define para un compuesto de la fórmula I, mediante su reacción (en un paso o en dos pasos) con formamida y con ácido p-toluen-sulfónico o de preferencia ácido p-toluen-sulfínico, en un solvente apropiado, por ejemplo, tolueno/acetonitrilo (con o sin dimetil-formamida) en la presencia de un haluro de sililo, tal como haluro de trimetil-sililo, de preferencia a una temperatura elevada, por ejemplo, en el intervalo de 30°C a 75°C. Por ejemplo, se pueden preparar como se describe en *Chem. Lett.* **1988**, *9*, 1531-1534.

Los compuestos de aldehído de la fórmula XVII son conocidos en la materia, se pueden preparar de acuerdo con los métodos que son conocidos en la materia, están comercialmente disponibles y/o se pueden preparar mediante, o en analogía a, los métodos descritos en los Ejemplos.

Los ácidos indol-borónicos de la fórmula V se puede obtener a partir de un compuesto de la fórmula XVIII:



(XVIII)

en donde X, Y, R^3 y R^A son como se definen para un

compuesto de la fórmula I, y halógeno es en especial bromo o yodo, o es trifluoro-metan-sulfonilo, mediante su reacción con un compuesto de Grignard o de preferencia con un compuesto de litio (por ejemplo, con alquil-litio, por ejemplo, butil-litio) (Li en lugar de halógeno en la fórmula XVIII), el cual entonces se hace reaccionar con un trialcoxi-borano o un bis-(dialcoxi-borano), hasta el compuesto correspondiente de la fórmula V, por ejemplo, de acuerdo con la reacción de borilación de Miyaura, de acuerdo con el método descrito en *Org. Lett.*, 2006, 8, 305-307, de acuerdo con el método descrito en *Org. Lett.*, 2006, 8, 261-263, o similares.

Los halo-imidazoles de la fórmula VI son conocidos en la materia, se pueden preparar de acuerdo con los métodos que son conocidos en la materia, están comercialmente disponibles y/o se pueden obtener mediante o en analogía al un método descrito en los Ejemplos. Esto también es cierto para los compuestos de la fórmula VII y para los alcoholes de la fórmula VIII.

Otros materiales de partida son conocidos en la materia, se pueden preparar de acuerdo con los métodos que son conocidos en la materia, están comercialmente disponibles y/o se pueden preparar de acuerdo con, o en analogía a, los métodos descritos en los Ejemplos.

Ejemplos:

Los siguientes ejemplos sirven para ilustrar la invención sin limitar su alcance. Observe que en algunos casos, los compuestos mencionados como intermediarios son también compuestos de la

fórmula I de acuerdo con la invención (entonces se menciona que los compuestos caen bajo la fórmula I).

Abreviaturas

Ac	acetilo
AcOH	ácido acético
$AlCl_3$	tricloruro de aluminio
aq.	acuoso
Boc	terbutoxi-carbonilo
Salmuera	solución saturada de cloruro de sodio (a temperatura ambiente)
^tBu	butilo terciario
CDI	carbonil-di-imidazol
Celite	Marca comercial registrada de Celite Corp. (World Minerals Inc.), Santa Bárbara, CA, EUA, para auxiliar de filtración basado en sílice.
CH_3CN	acetonitrilo
conc.	concentrado
DCM	dicloro-metano
DMAP	4-dimetil-amino-piridina
DMF	N,N-dimetil-formamida
DMSO	sulfóxido de dimetilo
ES-MS	espectrometría de masas por electropulverización
Et	etilo
Et_3N	trietil-amina

Et_2O	dietil-éter
EtOAc	acetato de etilo
EtOH	etanol
h	hora(s)
HATU	hexafluorofosfato de O-(7-azabenzotriazol-1-il)-N,N,N',N'-tetrametil-uronio
HBr	bromuro de hidrógeno
HCl	cloruro de hidrógeno
HOAt	1-hidroxi-7-azabenzo-triazol
HPLC	cromatografía de líquidos a alta presión
HyFlo	auxiliar de filtración basado en tierra diatomácea, marca comercial registrada de Johns Manville Corp., Denver, CO, EUA
HV	alto vacío
IPr	isopropilo
K_2CO_3	carbonato de potasio
KHMDS	hexametil-disilazida de potasio
KO^tBu	terbutoxilato de potasio
KOH	hidróxido de potasio
K_3PO_4	fosfato de potasio
LAH	hidruro de litio y aluminio
LDA	di-isopropil-amida de litio
Me	metilo
MeI	yoduro de metilo
MeOH	metanol

$MgSO_4$	sulfato de magnesio
min	minuto(s)
mL	mililitro(s)
MS	Espectrometría de masas
MsCl	cloruro de metan-sulfonilo
NaH	hidruro de sodio
$NaHCO_3$	bicarbonato de sodio
Na_2CO_3	carbonato de sodio
NaOH	hidróxido de sodio
NaOMe	metoxilato de sodio
NaOEt	etoxilato de sodio
NaO^tBu	terbutoxilato de sodio
Na_2SO_4	sulfato de sodio
NBS	N-bromo-succinimida
NCS	N-cloro-succinimida
NH_4Cl	cloruro de amonio
NIS	N-yodo-succinimida
NMM	4-metil-morfolina
NMR	resonancia magnética nuclear
Ph	fenilo
PG	grupo protector
$POCl_3$	oxicloruro de fósforo (III)
rt (o RT)	temperatura ambiente
TBAF	fluoruro de tetrabutil-amonio
TBAHS	hidrosulfato de tetrabutil-amonio

TBTU	tetrafluoro-borato de O-(benzotriazol-1-il)-N,N,N',N'-tetrametil-amonio
TFA	ácido trifluoro-acético
TFAA	anhídrido trifluoroacético
THF	tetrahidrofurano
TMS	trimetil-sililo
TMSCl	cloruro de trimetil-sililo
t_{Ret}	tiempo de retención
TsCl	cloruro de p-toluen-sulfonilo
TsOH	ácido p-toluen-sulfónico
UV	ultravioleta

En donde no se indique la fuente específica, los materiales de partida son los que se pueden obtener con los proveedores acostumbrados, tales como Sigma-Aldrich, St. Louis, EUA, con Fluka, Suiza, Buchs, con Merck, Darmstadt, FRG, o con los proveedores indicados de una manera específica.

Síntesis

La cromatografía por evaporación instantánea se lleva a cabo utilizando gel de sílice (Merck; 40 - 63 micras). Para la cromatografía de capa delgada, se utilizan placas de gel de sílice previamente recubiertas (Merck 60 F254; Merck KgaA, Darmstadt, Alemania). Las mediciones de ^{1}RMN se llevan a cabo en un espectrómetro Varian Gemini 400 utilizando tetrametil-silano como estándar interno. Los cambios químicos (δ) se expresan en partes por millón campo abajo

a partir de tetrametil-silano. Los espectros de masas por electropulverización se obtienen con una Plataforma Fisons Instruments VG II. Para las síntesis, se utilizan los solventes y productos químicos comercialmente disponibles.

Condición de HPLC A:

Columna:	Nucleosil 100-3 C18, 70 x 4.0 milímetros.
Velocidad de flujo:	1.0 mililitro/minuto.
Fase móvil:	A) ácido trifluoro-acético/agua (0.1/100, volumen/volumen), B) ácido trifluoro-acético/CH_3CN (0.1/100, volumen/ volumen).
Gradiente:	Gradiente lineal desde el 20 por ciento de B hasta el 100 por ciento de B en 7 minutos.
Detección:	UV a 215 nanómetros.

Condición de HPLC B:

Columna:	Speed ROD RP18e, 50 x 4.6 milímetros.
Velocidad de flujo:	1.3 mililitros/minuto.
Fase móvil:	A) ácido trifluoro-acético/agua (0.1/100, volumen/volumen), B) ácido trifluoro-acético/ CH_3CN (0.1/100, volumen/ volumen).
Gradiente:	Gradiente lineal desde el 2 por ciento de

B hasta el 100 por ciento de B en 1 minuto, luego el 100 por ciento de B en 2 minutos.

Detección: UV a 215 nanómetros.

Condición de HPLC C:

Columna: Nucleosil 100-3 C 18 HD, 125 x 4.0 milímetros.

Velocidad de flujo: 1.0 mililitro/minuto.

Fase móvil: A) ácido trifluoro-acético/agua (0.1/100, volumen/volumen), B) ácido trifluoro-acético/ CH_3CN (0.1/100, volumen/ volumen).

Gradiente: Gradiente lineal desde el 2 por ciento de B hasta el 100 por ciento de B en 7 minutos, luego el 100 por ciento de B en 2 minutos.

Detección: UV a 215 nanómetros.

Condición de HPLC D:

Columna: Nucleosil 100-3 C 18 HD, 125 x 4.0 milímetros.

Velocidad de flujo: 2.0 mililitros/minuto.

Fase móvil: A) ácido trifluoro-acético/agua (0.1/100, volumen/volumen), B) ácido trifluoro-acético/ CH_3CN (0.1/100, volumen/ volumen).

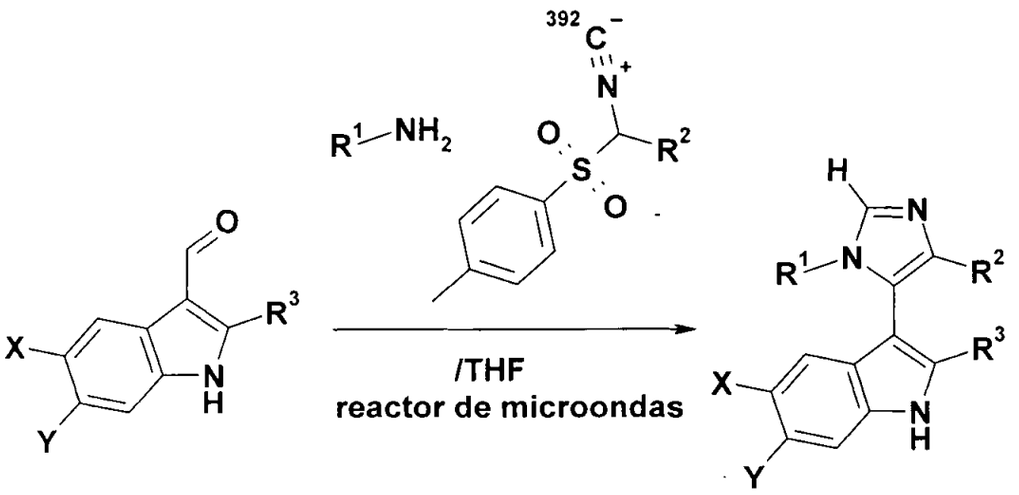
Gradiente:	Gradiente desde el 1 por ciento hasta el 20 por ciento de B en 1 minuto, desde el 20 por ciento hasta el 100 por ciento de B en 2 minutos, luego el 100 por ciento de B en 1 minuto.
Detección:	UV a 215 nanómetros.

Condición de HPLC E:

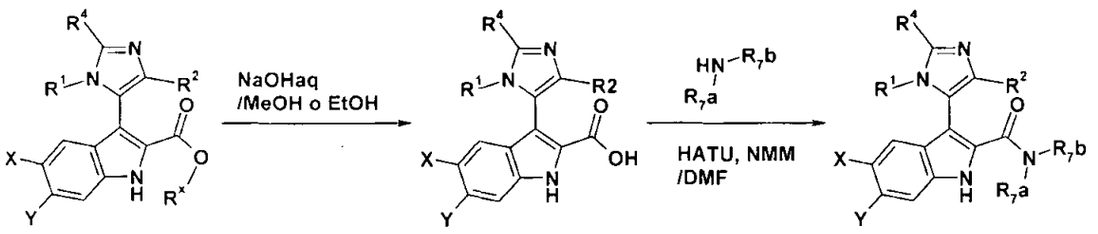
Columna:	Speed ROD RP18e, 50 x 4.6 milímetros.
Velocidad de flujo:	1.3 mililitros/minuto.
Fase móvil:	A) ácido trifluoro-acético/agua (0.1/100, volumen/volumen), B) ácido trifluoro-acético/acetonitrilo (0.1/100, volumen/volumen).
Gradiente:	Gradiente lineal desde el 0 por ciento de B hasta el 100 por ciento de B en 6 minutos luego 2 minutos con el 100 por ciento de B.
Detección:	UV a 215 nanómetros.

Las condiciones de HPLC A, B, C, D y E se pueden identificar por los prefijos suscritos de los valores T_{Ret} dados en los Ejemplos. Por ejemplo, B en ${}_{B}t_{Ret}$ = ... minutos, significa la condición-B en el caso de HPLC.

Esquema General 1

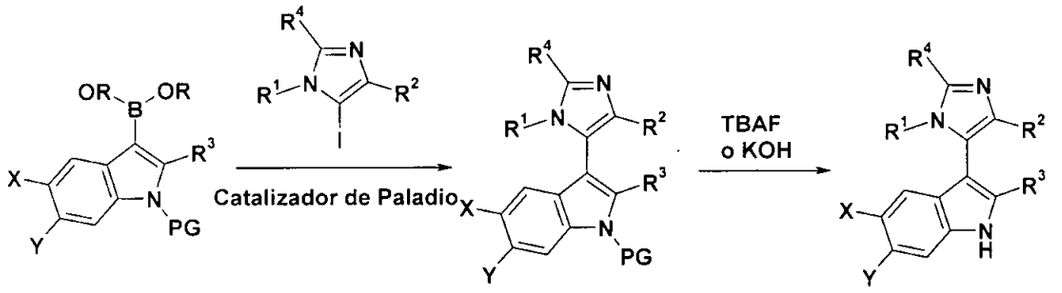


Esquema General 2



Rx = alquilo, por ejemplo, metilo, etilo; R^{7a}, R^{7b} = H, alquilo de 1 a 7 átomos de carbono, fenilo, fenil-metilo o similar, en especial como se muestra en los Ejemplos.

General Esquema-3



R = H, alquilo inferior o R + R forman 1,1,2,2-tetrametil-1,2-etileno.

Ejemplo 1: 6-cloro-3-[3-(4-cloro-bencil)-5-fenil-3H-imidazol-4-il]-1H-indol

Una mezcla del Intermediario **1.1** (100 miligramos, 0.55 milimoles), 4-cloro-bencil-amina (0.1 mililitros, 0.83 milimoles) y 1-(isociano-fenil-metan-sulfonil)-4-metil-benceno (comercialmente disponible en SynChem, Inc., Des Plaines, IL, EUA) (227 miligramos, 0.83 milimoles) en tetrahidrofurano (2 mililitros) se sella y se calienta mediante el reactor de microondas a 110°C durante 1 hora. Después de completarse, la mezcla de reacción se apaga mediante $NaHCO_3$ acuoso, se agrega EtOAc, y la capa orgánica se lava con salmuera, se seca sobre $MgSO_4$ y se evapora al vacío. La cromatografía por evaporación instantánea en gel de sílice del residuo proporciona el compuesto del título como un polvo incoloro; ES-MS: M+ = 418.0; HPLC: $_{A}t_{Ret}$ = 4.53 minutos.

Intermediario 1.1: 6-cloro-1H-indol-3-carbaldehído

Una mezcla de 6-cloro-1H-indol (2.0 gramos, 13.2 milimoles) y $POCl_3$ (1.34 mililitros, 14.5 milimoles) en dimetil-formamida (5 mililitros) se calienta a 45°C durante 1 hora. Después de completarse, la mezcla de reacción se apaga con $NaHCO_3$ acuoso, se agrega Et_2O, y la capa orgánica se lava con salmuera, se seca sobre $MgSO_4$ y se evapora al vacío. La cromatografía por evaporación instantánea en gel de sílice del residuo proporciona el compuesto del título como un polvo incoloro; ES-MS: M+ = 179.9; HPLC: ${}_At_{Ret}$ = 3.74 minutos.

Ejemplo 2: (2-morfolin-4-il-etil)-amida del ácido 6-cloro-3-[3-(4-cloro-bencil)-5-fenil-3H-imidazol-4-il]-1H-indol-2-carboxílico

Una mezcla del Intermediario **2.1** (200 miligramos, 0.43 milimoles), N-(4-amino-etil)-morfolina (68 miligramos, 0.52 milimoles), NMM (109 miligramos, 1.08 milimoles) y HATU (245 miligramos, 0.65 milimoles) en dimetil-formamida (2.2 mililitros), se calienta durante 1 hora a 50°C. Se agrega EtOAc, y la capa orgánica se lava con salmuera, se seca sobre $MgSO_4$ y se evapora al vacío. La cromatografía por evaporación instantánea en gel de sílice del residuo proporciona el compuesto del título como un cristal incoloro; ES-MS: M+H = 576.2; HPLC: ${}_At_{Ret}$ = 3.80 minutos.

Intermediario 2.1: Ácido 6-cloro-3-[3-(4-cloro-bencil)-5-fenil-3H-imidazol-4-il]-1H-indol-2-carboxílico (el cual también es un compuesto de la fórmula I)

Una mezcla del Intermediario **2.2** (900 miligramos, 1.84

milimoles) y NaOH acuoso 2M (35 mililitros) en EtOH (35 mililitros) se pone a reflujo durante 2.5 horas. La mezcla resultante se vierte en una mezcla de hielo y agua, y después de neutralizarse con HCl acuoso 4 M, se agrega EtOAc, y la capa orgánica se lava con salmuera, y se seca sobre $MgSO_4$. La concentración al vacío proporciona el compuesto del título como un cristal incoloro; ES-MS: M+ = 461.9; HPLC: $_At_{Ret}$ = 4.22 minutos.

Intermediario 2.2: Etil-éster del ácido 6-cloro-3-[3-(4-cloro-bencil)-5-fenil-3H-imidazol-4-il]-1H-indol-2-carboxílico (también un compuesto activo de la fórmula I)

Método A: Una mezcla del Intermediario **2.3** (1.0 gramos, 3.97 milimoles), 4-cloro-bencil-amina (731 miligramos, 5.17 milimoles) y 1-(isociano-fenil-metan-sulfonil)-4-metil-benceno (1.62 gramos, 5.96 milimoles) en tetrahidrofurano (15 mililitros) se sella y se calienta por medio de un reactor de microondas a 110°C durante 1 hora. Después de completarse, la mezcla de reacción se apaga mediante $NaHCO_3$ acuoso, se agrega EtOAc, y la capa orgánica se lava con salmuera, se seca sobre $MgSO_4$ y se evapora al vacío. La cromatografía por evaporación instantánea en gel de sílice del residuo proporciona el compuesto del título como un polvo incoloro; ES-MS: M+ = 490.1; HPLC: $_At_{Ret}$ = 4.62 minutos.

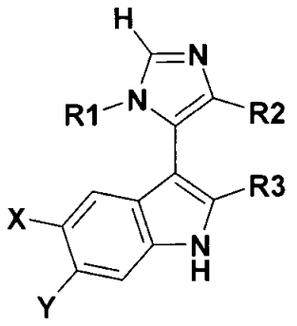
Método B: Una mezcla del Intermediario **2.3** (6.09 gramos, 24.2 milimoles), 4-cloro-bencil-amina (3.55 mililitros, 29.0 milimoles), Et_3N (10.1 mililitros, 72.6 milimoles) y 1-(isociano-fenil-metan-sulfonil)-4-metil-benceno (7.87 gramos, 29.0 milimoles) en EtOH (120

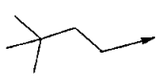
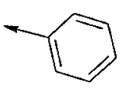
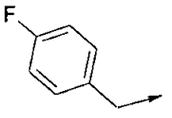
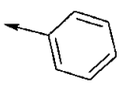
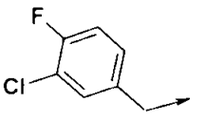
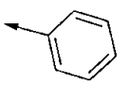
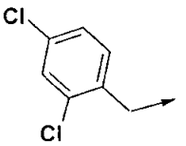
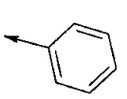
mililitros) se calienta a 60°C durante 3 horas. Después de completarse, la mezcla de reacción se concentra al vacío y se apaga mediante $NaHCO_3$ acuoso, se agrega EtOAc, y la capa orgánica se lava con salmuera, se seca sobre $MgSO_4$ y se evapora al vacío. La cromatografía por evaporación instantánea en gel de sílice del residuo proporciona el compuesto del título como un polvo incoloro.

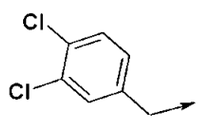
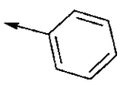
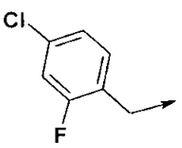
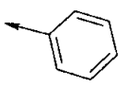
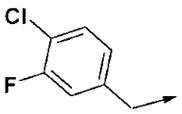
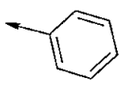
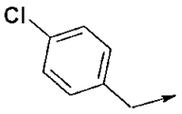
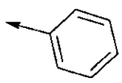
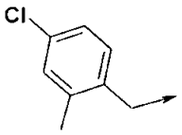
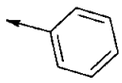
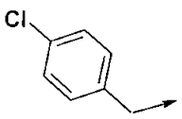
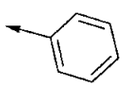
Intermediario 2.3: Etil-éster del ácido 6-cloro-3-formil-1H-indol-2-carboxílico

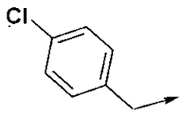
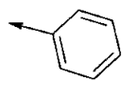
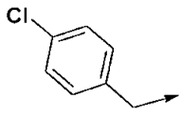
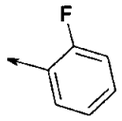
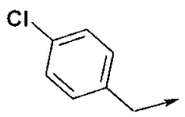
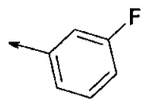
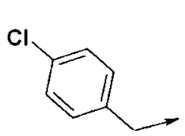
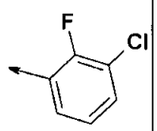
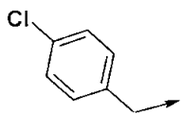
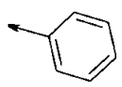
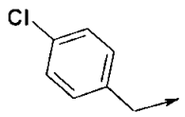
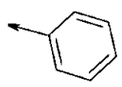
El compuesto del título se prepara de acuerdo con un procedimiento publicado en la literatura (véase J. Med. Chem. 2005, 48, 995-1018). Una solución del etil-éster del ácido 6-cloro-1H-indol-2-carboxílico (5.0 gramos, 22.4 milimoles) (comercialmente disponible en 3D Medical Systems Inc.) y $POCl_3$ (2.46 mililitros, 26.8 milimoles) en dimetil-formamida (15 mililitros) se calienta a 50°C durante 28 horas. Después de completarse, la mezcla de reacción se apaga mediante $NaHCO_3$ acuoso, se agrega Et_2O, y la capa orgánica se lava con salmuera, se seca sobre $MgSO_4$ y se evapora al vacío. La cromatografía por evaporación instantánea en gel de sílice del residuo proporciona el compuesto del título como un polvo incoloro; ES-MS: M- = 250.1; HPLC: $_At_{Ret}$ = 4.67 minutos.

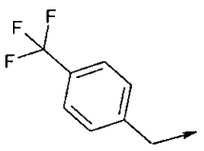
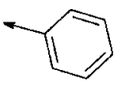
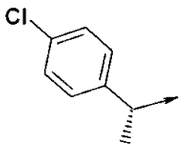
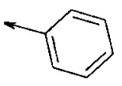
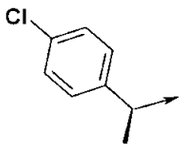
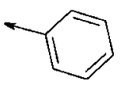
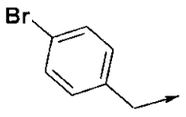
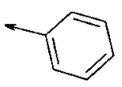
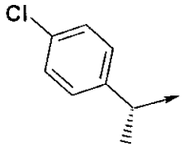
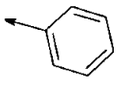
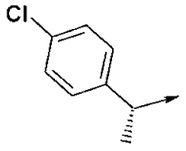
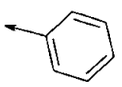
Tabla 1 de Ejemplos Adicionales:

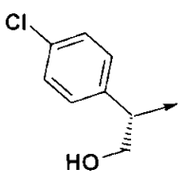
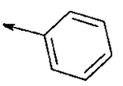
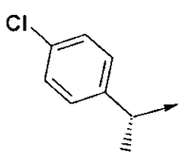
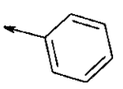
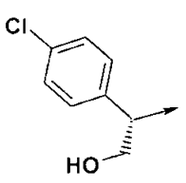
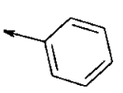
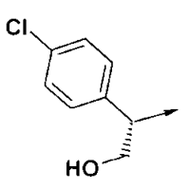
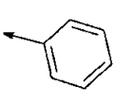
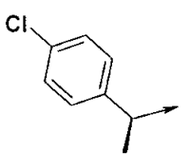
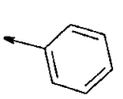


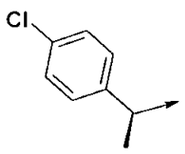
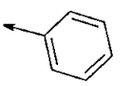
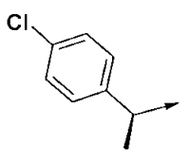
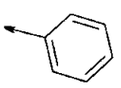
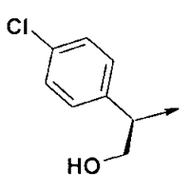
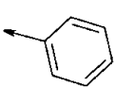
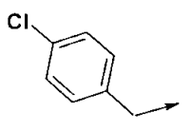
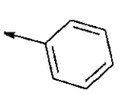
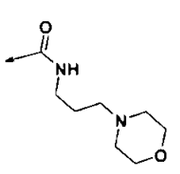
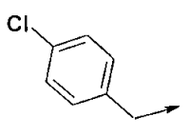
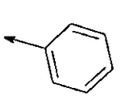
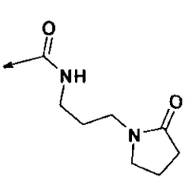
Ejem-plo	X e Y	R^1	R^2	R^3	Análisis MS/HPLC/RMN
3	X=H Y=Cl			H	M+ = 378.0 $_At_{Ret}$ = 4.61 min
4	X=H Y=Cl			H	M+ = 402.0 $_At_{Ret}$ = 4.37 min
5	X=H Y=Cl			H	M+ = 435.9 $_At_{Ret}$ = 4.49 min
6	X=H Y=Cl			H	M+H= 453.7 $_At_{Ret}$ = 4.65 min

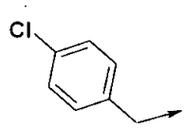
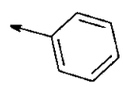
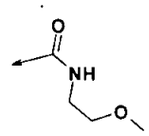
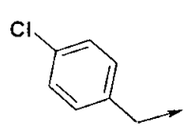
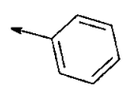
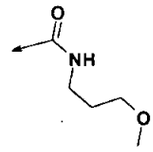
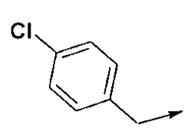
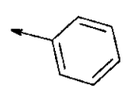
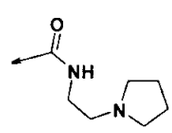
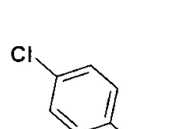
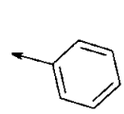
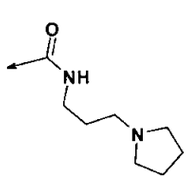
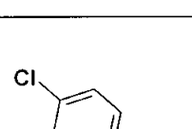
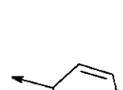
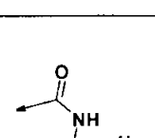
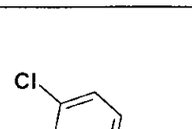
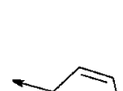
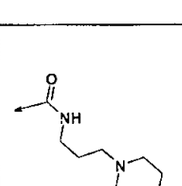
Ejemplo	X e Y	R^1	R^2	R^3	Análisis MS/HPLC/RMN
7	X=H Y=Cl			H	M+H= 455.8 $_At_{Ret}$ = 4.65 min
8	X=H Y=Cl			H	M+= 436.0 $_At_{Ret}$ = 4.50 min
9	X=H Y=Cl			H	M- = 436.1 $_At_{Ret}$ = 4.54 min
10	X=F Y=Cl			H	M+= 436.0 $_At_{Ret}$ = 4.53 min
11	X=H Y=Cl			H	M- = 432.1 $_At_{Ret}$ = 4.68 min
12	X=H Y=Br			H	M+= 436.9 $_At_{Ret}$ = 4.61 min

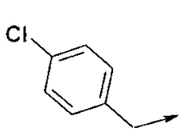
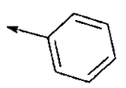
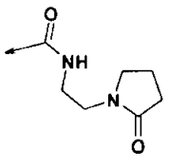
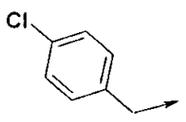
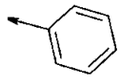
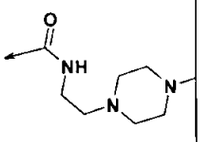
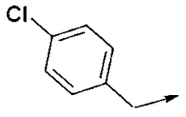
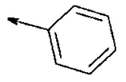
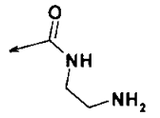
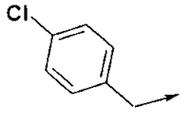
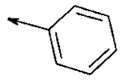
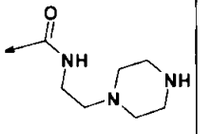
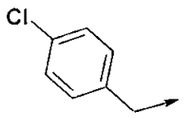
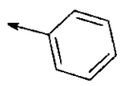
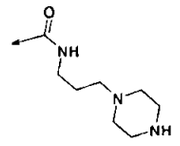
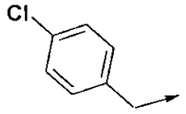
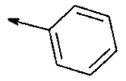
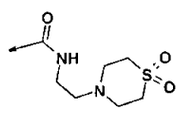
Ejemplo	X e Y	R^1	R^2	R^3	Análisis MS/HPLC/RMN
13	X=H Y=Me			H	M- = 398.1 $_{A}t_{Ret}$ = 4.51 min
14	X=H Y=Cl			H	M- = 436.0 $_{A}t_{Ret}$ = 4.47 min
15	X=H Y=Cl			H	M+= 436.0 $_{A}t_{Ret}$ = 4.61 min
16	X=H Y=Cl			H	M+H= 471.9 $_{A}t_{Ret}$ = 4.69 min
17	X=H Y=CN			H	M+H= 409.0 $_{C}t_{Ret}$ = 5.82 min
18	X=F Y=F			H	M+H= 420.0 $_{C}t_{Ret}$ = 6.20 min

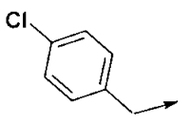
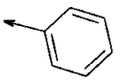
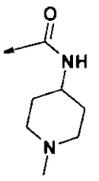
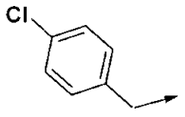
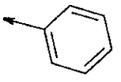
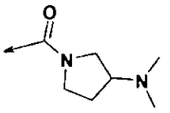
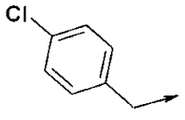
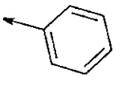
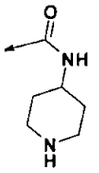
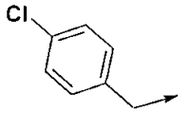
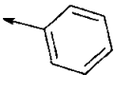
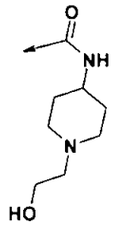
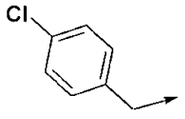
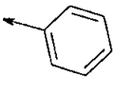
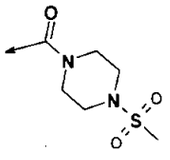
Ejemplo	X e Y	R^1	R^2	R^3	Análisis MS/HPLC/RMN
19	X=H Y=Cl			H	M+H= 452.1 $_At_{Ret}$ = 4.60 min
20	X=H Y=Cl			H	M+= 432.1 $_At_{Ret}$ = 4.65 min
21	X=H Y=Cl			H	M+= 432.1 $_At_{Ret}$ = 4.65 min
22	X=H Y=Cl			H	M+H= 463.9 $_At_{Ret}$ = 4.59 min
23	X=F Y=Cl			H	M+H= 450.0 $_ct_{Ret}$ = 6.48 min
24	X=F Y=F			H	M+H= 434.0 $_ct_{Ret}$ = 6.25 min

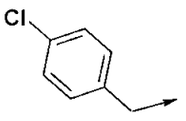
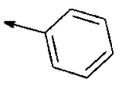
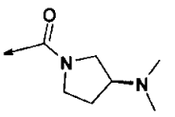
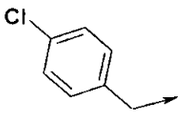
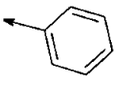
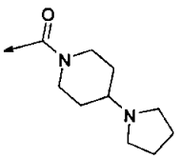
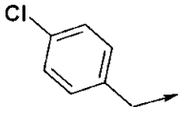
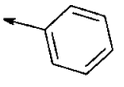
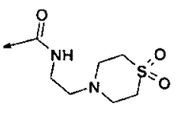
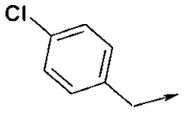
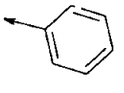
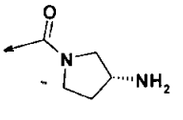
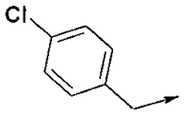
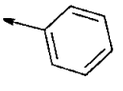
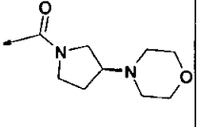
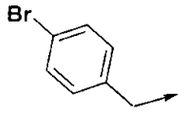
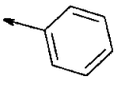
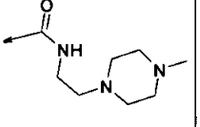
Ejemplo	X e Y	R^1	R^2	R^3	Análisis MS/HPLC/RMN
25	X=H Y=Cl			H	M+= 448.0 $_At_{Ret}$ = 4.35 min
26	X=H Y=CN			H	M+= 423.1 $_At_{Ret}$ = 4.14 min
27	X=F Y=Cl			H	M+= 466.0 $_At_{Ret}$ = 4.32 min
28	X=H Y=CN			H	M+= 439.1 $_At_{Ret}$ = 3.87 min
29	X=F Y=Cl			H	M+= 450.1 $_At_{Ret}$ = 4.59 min

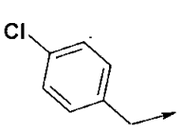
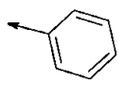
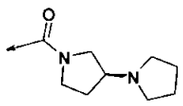
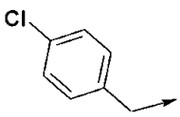
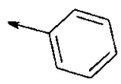
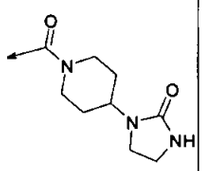
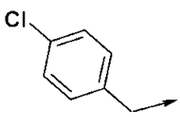
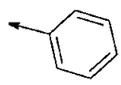
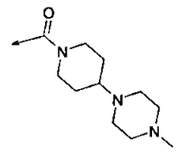
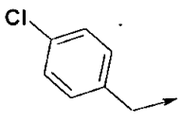
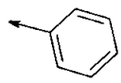
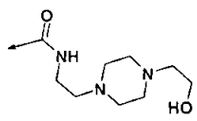
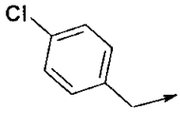
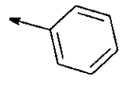
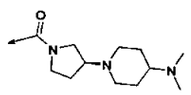
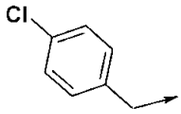
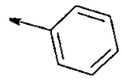
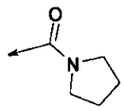
Ejemplo	X e Y	R^1	R^2	R^3	Análisis MS/HPLC/RMN
30	X=H Y=CN			H	M+= 423.1 $_At_{Ret}$ = 4.14 min
31	X=F Y=F			H	M+= 434.1 $_At_{Ret}$ = 4.42 min
32	X=F Y=Cl			H	M+= 466.0 $_At_{Ret}$ = 4.33 min
33	X=H Y=Cl				M+= 587.8 $_At_{Ret}$ = 3.96 min
34	X=H Y=Cl				M+= 586.2 $_At_{Ret}$ = 4.35 min

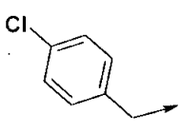
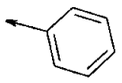
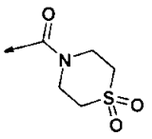
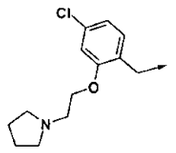
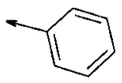
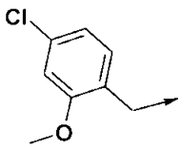
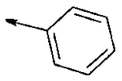
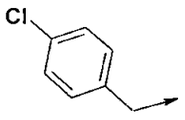
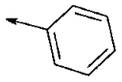
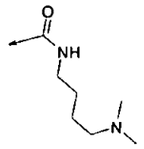
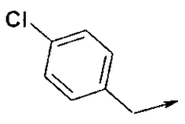
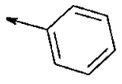
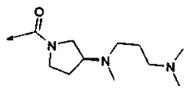
Ejemplo	X e Y	R^1	R^2	R^3	Análisis MS/HPLC/RMN
35	X=H Y=Cl				M+= 520.9 $_At_{Ret}$ = 4.34 min
36	X=H Y=Cl				M+= 534.9 $_At_{Ret}$ = 4.41 min
37	X=H Y=Cl				M+= 559.9 $_At_{Ret}$ = 3.91 min
38	X=H Y=Cl				M+= 573.9 $_At_{Ret}$ = 3.87 min
39	X=H Y=Cl				M+= 519.9 $_At_{Ret}$ = 3.76 min
40	X=H Y=Cl				M+= 603.3 $_At_{Ret}$ = 3.51 min

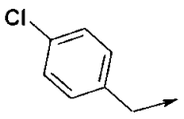
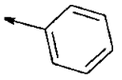
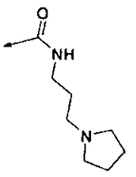
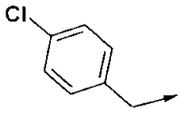
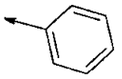
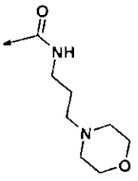
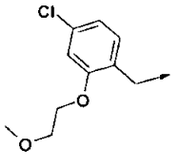
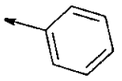
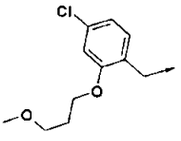
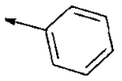
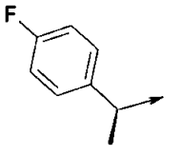
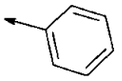
Ejemplo	X e Y	R^1	R^2	R^3	Análisis MS/HPLC/RMN
41	X=H Y=Cl				M+= 573.9 $_At_{Ret}$ = 4.22 min
42	X=H Y=Cl				M+= 589.3 $_At_{Ret}$ = 3.61 min
43	X=H Y=Cl				M+= 504.0 $_At_{Ret}$ = 3.67 min
44	X=H Y=Cl				M+= 574.4 $_At_{Ret}$ = 3.52 min
45	X=H Y=Cl				M+= 588.4 $_At_{Ret}$ = 3.49 min
46	X=H Y=Cl				M+= 621.9 $_At_{Ret}$ = 3.97 min

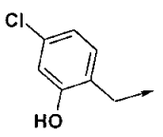
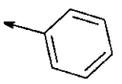
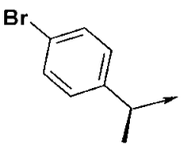
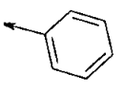
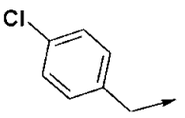
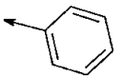
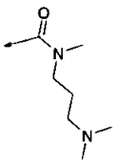
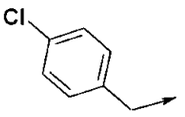
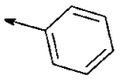
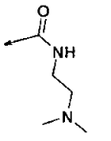
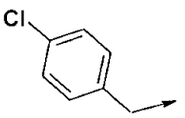
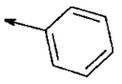
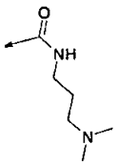
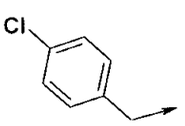
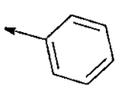
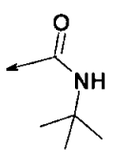
Ejemplo	X e Y	R^1	R^2	R^3	Análisis MS/HPLC/RMN
47	X=H Y=Cl				M+= 558.0 $_At_{Ret}$ = 3.78 min
48	X=H Y=Cl				M+= 558.0 $_At_{Ret}$ = 3.73 min
49	X=H Y=Cl				M+= 544.0 $_At_{Ret}$ = 3.71 min
50	X=H Y=Cl				M+= 588.0 $_At_{Ret}$ = 3.73 min
51	X=H Y=Cl				M+= 607.9 $_At_{Ret}$ = 4.36 min

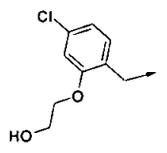
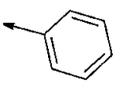
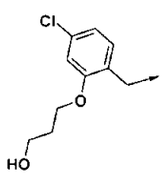
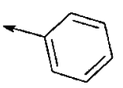
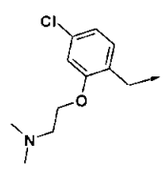
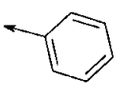
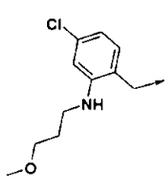
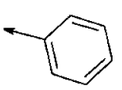
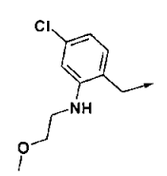
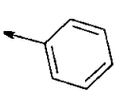
Ejemplo	X e Y	R^1	R^2	R^3	Análisis MS/HPLC/RMN
85	X=F Y=Cl				M+= 578.3 $_{A}t_{Ret}$ = 3.72 min
86	X=F Y=Cl				M+= 618.2 $_{A}t_{Ret}$ = 3.85 min
87	X=F Y=Cl				M+= 642.1 $_{A}t_{Ret}$ = 3.95 min
88	X=H Y=Cl				M+ = 529.9 $_{B}t_{ret}$ = 2.05 min
89	X=H Y=Cl				M+ = 599.9 $_{B}t_{ret}$ = 1.99 min
90	X=H Y=Cl				M+= 634.2 $_{A}t_{Ret}$ = 3.64 min

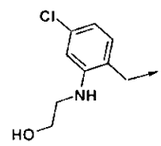
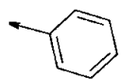
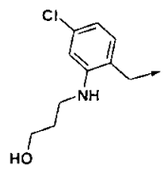
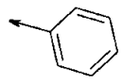
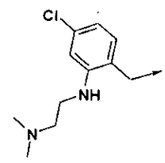
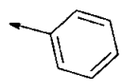
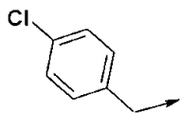
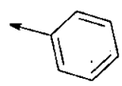
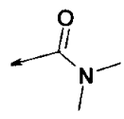
Ejemplo	X e Y	R^1	R^2	R^3	Análisis MS/HPLC/RMN
91	X=H Y=Cl				M+ = 584.6 $_{B}t_{ret}$ = 2.04 min
92	X=F Y=Cl				M- = 631.3 $_{A}t_{Ret}$ = 4.18 min
93	X=F Y=Cl				M- = 643.0 $_{A}t_{Ret}$ = 3.69 min
94	X=H Y=Cl				M-H = 651.2 $_{B}t_{ret}$ = 2.00 min
95	X=H Y=Cl				M+ = 641.0 $_{B}t_{ret}$ = 1.96 min
96	X=H Y=Cl				M+ = 515.1 $_{B}t_{ret}$ = 2.13 min

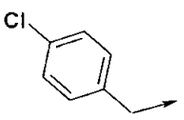
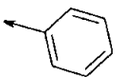
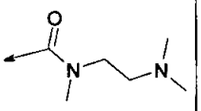
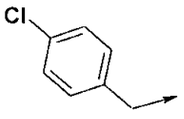
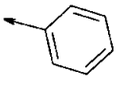
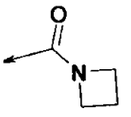
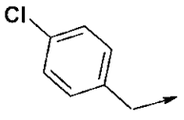
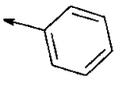
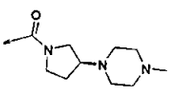
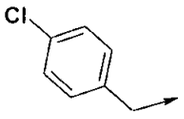
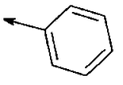
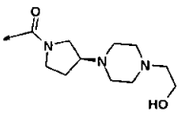
Ejemplo	X e Y	R^1	R^2	R^3	Análisis MS/HPLC/RMN
97	X=H Y=Cl				M+ = 578.8 $_Bt_{ret}$ = 2.13 min
98	X=F Y=Cl			H	M+ = 549.0 $_At_{Ret}$ = 3.87 min
99	X=F Y=Cl			H	M+= 466.0 $_At_{Ret}$ = 4.63 min
100	X=H Y=Cl				M+ = 560.0 $_Ct_{Ret}$ = 5.57 min
101	X=H Y=Cl				M-H = 637.1 $_Ct_{ret}$ = 5.46

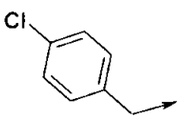
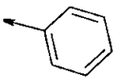
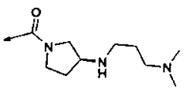
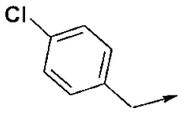
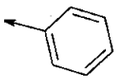
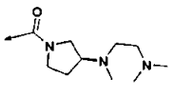
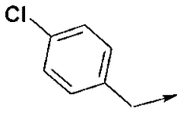
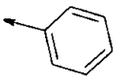
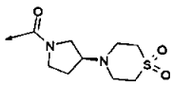
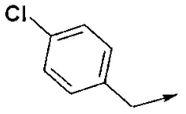
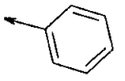
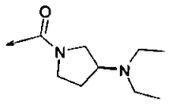
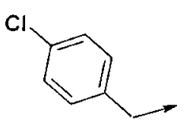
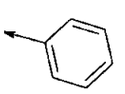
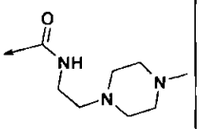
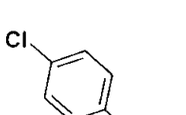
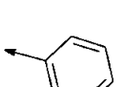
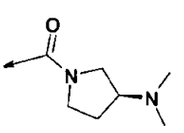
Ejemplo	X e Y	R^1	R^2	R^3	Análisis MS/HPLC/RMN
102	X=F Y=Cl				M+ = 591.5 $_At_{Ret}$ = 3.89 min
103	X=F Y=Cl				M+ = 606.0 $_At_{Ret}$ = 3.78 min
104	X=F Y=Cl			H	M+ = 510.0 $_At_{Ret}$ = 4.65 min
105	X=F Y=Cl			H	M+ = 524.0 $_At_{Ret}$ = 4.75 min
106	X=F Y=Cl			H	M+ = 434.1 $_At_{Ret}$ = 4.45 min

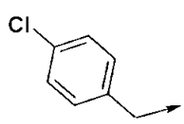
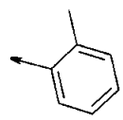
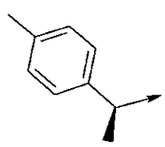
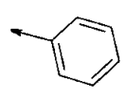
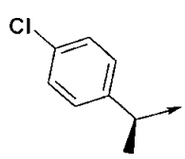
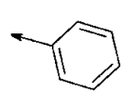
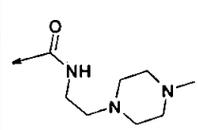
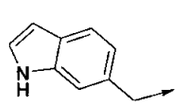
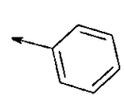
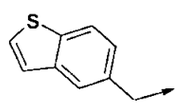
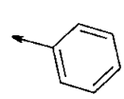
Ejemplo	X e Y	R^1	R^2	R^3	Análisis MS/HPLC/RMN
107	X=F Y=Cl			H	M+ = 452.0 $_At_{Ret}$ = 4.36 min
108	X=F Y=Cl			H	M+ = 495.8 $_At_{Ret}$ = 4.65 min
109	X=H Y=Cl				M-H = 558.1 $_Bt_{ret}$ = 2.01 min
110	X=H Y=Cl				M-H = 530.2 $_Bt_{ret}$ = 2.01 min
111	X=H Y=Cl				M-H = 544.2 $_Bt_{ret}$ = 2.00 min
112	X=H Y=Cl				M+H = 518.8 $_Bt_{ret}$ = 2.17 min

Ejemplo	X e Y	R^1	R^2	R^3	Análisis MS/HPLC/RMN
113	X=F Y=Cl			H	M+= 496.0 $_At_{Ret}$ = 4.32 min
114	X=F Y=Cl			H	M+= 510.0 $_At_{Ret}$ = 4.35 min
115	X=F Y=Cl			H	M+= 523.0 $_At_{Ret}$ = 4.81 min
116	X=F Y=Cl			H	M+= 523.0 $_At_{Ret}$ = 4.81 min
117	X=F Y=Cl			H	M+= 509.0 $_At_{Ret}$ = 4.71 min

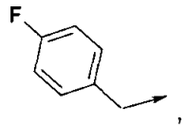
Ejemplo	X e Y	R^1	R^2	R^3	Análisis MS/HPLC/RMN
118	X=F Y=Cl			H	M+= 495.0 $_At_{Ret}$ = 4.35 min
119	X=F Y=Cl			H	M+= 509.0 $_At_{Ret}$ = 4.39 min
120	X=F Y=Cl			H	M+= 522.1 $_At_{Ret}$ = 3.88 min
121	X=H Y=Cl				M-H = 488.1 ^{1}H-RMN ($CDCl_3$) 9.01 (s, 1H), 7.79 (s, 1H), 7.60 (d, 2H), 7.41 (s, 1H), 7.21-7.17 (m, 3H), 7.03 (d, 2H), 6.97 (s, 2H), 6.79 (d, 2H), 4.89 (d, 1H), 4.79 (d, 1H), 1.59 (s, 1H).

Ejemplo	X e Y	R^1	R^2	R^3	Análisis MS/HPLC/RMN
122	X=H Y=Cl				M-H = 544.2 ^{1}H-RMN ($CDCl_3$) 7.64 (s, 1H), 7.51(d, 2H), 7.39 (s, 1H), 7.18-7.03 (m, 6H), 6.98-6.87 (m, 4H), 5.00 (s, 2H), 2.82-2.75 (m, 2H), 2.59-2.41 (m, 5H), 1.58 (s, 6H).
123	X=H Y=Cl				M+H = 502.8 $_Bt_{ret}$ = 2.10 min
124	X=H Y=Cl				M+= 613.0 $_Ct_{Ret}$ = 5.60 min
125	X=H Y=Cl				M-H = 641.3 $_Bt_{ret}$ = 1.98 min

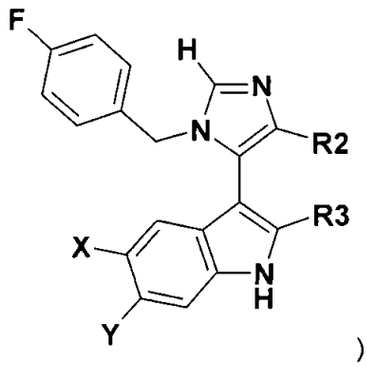
Ejemplo	X e Y	R^1	R^2	R^3	Análisis MS/HPLC/RMN
126	X=H Y=Cl				M+= 615.0 $_{C}t_{Ret}$ = 5.46 min
127	X=H Y=Cl				M-H = 613.3 $_{B}t_{ret}$ = 1.98 min
128	X=H Y=Cl				M-H = 646.2 $_{B}t_{ret}$ = 1.99 min
129	X=H Y=Cl				M-H = 584.2 $_{B}t_{ret}$ = 2.01 min
130	X=H Y=CN				M+= 578.1 $_{A}t_{Ret}$ = 3.35 min
131	X=H Y=CN				M+= 549.1 $_{A}t_{Ret}$ = 3.36 min

Ejemplo	X e Y	R^1	R^2	R^3	Análisis MS/HPLC/RMN
132	X=F Y=Cl			H	M+= 451.9 $_{A}t_{Ret}$ = 4.60 min
133	X=F Y=Cl			H	M+= 430.0 $_{C}t_{Ret}$ = 6.56 min
134	X=H Y=Cl				M+= 601.0 $_{A}t_{Ret}$ = 3.79 min
135	X=F Y=Cl			H	M+= 441.0 $_{C}t_{Ret}$ = 6.26 min
136	X=F Y=Cl			H	M+= 458.0 $_{C}t_{Ret}$ = 6.46 min

(En la tabla, la punta de la flecha significa el final del enlace en donde se enlaza la fracción respectiva al resto de la molécula en la fórmula; por ejemplo, si R^1 tiene la fórmula:



entonces el compuesto correspondiente tiene la fórmula:



).

Intermediario 10.1: 6-cloro-5-fluoro-1H-indol-3-carbaldehído

El compuesto del título se sintetiza mediante la formilación del 6-cloro-5-fluoro-1H-indol de una manera análoga a la preparación del Intermediario **1.1** como un sólido blanco; ES-MS: M+ = 198.0; HPLC: $_At_{Ret}$ = 3.98 minutos.

Intermediario 16.1: 1-cloro-2-fluoro-3-[isociano-(toluen-4-sulfonil)-metil]-benceno

El Intermediario **16.1** se prepara en analogía al un procedimiento publicado en la literatura (*Chem. Lett.* 1988, *9*, 1531-1534). Se agrega $POCl_3$ (0.33 mililitros, 3.66 milimoles) a una solución del Intermediario **16.2** (500 miligramos, 1.46 milimoles) en

tetrahidrofurano (7 mililitros) a 0°C. Después de 30 minutos, se agrega Et_3N (1.32 mililitros, 9.51 milimoles) a la mezcla de reacción, entonces la mezcla se agita durante 1 hora adicional, y entonces se apaga mediante H_2O, se agrega EtOAc, y la capa orgánica se lava con salmuera, se seca sobre $MgSO_4$ y se evapora al vacío. La cromatografía por evaporación instantánea en gel de sílice del residuo proporciona el compuesto del título como un polvo incoloro; ES-MS: M+H = 325.0; HPLC: $_{A}t_{Ret}$ = 5.03 minutos.

Intermediario 16.2: N-[(3-cloro-2-fluoro-fenil)-(toluen-4-sulfonil)-metil]-formamida

El Intermediario **16.2** se prepara en analogía al un procedimiento publicado en la literatura (*Chem. Lett.* 1988, *9*, 1531-1534). Una mezcla del 3-cloro-2-fluoro-benzaldehído (2.00 gramos, 12.6 milimoles), ácido p-toluen-sulfínico (2.96 gramos, 18.9 milimoles), TMSCl (1.75 mililitros, 13.9 milimoles) y formamida (1.25 mililitros, 31.5 milimoles) en tolueno (7 mililitros) y CH_3CN (7 mililitros), se calienta a 50°C durante 5 horas. Después de completarse, la mezcla de reacción se apaga mediante H_2O, se agrega EtOAc, y la capa orgánica se lava con salmuera, se seca sobre $MgSO_4$ y se evapora al vacío. La cromatografía por evaporación instantánea en gel de sílice del residuo proporciona el compuesto del título como un polvo incoloro; HPLC: $_{A}t_{Ret}$ = 4.21 minutos; ^{1}H-RMN ($CDCl_3$) 8.18 (s, 1H), 7.72 (d, 2H), 7.50-7.45 (m, 1H), 7.40-7.30 (m, 3H), 7.20-7.10 (m, 1H), 7.00 (d, 1H), 6.60 (d, 1H), 2.45 (s, 3H).

Intermediario 17.1: 3-formil-1H-indol-6-carbonitrilo

El compuesto del título se sintetiza mediante la formilación del 1H-indol-6-carbonitrilo de una manera análoga a la preparación del Intermediario **1.1** como un sólido blanco; ES-MS: M-H = 169.0; HPLC: $_{c}t_{Ret}$ = 4.96 minutos.

Intermediario 18.1: 5,6-difluoro-1H-indol-3-carbaldehído

El compuesto del título se sintetiza mediante la formilación del 5,6-difluoro-1H-Indol de una manera análoga a la preparación del Intermediario **1.1** como un sólido blanco; ES-MS: M-H = 180.0; HPLC: $_{c}t_{Ret}$ = 5.47 minutos.

Intermediario 25.1: (S)-2-amino-2-(4-cloro-fenil)-etanol

Una mezcla de la L-4-cloro-fenil-glicina (1.74 gramos, 9.37 milimoles) y LAH (712 miligramos, 18.75 milimoles) en tetrahidrofurano (40 mililitros), se pone a reflujo durante 1.5 horas. Después de completarse, la mezcla de reacción se apaga mediante $Na_2SO_4 \cdot 10H_2O$ y el producto se aísla mediante filtración con Celite, se lava con tetrahidrofurano, y se seca bajo presión reducida para dar el compuesto del título como un aceite; HPLC: $_{A}t_{Ret}$ = 1.46 minutos; ^{1}H-RMN (DMSO-d_6) 7.35 (d, 2H), 7.30 (d, 2H), 4.80 (bs, 1H), 3.85-3.80 (m, 1H), 3.45-3.20 (m, 2H), 1.85 (bs, 2H).

Intermediario 32.1: (R)-2-amino-2-(4-cloro-fenil)-etanol

El compuesto del título se sintetiza mediante la reducción de la D-4-cloro-fenil-glicina de una manera análoga a la preparación del Intermediario **25.1** como un aceite incoloro; ES-MS: HPLC: $_{A}t_{Ret}$ = 1.47 minutos; ^{1}H-RMN (DMSO-d_6) 7.35 (d, 2H), 7.30 (d, 2H), 4.80

(bs, 1H), 3.85-3.80 (m, 1H), 3.45-3.20 (m, 2H), 1.85 (bs, 2H).

El **Ejemplo 43** se prepara en analogía al un procedimiento publicado en la literatura (*J. Med. Chem.* **1989**, *32*, 1728-1732). Una mezcla del Intermediario **43.1** (102 miligramos, 0.16 milimoles) e hidrato de hidrazina (12 miligramos, 0.24 milimoles) en EtOH (0.8 mililitros) se pone a reflujo durante 2 horas; después de completarse, la mezcla de reacción se apaga mediante H_2O, se agrega EtOAc, y la capa orgánica se lava con salmuera, se seca sobre $MgSO_4$ y se evapora al vacío. La cromatografía por evaporación instantánea en gel de sílice del residuo proporciona el compuesto del título como un polvo incoloro.

Intermediario 43.1: [2-(1,3-dioxo-1,3-dihidro-isoindol-2-il)-etil]-amida del ácido 6-cloro-3-[3-(4-cloro-bencil)-5-fenil-3H-imidazol-4-il]-1H-indol-2-carboxílico (también un compuesto de la fórmula I)

El compuesto del título se sintetiza mediante la condensación del **Intermediario 2.1** y 2-(2-amino-etil)-isoindol-1,3-diona de una manera análoga a la preparación del Ejemplo **2** como un sólido incoloro; ES-MS: M+ = 636.1; HPLC: ${}_At_{Ret}$ = 4.64 minutos.

El **Ejemplo 44** se prepara en analogía al un procedimiento publicado en la literatura (*J. Med. Chem.* **2003**, *46*, 3957-3960). Una solución del Intermediario **44.1** (97 miligramos, 0.14 milimoles) en dioxano (0.5 mililitros) se trata con una solución en dioxano 4M de HCl (4 mililitros) durante 14 horas. Después de completarse, la mezcla de reacción se apaga mediante $NaHCO_3$ acuoso saturado, se

agrega EtOAc, y la capa orgánica se lava con salmuera, se seca sobre $MgSO_4$ y se evapora al vacío. La cromatografía por evaporación instantánea en gel de sílice del residuo proporciona el compuesto del título como un polvo incoloro.

Los **Ejemplos 45, 49, 80 y 88** se preparan también en analogía al **Ejemplo 44**.

Intermediario 44.1: Terbutil-éster del ácido 4-[2-({6-cloro-3-[3-(4-cloro-bencil)-5-fenil-3H-imidazol-4-il]-1H-indol-2-carbonil}-amino)-etil]-piperazin-1-carboxílico (también un compuesto de la fórmula I)

El compuesto del título se sintetiza mediante la condensación del **Intermediario 2.1** y el terbutil-éster del ácido 4-(2-amino-etil)-piperazin-1-carboxílico, de una manera análoga a la preparación del Ejemplo **2** como un sólido incoloro; ES-MS: M+ = 675.3; HPLC: $_At_{Ret}$ = 4.29 minutos.

Intermediario 45.1: Terbutil-éster del ácido 4-[3-({6-cloro-3-[3-(4-cloro-bencil)-5-fenil-3H-imidazol-4-il]-1H-indol-2-carbonil}-amino)-propil]-piperazin-1-carboxílico (también un compuesto de la fórmula I)

El compuesto del título se sintetiza mediante la condensación del **Intermediario 2.1** y el terbutil-éster del ácido 4-(3-amino-propil)-piperazin-1-carboxílico, de una manera análoga a la preparación del Ejemplo **2** como un sólido incoloro; ES-MS: M+ = 689.3; HPLC: $_At_{Ret}$ = 4.24 minutos.

Intermediario 49.1: Terbutil-éster del ácido 4-({6-cloro-3-[3-(4-cloro-bencil)-5-fenil-3H-imidazol-4-il]-1H-indol-2-carbonil}-amino)-piperidin-1-carboxílico (también un compuesto de la fórmula I)

El compuesto del título se sintetiza mediante la condensación del **Intermediario 2.1** y el terbutil-éster del ácido 4-amino-piperidin-1-carboxílico, de una manera análoga a la preparación del Ejemplo **2** como un sólido incoloro; ES-MS: M+ = 643.7; HPLC: $_{A}t_{Rel}$ = 4.88 minutos.

El **Ejemplo 56** se prepara en analogía al un procedimiento publicado en la literatura (J. Org. Chem. **2006**, 71, 1442-1448). Una solución del Intermediario **56.1** (142 miligramos, 0.22 milimoles) en dicloro-metano (1.5 mililitros) se trata con una solución en tetrahidrofurano 1M de TBAF (0.45 mililitros) durante 47 horas. Después de completarse, la mezcla de reacción se apaga mediante $NaHCO_3$ acuoso saturado, se agrega EtOAc, y la capa orgánica se lava con salmuera, se seca sobre $MgSO_4$ y se evapora al vacío. La cromatografía por evaporación instantánea en gel de sílice del residuo proporciona el compuesto del título como un polvo incoloro.

El **Ejemplo 57** también se prepara en analogía al **Ejemplo 56**.

Intermediario 56.1: [2-(terbutil-dimetil-silaniloxi)-etil]-amida del ácido 6-cloro-3-[3-(4-cloro-bencil)-5-fenil-3H-imidazol-4-il]-1H-indol-2-carboxílico (también un compuesto de la fórmula I)

El compuesto del título se sintetiza mediante la condensación del **Intermediario 2.1** y 2-(terbutil-dimetil-silaniloxi)-etil-amina de

una manera análoga a la preparación del Ejemplo **2** como un sólido *incoloro*; ES-MS: M+ = 619.0; HPLC: $_{c}t_{Ret}$ = 7.37 *minutos*.

Intermediario 56.2: 2-(terbutil-dimetil-silaniloxi)-etil-amina

Una mezcla de etanolamina (0.5 mililitros, 8.1 milimoles), terbutil-dimetil-cloro-silano (1.42 gramos, 8.9 milimoles), Et_3N (1.25 mililitros, 8.9 milimoles) y DMAP (51 miligramos, 0.41 milimoles) en dicloro-metano (25 mililitros), se agita a temperatura ambiente durante 18 horas. La mezcla de reacción se apaga mediante H_2O, se agrega dicloro-metano, y la capa orgánica se lava con salmuera, se seca sobre $MgSO_4$ y se evapora al vacío. La cromatografía por evaporación instantánea en gel de sílice del residuo proporciona el compuesto del título como un aceite incoloro; ES-MS: M+ = 176.2; ^{1}H-RMN ($CDCl_3$) 3.95-3.85 (m, 2H), 3.15-3.10 (m, 2H), 0.90 (s, 9H), 0.05 (s, 6H), falta NH_2.

Intermediario 57.1: [3-(terbutil-dimetil-silaniloxi)-propil]-amida del ácido 6-cloro-3-[3-(4-cloro-bencil)-5-fenil-3H-imidazol-4-il]-1H-indol-2-carboxílico (también un compuesto de la fórmula I)

El compuesto del título se sintetiza mediante la condensación del **Intermediario 2.1** y 2-(terbutil-dimetil-silaniloxi)-propil-amina de una manera análoga a la preparación del Ejemplo **2** como un sólido *incoloro*; ES-MS: M+ = 633.0; HPLC: $_{c}t_{Ret}$ = 7.52 *minutos*.

Intermediario 57.2: 2-(terbutil-dimetil-silaniloxi)-propil-amina

El compuesto del título se sintetiza mediante la condensación del 3-amino-1-propanol y terbutil-dimetil-cloro-silano de una manera análoga a la preparación del Intermediario **56.2** como un aceite

incoloro; ES-MS: M+ = 190.2; ^{1}H-RMN ($CDCl_3$) 3.80-3.70 (m, 2H), 3.10-3.05 (m, 2H), 1.95-1.85 (m, 2H), 0.90 (s, 9H), 0.03 (s, 6H), falta NH_2.

Intermediario 80.1: Terbutil-éster del ácido ((S)-1-{6-cloro-3-[3-(4-cloro-bencil)-5-fenil-3H-imidazol-4-il]-1H-indol-2-carbonil}-pirrolidin-3-il)-carbámico (también un compuesto de la fórmula I)

El compuesto del título se sintetiza mediante la condensación del **Intermediario 2.1** y el terbutil-éster del ácido (S)-pirrolidin-3-il-carbámico, de una manera análoga a la preparación del Ejemplo **2** como un sólido incoloro; ES-MS: M+H = 531.8; HPLC: $_Bt_{Ret}$ = 2.17 minutos.

Intermediario 84.1: Ácido 6-cloro-3-[3-(4-cloro-bencil)-5-fenil-3H-imidazol-4-il]-5-fluoro-1H-indol-2-carboxílico (también un compuesto de la fórmula I)

El compuesto del título se sintetiza mediante la hidrólisis del Intermediario **84.2** de una manera análoga a la preparación del Intermediario **2.1** como un sólido incoloro; ES-MS: M+ = 480.0; HPLC: $_At_{Ret}$ = 4.23 minutos.

Intermediario 84.2: Metil-éster del ácido 6-cloro-3-[3-(4-cloro-bencil)-5-fenil-3H-imidazol-4-il]-5-fluoro-1H-indol-2-carboxílico (también un compuesto de la fórmula I)

El compuesto del título se sintetiza mediante la condensación del **Intermediario 84.3**, 4-cloro-bencil-amina y 1-(isociano-fenil-metan-sulfonil)-4-metil-benceno de una manera análoga a la preparación del Intermediario **2.2** como un sólido incoloro; ES-MS:

HPLC: $_At_{Ret}$ = 4.51 minutos; ^{1}H-RMN (DMSO-d_6) 12.5 (s, 1H), 8.05 (s, 1H), 7.58 (d, 1H), 7.35-7.30 (m, 2H), 7.10-7.00 (m, 5H), 6.75-6.65 (m, 3H), 5.00 (d, 1H), 4.85 (d, 1H), 3.65 (s, 3H).

Intermediario 84.3: Metil-éster del ácido 6-cloro-5-fluoro-3-formil-1H-indol-2-carboxílico

El compuesto del título se sintetiza mediante la formilación del Intermediario **84.4** de una manera análoga a la preparación del Intermediario **2.3** como un sólido blanco; $_At_{Ret}$ = 4.47 minutos; ^{1}H-RMN (DMSO-d_6) 13.1 (bs, 1H), 10.5 (s, 1H), 8.05 (d, 1H), 7.70 (d, 1H), 4.00 (s, 3H).

Intermediario 84.4: Metil-éster del ácido 6-cloro-5-fluoro-1H-indol-2-carboxílico

El **Intermediario 84.4** se prepara en analogía a un procedimiento publicado en la literatura (*Org. Lett.* **2004**, *6*, 2953-2956.). Una mezcla del Intermediario **84.5** (330 miligramos, 1.08 milimoles) y una solución en tetrahidrofurano 1M de TBAF (5.0 mililitros, 5.0 milimoles) se agita a temperatura ambiente durante 1.5 horas. La mezcla de reacción se apaga mediante NH_4Cl acuoso saturado, se agrega EtOAc, y la capa orgánica se lava con salmuera, se seca sobre $MgSO_4$ y se evapora al vacío. La cromatografía por evaporación instantánea en gel de sílice del residuo proporciona el compuesto del título como un polvo incoloro; ES-MS: M- = 226.1; HPLC: $_At_{Ret}$ = 4.71 minutos.

Intermediario 84.5: Metil-éster del ácido 6-cloro-5-fluoro-1-metan-sulfonil-1H-indol-2-carboxílico

El **Intermediario 84.5** se prepara en analogía a un procedimiento publicado en la literatura (*Org. Lett.* **2004**, *6*, 2953-2956.). Una mezcla del Intermediario **84.6** (3.00 gramos, 8.58 milimoles), propiolato de metilo (1.4 mililitros, 17.16 milimoles), N-etil-di-isopropil-amina (8.8 mililitros, 51.4 milimoles), bromuro de zinc (5.8 gramos, 25.7 milimoles) y tetraquis-trifenil-fosfina-paladio (300 miligramos, 0.26 milimoles) en dioxano (60 mililitros), se calienta a reflujo durante 2 horas. La mezcla de reacción se apaga mediante H_2O, se agrega EtOAc, y la capa orgánica se lava con salmuera, se seca sobre $MgSO_4$ y se evapora al vacío. La cromatografía por evaporación instantánea en gel de sílice del residuo proporciona el compuesto del título como un polvo incoloro; ES-MS: M+ = 306.0; HPLC: ${}_At_{Ret}$ = 4.85 minutos.

Intermediario 84.6: N-(5-cloro-4-fluoro-2-yodo-fenil)-metan-sulfonamida

Una mezcla de la 3-cloro-4-fluoro-anilina (12.9 gramos, 88.9 milimoles) y NIS (22.0 gramos, 97.8 milimoles) en AcOH (90 mililitros) se agita a temperatura ambiente durante 1.5 horas. Después de completarse, la mezcla de reacción se apaga mediante H_2O, se agrega dicloro-metano, y la capa orgánica se lava con salmuera, se seca sobre $MgSO_4$ y se evapora al vacío. La cromatografía por evaporación instantánea en gel de sílice del residuo proporciona la 5-cloro-4-fluoro-2-yodo-anilina como un polvo incoloro; HPLC: ${}_At_{Ret}$ = 4.75 minutos; ^{1}H-RMN ($CDCl_3$) 7.40 (d, 1H), 6.75 (d, 1H), 4.00 (bs, 2H).

Se agrega MsCl (11.8 mililitros, 152.0 milimoles) a una mezcla de 5-cloro-4-fluoro-2-yodo-anilina (15.8 gramos, 58.4 milimoles) y piridina (16.5 mililitros, 204.6 milimoles) en dicloro-metano (200 mililitros) a temperatura ambiente, y se calienta a 50°C durante 18 horas. La mezcla de reacción se apaga mediante $NaHCO_3$ acuoso saturado, se agrega dicloro-metano, y la capa orgánica se lava con salmuera. El lavado se extrae repetidamente con dicloro-metano, y los extractos combinados se lavan con salmuera, se secan y se concentran para dar la N-(5-cloro-4-fluoro-2-yodo-fenil)-bis-metan-sulfonamida como un sólido amarillo, la cual se somete al siguiente paso sin mayor purificación.

Una mezcla de la N-(5-cloro-4-fluoro-2-yodo-fenil)-bis-metan-sulfonamida y K_2CO_3 (10.5 gramos, 76.0 milimoles) en metanol (100 mililitros) y tetrahidrofurano (100 mililitros), se agita a temperatura ambiente durante 18 horas. La mezcla de reacción se apaga mediante NH_4Cl acuoso saturado, se agrega EtOAc, y la capa orgánica se lava con salmuera, se seca sobre $MgSO_4$ y se evapora al vacío. La cromatografía por evaporación instantánea en gel de sílice del residuo proporciona el compuesto del título como un polvo incoloro; HPLC: $_At_{Ret}$ = 4.11 minutos; ^{1}H-RMN (DMSO-d_6) 9.50(s, 1H), 7.95 (d, 1H), 7.50 (d, 1H), 3.00 (s, 3H).

Intermediario 88.1: Terbutil-éster del ácido ((R)-1-{6-cloro-3-[3-(4-cloro-bencil)-5-fenil-3H-imidazol-4-il]-1H-indol-2-carbonil}-pirrolidin-3-il)-carbámico (también un compuesto de la fórmula I)

El compuesto del título se sintetiza mediante la condensación

del **Intermediario 2.1** y el terbutil-éster del ácido (R)-pirrolidin-3-il-carbámico, de una manera análoga a la preparación del Ejemplo **2** como un sólido incoloro; ES-MS: M+H = 531.8; HPLC: $_{B}t_{Ret}$ = 2.18 minutos.

Intermediario 89.1: Sal de (S)-4-pirrolidin-3-il-morfolina·2HBr

El **Intermediario 89.1** se prepara en analogía a un procedimiento publicado en la literatura (*J. Org. Chem.* **1998**, *63*, 8266-8275.). El **Intermediario 89.2** se disuelve en una solución de HBr/AcOH al 33 por ciento, y se calienta a reflujo durante 2.5 horas. La reacción se deja entonces enfriar a temperatura ambiente, después de lo cual, se precipita el producto. Se aísla mediante filtración, subsiguientemente se lava con AcOH, EtOAc y se seca para dar el compuesto del título como un polvo amarillo. ES-MS: M+H = 157.4 (base libre); ^{1}H-RMN (MeOH-d_4) δ 4.18-4.01 (m, 2H), 3.99-3.90 (m, 4H), 3.86-3.82 (m, 2H), 3.71-3.62 (m, 2H), 3.48-3.37 (m, 2H), 2.63.2.56 (m, 2H), 2.42-2.35 (m, 2H).

Intermediario 89.2: 4-[(S)-1-(toluen-4-sulfonil)-pirrolidin-3-il]-morfolina

El **Intermediario 89.3** (1.0 gramos, 2.5 milimoles) se disuelve en morfolina (5 mililitros) y se calienta a 85°C en un baño de aceite durante 12 horas. Después de completarse, la mezcla de reacción se deja enfriar a temperatura ambiente, se diluye con EtOAc y se lava con una solución acuosa de NaOH 4M. El lavado se extrae repetidamente con EtOAc, y los extractos combinados se lavan con salmuera, se secan y se concentran para dar el compuesto del título

como un aceite amarillo, el cual se somete al siguiente paso sin mayor purificación. ^{1}H-RMN ($CDCl_3$) δ 7.78 (d, 2H), 7.58 (d, 2H), 3.69-3.61 (m, 4H), 3.55 (dd, 1H), 3.38 (dd, 1H), 3.29-3.21 (m, 1H), 2.98 (dd, 1H), 2.76 (m, 1H), 2.44 (s, 3H), 2.43-2.21 (m, 4H), 2.02-1.98 (m, 1H), 1.71-1.64 (m, 1H).; HPLC: $_Bt_{Ret}$ = 1.87 minutos.

Intermediario 89.3

Se disuelve R-Prolinol (7.0 gramos, 80.3 milimoles, 1 equivalente) en dicloro-metano (40 mililitros). Se agregan piridina (33 mililitros) y DMAP (980 miligramos, 8.0 milimoles, 0.1 equivalentes) a temperatura ambiente, y la reacción se enfría en un baño de hielo, seguido por la adición de TsCl (38.3 gramos, 200.8 milimoles, 2.5 equivalentes). Entonces se deja que la reacción alcance la temperatura ambiente, y se agita durante 2 días. Se concentra y se suspende con hexanos/dietil-éter (1:1, 150 mililitros). El producto sólido se aísla mediante filtración y se seca. Subsiguientemente se disuelve en dietil-éter/tetrahidrofurano (3:1, 600 mililitros), se lava con salmuera, se seca y se concentra para dar el compuesto del título como un polvo amarillo claro. ES-MS: M+H = 397.3; HPLC: $_Bt_{Ret}$ = 2.33 minutos.

Intermediario 90.1: Ácido 3-[3-(4-bromo-bencil)-5-fenil-3H-imidazol-4-il]-6-cloro-1H-indol-2-carboxílico (también un compuesto de la fórmula I)

El compuesto del título se sintetiza mediante la hidrólisis del Intermediario **90.2** de una manera análoga a la preparación del Intermediario **2.1** como un sólido incoloro; HPLC: $_At_{Ret}$ = 4.28

minutos.; ^{1}H-RMN (DMSO-d_6) 12.4 (s, 1H), 7.45-7.05 (m, 10H), 6.90 (s, 1H), 6.75 (d, 2H), 5.10 (d, 1H), 4.90 (d, 1H).

Intermediario 90.2: Etil-éster del ácido 3-[3-(4-bromo-bencil)-5-fenil-3H-imidazol-4-il]-6-cloro-1H-indol-2-carboxílico (también un compuesto de la fórmula I)

El compuesto del título se sintetiza mediante la condensación del **Intermediario 2.3**, 4-bromo-bencil-amina y 1-(isociano-fenil-metan-sulfonil)-4-metil-benceno de una manera análoga a la preparación del Intermediario **2.2** como un sólido incoloro; HPLC: $_At_{Rel}$ = 4.71 minutos. ^{1}H-RMN (DMSO-d_6) 12.3 (s, 1H), 8.05 (s, 1H), 7.50-7.00 (m, 9H), 6.95 (s, 1H), 6.65 (d, 2H), 5.05 (d, 1H), 4.90 (d, 1H), 4.00 (q, 2H), 1.00 (t, 3H).

Intermediario 91.1: Sal de (S)-[1,3']-bipirrolidinilo·2HBr

El compuesto del título se sintetiza mediante la condensación del **Intermediario 89.3** y pirrolidina de una manera análoga a la preparación del Intermediario **89.1** como un polvo amarillo; ES-MS: M+H = 141.5 (base libre); ^{1}H-RMN (DMSO-d_6) δ 9.19 (s, 1H), 4.17-3.99 (m, 1H), 3.69-3-49 (m, 2H), 3.43-3.35 (m, 2H), 3.24-3.19 (m, 1H), 3.18-2.99 (m, 2H), 2.60-2.49 (m, 1H), 2.21-2.10 (m, 1H), 2.05-1.95 (m, 2H), 1.94-1.78 (m, 3H).

Intermediario 94.1: 2-[4-(2-amino-etil)-piperazin-1-il]-etanol

La 2-{2-[4-(2-hidroxi-etil)-piperazin-1-il]-etil}-isoindol-1,3-diona (370 miligramos, 1.2 milimoles) se disuelve en EtOH (8 mililitros) y se agrega hidrato de hidrazina (88 mililitros, 1.8 milimoles) a temperatura ambiente. La mezcla de reacción se pone

entonces a reflujo durante 3 horas, y de nuevo se deja enfriar a temperatura ambiente. El producto precipitado se aísla mediante filtración, se lava subsiguientemente con EtOH frío y se seca en un alto vacío para dar el compuesto del título como un polvo blanco. ES-MS: M+H = 174.2. ^{1}H-RMN (MeOH-d4) δ 4.24 (bs, 2H), 3.41 (t, 2H), 2.62 (t, 2H), 2.54-2.50 (m, 2H), 2-39-2.201 (m, 10H).

Intermediario 94.2: 2-{2-[4-(2-hidroxi-etil)-piperazin-1-il]-etil}-isoindol-1,3-diona

El 2-piperazin-1-il-etanol (510 miligramos, 3.9 milimoles) se disuelve en CH_3CN (5 mililitros). Se agregan N-(2-bromo-etil)-ftalimida (995 miligramos, 3.9 milimoles) y K_2CO_3 anhidro (1.1 gramos, 7.8 milimoles) a temperatura ambiente, y entonces la mezcla de reacción se pone a reflujo durante 5 horas. La mezcla de reacción se deja enfriar a temperatura ambiente nuevamente, y el producto crudo precipitado se aísla mediante filtración. Entonces se purifica mediante cromatografía por evaporación instantánea (SiO_2; DCM/MeOH, gradiente del 1 al 5 por ciento de MeOH) para dar el compuesto del título como un polvo blanco. : M+H = 304.1; HPLC: $_ct_{Ret}$ = 1.73 minutos.

Intermediario 95.1: Sal de dimetil-((S)-1-pirrolidin-3-il-piperidin-4-il)-amina • 2HBr

El compuesto del título se sintetiza mediante la condensación del **Intermediario 89.3** y dimetil-piperidin-4-il-amina de una manera análoga a la preparación del Intermediario **89.1** como un polvo amarillo; ES-MS: M+H = 198.4 (base libre); ^{1}H-RMN (DMSO-d_6) δ

9.87 (s, 1H), 3.99 (m 1H), 3.45-3.34 (m, 5H), 3.23-2.95 (m, 4H), 2.48-2.03 (m, 4H), 1.99-1.78 (m, 2H).

Intermediario 98.1: 4-cloro-2-(2-pirrolidin-1-il-etoxi)-bencil-amina

Una mezcla del 4-cloro-2-fluoro-benzonitrilo (869 miligramos, 5.58 milimoles) y 2-pirrolidin-1-il-etanol (0.80 mililitros, 6.70 milimoles) en tetrahidrofurano (30 mililitros) se trata con una solución en tolueno 0.5M de KHMDS (13.4 mililitros, 6.7 milimoles) a 0°C. Después de completarse la reacción a temperatura ambiente, la mezcla de reacción se apaga mediante H_2O. Se agrega EtOAc, y la capa orgánica se lava con salmuera, y se seca sobre $MgSO_4$. La concentración al vacío proporciona el 4-cloro-2-(2-pirrolidin-1-il-etoxi)-benzonitrilo correspondiente. Una solución en tetrahidrofurano (7 mililitros) del 4-cloro-2-(2-pirrolidin-1-il-etoxi)-benzonitrilo se agrega a una suspensión de LAH (293 miligramos, 7.71 milimoles) en tetrahidrofurano (50 mililitros) a 0°C. La reacción se deja agitándose durante 2 horas a temperatura ambiente, y entonces se apaga mediante $Na_2SO_4 \cdot 10H_2O$, y el producto se aísla mediante filtración con Celite y se lava con tetrahidrofurano y se seca bajo presión reducida, para dar el compuesto del título como un aceite; ES-MS: M+ = 255.2; HPLC: ${}_At_{Ret}$ = 1.22 minutos.

Intermediario 99.1: 4-cloro-2-metoxi-bencil-amina

El compuesto del título se sintetiza mediante acoplamiento, seguido por reducción de 4-cloro-2-fluoro-benzonitrilo y metanol de una manera análoga a la preparación del Intermediario **98.1** como un aceite incoloro; HPLC: ${}_At_{Ret}$ = 2.24 minutos; ^{1}H-RMN ($CDCl_3$) δ 7.20-

7.10 (m, 1H), 7.00-6.80 (m 2H), 3.90-3.80 (m, 5H), 1.80 (bs, 2H).

Intermediario 101.1: Sal de N,N,N'-trimetil-N'-(S)-pirrolidin-3-il-propan-1,3-diamina • 3HBr

El compuesto del título se sintetiza mediante la condensación del **Intermediario 89.3** y N,N,N'-trimetil-propan-1,3-diamina de una manera análoga a la preparación del Intermediario **89.1** como un polvo amarillo; ES-MS: M+H = 186.2 (base libre); ^{1}H-RMN (DMSO-d_6) δ 9.19 (s, 1H), 4.09-4.03 (m, 1H), 3.65-3.59 (m, 1H), 3.31-3.02 (m, 5H), 3.83 (s, 3H), 3.79 (s, 6H), 2.42-2.36 (m, 2H), 2.22-2.03 (m, 4H).

Intermediario 104.1: 4-cloro-2-(2-metoxi-etoxi)-bencil-amina

El compuesto del título se sintetiza mediante acoplamiento, seguido por reducción de 4-cloro-2-fluoro-benzonitrilo y 2-metoxi-etanol de una manera análoga a la preparación del Intermediario **98.1** como un sólido incoloro; ES-MS: M+ = 216.1; HPLC: $_At_{Ret}$ = 2.51 minutos.

Intermediario 106.1: 4-cloro-2-(3-metoxi-propoxi)-bencil-amina

El compuesto del título se sintetiza mediante acoplamiento, seguido por reducción de 4-cloro-2-fluoro-benzonitrilo y 3-metoxi-propanol, de una manera análoga a la preparación del Intermediario **98.1** como un sólido incoloro; ES-MS: M+ = 230.1; HPLC: $_At_{Ret}$ = 2.81 minutos.

Intermediario 107.1: 3-[3-(2-terbutoxi-4-cloro-bencil)-5-fenil-3H-imidazol-4-il]-6-cloro-5-fluoro-1H-indol (también un compuesto de la fórmula I)

El compuesto del título se sintetiza mediante la condensación del **Intermediario 10.1**, el **Intermediario 107.2** y 1-(isociano-fenil-metan-sulfonil)-4-metil-benceno, de una manera análoga a la preparación del Ejemplo **1** como un sólido incoloro; ES-MS: M+ = 508.0; HPLC: $_At_{Ret}$ = 4.98 minutos.

Intermediario 107.2: 2-terbutoxi-4-cloro-bencil-amina

El compuesto del título del Intermediario **113.1** se sintetiza mediante acoplamiento, seguido por reducción de 4-cloro-2-fluoro-benzonitrilo y terbutanol de una manera análoga a la preparación del Intermediario **98.1** como un aceite incoloro; ES-MS: M+H-^{t}Bu = 158.0; HPLC: $_At_{Ret}$ = 3.19 minutos.

Intermediario 113.1: 2-(2-amino-metil-5-cloro-fenoxi)-etanol

Una mezcla del 4-cloro-2-fluoro-benzonitrilo (1.00 gramos, 6.43 milimoles), etilenglicol (3.59 mililitros, 64.3 milimoles) y K_2CO_3 (1.33 gramos, 9.64 milimoles) en dimetil-formamida (30 mililitros), se agita a temperatura ambiente durante 12 horas. La mezcla de reacción se apaga mediante H_2O. Se agrega EtOAc, y la capa orgánica se lava con salmuera, y se seca sobre $MgSO_4$. La concentración al vacío proporciona el 4-cloro-2-(2-hidroxi-etoxi)-benzonitrilo correspondiente. Una solución en tetrahidrofurano (6 mililitros) de 4-cloro-2-(2-hidroxi-etoxi)-benzonitrilo (875 miligramos, 4.43 milimoles) se agrega a una suspensión de LAH (504 miligramos, 13.2 milimoles) en tetrahidrofurano (45 mililitros) a 0°C. La reacción se deja agitándose durante 2 horas a temperatura ambiente y entonces se apaga mediante $Na_2SO_4 \cdot 10H_2O$, y el producto se aísla

mediante filtración con Celite, y se lava con tetrahidrofurano, y se seca bajo presión reducida, para dar el compuesto del título como un sólido incoloro; ES-MS: M+ = 202.1; HPLC: $_{A}t_{Ret}$ = 1.90 minutos.

Intermediario 114.1: 3-(2-amino-metil-5-cloro-fenoxi)-propan-1-ol

El compuesto del título se sintetiza mediante acoplamiento, seguido por reducción de 4-cloro-2-fluoro-benzonitrilo y 1,3-propandiol de una manera análoga a la preparación del Intermediario **113.1** como un sólido incoloro; ES-MS: M+ = 216.1; HPLC: $_{A}t_{Ret}$ = 2.23 minutos.

Intermediario 115.1: [2-(2-amino-metil-5-cloro-fenoxi)-etil]-dimetil-amina

El compuesto del título se sintetiza mediante acoplamiento, seguido por reducción de 4-cloro-2-fluoro-benzonitrilo y 2-dimetil-amino-etanol de una manera análoga a la preparación del Intermediario **113.1**. Aceite incoloro; ES-MS: M+ = 229.2; HPLC: $_{A}t_{Ret}$ = 1.18 minutos.

Intermediario 116.1: (2-amino-metil-5-cloro-fenil)-(3-metoxi-propil)-amina

El compuesto del título se sintetiza mediante acoplamiento, seguido por reducción de 4-cloro-2-fluoro-benzonitrilo y 3-metoxi-propil-amina de una manera análoga a la preparación del Intermediario **113.1**. Aceite incoloro; ES-MS: M- = 227.1; HPLC: $_{A}t_{Ret}$ = 2.97 minutos.

Intermediario 117.1: (2-amino-metil-5-cloro-fenil)-(2-metoxi-etil)-amina

El compuesto del título se sintetiza mediante acoplamiento, seguido por reducción de 4-cloro-2-fluoro-benzonitrilo y 3-metoxi-etil-amina de una manera análoga a la preparación del Intermediario **113.1** como un aceite incoloro; ES-MS: M- = 213.2; HPLC: $_At_{Ret}$ = 2.73 minutos.

Intermediario 118.1: 2-(2-amino-metil-5-cloro-fenil-amino)-etanol

El compuesto del título se sintetiza mediante acoplamiento, seguido por reducción de 4-cloro-2-fluoro-benzonitrilo y 2-amino-etanol de una manera análoga a la preparación del Intermediario **113.1**. Polvo incoloro; ES-MS: M- = 199.1; HPLC: $_At_{Ret}$ = 1.90 minutos.

Intermediario 119.1: 3-(2-amino-metil-5-cloro-fenil-amino)-propan-1-ol

El compuesto del título se sintetiza mediante acoplamiento, seguido por reducción de 4-cloro-2-fluoro-benzonitrilo y 3-amino-propanol de una manera análoga a la preparación del Intermediario **113.1**. Aceite incoloro; ES-MS: M- = 213.1; HPLC: $_At_{Ret}$ = 2.27 minutos.

Intermediario 120.1: N-(2-amino-metil-5-cloro-fenil)-N',N'-dimetil-etan-1,2-diamina

El compuesto del título se sintetiza mediante acoplamiento, seguido por reducción de 4-cloro-2-fluoro-benzonitrilo y 2-dimetil-

amino-etil-amina de una manera análoga a la preparación del Intermediario **113.1** como un aceite incoloro; ^{1}H-RMN ($CDCl_3$) δ 9.20 (bs, 1H), 7.18-7.10 (m, 2H), 6.95 (d, 1H), 4.60 (s, 2H), 3.80 (s, 2H), 3.25-3.05 (m, 4H), 2.25 (s, 6H).;HPLC: $_At_{Rel}$ = 1.26 minutos.

Intermediario 124.1: Sal de 1-metil-4-(S)-pirrolidin-3-il-piperazina • 2HBr

El compuesto del título se sintetiza mediante la condensación del **Intermediario 89.3** y 1-metil-piperazina de una manera análoga a la preparación del Intermediario **89.1** como un polvo amarillo; ES-MS: M+H = 170.2 (base libre); ^{1}H-RMN (DMSO-d_6) δ 9.48 (s, 1H), 4.76-4.59 (m, 1H), 3.42 (d, 2H), 3.39-3-22 (m, 2H), 3.18-2.82 (m, 6H), 2.79 (s, 3H), 2.43-2.14 (m, 2H), 2.09-2.03 (m, 1H), 1.79-1.72 (m, 1H).

Intermediario 125.1: Sal de 2-((S)-4-pirrolidin-3-il-piperazin-1-il)-etanol • 2HBr

El compuesto del título se sintetiza mediante la condensación del **Intermediario 89.3** y 2-piperazin-1-il-etanol de una manera análoga a la preparación del Intermediario **89.1** como un polvo amarillo; ES-MS: M+2H = 402.0; ^{1}H-RMN (MeOH-d_4) δ 4.42-4.40 (m, 2H), 3.98-3.94 (m, 1H), 3.79-3.76 (m, 1H), 3.65-3.61 (m, 1H), 3.59-3.39 (m, 6H), 3.21-2.99 (m, 4H), 2.39-2.23 (m, 2H), 2.19-2.14 (m, 2H).

Intermediario 126.1: Sal de N,N-dimetil-N'-(S)-pirrolidin-3-il-propan-1,3-diamina · 3HBr

El compuesto del título se sintetiza mediante la condensación del **Intermediario 89.3** y 3-dimetil-amino-propil-amina de una manera

análoga a la preparación del Intermediario **89.1** como un polvo amarillo; ES-MS: ES-MS: M+H = 158.1;. ^{1}H-RMN (MeOH-d_4) δ 4.29.4.19 (m, 1H), 3.84 (dd, 1H), 3.69-3.60 (m, 3H), 3.49-3.41 (m, 1H), 3.39-3.25 (m, 4H), 2.97 (s, 6H), 2.62-2.57 (m, 1H), 2.42-2.37 (m, 1H), 2.35-2.21 (m, 2H).

Intermediario 127.1: Sal de N,N,N'-Trimetil-N'-(S)-pirrolidin-3-il-etan-1,2-diamina · 3HBr

El compuesto del título se sintetiza mediante la condensación del **Intermediario 89.3** y 2-dimetil-amino-etil-amina de una manera análoga a la preparación del Intermediario **89.1** como un polvo amarillo; ES-MS: M+H = 172.1; ^{1}H-RMN (MeOH-d_4) δ 4.47-4.39 (m, 1H), 3.95-3.94 (m, 1H), 3.81-3.73 (m, 5H), 3.68-3.62 (m, 1H), 3.45-3.38 (m, 1H), 3.08-2.97 (m, 9H), 2.70-2.62 (m, 1H), 2.50-2.43 (m, 1H).

Intermediario 128.1: Sal de 1,1-dióxido de (S)-4-pirrolidin-3-il-tiomorfolina · 2HBr

El compuesto del título se sintetiza mediante la condensación del **Intermediario 89.3** y 1,1-dióxido de tiomorfolina, de una manera análoga a la preparación del Intermediario **89.1** como un polvo amarillo; ES-MS: M+H = 201.5..

Intermediario 129.1: Sal de dietil-(S)-pirrolidin-3-il-amina • 2HBr

El compuesto del título se sintetiza mediante la condensación del **Intermediario 89.3** y dietil-amina, de una manera análoga a la preparación del Intermediario **89.1** como un polvo amarillo; ES-MS:

M+H = 143.1; ^{1}H-RMN (MeOH-d_4) δ 4.37 (quinteto, 1H), 3.91-3.83 (m, 1H), 3.69-3.61 (m, 2H), 3.44-3.23 (m, 5H), 2.62-2.58 (m, 1H), 2.39-2.28 (m, 2H), 1.39 (t, 6H).

Intermediario 130.1: Ácido 3-[3-(4-cloro-bencil)-5-fenil-3H-imidazol-4-il]-6-ciano-1H-indol-2-carboxílico (el cual también es un compuesto de la fórmula I de acuerdo con la invención)

El compuesto del título se sintetiza mediante la hidrólisis del Intermediario **130.2** de una manera análoga a la preparación del Intermediario **2.1** como un sólido incoloro; ES-MS: M+ = 453.1; HPLC: $_At_{Ret}$ = 3.81 minutos.

Intermediario 130.2: Metil-éster del ácido 3-[3-(4-cloro-bencil)-5-fenil-3H-imidazol-4-il]-6-ciano-1H-indol-2-carboxílico (el cual también es un compuesto de la fórmula I de acuerdo con la invención)

El compuesto del título se sintetiza mediante la condensación del **Intermediario 130.3**, 4-cloro-bencil-amina, y 1-(isociano-fenil-metan-sulfonil)-4-metil-benceno de una manera análoga a la preparación del Intermediario **2.2** como un sólido color café; ES-MS: M+ = 467.1; HPLC: $_At_{Ret}$ = 4.08 minutos.

Intermediario 130.3: Metil-éster del ácido 6-ciano-3-formil-1H-indol-2-carboxílico

El compuesto del título se sintetiza mediante la formilación del metil-éster del ácido 6-ciano-1H-indol-2-carboxílico de una manera análoga a la preparación del Intermediario **2.3** como un sólido blanco; ES-MS: M- = 227.1; HPLC: $_At_{Ret}$ = 3.79 minutos.

Intermediario 132.1: 1-[isociano-(toluen-4-sulfonil)-metil]-2-metil-benceno

El compuesto del título se sintetiza mediante la condensación del 2-metil-benzaldehído de una manera análoga a la preparación del Intermediario **16.1** como un sólido blanco; ES-MS: M- = 284.1; HPLC: $_{A}t_{Ret}$ = 4.94 minutos.

Intermediario 134.1: Ácido 6-cloro-3-{3-[(S)-1-(4-cloro-fenil)-etil]-5-fenil-3H-imidazol-4-il}-1H-indol-2-carboxílico (el cual también es un compuesto de la fórmula I de acuerdo con la invención)

El compuesto del título se sintetiza mediante la hidrólisis del Intermediario **134.2** de una manera análoga a la preparación del Intermediario **2.1** como un sólido incoloro; ES-MS: M+ = 476.0; HPLC: $_{A}t_{Ret}$ = 4.33 minutos.

Intermediario 134.2: Etil-éster del ácido 6-cloro-3-{3-[(S)-1-(4-cloro-fenil)-etil]-5-fenil-3H-imidazol-4-il}-1H-indol-2-carboxílico (el cual también es un compuesto de la fórmula I de acuerdo con la invención)

El compuesto del título se sintetiza mediante la condensación del **Intermediario 2.3**, (S)-1-(4-cloro-fenil)-etil-amina, y 1-(isociano-fenil-metan-sulfonil)-4-metil-benceno de una manera análoga a la preparación del Intermediario **2.2** como un sólido color café; ES-MS: M+ = 504.0; HPLC: $_{A}t_{Ret}$ = 4.77 minutos.

Ejemplo 137: Amida del ácido 6-cloro-3-[3-(3,3-dimetil-butil)-5-fenil-3H-imidazol-4-il]-1H-indol-2-carboxílico

Una mezcla del Intermediario **137.1** (50 miligramos, 0.11 milimoles) y una solución en metanol 7M de amoníaco (2 mililitros, 14 milimoles) se calienta a 60°C. Después de completarse, la mezcla de reacción se deja enfriar a temperatura ambiente, se diluye con EtOAc, y se lava con salmuera, se seca sobre $MgSO_4$ y se evapora al vacío. La cromatografía por evaporación instantánea en gel de sílice del residuo proporciona el compuesto del título como un polvo incoloro; ES-MS: M+ = 421.1; HPLC: ${}_At_{Ret}$ = 4.18 minutos.

Intermediario 137.1: Etil-éster del ácido 6-cloro-3-[3-(3,3-dimetil-butil)-5-fenil-3H-imidazol-4-il]-1H-indol-2-carboxílico (el cual también es un compuesto de la fórmula I de acuerdo con la invención)

El compuesto del título se sintetiza mediante la condensación del **Intermediario 2.3**, 3,3-dimetil-butil-amina, y 1-(isociano-fenil-metan-sulfonil)-4-metil-benceno, de una manera análoga a la preparación del Intermediario **2.2** como un sólido incoloro; ES-MS: M+ = 450.0; HPLC: ${}_At_{Ret}$ = 4.77 minutos.

Ejemplo 138: Amida del ácido 6-cloro-3-[3-(3,3-dimetil-butil)-5-fenil-3H-imidazol-4-il]-1H-indol-2-carboxílico

El compuesto del título se sintetiza mediante la condensación del **Intermediario 2.2** de una manera análoga a la preparación del Ejemplo **137** como un sólido incoloro; ES-MS: M+ = 462.9; HPLC: ${}_At_{Ret}$ = 4.17 minutos.

Ejemplo 139: 6-cloro-3-[3-(4-cloro-bencil)-5-fenil-3H-imidazol-4-il]-2-(1H-tetrazol-5-il)-1H-indol

Una mezcla del Ejemplo **139.1** (37 miligramos, 0.08 milimoles) y azida de sodio (16 miligramos, 0.25 moles) en 2-metoxi-etanol (0.5 mililitros) se calienta a 130°C. Después de completarse, la mezcla de reacción se deja enfriar a temperatura ambiente, se diluye con EtOAc, y se lava con salmuera, se seca sobre $MgSO_4$ y se evapora al vacío. La cromatografía por evaporación instantánea en gel de sílice del residuo proporciona el compuesto del título como un polvo incoloro; ES-MS: M+H = 487.9; HPLC: ${}_At_{Ret}$ = 4.32 minutos.

Intermediario 139.1: 6-cloro-3-[3-(4-cloro-bencil)-5-fenil-3H-imidazol-4-il]-1H-indol-2-carbonitrilo (al mismo tiempo un compuesto de la fórmula I de acuerdo con la invención)

Una mezcla del Ejemplo **138** (150 miligramos, 0.33 milimoles) y TFAA (1.5 mililitros) en dicloro-metano (1.5 mililitros) se calienta a reflujo. Después de completarse, la mezcla de reacción se apaga mediante $NaHCO_3$ acuoso saturado. Se agrega dicloro-metano, y la capa orgánica se lava con salmuera, se seca sobre $MgSO_4$ y se evapora al vacío. La cromatografía por evaporación instantánea en gel de sílice del residuo proporciona el compuesto del título como un polvo incoloro; ES-MS: M+H = 444.9: ${}_At_{Ret}$ = 4.44.

Ejemplo 140: {6-cloro-3-[3-(4-cloro-bencil)-5-fenil-3H-imidazol-4-il]-1H-indol-2-il}-metanol

Una mezcla del Intermediario **2.2** (470 miligramos, 0.92

milimoles) y LAH (70 miligramos, 1.84 milimoles) en tetrahidrofurano (4.8 mililitros) se agita a temperatura ambiente durante 1 hora y entonces se pone a reflujo durante 2 horas. Se agrega EtOAc, y la capa orgánica se lava con salmuera, se seca sobre $MgSO_4$ y se evapora al vacío. La cromatografía por evaporación instantánea en gel de sílice del residuo proporciona el compuesto del título como un polvo incoloro; ES-MS: M+H = 449.9; HPLC: ${}_At_{Ret}$ = 4.29 minutos.

Ejemplo 141: {6-cloro-3-[3-(4-cloro-bencil)-5-fenil-3H-imidazol-4-il]-1H-indol-2-il-metil}-(2-morfolin-4-il-etil)-amina

Una mezcla del Ejemplo **2** (101 miligramos, 0.18 milimoles), $AlCl_3$ (117 miligramos, 0.88 milimoles), y LAH (33 miligramos, 0.88 milimoles), en tetrahidrofurano (2 mililitros), se pone a reflujo. Después de completarse, la mezcla de reacción se apaga mediante tartrato de sodio y potasio, y se neutraliza mediante $NaHCO_3$ acuoso saturado. Se agrega EtOA, y la capa orgánica se lava con salmuera, se seca sobre $MgSO_4$ y se evapora al vacío. La cromatografía por evaporación instantánea en gel de sílice del residuo proporciona el compuesto del título como un polvo incoloro; ES-MS: M+H = 561.8: ${}_At_{Ret}$ = 3.74 minutos.

Ejemplo 142: 3-[1-(4-cloro-bencil)-5-(6-cloro-5-fluoro-1H-indol-3-il)-1H-imidazol-4-il]-fenol

Una solución del Intermediario **142.1** (40 miligramos, 0.08 milimoles) en dicloro-metano (2 mililitros) se trata mediante una solución 1M de BBr_3 (0.34 mililitros, 0.34 milimoles) en dicloro-metano a temperatura ambiente y se calienta a 40°C. Después de

completarse, la mezcla de reacción se apaga mediante MeOH, y se neutraliza mediante $NaHCO_3$ acuoso saturado. Se agrega diclorometano, y la capa orgánica se lava con salmuera, se seca sobre $MgSO_4$ y se evapora al vacío. La cromatografía por evaporación instantánea en gel de sílice del residuo proporciona el compuesto del título como un polvo incoloro; ES-MS: M+ = 452.0: $_At_{Ret}$ = 4.20 minutos.

Intermediario 142.1: 6-cloro-3-[3-(4-cloro-bencil)-5-(3-metoxi-fenil)-3H-imidazol-4-il]-5-fluoro-1H-indol (al mismo tiempo un compuesto de la fórmula I de acuerdo con la invención)

El compuesto del título se sintetiza mediante la condensación del **Intermediario 10.1**, 4-cloro-bencil-amina, y el **Intermediario 142.2**, de una manera análoga a la preparación del Intermediario **2.2** como un sólido incoloro; ES-MS: M+ = 466.0; HPLC: $_At_{Ret}$ = 4.55 minutos.

Intermediario 142.2: 1-[isociano-(toluen-4-sulfonil)-metil]-3-metoxi-benceno

El compuesto del título se sintetiza mediante la condensación del 3-metoxi-benzaldehído de una manera análoga a la preparación del Intermediario **16.1** como un sólido incoloro; ^{1}H-RMN (DMSO-d_6) δ 7.65 (d, 2H), 7.50 (d, 2H), 7.40 (t, 1H), 7.10-7.05 (m, 1H), 6.90-6.80 (m, 3H), 3.70 (s, 3H), 2.40 (s, 3H);HPLC: $_At_{Ret}$ = 4.75 minutos.

Ejemplo 143: {6-cloro-3-[3-(4-cloro-bencil)-5-(3-hidroxi-fenil)-3H-imidazol-4-il]-1H-indol-2-il}-((S)-3-dimetil-amino-pirrolidin-1-il)-metanona

El compuesto del título se sintetiza mediante la desalquilación del Intermediario **143.1** de una manera análoga a la preparación del Ejemplo **142** como un sólido incoloro; ES-MS: M+ = 574.0; HPLC: $_{A}t_{Ret}$ = 3.56 minutos.

Intermediario 143.1: {6-cloro-3-[3-(4-cloro-bencil)-5-(3-metoxi-fenil)-3H-imidazol-4-il]-1H-indol-2-il}-((S)-3-dimetil-amino-pirrolidin-1-il)-metanona (al mismo tiempo un compuesto de la fórmula I de acuerdo con la invención)

El compuesto del título se sintetiza mediante la condensación del **Intermediario 143.2**, 4-cloro-bencil-amina, y el Intermediario **142.2**, de una manera análoga a la preparación del Intermediario **2.2** como un sólido incoloro; ES-MS: M+ = 588.0; HPLC: $_{A}t_{Ret}$ = 3.80 minutos.

Intermediario 143.2: 6-cloro-2-((S)-3-dimetil-amino-pirrolidin-1-carbonil)-1H-indol-3-carbaldehído

El compuesto del título se sintetiza mediante la formilación del Intermediario **143.3** de una manera análoga a la preparación del Intermediario **2.3** como un sólido color café; ES-MS: M+ = 320.2; HPLC: $_{A}t_{Ret}$ = 2.91 minutos.

Intermediario 143.3: (6-cloro-1H-indol-2-il)-((S)-3-dimetil-amino-pirrolidin-1-il)-metanona

El compuesto del título se sintetiza mediante la condensación del ácido 6-cloro-1H-indol-2-carboxílico y dimetil-(S)-pirrolidin-3-il-amina, de una manera análoga a la preparación del Ejemplo **2**, como un sólido incoloro; ES-MS: M+ = 292.2; HPLC: $_{A}t_{Ret}$ = 3.15 minutos.

Ejemplo 144: 6-cloro-3-[3-(4-cloro-bencil)-2-metil-5-fenil-3H-imidazol-4-il]-1H-indol

El **Intermediario 144.1** (100 miligramos, 0.24 milimoles) y el Intermediario **144.3** (127 miligramos, 0.29 milimoles) se disuelven en 1,2 dimetoxi-etano (1 mililitro). $Pd(PPh_3)_4$ (14.6 miligramos, 0.012 milimoles), se agregan K_3PO_4 (210 miligramos, 0.96 milimoles) y H_2O (0.5 mililitros), y el recipiente de reacción se sella y se calienta a 100°C durante 3 horas. La mezcla se deja entonces enfriar a temperatura ambiente y se diluye con EtOAc. La capa orgánica se lava repetidamente con salmuera, y los lavados acuosos combinados se extraen con EtOAc . Los extractos combinados se secan y se concentran, para dar el producto crudo, el cual se purifica mediante trituración con hexanos/EtOAc, para dar el compuesto del título como un polvo grisáceo. ES-MS: M+H = 590.0, ^{1}H-RMN (DMSO-d_6) δ 8.02 (s, 1H), 7.92 (s, 1H), 7.85 (d, 2H), 7.37 (d, 2H), 7.29-7.26 (m, 2H), 7.12-7.09 (m, 3H), 7.04-7.02 (m, 3H), 6.83 (d, 1H), 6.65 (d, 2H), 4.92 (s, 2H), 2.35 (s, 3H), 2.32 (s, 3H).

Intermediario 144.1: 6-cloro-3-(4,4,5,5-tetrametil-[1,3,2]-dioxaborolan-2-il)-1-(toluen-4-sulfonil)-1H-indol

El **Intermediario 144.2** (1.0 gramos, 2.3 milimoles) se disuelve en sulfóxido de dimetilo (20 mililitros). Se agregan bis-(pinacolato)-diboro (0.89 gramos, 3.5 milimoles), $Pd(dppf)Cl_2$ (0.21 gramos, 0.23 milimoles), y KOAc (0.68 gramos, 6.9 milimoles). El recipiente de reacción se sella y se calienta con agitación a 100°C

durante 2 horas. Se deja enfriar a temperatura ambiente de nuevo, se diluye con EtOAc, y la capa orgánica se lava repetidamente con una solución acuosa saturada de $NaHCO_3$. Después del secado y la evaporación de los solventes, el producto crudo se purifica mediante cromatografía por evaporación instantánea (SiO_2; hexanos/EtOAc, gradiente del 0 al 30 por ciento de EtOAc), para dar el compuesto del título como un polvo blanco. ^{1}H-RMN ($CDCl_3$) δ 7.95 (s, 2H), 7.84-7.79 (m, 3H), 7.27-7.20 (m, 3H), 1.35 (s, 12H).

Intermediario 144.2: 6-cloro-3-yodo-1-(toluen-4-sulfonil)-1H-indol

Una mezcla del 6-cloro-1H-indol (2.0 gramos, 13.2 milimoles) y NIS (4.45 gramos, 19.8 milimoles) en tetrahidrofurano (60 mililitros) se agita a 0°C. Después de completarse, la mezcla de reacción se apaga mediante H_2O. Se agrega EtOAc, y la capa orgánica se lava con salmuera, se seca sobre $MgSO_4$ y se evapora al vacío. La cromatografía por evaporación instantánea en gel de sílice del residuo proporciona el 6-cloro-3-yodo-1H-indol como un polvo incoloro. Una mezcla del 6-cloro-3-yodo-1H-indol (4.14 gramos, 13.2 milimoles), TsCl (3.77 gramos, 19.8 milimoles), TBAHS (672 miligramos, 1.98 milimoles) y NaOH (16.0 gramos, 400 milimoles) en tetrahidrofurano (60 mililitros) y H_2O (25 mililitros), se agita a temperatura ambiente. Después de completarse, la mezcla de reacción se apaga mediante H_2O. Se agrega EtOAc, y la capa orgánica se lava con salmuera, se seca sobre $MgSO_4$ y se evapora al vacío. la recristalización a partir de EtOAc del residuo proporciona el

compuesto del título como un polvo incoloro; ES-MS: M-H = 430.0: $_{CT}t_{Ret}$ = 8.66 minutos.

Intermediario 144.3: 1-(4-cloro-bencil)-5-yodo-2-metil-4-fenil-1H-imidazol

Una mezcla del Intermediario **144.4** (1.0 gramos, 3.53 milimoles) y NIS (872 miligramos, 3.88 milimoles) en CH_3CN (18 mililitros) se agita a 50°C. Después de completarse, la mezcla de reacción se apaga mediante H_2O. Se agrega EtOAc, y la capa orgánica se lava con salmuera, se seca sobre $MgSO_4$ y se evapora al vacío. La cromatografía por evaporación instantánea en gel de sílice del residuo proporciona el compuesto del título como un polvo incoloro; ES-MS: M+ = 409.0: $_{A}t_{Ret}$ = 4.06 minutos.

Intermediario 144.4: 1-(4-cloro-bencil)-2-metil-4-fenil-1H-imidazol

Una mezcla de la sal de HCl de 2-metil-4-fenil-1H-imidazol (1.51 gramos, 7.75 milimoles), bromuro de 4-cloro-bencilo (1.75 gramos, 8.53 milimoles), y NaH (745 miligramos, 18.6 milimoles) en dimetil-formamida (20 mililitros), se agita a temperatura ambiente. Después de completarse, la mezcla de reacción se apaga mediante H_2O. Se agrega EtOAc, y la capa orgánica se lava con salmuera, se seca sobre $MgSO_4$ y se evapora al vacío. La cromatografía por evaporación instantánea en gel de sílice del residuo proporciona el compuesto del título como un polvo incoloro; ES-MS: M+ = 283.1: $_{A}t_{Ret}$ = 3.93 minutos.

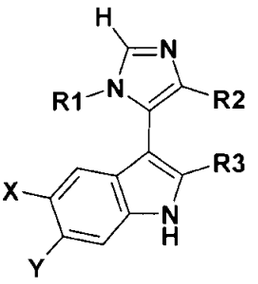
Ejemplo 145: Etil-éster del ácido 6-bromo-3-[2-cloro-3-(4-cloro-bencil)-5-fenil-3H-imidazol-4-il]-1H-indol-2-carboxílico

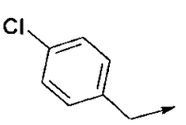
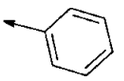
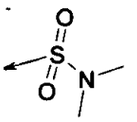
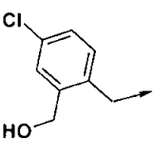
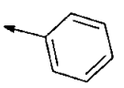
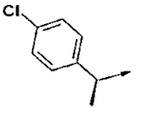
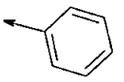
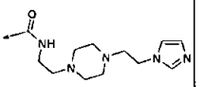
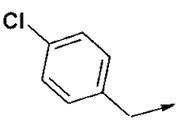
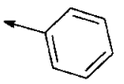
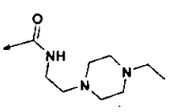
Una mezcla del Intermediario **2.2** (98 miligramos, 0.20 milimoles) y NBS (39 miligramos, 0.22 milimoles) en tetrahidrofurano (1.0 mililitros) se agita a temperatura ambiente durante 3 horas. Después de completarse, la mezcla de reacción se apaga mediante $NaHCO_3$ acuoso saturado. Se agrega EtOAc, y la capa orgánica se lava con salmuera, se seca sobre $MgSO_4$ y se evapora al vacío. La cromatografía por evaporación instantánea en gel de sílice del residuo proporciona el compuesto del título como un polvo incoloro; ES-MS: M+ = 569.7: ${}_{A}t_{Ret}$ = 5.76 minutos.

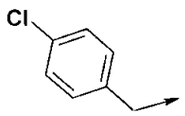
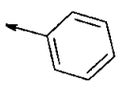
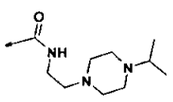
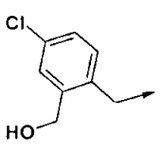
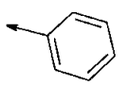
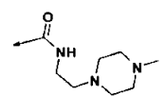
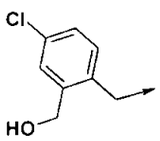
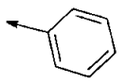
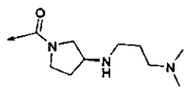
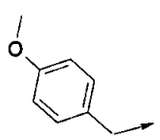
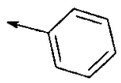
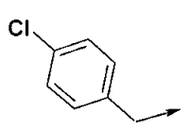
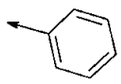
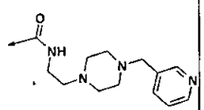
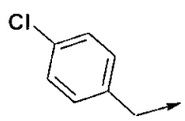
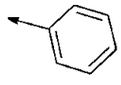
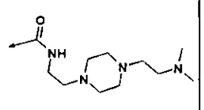
Ejemplo 146: Etil-éster del ácido 6-cloro-3-[2-cloro-3-(4-cloro-bencil)-5-fenil-3H-imidazol-4-il]-1H-indol-2-carboxílico

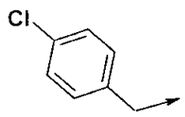
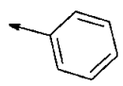
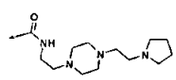
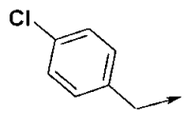
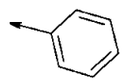
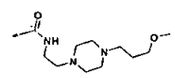
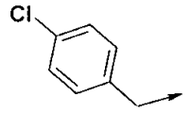
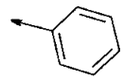
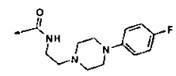
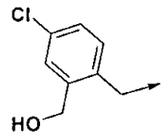
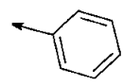
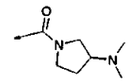
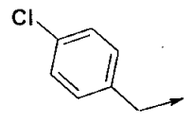
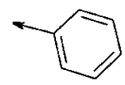
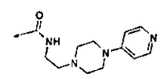
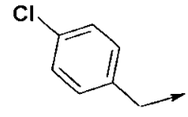
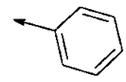
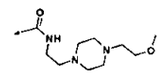
Una mezcla del Intermediario **2.2** (151 miligramos, 0.31 milimoles) y NCS (90 miligramos, 0.67 milimoles) en tetrahidrofurano (1.5 mililitros) se agita a 60°C durante 1 hora. Después de completarse, la mezcla de reacción se apaga mediante $NaHCO_3$ acuoso saturado. Se agrega EtOAc, y la capa orgánica se lava con salmuera, se seca sobre $MgSO_4$ y se evapora al vacío. La cromatografía por evaporación instantánea en gel de sílice del residuo proporciona el compuesto del título como un polvo incoloro; ES-MS: M+H = 525.8: ${}_{A}t_{Ret}$ = 5.83 minutos.

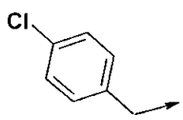
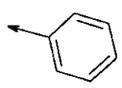
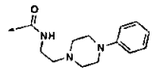
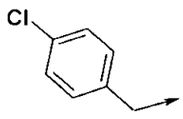
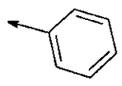
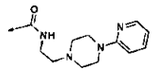
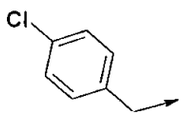
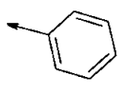
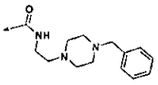
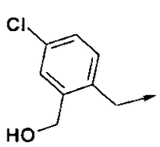
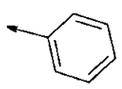
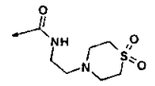
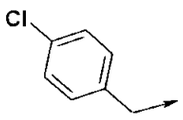
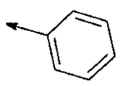
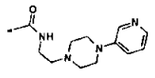
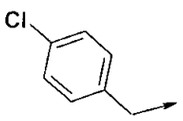
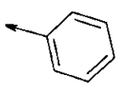
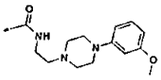
Tabla 2 de Ejemplos Adicionales:

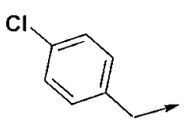
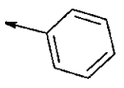
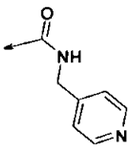
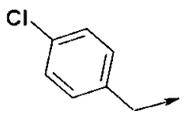
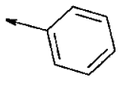
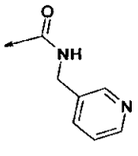
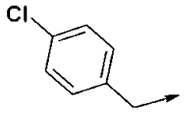
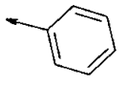
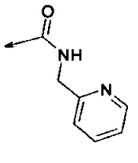
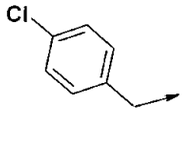
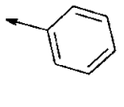
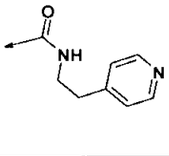
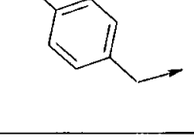
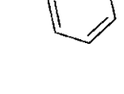
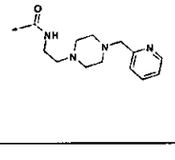
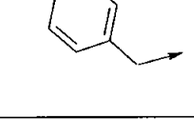
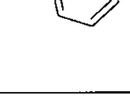
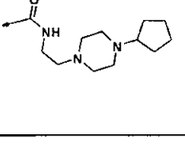


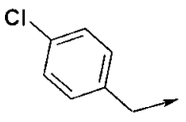
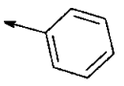
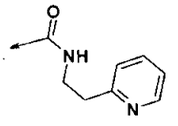
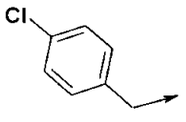
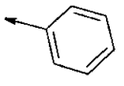
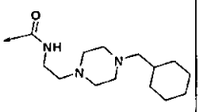
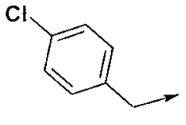
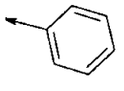
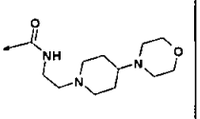
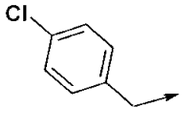
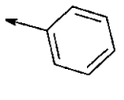
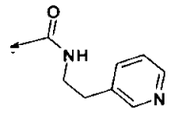
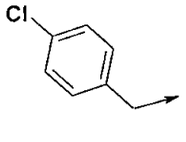
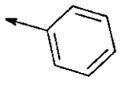
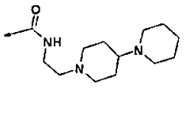
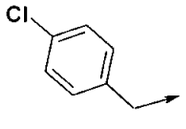
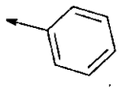
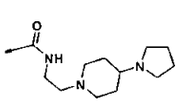
Ejemplo	X e Y	R^1	R^2	R^3	Análisis MS/HPLC/RMN
147	X=H Y=Cl				M+= 525.0 $_At_{Ret}$ = 4.51 min
148	X=F Y=Cl			H	M+H= 466.0 $_Ct_{Ret}$ = 6.07 min
149	X=H Y=Cl				M+H= 681.0 $_Ct_{Ret}$ = 5.45 min
150	X=H Y=Cl				M+= 601.0 $_At_{Ret}$ = 3.69 min

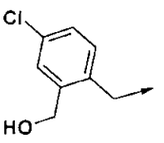
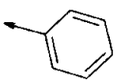
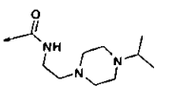
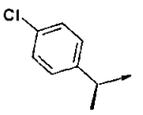
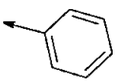
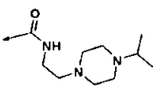
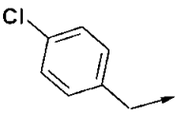
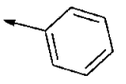
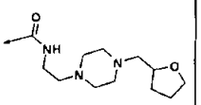
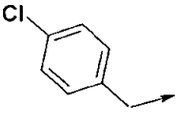
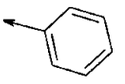
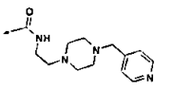
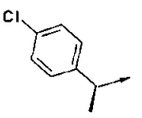
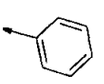
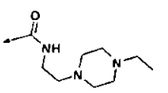
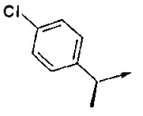
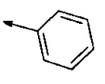
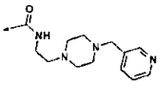
Ejemplo	X e Y	R^1	R^2	R^3	Análisis MS/HPLC/RMN
151	X=H Y=Cl				M+= 615.0 $_{A}t_{Ret}$ = 3.67 min
152	X=H Y=Cl				M+H= 617.0 $_{C}t_{Ret}$ = 5.26 min
153	X=H Y=Cl				M+H= 659.0 $_{C}t_{Ret}$ = 5.12 min
154	X=F Y=Cl			H	M+H= 432.1 $_{C}t_{Ret}$ = 6.18 min
155	X=H Y=Cl				M+= 664.0 $_{A}t_{Ret}$ = 3.59 min
156	X=H Y=Cl				M+= 643.9 $_{A}t_{Ret}$ = 3.67 min

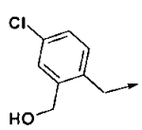
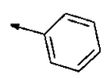
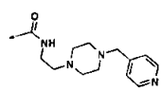
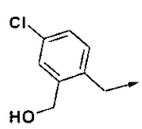
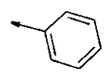
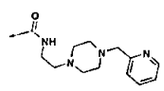
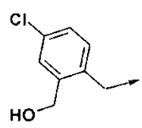
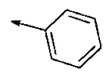
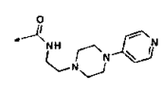
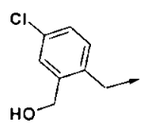
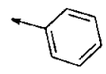
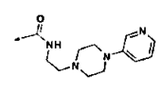
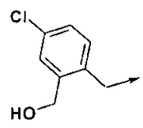
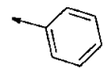
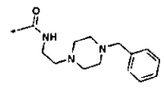
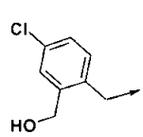
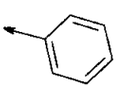
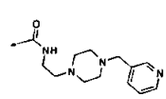
Ejemplo	X e Y	R^1	R^2	R^3	Análisis MS/HPLC/RMN
157	X=H Y=Cl				M+= 670.0 $_{A}t_{Ret}$ = 3.66 min
158	X=H Y=Cl				M+= 645.1 $_{A}t_{Ret}$ = 3.77 min
159	X=H Y=Cl				M+= 666.9 $_{A}t_{Ret}$ = 4.34 min
160	X=H Y=Cl				M+H= 588.0 $_{C}t_{Ret}$ = 5.31 min
161	X=H Y=Cl				M+= 650.0 $_{A}t_{Ret}$ = 3.66 min
162	X=H Y=Cl				M+= 631.0 $_{A}t_{Ret}$ = 3.69 min

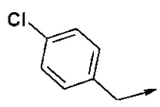
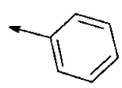
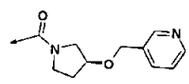
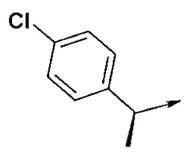
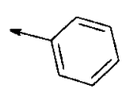
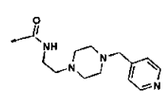
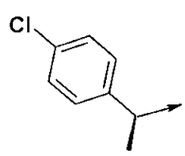
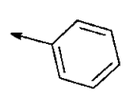
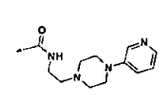
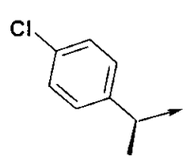
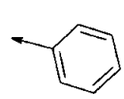
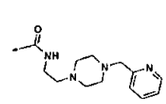
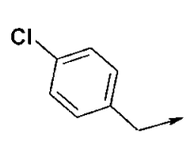
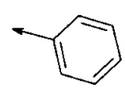
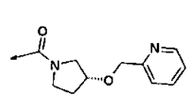
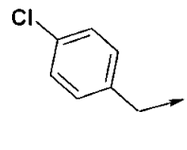
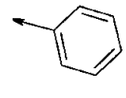
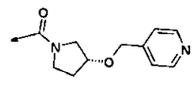
Ejem-plo	X e Y	R^1	R^2	R^3	Análisis MS/HPLC/RMN
163	X=H Y=Cl				M+= 648.9 $_At_{Ret}$ = 4.23 min
164	X=H Y=Cl				M+= 649.9 $_At_{Ret}$ = 3.65 min
165	X=H Y=Cl				M+= 662.9 $_At_{Ret}$ = 3.99 min
166	X=H Y=Cl				M+H= 651.9 $_Ct_{Ret}$ = 5.57 min
167	X=H Y=Cl				M+= 649.9 $_At_{Ret}$ = 3.58 min
168	X=H Y=Cl				M+= 678.9 $_At_{Ret}$ = 4.30 min

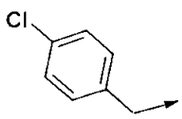
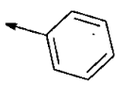
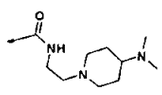
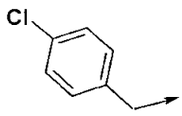
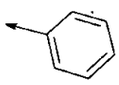
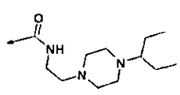
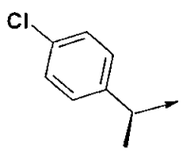
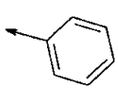
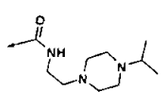
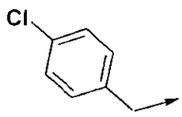
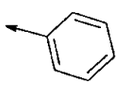
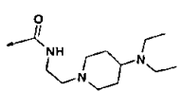
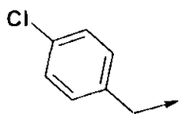
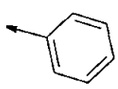
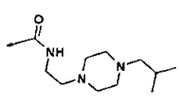
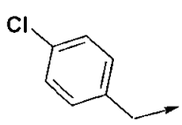
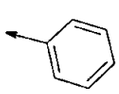
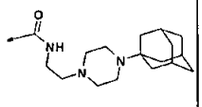
Ejemplo	X e Y	R^1	R^2	R^3	Análisis MS/HPLC/RMN
169	X=H Y=Cl				M+= 551.9 $_At_{Ret}$ = 3.71 min
170	X=H Y=Cl				M+= 551.9 $_At_{Ret}$ = 3.73 min
171	X=H Y=Cl				M+= 551.9 $_At_{Ret}$ = 3.81 min
172	X=H Y=Cl				M+= 565.9 $_At_{Ret}$ = 3.74 min
173	X=H Y=Cl				M+= 664.0 $_At_{Ret}$ = 3.72 min
174	X=H Y=Cl				M+= 641.0 $_At_{Ret}$ = 3.91 min

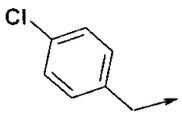
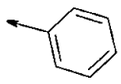
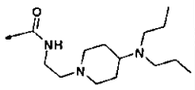
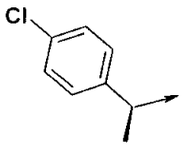
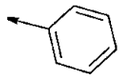
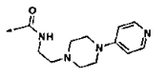
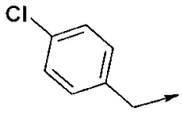
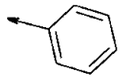
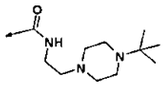
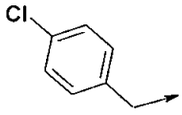
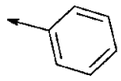
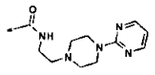
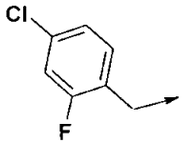
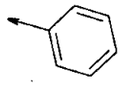
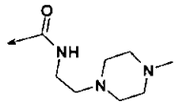
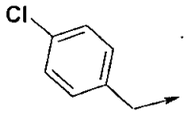
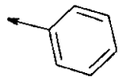
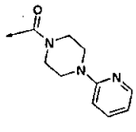
Ejemplo	X e Y	R^1	R^2	R^3	Análisis MS/HPLC/RMN
175	X=H Y=Cl				M+= 566.0 $_At_{Ret}$ = 3.80 min
176	X=H Y=Cl				M+= 669.0 $_At_{Ret}$ = 4.11 min
177	X=H Y=Cl				M+= 656.9 $_At_{Ret}$ = 3.61 min
178	X=H Y=Cl				M+= 565.9 $_At_{Ret}$ = 3.82 min
179	X=H Y=Cl				M+= 655.0 $_At_{Ret}$ = 3.67 min
180	X=H Y=Cl				M+= 641.0 $_At_{Ret}$ = 3.62 min

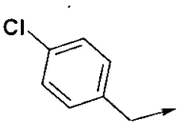
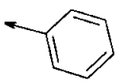
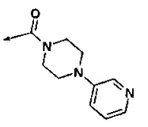
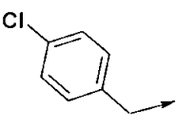
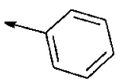
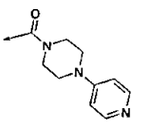
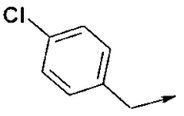
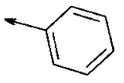
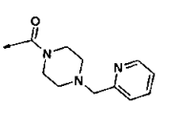
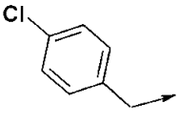
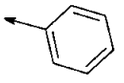
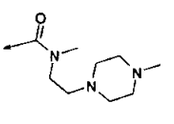
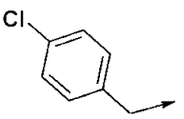
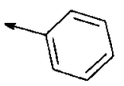
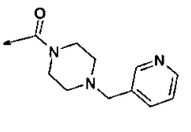
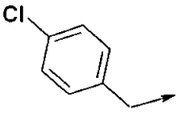
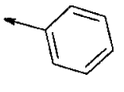
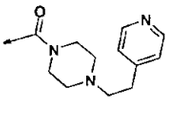
Ejem-plo	X e Y	R^1	R^2	R^3	Análisis MS/HPLC/RMN
181	X=H Y=Cl				M+H= 644.9 $_{C}t_{Ret}$ = 5.36 min
182	X=H Y=Cl				M+H= 629.0 $_{C}t_{Ret}$ = 5.70 min
183	X=H Y=Cl				M+= 656.9 $_{A}t_{Ret}$ = 3.82 min
184	X=H Y=Cl				M+= 663.9 $_{A}t_{Ret}$ = 3.50 min
185	X=H Y=Cl				M+H= 614.9 $_{C}t_{Ret}$ = 5.64 min
186	X=H Y=Cl				M+H= 677.9 $_{C}t_{Ret}$ = 5.53 min

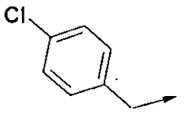
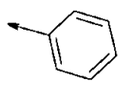
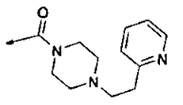
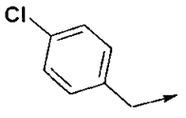
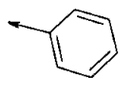
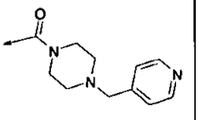
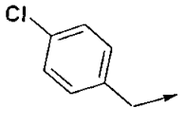
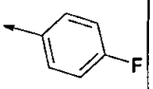
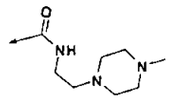
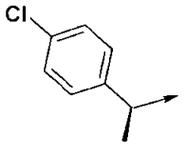
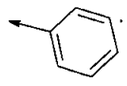
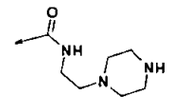
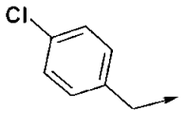
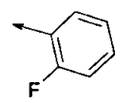
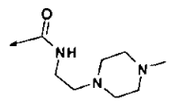
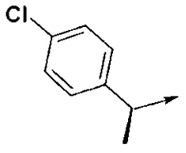
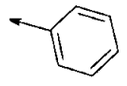
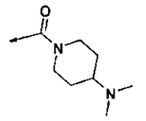
Ejemplo	X e Y	R^1	R^2	R^3	Análisis MS/HPLC/RMN
187	X=H Y=Cl				M+= 693.9 $_At_{Ret}$ = 3.33 min
188	X=H Y=Cl				M+= 693.9 $_At_{Ret}$ = 3.44 min
189	X=H Y=Cl				M+= 680.0 $_At_{Ret}$ = 3.32 min
190	X=H Y=Cl				M+= 679.9 $_At_{Ret}$ = 3.31 min
191	X=H Y=Cl				M+= 692.9 $_At_{Ret}$ = 3.86 min
192	X=H Y=Cl				M+= 693.9 $_At_{Ret}$ = 3.37 min

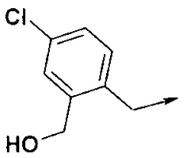
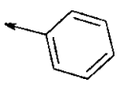
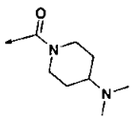
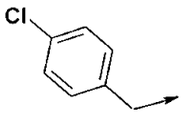
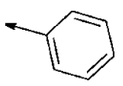
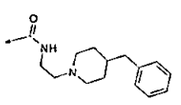
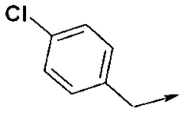
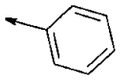
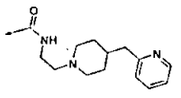
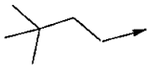
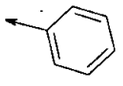
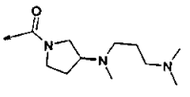
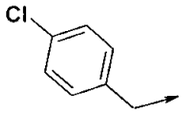
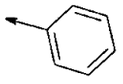
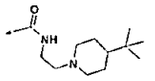
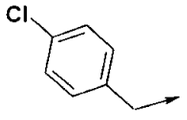
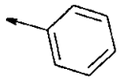
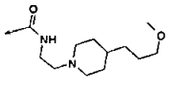
Ejemplo	X e Y	R^1	R^2	R^3	Análisis MS/HPLC/RMN
193	X=H Y=Cl				M+= 621.9 $_{A}t_{Ret}$ = 3.82 min
194	X=H Y=Cl				M+H= 678.0 $_{C}t_{Ret}$ = 5.53 min
195	X=H Y=Cl				M+H= 664.0 $_{C}t_{Ret}$ = 5.55 min
196	X=H Y=Cl				M+H= 678.1 $_{C}t_{Ret}$ = 5.59 min
197	X=H Y=Cl				M+= 621.9 $_{A}t_{Ret}$ = 3.87 min
198	X=H Y=Cl				M+= 622.0 $_{A}t_{Ret}$ = 3.79 min

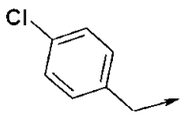
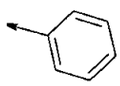
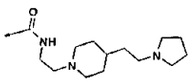
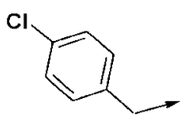
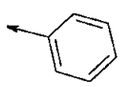
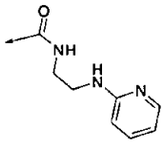
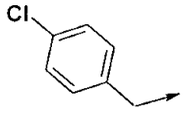
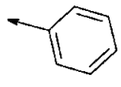
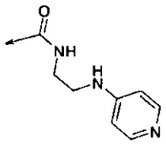
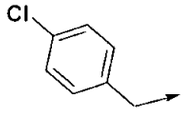
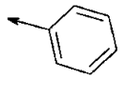
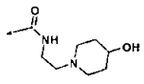
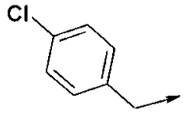
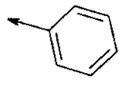
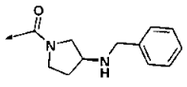
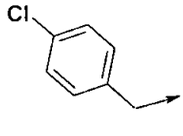
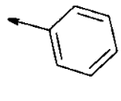
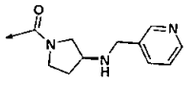
Ejemplo	X e Y	R^1	R^2	R^3	Análisis MS/HPLC/RMN
199	X=H Y=Cl				M+= 615.0 $_At_{Ret}$ = 3.54 min
200	X=H Y=Cl				M+= 643.0 $_At_{Ret}$ = 3.94 min
201	X=H Y=Cl				M+H= 629.0 $_Ct_{Ret}$ = 5.47 min
202	X=H Y=Cl				M+= 643.0 $_At_{Ret}$ = 3.75 min
203	X=H Y=Cl				M+= 629.0 $_At_{Ret}$ = 3.91 min
204	X=H Y=Cl				M+= 707.0 $_At_{Ret}$ = 4.20 min

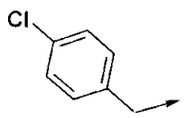
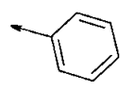
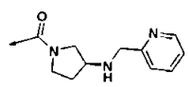
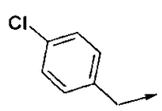
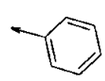
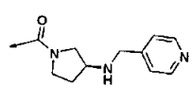
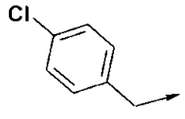
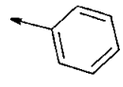
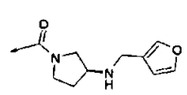
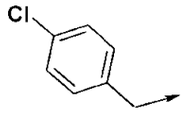
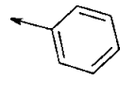
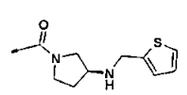
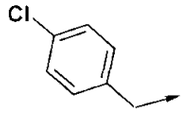
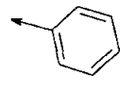
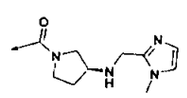
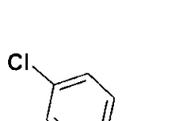
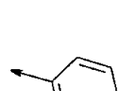
Ejem-plo	X e Y	R^1	R^2	R^3	Análisis MS/HPLC/RMN
205	X=H Y=Cl				M+= 671.0 $_At_{Ret}$ = 3.96 min
206	X=H Y=Cl				M+H= 663.9 $_Ct_{Ret}$ = 5.66 min
207	X=H Y=Cl				M+= 628.9 $_At_{Ret}$ = 3.72 min
208	X=H Y=Cl				M+= 651.0 $_At_{Ret}$ = 4.01 min
209	X=H Y=Cl				M+H= 604.8 $_Ct_{Ret}$ = 5.69 min
210	X=H Y=Cl				M+H= 607.0 $_Ct_{Ret}$ = 5.77 min

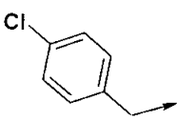
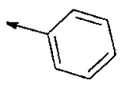
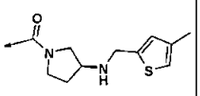
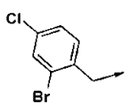
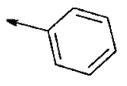
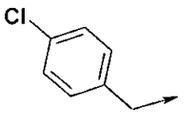
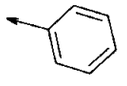
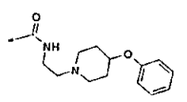
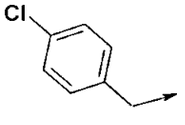
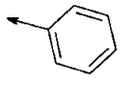
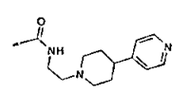
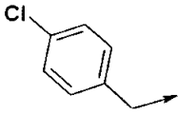
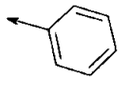
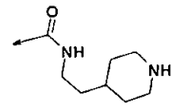
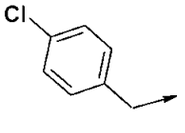
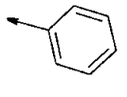
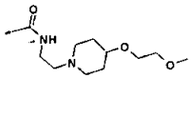
Ejemplo	X e Y	R^1	R^2	R^3	Análisis MS/HPLC/RMN
211	X=H Y=Cl				M+H= 607.0 $_ct_{Ret}$ = 5.72 min
212	X=H Y=Cl				M+H= 607.0 $_ct_{Ret}$ = 5.72 min
213	X=H Y=Cl				M+H= 621.0 $_ct_{Ret}$ = 5.81 min
214	X=H Y=Cl				M+H= 601.0 $_ct_{Ret}$ = 5.54 min
215	X=H Y=Cl				M+H= 621.0 $_ct_{Ret}$ = 5.56 min
216	X=H Y=Cl				M+H= 635.0 $_ct_{Ret}$ = 5.40 min

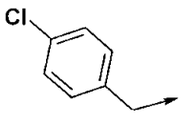
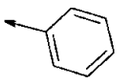
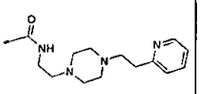
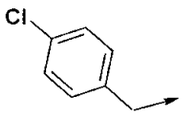
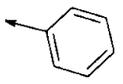
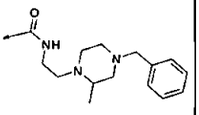
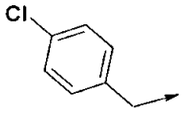
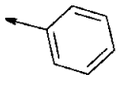
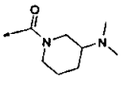
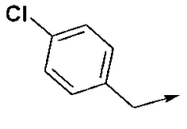
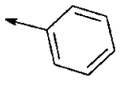
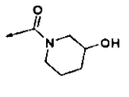
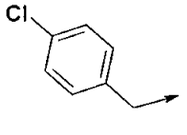
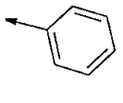
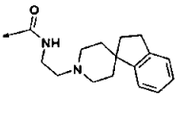
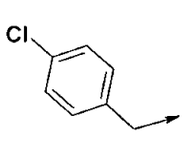
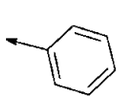
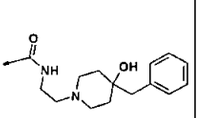
Ejemplo	X e Y	R^1	R^2	R^3	Análisis MS/HPLC/RMN
217	X=H Y=Cl				M+H= 635.0 $_{c}t_{Ret}$ = 5.56 min
218	X=H Y=Cl				M+H= 621.0 $_{c}t_{Ret}$ = 5.61 min
219	X=H Y=Cl				M+H= 605.0 $_{c}t_{Ret}$ = 5.58 min
220	X=H Y=Cl				M+H= 587.1 $_{c}t_{Ret}$ = 5.52 min
221	X=H Y=Cl				M+H= 605.0 $_{c}t_{Ret}$ = 5.48 min
222	X=H Y=Cl				M+H= 586.0 $_{c}t_{Ret}$ = 5.76 min

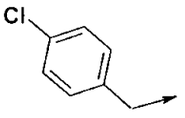
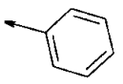
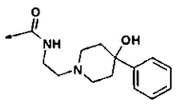
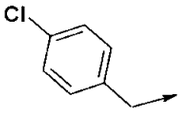
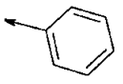
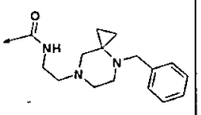
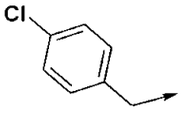
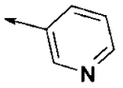
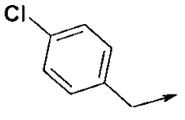
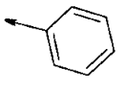
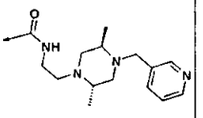
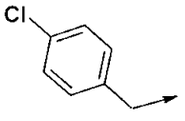
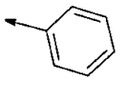
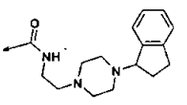
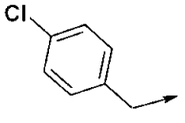
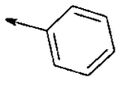
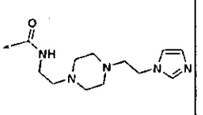
Ejem-plo	X e Y	R^1	R^2	R^3	Análisis MS/HPLC/RMN
223	X=H Y=Cl				M+H= 602.0 $_{C}t_{Ret}$ = 5.38 min
224	X=H Y=Cl				M+= 662.0 $_{A}t_{Ret}$ = 4.52 min
225	X=H Y=Cl				M+= 663.0 $_{A}t_{Ret}$ = 3.60 min
226	X=H Y=Cl				M+H= 589.2 $_{C}t_{Ret}$ = 5.35 min
227	X=H Y=Cl				M+H= 628.1 $_{C}t_{Ret}$ = 6.38 min
228	X=H Y=Cl				M+H= 644.0 $_{C}t_{Ret}$ = 6.00 min

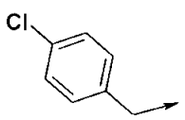
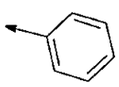
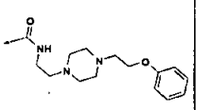
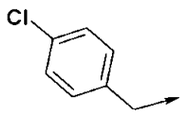
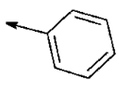
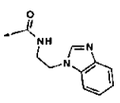
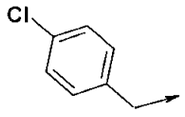
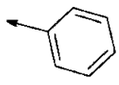
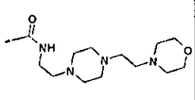
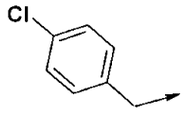
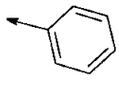
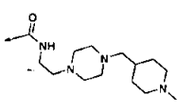
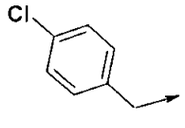
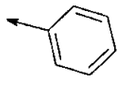
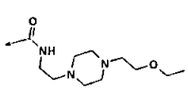
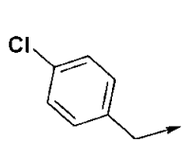
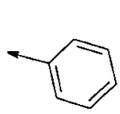
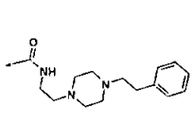
Ejemplo	X e Y	R^1	R^2	R^3	Análisis MS/HPLC/RMN
229	X=H Y=Cl				M+H= 669.0 $_{C}t_{Ret}$ = 5.52 min
230	X=H Y=Cl				M+H= 581.0 $_{C}t_{Ret}$ = 5.79 min
231	X=H Y=Cl				M+H= 581.0 $_{C}t_{Ret}$ = 5.62 min
232	X=H Y=Cl				M+H= 588.0 $_{C}t_{Ret}$ = 5.56 min
233	X=H Y=Cl				M-H = 618.0 $_{E}t_{ret}$ = 4.16 min
234	X=H Y=Cl				M-H = 620.0 $_{E}t_{ret}$ = 3.77 min

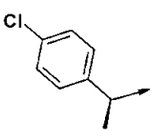
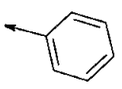
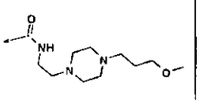
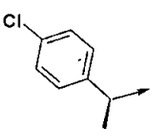
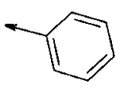
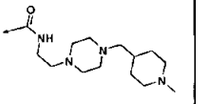
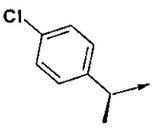
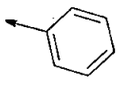
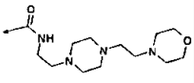
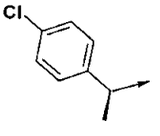
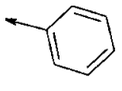
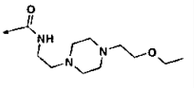
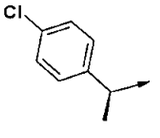
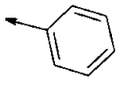
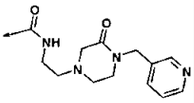
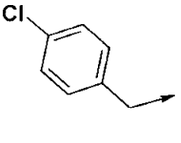
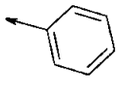
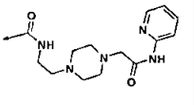
Ejemplo	X e Y	R^1	R^2	R^3	Análisis MS/HPLC/RMN
235	X=H Y=Cl				M-H = 619.0 $_Et_{ret}$ = 3.97 min
236	X=H Y=Cl				M-H = 619.2 $_Et_{ret}$ = 3.79 min
237	X=H Y=Cl				M-H = 608.1 $_Et_{ret}$ = 4.03 min
238	X=H Y=Cl				M-H = 624.0 $_Et_{ret}$ = 4.00 min
239	X=H Y=Cl				M-H = 622.1 $_Et_{ret}$ = 3.79 min
240	X=H Y=Cl				M-H = 625.0 $_Et_{ret}$ = 3.98 min

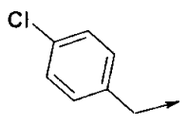
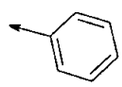
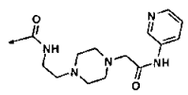
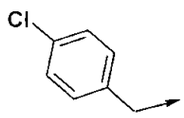
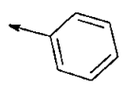
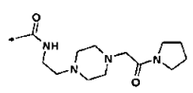
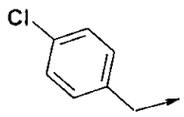
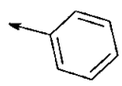
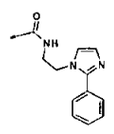
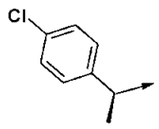
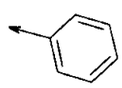
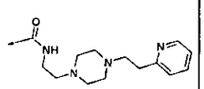
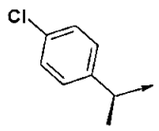
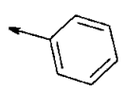
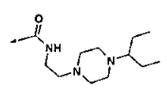
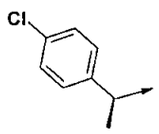
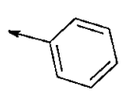
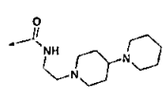
Ejemplo	X e Y	R^1	R^2	R^3	Análisis MS/HPLC/RMN
241	X=H Y=Cl				M-H = 638.0 $_Et_{ret}$ = 4.22 min
242	X=F Y=Cl			H	M+H= 515.8 $_Ct_{Ret}$ = 6.55 min
243	X=H Y=Cl				M+H= 664.0 $_Ct_{Ret}$ = 5.25 min
244	X=H Y=Cl				M+H= 649.0 $_Ct_{Ret}$ = 5.42 min
245	X=H Y=Cl				M+H= 572.0 $_Ct_{Ret}$ = 5.58 min
246	X=H Y=Cl				M+= 646.0 $_At_{Ret}$ = 3.91 min

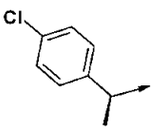
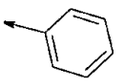
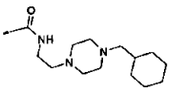
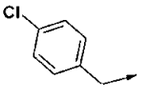
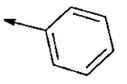
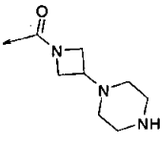
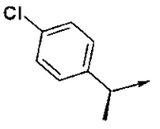
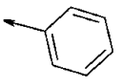
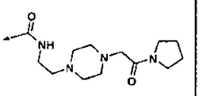
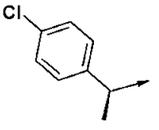
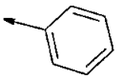
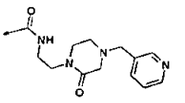
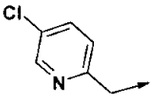
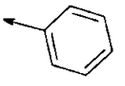
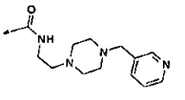
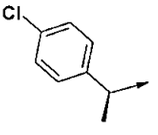
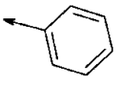
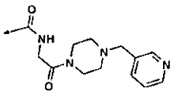
Ejemplo	X e Y	R^1	R^2	R^3	Análisis MS/HPLC/RMN
247	X=H Y=Cl				M+H= 678.0 $_{C}t_{Ret}$ = 5.44 min
248	X=H Y=Cl				M+H= 677.0 $_{C}t_{Ret}$ = 5.95 min
249	X=H Y=Cl				M+= 572.0 $_{A}t_{Ret}$ = 3.85 min
250	X=H Y=Cl				M+= 545.0 $_{A}t_{Ret}$ = 4.29 min
251	X=H Y=Cl				M+= 674.0 $_{A}t_{Ret}$ = 4.55 min
252	X=H Y=Cl				M+H= 678.0 $_{C}t_{Ret}$ = 6.09 min

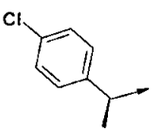
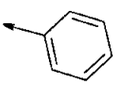
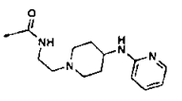
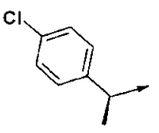
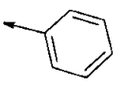
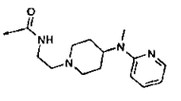
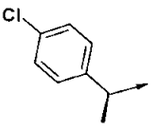
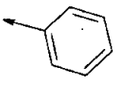
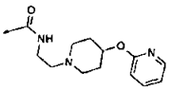
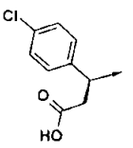
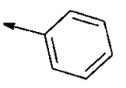
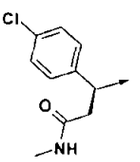
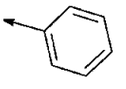
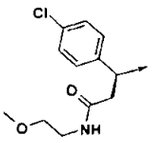
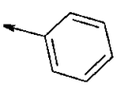
Ejemplo	X e Y	R^1	R^2	R^3	Análisis MS/HPLC/RMN
253	X=H Y=Cl				M+H= 664.0 $_{c}t_{Ret}$ = 6.06 min
254	X=H Y=Cl				M+H= 689.1 $_{c}t_{Ret}$ = 6.23 min
255	X=F Y=Cl			H	M+H= 437.0 $_{c}t_{Ret}$ = 5.57 min
256	X=H Y=Cl				M+H= 692.0 $_{c}t_{Ret}$ = 5.42 min
257	X=H Y=Cl				M+H= 689.0 $_{c}t_{Ret}$ = 5.95 min
258	X=H Y=Cl				M+H= 667.0 $_{c}t_{Ret}$ = 5.39 min

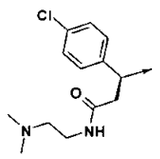
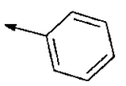
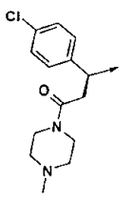
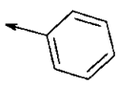
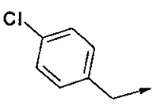
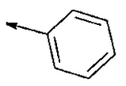
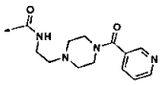
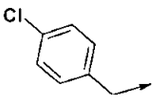
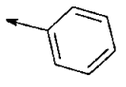
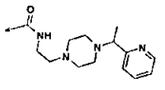
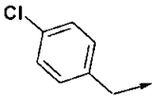
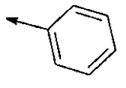
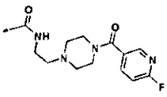
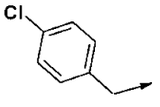
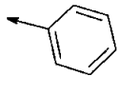
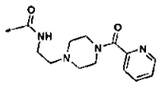
Ejem-plo	X e Y	R^1	R^2	R^3	Análisis MS/HPLC/RMN
259	X=H Y=Cl				M+H= 693.0 ct_{Ret} = 5.97 min
260	X=H Y=Cl				M+H= 605.0 ct_{Ret} = 5.74 min
261	X=H Y=Cl				M+H= 686.0 ct_{Ret} = 5.40 min
262	X=H Y=Cl				M+H= 684.0 ct_{Ret} = 5.34 min
263	X=H Y=Cl				M+H= 645.0 ct_{Ret} = 5.61 min
264	X=H Y=Cl				M+H= 677.0 ct_{Ret} = 5.92 min

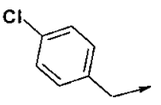
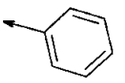
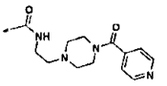
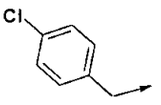
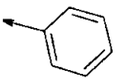
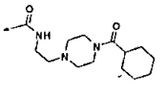
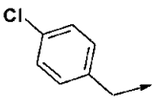
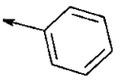
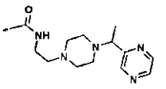
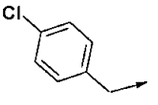
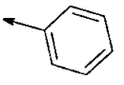
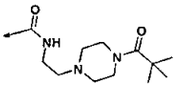
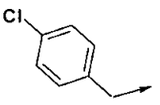
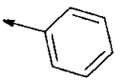
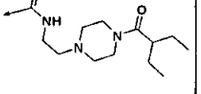
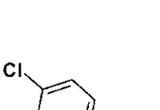
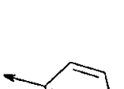
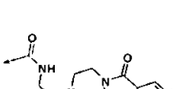
Ejemplo	X e Y	R^1	R^2	R^3	Análisis MS/HPLC/RMN
265	X=H Y=Cl				M+H= 659.0 ct_{Ret} = 5.67 min
266	X=H Y=Cl				M+H= 698.0 ct_{Ret} = 5.44 min
267	X=H Y=Cl				M+H= 700.0 ct_{Ret} = 5.51 min
268	X=H Y=Cl				M+H= 659.0 ct_{Ret} = 5.74 min
269	X=H Y=Cl				M+H= 691.9 ct_{Ret} = 5.49 min
270	X=H Y=Cl				M+H= 707.0 ct_{Ret} = 5.50 min

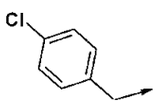
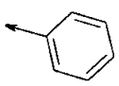
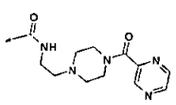
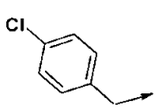
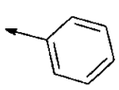
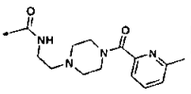
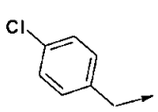
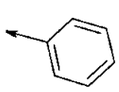
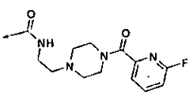
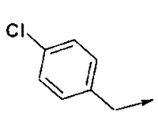
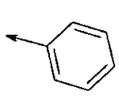
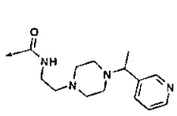
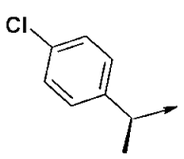
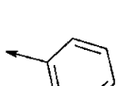
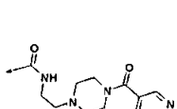
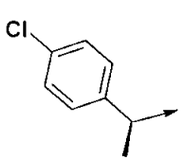
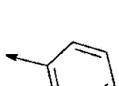
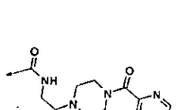
Ejemplo	X e Y	R^1	R^2	R^3	Análisis MS/HPLC/RMN
271	X=H Y=Cl				M+H= 707.0 ct_{Ret} = 5.35 min
272	X=H Y=Cl				M+H= 684.0 ct_{Ret} = 5.62 min
273	X=H Y=Cl				M+H= 631.0 ct_{Ret} = 5.75 min
274	X=H Y=Cl				M+H= 692.0 ct_{Ret} = 5.54 min
275	X=H Y=Cl				M+H= 657.1 ct_{Ret} = 5.82 min
276	X=H Y=Cl				M+H= 669.0 ct_{Ret} = 5.57 min

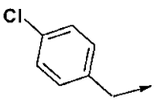
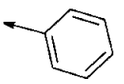
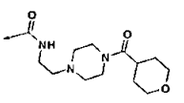
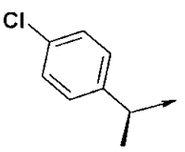
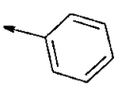
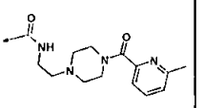
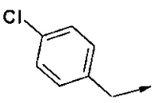
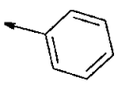
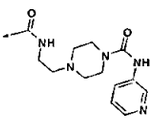
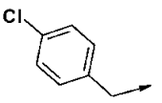
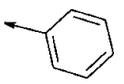
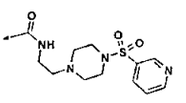
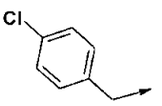
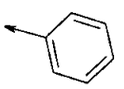
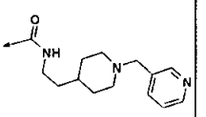
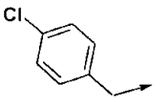
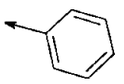
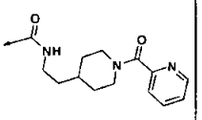
Ejemplo	X e Y	R^1	R^2	R^3	Análisis MS/HPLC/RMN
277	X=H Y=Cl				M+H= 683.0 $_{C}t_{Ret}$ = 6.03 min
278	X=H Y=Cl				M+= 585.0 $_{A}t_{Ret}$ = 3.60 min
279	X=H Y=Cl				M+H= 698.0 $_{C}t_{Ret}$ = 5.72 min
280	X=H Y=Cl				M+H= 691.8 $_{C}t_{Ret}$ = 5.63 min
281	X=H Y=Cl				M+H= 664.8 $_{C}t_{Ret}$ = 5.10 min
282	X=H Y=Cl				M+H= 692.0 $_{C}t_{Ret}$ = 5.41 min

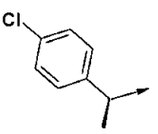
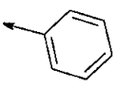
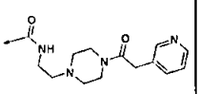
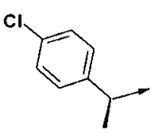
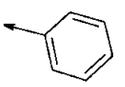
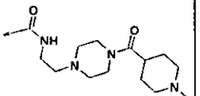
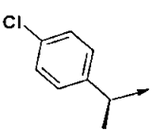
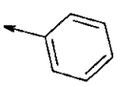
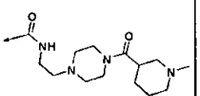
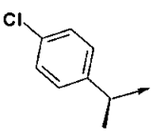
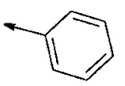
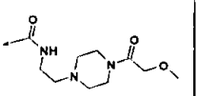
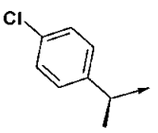
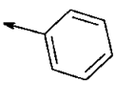
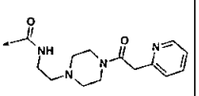
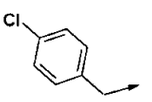
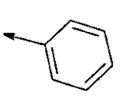
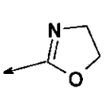
Ejemplo	X e Y	R^1	R^2	R^3	Análisis MS/HPLC/RMN
283	X=H Y=Cl				M+H= 678.0 $_{A}t_{Ret}$ = 5.41 min
284	X=H Y=Cl				M+H= 691.9 $_{A}t_{Ret}$ = 5.41 min
285	X=H Y=Cl				M+H= 679.0 $_{D}t_{Ret}$ = 2.88 min
286	X=F Y=Cl			H	M+H= 495.7 $_{A}t_{Ret}$ = 4.28 min
287	X=F Y=Cl			H	M+H= 507.0 $_{C}t_{Ret}$ = 6.17 min
288	X=F Y=Cl			H	M+H= 551.0 $_{C}t_{Ret}$ = 6.23 min

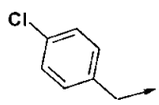
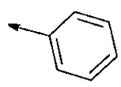
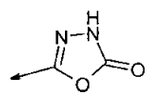
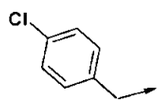
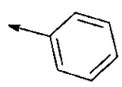
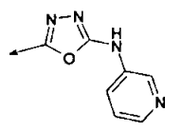
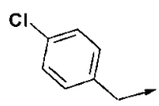
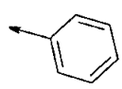
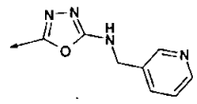
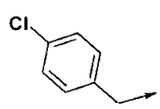
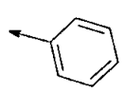
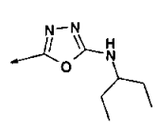
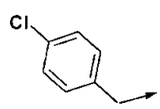
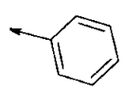
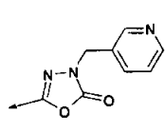
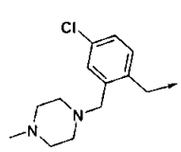
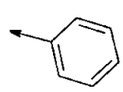
Ejemplo	X e Y	R^1	R^2	R^3	Análisis MS/HPLC/RMN
289	X=F Y=Cl			H	M+H= 564.0 $_{C}t_{Ret}$ = 5.72 min
290	X=F Y=Cl			H	M+H= 576.0 $_{C}t_{Ret}$ = 5.73 min
291	X=H Y=Cl				M+= 677.8 $_{A}t_{Ret}$ = 3.71 min
292	X=H Y=Cl				M+= 677.9 $_{A}t_{Ret}$ = 3.65 min
293	X=H Y=Cl				M+= 695.9 $_{A}t_{Ret}$ = 3.92 min
294	X=H Y=Cl				M+= 678.0 $_{A}t_{Ret}$ = 3.82 min

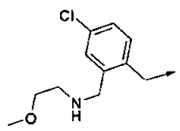
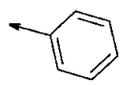
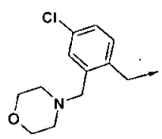
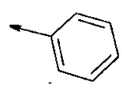
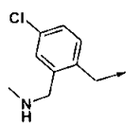
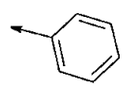
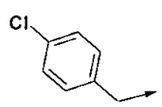
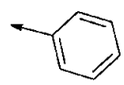
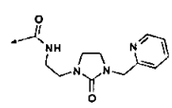
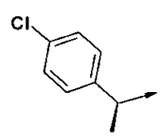
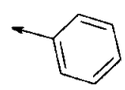
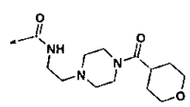
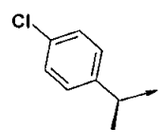
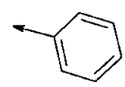
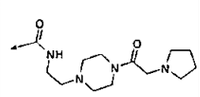
Ejemplo	X e Y	R^1	R^2	R^3	Análisis MS/HPLC/RMN
295	X=H Y=Cl				M+= 677.9 $_At_{Ret}$ = 3.59 min
296	X=H Y=Cl				M+= 683.0 $_At_{Ret}$ = 4.24 min
297	X=H Y=Cl				M+= 679.0 $_At_{Ret}$ = 3.80 min
298	X=H Y=Cl				M+= 657.0 $_At_{Ret}$ = 4.05 min
299	X=H Y=Cl				M-H= 670.6 $_At_{Ret}$ = 4.15 min
300	X=H Y=Cl				M+= 691.9 $_At_{Ret}$ = 3.58 min

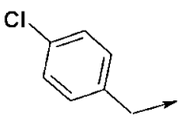
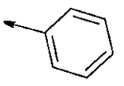
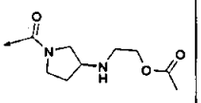
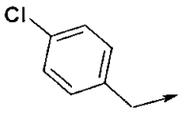
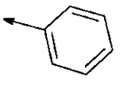
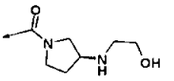
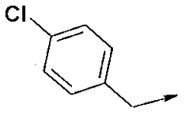
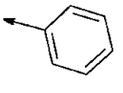
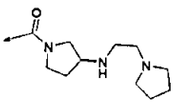
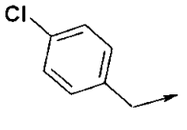
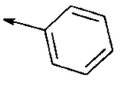
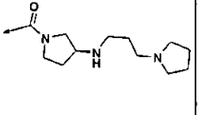
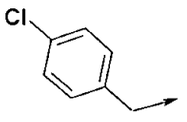
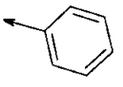
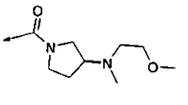
Ejem-plo	X e Y	R^1	R^2	R^3	Análisis MS/HPLC/RMN
301	X=H Y=Cl				M+= 678.9 $_At_{Ret}$ = 3.78 min
302	X=H Y=Cl				M+= 692.0 $_At_{Ret}$ = 3.82 min
303	X=H Y=Cl				M+= 695.9 $_At_{Ret}$ = 3.96 min
304	X=H Y=Cl				M+= 678.0 $_At_{Ret}$ = 3.60 min
305	X=H Y=Cl				M+= 692.9 $_At_{Ret}$ = 3.75 min
306	X=H Y=Cl				M+= 692.9 $_At_{Ret}$ = 3.88 min

Ejemplo	X e Y	R^1	R^2	R^3	Análisis MS/HPLC/RMN
307	X=H Y=Cl				M+= 685.0 $_At_{Ret}$ = 3.78 min
308	X=H Y=Cl				M+= 706.0 $_At_{Ret}$ = 3.97 min
309	X=H Y=Cl				M+= 693.0 $_At_{Ret}$ = 3.55 min
310	X=H Y=Cl				M+= 713.9 $_At_{Ret}$ = 4.02 min
311	X=H Y=Cl				M+H= 663.0 $_Ct_{Ret}$ = 5.51 min
312	X=H Y=Cl				M+H= 677.0 $_Ct_{Ret}$ = 6.15 min

Ejem-plo	X e Y	R^1	R^2	R^3	Análisis MS/HPLC/RMN
313	X=H Y=Cl				M+H= 706.0 $_{c}t_{Ret}$ = 5.35 min
314	X=H Y=Cl				M+H= 712.0 $_{c}t_{Ret}$ = 5.34 min
315	X=H Y=Cl				M+H= 712.0 $_{c}t_{Ret}$ = 5.38 min
316	X=H Y=Cl				M+H= 659.0 $_{c}t_{Ret}$ = 5.59 min
317	X=H Y=Cl				M+H= 706.0 $_{c}t_{Ret}$ = 5.38 min
318	X=H Y=Cl				M+H = 487.0 $_{c}t_{Ret}$ = 6.27 min

Ejemplo	X e Y	R^1	R^2	R^3	Análisis MS/HPLC/RMN
319	X=H Y=Cl				M+ = 502.0. $_At_{Ret}$ = 4.23 min
320	X=H Y=Cl				M+ = 578.0 $_At_{Ret}$ = 3.86 min
321	X=H Y=Cl				M+ = 592.0 $_At_{Ret}$ = 3.72 min
322	X=H Y=Cl				M+ = 571.0 $_At_{Ret}$ = 4.70 min
323	X=H Y=Cl				M+ = 592.9 $_At_{Ret}$ = 3.87 min
324	X=F Y=Cl			H	M+H= 548.1 $_Ct_{Ret}$ = 5.59 min

Ejemplo	X e Y	R^1	R^2	R^3	Análisis MS/HPLC/RMN
325	X=F Y=Cl			H	M+H= 523.0 ct_{Ret} = 5.50 min
326	X=F Y=Cl			H	M+H= 535.0 ct_{Ret} = 5.45 min
327	X=F Y=Cl			H	M+H= 479.0 ct_{Ret} = 5.38 min
328	X=H Y=Cl				M+H= 664.0 ct_{Ret} = 5.63 min
329	X=H Y=Cl				M+H= 698.9 ct_{Ret} = 5.63 min
330	X=H Y=Cl				M+H= 691.9 ct_{Ret} = 5.23 min

Ejemplo	X e Y	R^1	R^2	R^3	Análisis MS/HPLC/RMN
331	X=H Y=Cl				M-H= 614.0 $_{E}t_{Ret}$ = 4.00 min
332	X=H Y=Cl				M-H= 601.9 $_{E}t_{Ret}$ = 3.89 min
333	X=H Y=Cl				M-H= 625.0 $_{E}t_{Ret}$ = 3.79 min
334	X=H Y=Cl				M-H= 639.1 $_{E}t_{Ret}$ = 3.77 min
335	X=H Y=Cl				M-H= 601.9 $_{E}t_{Ret}$ = 3.89 min

El **Ejemplo 147** se sintetiza mediante la condensación de la 4-cloro-bencil-amina, el **Intermediario 147.1** y 1-(isociano-fenil-metan-sulfonil)-4-metil-benceno, de una manera análoga a la preparación del Intermediario **2.2** como un sólido incoloro.

Intermediario 147.1: Dimetil-amida del ácido 6-cloro-3-formil-1H-indol-2-sulfónico

El compuesto del título se sintetiza mediante la formilación del Intermediario **147.2** de una manera análoga a la preparación del Intermediario **1.1** como un sólido blanco; ES-MS: M+ = 287.1; HPLC: $_{A}t_{Ret}$ = 4.33 minutos.

Intermediario 147.2: Dimetil-amida del ácido 6-cloro-1H-indol-2-sulfónico

Paso 1: Una solución del Intermediario **147.3** (1.0 gramos, 3.27 milimoles) en la mezcla de hexano (11 mililitros) y Et_2O (11 mililitros), se trata con una solución en tetrahidrofurano 2M/heptano de LDA (1.8 mililitros, 3.6 milimoles) durante 1 hora a 0°C. La mezcla de reacción se enfría a -30°C, y se trata con cloruro de sulfurilo (0.52 mililitros, 6.5 milimoles) durante 4 horas. La mezcla de reacción se apaga mediante H_2O y se diluye con EtOAc, entonces la capa orgánica se seca sobre Na_2SO_4 y se evapora al vacío para proporcionar el producto crudo, el cual se somete al siguiente paso sin mayor purificación.

Paso 2: Una solución de cloruro de 6-cloro-1-(toluen-4-sulfonil)-1H-indol-2-sulfonilo en tetrahidrofurano (17 mililitros) se trata con un exceso de una solución en tetrahidrofurano 2M de

dimetil-amina (17.3 mililitros, 34.6 milimoles) a temperatura ambiente. Después de completarse, la mezcla de reacción se apaga con $NaHCO_3$ acuoso saturado, y se diluye con EtOAc. La capa orgánica se seca sobre Na_2SO_4 y se evapora al vacío. La cromatografía por evaporación instantánea en gel de sílice del residuo proporciona la dimetil-amida del ácido 6-cloro-1-(toluen-4-sulfonil)-1H-indol-2-sulfónico como un sólido color rojo; ES-MS: M+ = 413.0: ${}_{A}t_{Ret}$ = 5.36 minutos.

Paso 3: Una mezcla de la dimetil-amida del ácido 6-cloro-1-(toluen-4-sulfonil)-1H-indol-2-sulfónico (160 miligramos, 0.39 milimoles) y una solución en tetrahidrofurano 1M de TBAF (1.8 mililitros) se agita a temperatura ambiente. Después de completarse, la mezcla de reacción se apaga mediante NH_4Cl acuoso saturado, se agrega EtOAc, y la capa orgánica se lava con salmuera, se seca sobre $MgSO_4$ y se evapora al vacío. La cromatografía por evaporación instantánea en gel de sílice del residuo proporciona el compuesto del título como un polvo blanco; ES-MS: M+ = 259.1: ${}_{A}t_{Ret}$ = 4.43 minutos.

Intermediario 147.3: 6-cloro-1-(toluen-4-sulfonil)-1H-indol

El **Intermediario 147.3** se prepara en analogía al procedimiento publicado en la literatura (*J. Med. Chem.* **2006**, 49, 3101-3115). Se agrega NaH al 55 por ciento en aceite mineral (881 miligramos, 20.2 milimoles) a una solución de 6-cloro-indol (3.0 gramos, 19.8 milimoles) en tetrahidrofurano (28 mililitros) a 0°C. Después de 1 hora, se agrega TsCl (3.85 gramos, 20.2 milimoles), y

la mezcla de reacción se agita a temperatura ambiente. Después de completarse, la mezcla de reacción se apaga mediante $NaHCO_3$ acuoso saturado, y se diluye con Et_2O. La capa orgánica se seca sobre Na_2SO_4 y se evapora al vacío para proporcionar un sólido crudo. El producto crudo se lava con una pequeña cantidad de Et_2O, para dar el compuesto del título como un cristal color naranja; ES-MS: M+ = 306.1: ${}_At_{Ret}$ = 5.60 minutos.

El **Ejemplo 148** se sintetiza mediante la condensación del **Intermediario 148.1**, el **Intermediario 10.1** y 1-(isociano-fenil-metan-sulfonil)-4-metil-benceno, de una manera análoga a la preparación del Intermediario **2.2** como un sólido incoloro.

Intermediario 148.1: (2-amino-metil-5-cloro-fenil)-metanol

El **Intermediario 148.1** se prepara en analogía al procedimiento publicado en la literatura (*J. Org. Chem.* **2004**, 69, 3620-3627).

Paso 1: Una mezcla del 2-bromo-5-cloro-benzoato de metilo (3 gramos, 12.0 milimoles) y cianuro de cobre (1.2 gramos, 13.2 milimoles) en dimetil-formamida (15 mililitros), se calienta a 90°C durante 4 horas, y entonces se enfría a 10°C. Se agrega tolueno (15 mililitros), seguido por la adición lenta de una solución acuosa de 9:1 (15 mililitros) de NH_4Cl al 10 por ciento (peso/volumen)/NH_4OH al 30 por ciento, para mantener la temperatura interna <25°C. La mezcla de reacción se expone al aire, y la mezcla bifásica resultante se agitó durante 14 horas. Entonces se remueve la capa acuosa azul, y este proceso se repite hasta que la capa

acuosa ya no es azul. La capa orgánica se seca sobre Na_2SO_4 y se evapora al vacío, para proporcionar un sólido crudo. La cromatografía por evaporación instantánea en gel de sílice del residuo proporciona el metil-éster del ácido 5-cloro-2-ciano-benzoico como un sólido amarillo; $_{ct}t_{Ret}$ = 6.82 minutos.

Paso 2: Una mezcla de $ZnCl_2$ (338 miligramos, 2.43 milimoles) y $LiBH_4$ (117 miligramos, 5.11 milimoles) en tetrahidrofurano (5.2 mililitros) se calienta a 60°C durante 90 minutos, seguido por la adición lenta de una solución en tolueno (2.6 mililitros) del metil-éster del ácido 5-cloro-2-ciano-benzoico (500 miligramos, 2.56 milimoles), y se agita durante 12 horas. La mezcla resultante se enfría a 10°C y se apaga mediante HCl 3N, y entonces esta mezcla bifásica se calienta a 40°C durante 30 minutos. Esta mezcla se neutraliza mediante NaOH 10N a un pH de 12, y la capa de tolueno se concentra al vacío. La cromatografía por evaporación instantánea en gel de sílice del residuo proporciona el compuesto del título como un sólido amarillo; ES-MS: M+H = 172.0: $_{ct}t_{Ret}$ = 3.88 minutos.

Intermediario 149.1: 2-[4-(2-imidazol-1-il-etil)-piperazin-1-il]-etil-amina

Una solución del Intermediario **149.2** (1.1 gramos, 5.0 milimoles) en tetrahidrofurano (15 mililitros) se trata mediante LAH (393 miligramos, 10.0 milimoles) a 0°C. Después de completarse, la mezcla de reacción se apaga mediante $Na_2SO_4 \cdot 10H_2O$ (8.4 gramos, exceso), y se agita durante 30 minutos. El producto se aísla

mediante filtración con Celite, y se lava con tetrahidrofurano, y se seca bajo presión reducida para dar el compuesto del título como un aceite; ES-MS: M+H = 224.2: ct_{Rel} = 1.58 minutos.

Intermediario 149.2: [4-(2-imidazol-1-il-etil)-piperazin-1-il]-acetonitrilo

Una mezcla de la 1-(2-imidazol-1-il-etil)-piperazina (comercialmente disponible en CHESS GmbH) (1.0 gramos, 5.44 milimoles), bromo-acetonitrilo (740 miligramos, 6.0 milimoles) y K_2CO_3 (1.65 gramos, 12.0 milimoles) en CH_3CN (15 mililitros), se agita a temperatura ambiente. Después de completarse, el producto se aísla mediante filtración con Celite, y se lava con CH_3CN y se seca bajo presión reducida, para dar el compuesto del título como un aceite; ES-MS: M+H = 220.2: ct_{Rel} = 1.70 minutos.

Intermediario 150.1: 2-(4-etil-piperazin-1-il)-etil-amina

El compuesto del título se sintetiza mediante la reducción del Intermediario **150.2** de una manera análoga a la preparación del Intermediario **149.1** como un aceite color naranja; ES-MS: M+H= 158.2: ^{1}H-RMN (DMSO-d_6) 2.60-2.20 (m, 16H), 0.95 (t, 3H).

Intermediario 150.2: (4-etil-piperazin-1-il)-acetonitrilo

El compuesto del título se sintetiza mediante el acoplamiento de la 1-etil-piperazina y bromo-acetonitrilo de una manera análoga a la preparación del Intermediario **149.2,** como un aceite color naranja; ES-MS: M+ = 154.1: ^{1}H-RMN (DMSO-d_6) 3.70 (s, 2H), 2.40-2.20 (m, 10H), 0.95 (t, 3H).

Intermediario 151.1: 2-(4-isopropil-piperazin-1-il)-etil-amina

El compuesto del título se sintetiza mediante la reducción del Intermediario **151.2** de una manera análoga a la preparación del Intermediario **149.1,** como un aceite incoloro; ES-MS: M+ = 172.2: ^{1}H-RMN (DMSO-d_6) 2.60-2.20 (m, 15H), 0.95 (d, 6H).

Intermediario 151.2: (4-isopropil-piperazin-1-il)-acetonitrilo

El compuesto del título se sintetiza mediante el acoplamiento de la 1-isopropil-piperazina y bromo-acetonitrilo de una manera análoga a la preparación del Intermediario **149.2,** como un aceite incoloro; ES-MS: M+ = 168.1; ^{1}H-RMN (DMSO-d_6) 3.70 (s, 2H), 2.70-2.40 (m, 9H), 0.95 (d, 6H).

Intermediario 152.1: Ácido 6-cloro-3-[3-(4-cloro-2-hidroxi-metil-bencil)-5-fenil-3H-imidazol-4-il]-1H-indol-2-carboxílico (el cual también es un compuesto de la fórmula I de acuerdo con la invención)

El compuesto del título se sintetiza mediante la hidrólisis del Intermediario **152.2** de una manera análoga a la preparación del Intermediario **2.1,** como un sólido incoloro; ES-MS: M+H = 492.0: ct_{Rel} = 5.85.

Intermediario 152.2: Etil-éster del ácido 6-cloro-3-[3-(4-cloro-2-hidroxi-metil-bencil)-5-fenil-3H-imidazol-4-il]-1H-indol-2-carboxílico (el cual también es un compuesto de la fórmula I de acuerdo con la invención)

El compuesto del título se sintetiza mediante la condensación del **Intermediario 2.3**, el **Intermediario 148.1** y 1-(isociano-fenil-

metan-sulfonil)-4-metil-benceno, de una manera análoga a la preparación del Intermediario **2.2,** como un sólido incoloro; ES-MS: M+H = 520.0: $_{c}t_{Ret}$ = 6.20 minutos.

Intermediario 155.1: 2-(4-piridin-3-il-metil-piperazin-1-il)-etil-amina

El compuesto del título se sintetiza mediante la reducción del Intermediario **155.2** de una manera análoga a la preparación del Intermediario **149.1** como un aceite incoloro; ES-MS: M+ = 221.2: ^{1}H-RMN (DMSO-d_6) 8.45-8.40 (m, 2H), 7.65-7.60 (m, 1H), 7.45-7.30 (m, 1H), 3.45 (s, 2H), 2.55 (t, 2H), 2.40-2.20 (m, 12H).

Intermediario 155.2: (4-piridin-3-il-metil-piperazin-1-il)-acetonitrilo

El compuesto del título se sintetiza mediante el acoplamiento de la 1-piridin-3-il-metil-piperazina (comercialmente disponible en CHESS GmbH) y bromo-acetonitrilo, de una manera análoga a la preparación del Intermediario **149.2** como un aceite incoloro; ES-MS: M+ = 217.2.

Intermediario 156.1: 2-[4-(2-dimetil-amino-etil)-piperazin-1-il]-etil-amina

El compuesto del título se sintetiza mediante la reducción del Intermediario **156.2** de una manera análoga a la preparación del Intermediario **149.1** como un aceite incoloro; ES-MS: M+H = 201.3.

Intermediario 156.2: [4-(2-dimetil-amino-etil)-piperazin-1-il]-acetonitrilo

El compuesto del título se sintetiza mediante el acoplamiento

de la dimetil-(2-piperazin-1-il-etil)-amina (comercialmente disponible en CHESS GmbH) y bromo-acetonitrilo, de una manera análoga a la preparación del Intermediario **149.2,** como un aceite incoloro; ES-MS: M+ = 197.2.

Intermediario 157.1: 2-[4-(2-pirrolidin-1-il-etil)-piperazin-1-il]-etil-amina

El compuesto del título se sintetiza mediante la reducción del Intermediario **157.2,** de una manera análoga a la preparación del Intermediario **149.1,** como un aceite incoloro; ES-MS: M+H = 227.3.

Intermediario 157.2: [4-(2-pirrolidin-1-il-etil)-piperazin-1-il]-acetonitrilo

El compuesto del título se sintetiza mediante el acoplamiento de la 1-(2-pirrolidin-1-il-etil)-piperazina (comercialmente disponible en ABCR GmbH) y bromo-acetonitrilo de una manera análoga a la preparación del Intermediario **149.2,** como un sólido incoloro; ES-MS: M+H = 223.3.

Intermediario 158.1: 2-[4-(3-metoxi-propil)-piperazin-1-il]-etil-amina

El compuesto del título se sintetiza mediante la reducción del Intermediario **158.2,** de una manera análoga a la preparación del Intermediario **149.1,** como un aceite incoloro; ES-MS: M+ = 202.2: ^{1}H-RMN (DMSO-d_6) 3.30 (t, 2H), 3.20 (s, 3H), 2.55 (t, 2H), 2.40-2.20 (m, 14H), 1.65-1.55 (m, 2H).

Intermediario 158.2: [4-(3-metoxi-propil)-piperazin-1-il]-acetonitrilo

El compuesto del título se sintetiza mediante el acoplamiento de la 1-(3-metoxi-propil)-piperazina (comercialmente disponible en CHESS GmbH) y bromo-acetonitrilo, de una manera análoga a la preparación del Intermediario **149.2,** como un aceite incoloro; ES-MS: M+ = 198.2: ^{1}H-RMN (DMSO-d_6) 3.65 (s, 2H), 3.30 (s, 3H), 2.45-2.20 (m, 12H), 1.65-1.55 (m, 2H).

Intermediario 159.1: 2-[4-(4-fluoro-fenil)-piperazin-1-il]-etil-amina

El compuesto del título se sintetiza mediante la reducción del Intermediario **159.2,** de una manera análoga a la preparación del Intermediario **149.1,** como un aceite incoloro; ES-MS: M+ = 224.2: $_At_{Ret}$ = 1.54.

Intermediario 159.2: 4-(4-fluoro-fenil)-piperazin-1-il]-acetonitrilo

El compuesto del título se sintetiza mediante el acoplamiento de la 1-(4-fluoro-fenil)-piperazina y bromo-acetonitrilo, de una manera análoga a la preparación del Intermediario **149.2,** como un aceite incoloro; ES-MS: M+ = 220.2: $_At_{Ret}$ = 2.48 minutos.

Intermediario 161.1: 2-(4-piridin-4-il-piperazin-1-il)-etil-amina

El compuesto del título se sintetiza mediante la reducción del Intermediario **161.2,** de una manera análoga a la preparación del Intermediario **149.1,** como un aceite incoloro; ES-MS: M+ = 207.2.

Intermediario 161.2: (4-piridin-4-il-piperazin-1-il)-acetonitrilo

El compuesto del título se sintetiza mediante el acoplamiento de la 1-piridin-4-il-piperazina y bromo-acetonitrilo, de una manera análoga a la preparación del Intermediario **149.2,** como un aceite incoloro; ES-MS: M+ = 202.2: ^{1}H-RMN (DMSO-d_6) 8.15 (d, 2H), 6.80 (d, 2H), 3.80 (s, 1H), 3.35 (t, 4H), 2.50 (t, 4H).

Intermediario 162.1: 2-[4-(2-metoxi-etil)-piperazin-1-il]-etil-amina

El compuesto del título se sintetiza mediante la reducción del Intermediario **162.2,** de una manera análoga a la preparación del Intermediario **149.1,** como un aceite incoloro; ES-MS: M+ = 188.2.

Intermediario 162.2: [4-(2-metoxi-etil)-piperazin-1-il]-acetonitrilo

El compuesto del título se sintetiza mediante el acoplamiento de la 1-(2-metoxi-etil)-piperazina y bromo-acetonitrilo de una manera análoga a la preparación del Intermediario **149.2,** como un aceite incoloro; ES-MS: M+ = 184.2.

Intermediario 163.1: 2-[4-fenil-piperazin-1-il]-etil-amina

El compuesto del título se sintetiza mediante la reducción del Intermediario **163.2,** de una manera análoga a la preparación del Intermediario **149.1,** como un aceite incoloro; ES-MS: M+ = 206.2: $_At_{Ret}$ = 1.20 minutos.

Intermediario 163.2: (4-fenil-piperazin-1-il)-acetonitrilo

El compuesto del título se sintetiza mediante el acoplamiento de la 1-fenil-piperazina y bromo-acetonitrilo, de una manera análoga a la preparación del Intermediario **149.2,** como un sólido blanco; ES-

MS: M+ = 202.2: $_{A}t_{Ret}$ = 1.95 minutos.

Intermediario 164.1: 2-(4-piridin-2-il-piperazin-1-il)-etil-amina

El compuesto del título se sintetiza mediante la reducción del Intermediario **164.2**, de una manera análoga a la preparación del Intermediario **149.1**, como un aceite incoloro; ES-MS: M+ = 207.2.

Intermediario 164.2: (4-piridin-2-il-piperazin-1-il)-acetonitrilo

El compuesto del título se sintetiza mediante el acoplamiento de la 1-piridin-2-il-piperazina y bromo-acetonitrilo, de una manera análoga a la preparación del Intermediario **149.2**, como un aceite incoloro; ES-MS: M+ = 203.2: ^{1}H-RMN (DMSO-d_6) 8.05 (dd, 1H), 7.50 (dd, 1H), 6.80 (d, 1H), 6.60 (dd, 1H), 3.80 (s, 1H), 3.50 (t, 4H), 2.50 (t, 4H).

Intermediario 165.1: 2-(4-bencil-piperazin-1-il)-etil-amina

El compuesto del título se sintetiza mediante la reducción del Intermediario **165.2**, de una manera análoga a la preparación del Intermediario **149.1**, como un aceite incoloro; ES-MS: M+ = 220.2: $_{A}t_{Ret}$ = 1.10.

Intermediario 165.2: (4-bencil-piperazin-1-il)-acetonitrilo

El compuesto del título se sintetiza mediante el acoplamiento de la 1-bencil-piperazina y bromo-acetonitrilo de una manera análoga a la preparación del Intermediario **149.2**, como un sólido blanco; ES-MS: M+ = 216.2: $_{A}t_{Ret}$ = 1.50.

Intermediario 167.1: 2-(4-piridin-3-il-piperazin-1-il)-etil-amina

El compuesto del título se sintetiza mediante la reducción del Intermediario **167.2**, de una manera análoga a la preparación del Intermediario **149.1**, como un aceite incoloro; ES-MS: M+ = 207.2.

Intermediario 167.2: (4-piridin-3-il-piperazin-1-il)-acetonitrilo

El compuesto del título se sintetiza mediante el acoplamiento de la 1-piridin-3-il-piperazina y bromo-acetonitrilo, de una manera análoga a la preparación del Intermediario **149.2**, como un sólido blanco; ES-MS: M+ = 203.2: $_{A}t_{Ret}$ = 1.10 minutos.

Intermediario 168.1: 2-[4-(3-metoxi-fenil)-piperazin-1-il]-etil-amina

El compuesto del título se sintetiza mediante la reducción del Intermediario **168.2**, de una manera análoga a la preparación del Intermediario **149.1**, como un aceite incoloro; ES-MS: M+ = 236.2: $_{A}t_{Ret}$ = 1.44 minutos.

Intermediario 168.2: [4-(3-metoxi-fenil)-piperazin-1-il]-acetonitrilo

El compuesto del título se sintetiza mediante el acoplamiento de la 1-(3-metoxi-fenil)-piperazina y bromo-acetonitrilo, de una manera análoga a la preparación del Intermediario **149.2**, como un sólido blanco; ES-MS: M+ = 232.2: $_{A}t_{Ret}$ = 2.62 minutos.

Intermediario 173.1: 2-(4-piridin-2-il-metil-piperazin-1-il)-etil-amina

El compuesto del título se sintetiza mediante la reducción del Intermediario **173.2**, de una manera análoga a la preparación del Intermediario **149.1** ,como un aceite incoloro; ES-MS: M+ = 221.2.

Intermediario 173.2: (4-piridin-2-il-metil-piperazin-1-il)-acetonitrilo

El compuesto del título se sintetiza mediante el acoplamiento de la 1-piridin-2-il-metil-piperazina (comercialmente disponible en CHESS GmbH) y bromo-acetonitrilo, de una manera análoga a la preparación del Intermediario **149.2**, como un sólido color café; ES-MS: M+ = 217.2: ^{1}H-RMN (DMSO-d_6) 8.45 (dd, 1H), 7.75 (td, 1H), 7.40 (d, 1H), 7.25-7.20 (m, 1H), 3.70 (s, 2H), 3.60 (s, 2H), 2.50-2.35 (m, 8H).

Intermediario 174.1: 2-(4-ciclopentil-piperazin-1-il)-etil-amina

El compuesto del título se sintetiza mediante la reducción del Intermediario **174.2**, de una manera análoga a la preparación del Intermediario **149.1**, como un aceite incoloro; ES-MS: M+ = 198.2: ^{1}H-RMN (DMSO-d_6) 2.55 (t, 2H), 2.40-2.30 (m, 10H), 2.25 (t, 2H), 1.80-1.70 (m, 2H), 1.60-1.40 (m, 4H), 1.30-1.20 (m, 3H).

Intermediario 174.2: (4-ciclopentil-piperazin-1-il)-acetonitrilo

El compuesto del título se sintetiza mediante el acoplamiento de la 1-ciclopentil-piperazina (comercialmente disponible en CHESS GmbH) y bromo-acetonitrilo, de una manera análoga a la preparación del Intermediario **149.2**, como un aceite incoloro; ES-MS: M+ =

194.2: ^{1}H-RMN (DMSO-d_6) 3.65 (s, 2H), 2.45-2.20 (m, 9H), 1.80-1.20 (m, 8H).

Intermediario 176.1: 2-(4-ciclohexil-metil-piperazin-1-il)-etil-amina

El compuesto del título se sintetiza mediante la reducción del Intermediario **176.2**, de una manera análoga a la preparación del Intermediario **149.1**, como un aceite incoloro; ES-MS: M+ = 226.3: ^{1}H-RMN (DMSO-d_6) 2.25 (t, 2H), 2.40-2.20 (m, 12H), 2.00 (d, 2H), 1.70-1.55 (m, 5H), 1.50-1.40 (m, 1H), 1.20-1.05 (m, 3H), 0.85-0.70 (m, 2H).

Intermediario 176.2: (4-ciclohexil-metil-piperazin-1-il)-acetonitrilo

El compuesto del título se sintetiza mediante el acoplamiento de la 1-ciclohexil-metil-piperazina (comercialmente disponible en Fluorochem Ltd) y bromo-acetonitrilo, de una manera análoga a la preparación del Intermediario **149.2**, como un aceite incoloro; ES-MS: M+ = 222.2: ^{1}H-RMN (DMSO-d_6) 3.65 (s, 2H), 2.45-2.20 (m, 8H), 2.00 (d, 2H), 1.70-1.55 (m, 5H), 1.50-1.40 (m, 1H), 1.20-1.05 (m, 3H), 0.85-0.70 (m, 2H).

Intermediario 177.1: 2-(4-morfolin-4-il-piperidin-1-il)-etil-amina

El compuesto del título se sintetiza mediante la reducción del Intermediario **177.2**, de una manera análoga a la preparación del Intermediario **149.1**, como un aceite incoloro; ES-MS: M+ = 214.3: : ^{1}H-RMN (DMSO-d_6) 3.55 (t, 4H), 3.30 (bs, 2H), 2.55 (t, 2H), 2.40 (t,

4H), 2.20 (t, 2H), 2.10-2.00 (m, 1H), 1.85-1.80 (m, 2H), 1.80-1.70 (m, 2H), 1.40-1.20 (m, 2H).

Intermediario 177.2: (4-morfolin-4-il-piperidin-1-il)-acetonitrilo

El compuesto del título se sintetiza mediante el acoplamiento de la 4-piperidin-4-il-morfolina (comercialmente disponible en CHESS GmbH) y bromo-acetonitrilo, de una manera análoga a la preparación del Intermediario **149.2,** como un aceite incoloro; ES-MS: M+ = 210.1: ^{1}H-RMN (DMSO-d_6) 3.65 (s, 2H), 3.55 (t, 4H), 2.80-2.75 (m, 2H), 2.40 (t, 4H), 2.15-2.00 (m, 3H), 1.80-1.70 (m, 2H), 1.40-1.30 (m, 2H).

Intermediario 179.1: 2-[1,4']-bipiperidinil-1'-il-etil-amina

El compuesto del título se sintetiza mediante la reducción del Intermediario **179.2,** de una manera análoga a la preparación del Intermediario **149.1,** como un aceite incoloro; ES-MS: M+ = 212.3: ^{1}H-RMN (DMSO-d_6) 3.30 (bs, 2H), 2.85-2.80 (m, 2H), 2.55 (t, 2H), 2.40 (t, 4H), 2.20 (t, 2H), 2.10-2.05 (m, 1H), 1.85-1.75 (m, 2H), 1.65-1.55 (m, 2H), 1.45-1.30 (m, 8H).

Intermediario 179.2: [1,4']-bipiperidinil-1'-il-acetonitrilo

El compuesto del título se sintetiza mediante el acoplamiento del [1,4']-bipiperidinilo (comercialmente disponible en Fluorochem Ltd) y bromo-acetonitrilo, de una manera análoga a la preparación del Intermediario **149.2,** como un aceite incoloro; ES-MS: M+ = 208.2.

Intermediario 180.1: 2-(4-pirrolidin-1-il-piperidin-1-il)-etil-amina

El compuesto del título se sintetiza mediante la reducción del Intermediario **180.2**, de una manera análoga a la preparación del Intermediario **149.1**, como un aceite incoloro; ES-MS: M+ = 198.2: ^{1}H-RMN (DMSO-d_6) 3.30 (bs, 2H), 2.80-2.75 (m, 2H), 2.55 (t, 2H), 2.45-2.35 (m, 4H), 2.20 (t, 2H), 1.90-1.55 (m, 9H), 1.40-1.30 (m, 2H).

Intermediario 180.2: (4-pirrolidin-1-il-piperidin-1-il)-acetonitrilo

El compuesto del título se sintetiza mediante el acoplamiento de la 4-pirrolidin-1-il-piperidina (comercialmente disponible en CHESS GmbH) y bromo-acetonitrilo, de una manera análoga a la preparación del Intermediario **149.2**, como un sólido blanco; ES-MS: M+ = 194.1: ^{1}H-RMN (DMSO-d_6) 3.65 (s, 2H), 2.75-2.70 (m, 2H), 2.45-2.40 (m, 4H), 2.20-2.10 (m, 2H), 1.90-1.75 (m, 3H), 1.65-1.60 (m, 4H), 1.45-1.30 (m, 2H).

Intermediario 183.1: 2-[4-(tetrahidro-furan-2-il-metil)-piperazin-1-il]-etil-amina

El compuesto del título se sintetiza mediante la reducción del Intermediario **183.2**, de una manera análoga a la preparación del Intermediario **149.1**, como un aceite incoloro; ES-MS: M+ = 214.3.

Intermediario 183.2: [4-(tetrahidro-furan-2-il-metil)-piperazin-1-il]-acetonitrilo

El compuesto del título se sintetiza mediante el acoplamiento de la 1-(tetrahidro-furan-2-il-metil)-piperazina (comercialmente

disponible en CHESS GmbH) y bromo-acetonitrilo, de una manera análoga a la preparación del Intermediario **149.2,** como un sólido blanco; ES-MS: M+ = 210.2.

Intermediario 184.1: 2-(4-piridin-4-il-metil-piperazin-1-il)-etil-amina

El compuesto del título se sintetiza mediante la reducción del Intermediario **184.2,** de una manera análoga a la preparación del Intermediario **149.1,** como un aceite incoloro; ES-MS: M+ = 221.2: ^{1}H-RMN ($CDCl_3$) 8.50 (d, 2H), 7.20 (d, 2H), 3.50 (s, 2H), 2.80 (t, 2H), 2.60-2.30 (m, 12H).

Intermediario 184.2: (4-piridin-4-il-metil-piperazin-1-il)-acetonitrilo

El compuesto del título se sintetiza mediante el acoplamiento de la 1-piridin-4-il-metil-piperazina (comercialmente disponible en ABCR GmbH) y bromo-acetonitrilo, de una manera análoga a la preparación del Intermediario **149.2,** como un aceite incoloro; ES-MS: M+ = 217.2: ^{1}H-RMN ($CDCl_3$) 8.55 (d, 2H), 7.25 (d, 2H), 3.50 (s, 4H), 2.70-2.40 (m, 8H).

Intermediario 193.1: Sal de 3-((R)-pirrolidin-3-iloxi-metil)-piridina • 2HCl

El **Intermediario 193.2** (609 miligramos, 2.19 milimoles) se trata con una solución en EtOH 1M de HCl (10 mililitros) a temperatura ambiente. Después de 5 horas, la mezcla de reacción se evapora al vacío, para proporcionar el compuesto del título como un sólido blanco con una alta pureza, el cual se somete al siguiente

paso sin mayor purificación; ES-MS: M+ = 179.1; ^{1}H-RMN (DMSO-d_6) 9.50 (bs, 2H), 8.95 (s, 1H), 8.80 (d, 1H), 8.50 (d, 1H), 7.95 (dd, 1H), 4.70 (s, 2H), 4.35 (t, 1H), 3.40-3.10 (m, 5H), 2.10-1.95 (m, 2H).

Intermediario 193.2: Terbutil-éster del ácido (R)-3-(piridin-3-il-metoxi)-pirrolidin-1-carboxílico

Se agrega NaH al 55 por ciento en aceite mineral (160 miligramos, 6.68 milimoles), a una solución de terbutil-éster del ácido (R)-3-hidroxi-pirrolidin-1-carboxílico (500 miligramos, 2.67 milimoles) en tetrahidrofurano (8 mililitros) a 0°C. Después de 15 minutos, se agrega sal de 3-cloro-metil-piridina•HCl (526 miligramos, 3.20 milimoles), y la mezcla de reacción se agita a 40°C. Después de completarse, la mezcla de reacción se apaga mediante H_2O, se agrega EtOAc, y la capa orgánica se lava con salmuera, se seca sobre $MgSO_4$ y se evapora al vacío. La cromatografía por evaporación instantánea en gel de sílice del residuo proporciona el compuesto del título como un polvo blanco; ES-MS: M+ = 279.2: $_At_{Ret}$ = 2.80 minutos.

Intermediario 197.1: Sal de 2-((R)-pirrolidin-2-iloxi-metil)-piridina • 2HCl

El compuesto del título se sintetiza mediante la desprotección del **Intermediario 197.2,** de una manera análoga a la preparación del Intermediario **193.1,** como un sólido blanco; ES-MS: M+ = 179.1; ^{1}H-RMN (DMSO-d_6) 9.60 (bs, 1H), 9.40 (bs, 1H), 8.75 (d, 1H), 8.35 (t, 1H), 7.90 (d, 1H), 7.80 (dd, 1H), 4.80 (s, 2H), 4.40 (t, 1H), 3.50-3.10 (m, 5H), 2.10-1.90 (m, 2H).

Intermediario 197.2: Terbutil-éster del ácido (R)-3-(piridin-2-il-metoxi)-pirrolidin-1-carboxílico

El compuesto del título se sintetiza mediante el acoplamiento del terbutil-éster del ácido (R)-3-hidroxi-pirrolidin-1-carboxílico y sal de 2-cloro-metil-piridina • HCl, de una manera análoga a la preparación del Intermediario **193.2**, como un sólido blanco; ES-MS: M+ = 279.2: $_{A}t_{Ret}$ = 2.81 minutos.

Intermediario 198.1: 4-((R)-pirrolidin-4-iloxi-metil)-piridina

El compuesto del título se sintetiza mediante la desprotección del **Intermediario 198.2**, de una manera análoga a la preparación del Intermediario **193.1**, como un sólido blanco; ES-MS: M+ = 179.1; ^{1}H-RMN (DMSO-d_6) 9.50 (bs, 2H), 8.85 (d, 2H), 7.95 (d, 2H), 4.80 (s, 2H), 4.40 (t, 1H), 3.40-3.15 (m, 5H), 2.20-1.90 (m, 2H).

Intermediario 198.2: Terbutil-éster del ácido (R)-3-(piridin-4-il-metoxi)-pirrolidin-1-carboxílico

El compuesto del título se sintetiza mediante el acoplamiento del terbutil-éster del ácido (R)-3-hidroxi-pirrolidin-1-carboxílico y sal de 4-cloro-metil-piridina • HCl, de una manera análoga a la preparación del Intermediario **193.2**, como un sólido blanco; ES-MS: M+ = 279.2: $_{A}t_{Ret}$ = 2.84 minutos.

Intermediario 199.1: [1-(2-amino-etil)-piperidin-4-il]-dimetil-amina

El compuesto del título se sintetiza mediante la reducción del Intermediario **199.2**, de una manera análoga a la preparación del

Intermediario **149.1,** como un aceite incoloro; ES-MS: M+ = 172.1: ^{1}H-RMN (DMSO-d_6) 3.30 (s, 2H), 2.85-2.75 (m, 2H), 2.55 (t, 2H), 2.20 (t, 2H), 2.10 (s, 6H), 2.00-1.95 (m, 1H), 1.90-1.80 (m, 2H), 1.70-1.60 (m, 2H), 1.40-1.20 (m, 2H).

Intermediario 199.2: (4-dimetil-amino-piperidin-1-il)-acetonitrilo

El compuesto del título se sintetiza mediante el acoplamiento de la dimetil-piperidin-4-il-amina y bromo-acetonitrilo, de una manera análoga a la preparación del Intermediario **149.2,** como un aceite incoloro; ES-MS: M+ = 168.1: ^{1}H-RMN (DMSO-d_6) 3.65 (s, 2H), 2.80-2.75 (m, 2H), 2.15-2.05 (m, 8H, incluyendo un singulete en 2.10), 2.00-1.95 (m, 1H), 1.75-1.65 (m, 2H), 1.40-1.30 (m, 2H).

Intermediario 200.1: 2-[4-(1-etil-propil)-piperazin-1-il]-etil-amina

El compuesto del título se sintetiza mediante la reducción del Intermediario **200.2,** de una manera análoga a la preparación del Intermediario **149.1,** como un aceite incoloro; ES-MS: M+ = 200.3: ^{1}H-RMN (DMSO-d_6) 3.30 (bs, 2H), 2.55 (t, 2H), 2.40-2.25 (m, 8H), 2.20 (t, 2H), 2.10-2.00 (m, 1H), 1.45-1.35 (m, 2H), 1.25-1.05 (m, 2H), 0.90 (t, 6H).

Intermediario 200.2: 4-(1-etil-propil)-piperazin-1-il]-acetonitrilo

El compuesto del título se sintetiza mediante el acoplamiento de la 1-(1-etil-propil)-piperazina (comercialmente disponible en CHESS GmbH) y bromo-acetonitrilo, de una manera análoga a la

preparación del Intermediario **149.2,** como un aceite incoloro; ES-MS: M+ = 196.2: ^{1}H-RMN (DMSO-d_6) 3.65 (s, 2H), 2.50-2.35 (m, 8H), 2.15-2.05 (m, 1H), 1.45-1.35 (m, 2H), 1.25-1.05 (m, 2H), 0.90 (t, 6H).

Intermediario 202.1: [1-(2-amino-etil)-piperidin-4-il]-dietil-amina

El compuesto del título se sintetiza mediante la reducción del Intermediario **202.2,** de una manera análoga a la preparación del Intermediario **149.1,** como un aceite incoloro; ES-MS: M+ = 200.3: ^{1}H-RMN (DMSO-d_6) 3.30 (bs, 2H), 2.85-2.75 (m, 2H), 2.55 (t, 2H), 2.45-2.30 (m, 5H), 2.20 (t, 2H), 1.90-1.80 (m, 2H), 1.60-1.55 (m, 2H), 1.40-1.30 (m, 2H), 0.95 (t, 6H).

Intermediario 202.2: (4-dietil-amino-piperidin-1-il)-acetonitrilo

El compuesto del título se sintetiza mediante el acoplamiento de la dietil-piperidin-4-il-amina (comercialmente disponible en CHESS GmbH) y bromo-acetonitrilo, de una manera análoga a la preparación del Intermediario **149.2,** como un aceite incoloro; ES-MS: M+ = 196.2: ^{1}H-RMN (DMSO-d_6) 3.65 (s, 2H), 2.80-2.75 (m, 2H), 2.45-2.30 (m, 5H), 2.15-2.05 (m, 2H), 1.70-1.60 (m, 2H), 1.45-1.35 (m, 2H), 0.95 (t, 6H).

Intermediario 203.1: 2-(4-isobutil-piperazin-1-il)-etil-amina

El compuesto del título se sintetiza mediante la reducción del Intermediario **203.2,** de una manera análoga a la preparación del Intermediario **149.1,** como un aceite incoloro; ES-MS: M+ = 186.2: : ^{1}H-RMN (DMSO-d_6) 3.30 (bs, 2H), 2.50 (t, 2H), 2.40-2.20 (m, 10H),

1.95 (d, 2H), 1.75-1.65 (m, 1H), 0.95 (d, 6H).

Intermediario 203.2: (4-isobutil-piperazin-1-il)-acetonitrilo

El compuesto del título se sintetiza mediante el acoplamiento de la 1-isobutil-piperazin-amina (comercialmente disponible en CHESS GmbH) y bromo-acetonitrilo, de una manera análoga a la preparación del Intermediario **149.2,** como un aceite incoloro; ES-MS: M+ = 182.2: ^{1}H-RMN (DMSO-d_6) 3.65 (s, 2H), 2.45-2.20 (m, 8H), 2.00 (d, 2H), 1.80-1.70 (m, 1H), 0.90 (d, 6H).

Intermediario 204.1: 2-(4-adamantan-1-il-piperazin-1-il)-etil-amina

El compuesto del título se sintetiza mediante la reducción del Intermediario **204.2,** de una manera análoga a la preparación del Intermediario **149.1,** como un aceite incoloro; ES-MS: M+ = 264.4: ^{1}H-RMN (DMSO-d_6) 3.30 (bs, 2H), 2.60-2.50 (m, 6H), 2.40-2.20 (m, 6H), 2.00 (bs, 3H), 1.60-1.50 (m, 12H).

Intermediario 204.2: (4-adamantan-1-il-piperazin-1-il)-acetonitrilo

El compuesto del título se sintetiza mediante el acoplamiento de la 1-adamantil-piperazina (comercialmente disponible en CHESS GmbH) y bromo-acetonitrilo, de una manera análoga a la preparación del Intermediario **149.2,** como un aceite incoloro; ES-MS: M+ = 260.3: ^{1}H-RMN (DMSO-d_6) 3.65 (s, 2H), 2.60-2.50 (m, 4H), 2.45-2.40 (m, 4H), 2.00 (bs, 3H), 1.60-1.50 (m, 12H).

Intermediario 205.1: [1-(2-amino-etil)-piperidin-4-il]-dipropil-amina

El compuesto del título se sintetiza mediante la reducción del Intermediario **205.2,** de una manera análoga a la preparación del Intermediario **149.1,** como un aceite incoloro; ES-MS: M+ = 228.3: ^{1}H-RMN (DMSO-d_6) 3.30 (bs, 2H), 2.85-2.80 (m, 2H), 2.60 (t, 2H), 2.40-2.25 (m, 5H), 2.20 (t, 2H), 1.85-1.80 (m, 2H), 1.60-1.50 (m, 2H), 1.40-1.25 (m, 6H), 0.90 (t, 6H).

Intermediario 205.2: (4-dipropil-amino-piperidin-1-il)-acetonitrilo

El compuesto del título se sintetiza mediante el acoplamiento de la dipropil-piperidin-4-il-amina (comercialmente disponible en CHESS GmbH) y bromo-acetonitrilo, de una manera análoga a la preparación del Intermediario **149.2,** como un aceite incoloro; ES-MS: M+ = 224.3: ^{1}H-RMN (DMSO-d_6) 3.65 (s, 2H), 2.80-2.75 (m, 2H), 2.40-2.30 (m, 5H), 2.15-2.05 (m, 2H), 1.65-1.60 (m, 2H), 1.50-1.30 (m, 6H), 0.90 (t, 6H).

Intermediario 207.1: 2-(4-terbutil-piperazin-1-il)-etil-amina

El compuesto del título se sintetiza mediante la reducción del Intermediario **207.2,** de una manera análoga a la preparación del Intermediario **149.1,** como un aceite incoloro; ES-MS: M+ = 186.2; ^{1}H-RMN (DMSO-d_6) 2.60 (t, 2H), 2.50-2.20 (m, 10H), 1.40 (bs, 2H), 0.95 (s, 9H).

Intermediario 207.2: (4-terbutil-piperazin-1-il)-acetonitrilo

El compuesto del título se sintetiza mediante el acoplamiento de la 1-terbutil-piperazina (comercialmente disponible en Wako Pure Chemical Industries, Ltd) y bromo-acetonitrilo, de una manera

análoga a la preparación del Intermediario **149.2,** como un aceite incoloro; ES-MS: M+ = 182.2: ^{1}H-RMN (DMSO-d_6) 3.65 (s, 2H), 2.50-2.40 (m, 8H), 1.00 (s, 9H).

Intermediario 208.1: 2-(4-pirimidin-2-il-piperazin-1-il)-etil-amina

El compuesto del título se sintetiza mediante la reducción del Intermediario **208.2,** de una manera análoga a la preparación del Intermediario **149.1,** como un aceite incoloro; ES-MS: M+ = 208.2.

Intermediario 208.2: (4-pirimidin-2-il-piperazin-1-il)-acetonitrilo

El compuesto del titulo se sintetiza mediante el acoplamiento de la 2-piperazin-1-il-pirimidina y bromo-acetonitrilo, de una manera análoga a la preparación del Intermediario **149.2,** como un sólido blanco; ES-MS: M+ = 204.2: ^{1}H-RMN (DMSO-d_6) 8.35 (d, 2H), 6.60 (t, 1H), 3.80-3.70 (m, 6H), 2.45-2.40 (m, 4H).

Intermediario 209.1: Ácido 6-cloro-3-[3-(4-cloro-2-fluoro-bencil)-5-fenil-3H-imidazol-4-il]-1H-indol-2-carboxílico (al mismo tiempo un compuesto de la fórmula I de acuerdo con la invención)

El compuesto del título se sintetiza mediante la hidrólisis del Intermediario **209.2,** de una manera análoga a la preparación del Intermediario **2.1,** como un sólido incoloro; ES-MS: M+ = 480.0: $_{At}t_{Ret}$ = 4.23 minutos.

Intermediario 209.2: Etil-éster del ácido 6-cloro-3-[3-(4-cloro-2-fluoro-bencil)-5-fenil-3H-imidazol-4-il]-1H-indol-2-

carboxílico (el cual también es un compuesto de la fórmula I de acuerdo con la invención)

El compuesto del título se sintetiza mediante la condensación del **Intermediario 2.3**, 4-cloro-2-fluoro-bencil-amina, y 1-(isociano-fenil-metan-sulfonil)-4-metil-benceno, de una manera análoga a la preparación del Intermediario **2.2,** como un sólido incoloro; ES-MS: M+ = 508.0: $_{A}t_{Ret}$ = 4.63 minutos.

Intermediario 219.1: Ácido 6-cloro-3-[3-(4-cloro-bencil)-5-(4-fluoro-fenil)-3H-imidazol-4-il]-1H-indol-2-carboxílico (el cual también es un compuesto de la fórmula I de acuerdo con la invención)

El compuesto del título se sintetiza mediante la hidrólisis del Intermediario **219.2**, de una manera análoga a la preparación del Intermediario **2.1**, como un sólido incoloro; ES-MS: M+H = 480.0: HPLC $_{C}t_{Ret}$ = 6.24 minutos.

Intermediario 219.2: Etil-éster del ácido 6-cloro-3-[3-(4-cloro-bencil)-5-(4-fluoro-fenil)-3H-imidazol-4-il]-1H-indol-2-carboxílico (el cual también es un compuesto de la fórmula I de acuerdo con la invención)

El compuesto del título se sintetiza mediante la condensación del **Intermediario 2.3**, 4-cloro-bencil-amina, y 1-(isociano-4-fluoro-fenil-metan-sulfonil)-4-metil-benceno (comercialmente disponible en SynChem, Inc) de una manera análoga a la preparación del Intermediario **2.2**, como un sólido incoloro; ES-MS: M+H = 508.0: HPLC $_{C}t_{Ret}$ = 6.59 minutos.

El **Ejemplo 220** se sintetiza mediante la desprotección del **Intermediario 220.1** de una manera análoga a la preparación del Ejemplo **44**, como un sólido incoloro; ES-MS: M+H = 587.0; HPLC: ct_{Ret} = 5.36 minutos.

Intermediario 220.1: Terbutil-éster del ácido 4-{2-[(6-cloro-3-{3-[(S)-1-(4-cloro-fenil)-etil]-5-fenil-3H-imidazol-4-il}-1H-indol-2-carbonil)-amino]-etil}-piperazin-1-carboxílico (el cual también es un compuesto de la fórmula I de acuerdo con la invención)

El compuesto del título se sintetiza mediante la condensación del **Intermediario 134.1** y el terbutil-éster del ácido 4-(2-amino-etil)-piperazin-1-carboxílico, de una manera análoga a la preparación del Ejemplo **2**, como un sólido incoloro; ES-MS: M+H = 687.0; HPLC: ct_{Ret} = 6.12 minutos.

Intermediario 221.1: Ácido 6-cloro-3-[3-(4-cloro-bencil)-5-(2-fluoro-fenil)-3H-imidazol-4-il]-1H-indol-2-carboxílico (el cual también es un compuesto de la fórmula I de acuerdo con la invención)

El compuesto del título se sintetiza mediante la hidrólisis del Intermediario **221.2**, de una manera análoga a la preparación del Intermediario **2.1**, como un sólido incoloro; ES-MS: M+H = 480.0: ct_{Ret} = 6.12 minutos.

Intermediario 221.2: Etil-éster del ácido 6-cloro-3-[3-(4-cloro-bencil)-5-(2-fluoro-fenil)-3H-imidazol-4-il]-1H-indol-2-carboxílico (el cual también es un compuesto de la fórmula I de

acuerdo con la invención)

El compuesto del título se sintetiza mediante la condensación del **Intermediario 2.3**, 4-cloro-bencil-amina, y 1-(isociano-2-fluoro-fenil-metan-sulfonil)-4-metil-benceno (comercialmente disponible en SpeedChemical Corp. Ltd) de una manera análoga a la preparación del Intermediario **2.2**, como un sólido incoloro; ES-MS: M+H = 508.0: $_{C}t_{Ret}$ = 6.50 minutos.

Intermediario 224.1: 2-(4-bencil-piperidin-1-il)-etil-amina

El compuesto del título se sintetiza mediante la reducción del Intermediario **224.2**, de una manera análoga a la preparación del Intermediario **149.1**, como un aceite incoloro; ES-MS: M+H = 219.3: $_{A}t_{Ret}$ = 2.04 minutos.

Intermediario 224.2: (4-bencil-piperidin-1-il)-acetonitrilo

El compuesto del título se sintetiza mediante el acoplamiento de la 4-bencil-piperidina y bromo-acetonitrilo, de una manera análoga a la preparación del Intermediario **149.2**, como un aceite incoloro; ES-MS: M+ = 215.2: $_{A}t_{Ret}$ = 2.90 minutos.

Intermediario 225.1: 2-(4-piridin-2-il-metil-piperidin-1-il)-etil-amina

El compuesto del título se sintetiza mediante la reducción del Intermediario **225.2**, de una manera análoga a la preparación del Intermediario **149.1**, como un aceite incoloro; ES-MS: M+ = 220.3.

Intermediario 225.2: (4-piridin-2-il-metil-piperidin-1-il)-acetonitrilo

El compuesto del título se sintetiza mediante el acoplamiento

de la 2-piperidin-4-il-metil-piridina (comercialmente disponible en Array Biopharma) y bromo-acetonitrilo de una manera análoga a la preparación del Intermediario **149.2,** como un aceite incoloro; ES-MS: M+ = 216.2.

Intermediario 226.1: Ácido 6-cloro-3-[3-(3,3-dimetil-butil)-5-fenil-3H-imidazol-4-il]-1H-indol-2-carboxílico (el cual también es un compuesto de la fórmula I de acuerdo con la invención)

El compuesto del título se sintetiza mediante la hidrólisis del Intermediario **137.1,** de una manera análoga a la preparación del Intermediario **2.1,** como un sólido incoloro; ES-MS: M+ = 422.0: $_{A}t_{Ret}$ = 4.30 minutos.

Intermediario 227.1: 2-(4-terbutil-piperidin-1-il)-etil-amina

El compuesto del título se sintetiza mediante la reducción del Intermediario **227.2,** de una manera análoga a la preparación del Intermediario **149.1,** como un aceite incoloro; ES-MS: M+H = 185.3; ^{1}H-RMN (DMSO-d_6) 3.40 (bs, 2H), 2.90-2.80 (m, 2H), 2.55 (t, 2H), 2.20 (t, 2H), 1.80-1.70 (m, 2H), 1.60-1.50 (m, 2H), 1.25-1.05 (m, 2H), 1.00-0.90 (m, 1H), 0.80 (s, 9H).

Intermediario 227.2: (4-terbutil-piperidin-1-il)-acetonitrilo

El compuesto del título se sintetiza mediante el acoplamiento de la 4-terbutil-piperidina (comercialmente disponible en Matrix Scientific) y bromo-acetonitrilo, de una manera análoga a la preparación del Intermediario **149.2,** como un aceite incoloro; ES-MS: M+ = 181.2; ^{1}H-RMN (DMSO-d_6) 3.65 (s, 2H), 2.80-2.75 (m, 2H), 2.05-2.00 (m, 2H), 1.65-1.60 (m, 2H), 1.25-1.05 (m, 2H), 1.00-0.90

(m, 1H), 0.80 (s, 9H).

Intermediario 228.1: 2-[4-(3-metoxi-propil)-piperidin-1-il]-etil-amina

El compuesto del título se sintetiza mediante la reducción del Intermediario **228.2**, de una manera análoga a la preparación del Intermediario **149.1**, como un aceite incoloro; ES-MS: M+H = 201.3.

Intermediario 228.2: [4-(3-metoxi-propil)-piperidin-1-il]-acetonitrilo

El compuesto del título se sintetiza mediante el acoplamiento de la 4-(3-metoxi-propil)-piperidina (comercialmente disponible en ChemBridge Corporation) y bromo-acetonitrilo, de una manera análoga a la preparación del Intermediario **149.2**, como un aceite incoloro; ES-MS: M+ = 197.2; ^{1}H-RMN (DMSO-d_6) 3.65 (s, 2H), 3.30 (t, 2H), 3.00 (s, 3H), 2.75-2.70 (m, 2H), 2.10-2.00 (m, 2H), 1.65-1.40 (m, 4H), 1.20-1.00 (m, 5H).

Intermediario 229.1: 2-[4-(2-pirrolidin-1-il-etil)-piperidin-1-il]-etil-amina

El compuesto del título se sintetiza mediante la reducción del Intermediario **229.2**, de una manera análoga a la preparación del Intermediario **149.1**, como un aceite incoloro; ES-MS: M+ = 226.3; ^{1}H-RMN (DMSO-d_6) 2.75 (d, 2H), 2.55 (t, 2H), 2.40-2.30 (m, 6H), 2.20 (t, 2H), 1.80-1.75 (m, 2H), 1.65-1.50 (m, 6H), 1.30-1.00 (m, 7H).

Intermediario 229.2: 4-(2-pirrolidin-1-il-etil)-piperidin-1-il]-acetonitrilo

El compuesto del título se sintetiza mediante el acoplamiento

de la 4-(2-pirrolidin-1-il-etil)-piperidina (comercialmente disponible en ABCR GmbH) y bromo-acetonitrilo, de una manera análoga a la preparación del Intermediario **149.2,** como un aceite incoloro; ES-MS: M+ = 222.3; ^{1}H-RMN ($CDCl_3$) 3.45 (s, 2H), 2.70 (d, 2H), 2.45-2.20 (m, 8H), 1.80-1.60 (m, 6H), 1.40-1.20 (m, 5H).

Ejemplo 233: ((S)-3-bencil-amino-pirrolidin-1-il)-{6-cloro-bencil)-5-fenil-3H imidazol-4-il]-1H-indol-2-il}-metanona

Se agrega ciano-borohidruro de sodio (9 miligramos, 0.12 milimoles) a una solución del Ejemplo **80** (50 miligramos, 0.09 milimoles) en 1,2-dicloro-etano (2 mililitros) a temperatura ambiente. Después de 1 hora de agitación, la mezcla de reacción se apaga mediante la adición de dicloro-metano y una solución saturada de $NaHCO_3$. La capa orgánica se separa y se lava con H_2O y salmuera, se seca y se concentra. La cromatografía por evaporación instantánea en gel de sílice del producto crudo proporciona el compuesto del título como un sólido blanco. ES-MS: M-H = 618.0; HPLC: $_{ET}t_{Ret}$ = 4.16 minutos.

Los **Ejemplos 234, 235, 236, 237, 238, 239, 240 y 241** se preparan también en analogía al **Ejemplo 233**.

Intermediario 243.1: 2-(4-fenoxi-piperidin-1-il)-etil-amina

El compuesto del título se sintetiza mediante la reducción del Intermediario **243.2,** de una manera análoga a la preparación del Intermediario **149.1,** como un aceite incoloro; ES-MS: M+H = 221.2: $_{CT}t_{Ret}$ = 3.95 minutos.

Intermediario 243.2: (4-fenoxi-piperidin-1-il)-acetonitrilo

El compuesto del título se sintetiza mediante el acoplamiento de la 4-fenoxi-piperidina (comercialmente disponible en Alfa Aesar) y bromo-acetonitrilo, de una manera análoga a la preparación del Intermediario **149.2**, como un aceite incoloro; ES-MS: M+H = 217.2: ct_{Ret} = 4.80 minutos.

Intermediario 244.1: 2-(3,4,5,6-Tetrahidro-2H-[4,4']-bipiridinil-1-il)-etil-amina

El compuesto del título se sintetiza mediante la reducción del Intermediario **244.2**, de una manera análoga a la preparación del Intermediario **149.1**, como un aceite incoloro; ES-MS: M+H = 206.2: ct_{Ret} = 1.60 minutos.

Intermediario 244.2: (3,4,5,6-tetrahidro-2H-[4,4']-bipiridinil-1-il)-acetonitrilo

El compuesto del título se sintetiza mediante el acoplamiento de la 1,2,3,4,5,6-hexahidro-[4,4']-bipiridinilo (comercialmente disponible en CHESS GmbH) y bromo-acetonitrilo, de una manera análoga a la preparación del Intermediario **149.2**, como un aceite incoloro; ES-MS: M+H = 202.2: ct_{Ret} = 2.41 minutos.

El **Ejemplo 245** se sintetiza mediante la desprotección del **Intermediario 245.1**, de una manera análoga a la preparación del Ejemplo **44**, como un sólido incoloro; ES-MS: M+H = 572.0; HPLC: ct_{Ret} = 5.58 minutos.

Intermediario 245.1: Terbutil-éster del ácido 4-[2-({6-cloro-3-[3-(4-cloro-bencil)-5-fenil-3H-imidazol-4-il]-1H-indol-2-carbonil}-amino)-etil]-piperidin-1-carboxílico (el cual también es

un compuesto de la fórmula I de acuerdo con la invención)

El compuesto del título se sintetiza mediante la condensación del **Intermediario 2.1** y el terbutil-éster del ácido 4-(2-amino-etil)-piperidin-1-carboxílico, de una manera análoga a la preparación del Ejemplo **2**, como un sólido incoloro; ES-MS: M+H = 672.0; HPLC: ct_{Rel} = 6.93 minutos.

Intermediario 246.1: 2-[4-(2-metoxi-etoxi)-piperidin-1-il]-etil-amina

El compuesto del título se sintetiza mediante la reducción del Intermediario **246.2**, de una manera análoga a la preparación del Intermediario **149.1**, como un aceite incoloro; ES-MS: M+ = 203.2; ^{1}H-RMN (DMSO-d_6) 3.45 (dd, 2H), 3.40 (dd, 2H), 3.25-3.20 (m, 4H), 2.70-2.50 (m, 4H), 2.20 (t, 2H), 2.05-1.70 (m, 4H), 1.40-1.20 (m, 4H).

Intermediario 246.2: 2-[4-(2-metoxi-etoxi)-piperidin-1-il]-acetonitrilo

El compuesto del título se sintetiza mediante el acoplamiento de la 4-(2-metoxi-etoxi)-piperidina (comercialmente disponible en ChemBridge Corporation) y bromo-acetonitrilo, de una manera análoga a la preparación del Intermediario **149.2**, como un aceite incoloro; ES-MS: M+ = 199.2; ^{1}H-RMN (DMSO-d_6) 3.65 (s, 2H), 3.50 (dd, 2H), 3.40 (dd, 2H), 3.30-3.25 (m, 1H), 3.20 (s, 3H), 2.70-2.60 (m, 2H), 2.25-2.20 (m, 2H), 1.85-1.80 (m, 2H), 1.50-1.40 (m, 2H).

Intermediario 247.1: 2-[4-(2-piridin-2-il-etil)-piperazin-1-il]-etil-amina

El compuesto del título se sintetiza mediante la reducción del

Intermediario **247.2**, de una manera análoga a la preparación del Intermediario **149.1**, como un aceite incoloro; ES-MS: M+H = 235.2: $_{c}t_{Ret}$ = 1.81 minutos.

Intermediario 247.2: [4-(2-piridin-2-il-etil)-piperazin-1-il]-acetonitrilo

El compuesto del título se sintetiza mediante el acoplamiento de la 1-(2-piridin-2-il-etil)-piperazina (comercialmente disponible en ABCR GmbH) y bromo-acetonitrilo, de una manera análoga a la preparación del Intermediario **149.2**, como un aceite incoloro; ES-MS: M+H = 231.2: $_{c}t_{Ret}$ = 2.17 minutos.

Intermediario 248.1: 2-(4-bencil-2-metil-piperazin-1-il)-etil-amina

El compuesto del título se sintetiza mediante la reducción del Intermediario **248.2**, de una manera análoga a la preparación del Intermediario **149.1**, como un aceite incoloro; ES-MS: M+ = 234.3; ^{1}H-RMN (DMSO-d_6) 7.35-7.20 (m, 5H), 3.40 (dd, 2H), 2.70-2.50 (m, 6H), 2.40-2.00 (m, 4H), 1.80 (t, 1H), 1.20 (bs, 2H), 0.90 (d, 3H).

Intermediario 248.2: (4-bencil-2-metil-piperazin-1-il)-acetonitrilo

El compuesto del título se sintetiza mediante el acoplamiento de la 4-bencil-2-metil-piperazina (comercialmente disponible en CHESS GmbH) y bromo-acetonitrilo, de una manera análoga a la preparación del Intermediario **149.2**, como un aceite incoloro; ES-MS: M+ = 230.2: $_{A}t_{Ret}$ = 1.86 minutos.

Intermediario 251.1:

El compuesto del título se sintetiza mediante la reducción del Intermediario **251.2**, de una manera análoga a la preparación del Intermediario **149.1**, como un aceite incoloro; ES-MS: M+ = 231.3: $_{A}t_{Ret}$ = 2.27 minutos.

Intermediario 251.2:

El compuesto del título se sintetiza mediante el acoplamiento de la 2,3-dihidro-espiro-[inden-1,4'-piperidina] (comercialmente disponible en Parkway Scientific) y bromo-acetonitrilo, de una manera análoga a la preparación del Intermediario **149.2**, como un aceite incoloro; ES-MS: M+ = 227.2: $_{A}t_{Ret}$ = 3.10.

Intermediario 252.1: 1-(2-amino-etil)-4-bencil-piperidin-4-ol

El compuesto del título se sintetiza mediante la reducción del Intermediario **252.2**, de una manera análoga a la preparación del Intermediario **149.1**, como un aceite incoloro; ES-MS: M+ = 235.2: $_{A}t_{Ret}$ = 1.27 minutos.

Intermediario 251.2: (4-bencil-4-hidroxi-piperidin-1-il)-acetonitrilo

El compuesto del título se sintetiza mediante el acoplamiento de la 4-bencil-4-hidroxi-piperidina (comercialmente disponible en ABCR GmbH) y bromo-acetonitrilo, de una manera análoga a la preparación del Intermediario **149.2**, como un aceite incoloro; ES-MS: M+ = 231.2: $_{A}t_{Ret}$ = 1.81 minutos.

Intermediario 253.1: 1-(2-amino-etil)-4-fenil-piperidin-4-ol

El compuesto del título se sintetiza mediante la reducción del Intermediario **253.2**, de una manera análoga a la preparación del

Intermediario **149.1**, como un aceite incoloro; ES-MS: M+ = 221.2; ^{1}H-RMN (DMSO-d_6) 7.50-7.40 (m, 2H), 7.30-7.10 (m, 3H), 3.30 (s, 2H), 2.70-2.60 (m, 4H), 2.40-2.20 (m, 4H), 1.95-1.70 (m, 3H), 1.60-1.50 (m, 2H).

Intermediario 253.2: (4-hidroxi-4-fenil-piperidin-1-il)-acetonitrilo

El compuesto del título se sintetiza mediante el acoplamiento de la 4-hidroxi-4-fenil-piperidina y bromo-acetonitrilo, de una manera análoga a la preparación del Intermediario **149.2**, como un aceite incoloro; ES-MS: M+ = 217.2: $_{A}t_{Ret}$ = 1.51 minutos.

Intermediario 254.1: 2-(4-bencil-4,7-diaza-espiro[2.5]-oct-7-il)-etil-amina

El compuesto del título se sintetiza mediante la reducción del Intermediario **254.2**, de una manera análoga a la preparación del Intermediario **149.1**, como un aceite incoloro; ES-MS: M+H = 246.3: $_{ct}t_{Ret}$ = 3.81 minutos.

Intermediario 254.2: (4-bencil-4,7-diaza-espiro[2.5]-oct-7-il)-acetonitrilo

El compuesto del título se sintetiza mediante el acoplamiento de la 4-bencil-4,7-diaza-espiro-[2.5]-octano (el cual se prepara en analogía a un procedimiento publicado en la literatura (Publicación Internacional Número WO030828859)) y bromo-acetonitrilo, de una manera análoga a la preparación del Intermediario **149.2**, como un aceite incoloro; ES-MS: M+H = 242.2: $_{ct}t_{Ret}$ = 3.84 minutos.

Intermediario 255.1: 3-[isociano-(toluen-4-sulfonil)-metil]-

piridina

El compuesto del título se sintetiza mediante la condensación del piridin-3-carbaldehído, de una manera análoga a la preparación del Intermediario **16.1**, como un sólido incoloro; ES-MS: M+H = 273.1: ct_{Rel} = 5.45 minutos.

Intermediario 256.1: 2-((2S,5R)-2,5-dimetil-4-piridin-3-il-metil-piperazin-1-il)-etil-amina

El compuesto del título se sintetiza mediante la reducción del Intermediario **256.2**, de una manera análoga a la preparación del Intermediario **149.1** como un aceite incoloro; ES-MS: M+H = 249.2; ^{1}H-RMN (DMSO-d_6) 8.50 (s, 1H), 8.40 (d, 1H), 7.65 (d, 1H), 7.35 (dd, 1H), 4.00 (d, 1H), 3.05 (d, 1H), 2.80-1.70 (m, 12H), 1.05 (d, 3H), 0.90 (d, 3H).

Intermediario 256.2: ((2S,5R)-2,5-dimetil-4-piridin-3-il-metil-piperazin-1-il)-acetonitrilo

El compuesto del título se sintetiza mediante el acoplamiento del Intermediario **256.3**, y bromo-acetonitrilo, de una manera análoga a la preparación del Intermediario **149.2**, como un aceite incoloro; ES-MS: M+H = 245.2: ct_{Rel} = 2.88 minutos.

Intermediario 256.3: (2R,5S)-2,5-dimetil-1-piridin-3-il-metil-piperazina

El compuesto del título se sintetiza mediante la desprotección del **Intermediario 256.4**, de una manera análoga a la preparación del Ejemplo **44**, como un sólido incoloro; ES-MS: M+H = 206.2; HPLC: ct_{Rel} = 2.56 minutos.

Intermediario 256.4: Terbutil-éster del ácido (2S,5R)-2,5-dimetil-4-piridin-3-il-metil-piperazin-1-carboxílico

El compuesto del título se sintetiza mediante la alquilación del **Intermediario 256.5** con clorhidrato de cloruro de 3-picolilo de una manera análoga a la preparación del Intermediario **149.2**, como un sólido incoloro; ES-MS: M+H = 306.3; HPLC: $_{ct}t_{Ret}$ = 5.14 minutos.

Intermediario 256.5: Terbutil-éster del ácido (2S,5R)-2,5-dimetil-piperazin-1-carboxílico

Una mezcla de la trans-2,5-dimetil-piperazina (1.0 gramos, 8.76 milimoles) (comercialmente disponible en ABCR GmbH), $(Boc)_2O$ (1.91 gramos, 8.76 milimoles), y Et_3N (2.44 mililitros, 17.5 milimoles) en dicloro-metano (50 mililitros), se agita durante 16 horas a temperatura ambiente. Después de completarse, la mezcla de reacción se apaga mediante H_2O, se agrega dicloro-metano, y la capa orgánica se lava con salmuera, se seca sobre $MgSO_4$ y se evapora al vacío. La cromatografía por evaporación instantánea en gel de sílice del residuo proporciona el compuesto del título como un aceite incoloro; ES-MS: M+H = 215.2: ^{1}H-RMN (DMSO-d_6) 3.95-3.90 (m, 1H), 3.35 (dd, 1H), 3.20 (bs, 1H), 3.05 (dd, 1H), 3.00-2.90 (m, 2H), 2.30 (dd, 1H), 1.40 (s, 9H), 1.05 (d, 3H), 1.00 (d, 3H).

Intermediario 257.1: 2-(4-Indan-1-il-piperazin-1-il)-etil-amina

El compuesto del título se sintetiza mediante la reducción del Intermediario **257.2**, de una manera análoga a la preparación del Intermediario **149.1**, como un aceite incoloro; ES-MS: M+H = 246.3:

$_{ct}t_{Ret}$ = 3.69 minutos.

Intermediario 257.2: (4-Indan-1-il-piperazin-1-il)-acetonitrilo

El compuesto del título se sintetiza mediante el acoplamiento de la 1-indan-1-il-piperazina (comercialmente disponible en CHESS GmbH) y bromo-acetonitrilo, de una manera análoga a la preparación del Intermediario **149.2**, como un aceite incoloro; ES-MS: M+H = 242.2: $_{ct}t_{Ret}$ = 4.25 minutos.

Intermediario 259.1: 2-[4-(2-fenoxi-etil)-piperazin-1-il]-etil-amina

El compuesto del título se sintetiza mediante la reducción del Intermediario **259.2**, de una manera análoga a la preparación del Intermediario **149.1**, como un aceite incoloro; ES-MS: M+H = 250.2: $_{ct}t_{Ret}$ = 3.78 minutos.

Intermediario 259.2: 2-[4-(2-fenoxi-etil)-piperazin-1-il]-acetonitrilo

El compuesto del título se sintetiza mediante el acoplamiento de la 1-(2-fenoxi-etil)-piperazina (comercialmente disponible en CHESS GmbH) y bromo-acetonitrilo, de una manera análoga a la preparación del Intermediario **149.2**, como un aceite incoloro; ES-MS: M+H = 246.2: $_{ct}t_{Ret}$ = 4.31 minutos.

Intermediario 260.1: 2-benzo-imidazol-1-il-etil-amina

El compuesto del título se sintetiza mediante la reducción del Intermediario **260.2**, de una manera análoga a la preparación del Intermediario **149.1**, como un aceite incoloro; ES-MS: M+H = 162.1: $_{ct}t_{Ret}$ = 3.45 minutos.

Intermediario 260.2: Benzo-imidazol-1-il-acetonitrilo

El compuesto del título se sintetiza mediante el acoplamiento del bencimidazol y bromo-acetonitrilo, de una manera análoga a la preparación del Intermediario **149.2,** como un sólido incoloro; ES-MS: M+H = 158.0: ct_{Ret} = 3.42 minutos.

Intermediario 261.1: 2-[4-(2-morfolin-4-il-etil)-piperazin-1-il]-etil-amina

El compuesto del título se sintetiza mediante la reducción del Intermediario **261.2,** de una manera análoga a la preparación del Intermediario **149.1,** como un aceite incoloro; ES-MS: M+H = 243.0; ^{1}H-RMN (DMSO-d_6) 7.95 (bs, 2H), 3.80-3.60 (m, 4H), 3.40-2.70 (m, 20H).

Intermediario 261.2: [4-(2-morfolin-4-il-etil)-piperazin-1-il]-acetonitrilo

El compuesto del título se sintetiza mediante el acoplamiento de la 4-(2-piperazin-1-il-etil)-morfolina (comercialmente disponible en ABCR GmbH) y bromo-acetonitrilo, de una manera análoga a la preparación del Intermediario **149.2,** como un aceite incoloro; ES-MS: M+H = 239.3; ^{1}H-RMN (DMSO-d_6) 3.70 (s, 2H), 3.30 (bs, 4H), 2.60-2.30 (m, 16H).

Intermediario 262.1: 2-[4-(1-metil-piperidin-4-il-metil)-piperazin-1-il]-etil-amina

El compuesto del título se sintetiza mediante la reducción del Intermediario **262.2,** de una manera análoga a la preparación del

Intermediario **149.1,** como un aceite incoloro; ES-MS: M+H = 241.0; ^{1}H-RMN (DMSO-d_6) 2.70-2.50 (m, 5H), 2.40-2.20 (m, 10H), 2.10 (s, 3H), 2.15-2.00 (m, 2H), 1.75 (t, 2H), 1.60 (d, 2H), 1.40-1.30 (m, 2H), 10.5 (dq, 2H).

Intermediario 262.2: [4-(1-metil-piperidin-4-il-metil)-piperazin-1-il]-acetonitrilo

El compuesto del título se sintetiza mediante el acoplamiento de la 1-(1-metil-piperidin-4-il-metil)-piperazina (comercialmente disponible en CHESS GmbH) y bromo-acetonitrilo, de una manera análoga a la preparación del Intermediario **149.2,** como un aceite incoloro; ES-MS: M+H = 237.3.

Intermediario 263.1: 2-[4-(2-etoxi-etil)-piperazin-1-il]-etil-amina

El compuesto del título se sintetiza mediante la reducción del Intermediario **263.2,** de una manera análoga a la preparación del Intermediario **149.1,** como un aceite incoloro; ES-MS: M+H = 202.2; ^{1}H-RMN (DMSO-d_6) 3.40 (q, 2H), 3.35 (q, 2H), 2.55 (t, 2H), 2.40-2.20 (m, 14H), 1.05 (t, 3H).

Intermediario 263.2: [4-(2-etoxi-etil)-piperazin-1-il]-acetonitrilo

El compuesto del título se sintetiza mediante el acoplamiento de la 4-(2-etoxi-etil)-piperazina (comercialmente disponible en ABCR GmbH) y bromo-acetonitrilo, de una manera análoga a la preparación del Intermediario **149.2,** como un aceite incoloro; ES-MS: M+H = 198.2; ^{1}H-RMN (DMSO-d_6) 3.70 (s, 2H), 3.45 (q, 2H), 3.40 (q, 2H),

2.40-2.30 (m, 10H), 1.05 (t, 3H).

Intermediario 264.1: 2-(4-fenetil-piperazin-1-il)-etil-amina

El compuesto del título se sintetiza mediante la reducción del Intermediario **264.2**, de una manera análoga a la preparación del Intermediario **149.1**, como un aceite incoloro; ES-MS: M+H = 234.3: ct_{Ret} = 3.74 minutos.

Intermediario 264.2: (4-fenetil-piperazin-1-il)-acetonitrilo

El compuesto del título se sintetiza mediante el acoplamiento de la 4-fenil-etil-piperazina (comercialmente disponible en ABCR GmbH) y bromo-acetonitrilo, de una manera análoga a la preparación del Intermediario **149.2**, como un aceite incoloro; ES-MS: M+H = 230.2: ct_{Ret} = 4.20 minutos.

Intermediario 269.1: 4-(2-amino-etil)-1-piridin-3-il-metil-piperazin-2-ona

El compuesto del título se sintetiza mediante la desprotección del **Intermediario 269.2**, de una manera análoga a la preparación del Ejemplo **44**, como un aceite incoloro; ES-MS: M+H = 235.2: ct_{Ret} = 1.76 minutos.

Intermediario 269.2: Terbutil-éster del ácido [2-(3-oxo-4-piridin-3-il-metil-piperazin-1-il)-etil]-carbámico

Una mezcla del Intermediario **269.3** (1.7 gramos, 6.44 milimoles), bromuro de 2-Boc-amino-etilo (1.58 gramos, 7.08 milimoles) y K_2CO_3 (5.34 gramos, 38.6 milimoles) en dimetil-formamida (30 mililitros), se agita a temperatura ambiente. Después de completarse, la mezcla de reacción se apaga mediante H_2O, se

agrega EtOAc, y la capa orgánica se lava con salmuera, se seca sobre $MgSO_4$ y se evapora al vacío. La cromatografía por evaporación instantánea en gel de sílice del residuo proporciona el compuesto del título como un aceite incoloro; ES-MS: M+H = 335.3: $_{ct}t_{Ret}$ = 3.73 minutos.

Intermediario 269.3: Sal de 1-piridin-3-il-metil-piperazin-2-ona • 2HCl

Una solución del intermediario **269.4** (2.03 gramos, 6.97 milimoles) en dioxano (25 mililitros) se trata mediante una solución en dioxano 4M de HCl (25 mililitros) a temperatura ambiente. Después de completarse, la mezcla de réacción se concentra al vacío para proporcionar el producto crudo, el cual se somete al siguiente paso sin mayor purificación; ES-MS: M+H = 192.1: $_{ct}t_{Ret}$ = 1.40 minutos.

Intermediario 269.4: Terbutil-éster del ácido 3-oxo-4-piridin-3-il-metil-piperazin-1-carboxílico

Una mezcla del terbutil-éster del ácido 3-oxo-piperazin-1-carboxílico (2.0 gramos, 9.99 milimoles) y clorhidrato de cloruro de 3-picolilo (1.63 gramos, 9.99 milimoles) en dimetil-formamida (20 mililitros), se trata mediante NaH al 60 por ciento en aceite mineral (0.80 gramos, 19.98 milimoles) a 0°C. Después de completarse, la mezcla de reacción se apaga mediante H_2O, se agrega EtOAc, y la capa orgánica se lava con salmuera, se seca sobre $MgSO_4$ y se evapora al vacío. La cromatografía por evaporación instantánea en gel de sílice del residuo proporciona el compuesto del título como un

aceite incoloro; ES-MS: M+H = 292.2: $_{ct}t_{Ret}$ = 4.15 minutos.

Intermediario 270.1: 2-[4-(2-amino-etil)-piperazin-1-il]-N-piridin-2-il-acetamida

El compuesto del título se sintetiza mediante la desprotección del **Intermediario 270.2**, de una manera análoga a la preparación del Ejemplo **44**, como un aceite incoloro; ES-MS: M+H = 264.2: $_{ct}t_{Ret}$ = 2.70 minutos.

Intermediario 270.2: Terbutil-éster del ácido {2-[4-(piridin-2-il-carbamoil-metil)-piperazin-1-il]-etil}-carbámico

El compuesto del título se sintetiza mediante el acoplamiento del deshidrato de triclorhidrato de 2-piperazin-1-il-N-piridin-2-il-acetamida (comercialmente disponible en ABCR GmbH) y el terbutil-éster del ácido (2-bromo-etil)-carbámico, de una manera análoga a la preparación del Intermediario **269.2**, como un aceite incoloro; ES-MS: M+H = 364.3: $_{ct}t_{Ret}$ = 4.07 minutos.

Intermediario 271.1: 2-[4-(2-amino-etil)-piperazin-1-il]-N-piridin-3-il-acetamida

El compuesto del título se sintetiza mediante la desprotección del **Intermediario 271.2**, de una manera análoga a la preparación del Ejemplo **44**, como un aceite incoloro; ES-MS: M+H = 264.2: $_{ct}t_{Ret}$ = 1.62 minutos.

Intermediario 271.2: Terbutil-éster del ácido {2-[4-(piridin-3-il-carbamoil-metil)-piperazin-1-il]-etil}-carbámico

El compuesto del título se sintetiza mediante el acoplamiento del triclorhidrato de 2-piperazin-1-il-N-piridin-2-il-acetamida

(comercialmente disponible en CHESS GmbH) y el terbutil-éster del ácido (2-bromo-etil)-carbámico, de una manera análoga a la preparación del Intermediario **269.2**, como un aceite incoloro; ES-MS: M+H = 364.2: ct_{Rel} = 3.88 minutos.

Intermediario 272.1: 2-[4-(2-amino-etil)-piperazin-1-il]-1-pirrolidin-1-il-etanona

El compuesto del título se sintetiza mediante la desprotección del **Intermediario 272.2**, de una manera análoga a la preparación del Ejemplo **44**, como un aceite incoloro; ES-MS: M+H = 241.3: ct_{Rel} = 2.88 minutos.

Intermediario 272.2: Terbutil-éster del ácido {2-[4-(2-oxo-2-pirrolidin-1-il-etil)-piperazin-1-il]-etil}-carbámico

El compuesto del título se sintetiza mediante el acoplamiento de la 2-piperazin-1-il-1-pirrolidin-1-il-etanona (comercialmente disponible en CHESS GmbH) y el terbutil-éster del ácido (2-bromo-etil)-carbámico, de una manera análoga a la preparación del Intermediario **269.2**, como un aceite incoloro; ES-MS: M+H = 341.3: ct_{Rel} = 4.08 minutos.

Intermediario 273.1: 2-(2-fenil-imidazol-1-il)-etil-amina

El compuesto del título se sintetiza mediante la reducción del Intermediario **273.2**, de una manera análoga a la preparación del Intermediario **149.1**, como un aceite incoloro; ES-MS: M+H = 188.1: ct_{Rel} = 2.37 minutos.

Intermediario 273.2: (2-fenil-imidazol-1-il)-acetonitrilo

El compuesto del título se sintetiza mediante el acoplamiento

del 2-fenil-1H-imidazol y bromo-acetonitrilo, de una manera análoga a la preparación del Intermediario **269.4**, como un aceite incoloro; ES-MS: M+H = 184.1: $_{c}t_{Ret}$ = 3.48 minutos.

El **Ejemplo 278** se sintetiza mediante la desprotección del **Intermediario 278.1**, de una manera análoga a la preparación del Ejemplo **44**, como un sólido incoloro.

Intermediario 278.1: Terbutil-éster del ácido 4-(1-{6-cloro-3-[3-(4-cloro-bencil)-5-fenil-3H-imidazol-4-il]-1H-indol-2-carbonil}-azetidin-3-il)-piperazin-1-carboxílico (el cual también es un compuesto de la fórmula I de acuerdo con la invención)

El compuesto del título se sintetiza mediante la condensación del **Intermediario 2.1** y el **Intermediario 278.2**, de una manera análoga a la preparación del Ejemplo **2**, como un sólido incoloro; ES-MS: M+ = 685.0; HPLC: $_{A}t_{Ret}$ = 4.21 minutos.

Intermediario 278.2: Terbutil-éster del ácido 4-azetidin-3-il-piperazin-1-carboxílico

Una mezcla del Intermediario **278.3** (1.0 gramos, 2.45 milimoles) y Pd/C al 5 por ciento (200 miligramos) en metanol, se agita bajo una atmósfera de H_2 (1 bar). Después de 22 horas, la mezcla de reacción se filtra a través de Celite, y se lava cuidadosamente con tetrahidrofurano. Concentración al vacío para proporcionar el producto crudo, el cual se somete al siguiente paso sin mayor purificación; ES-MS: M+ = 242.3.

Intermediario 278.3: Terbutil-éster del ácido 4-(1-benzhidril-azetidin-3-il)-piperazin-1-carboxílico

El compuesto del título se sintetiza mediante la condensación del terbutil-éster del ácido piperazin-1-carboxílico y 1-benzhidril-azetidin-3-il-éster del ácido metan-sulfónico (comercialmente disponible en Fluorochem Ltd), de una manera análoga a la preparación del Intermediario **149.2**, como un sólido blanco; ES-MS: M+ = 408.3; HPLC: $_{A}t_{Ret}$ = 3.84 minutos.

Intermediario 280.1: 1-(2-amino-etil)-4-piridin-3-il-metil-piperazin-2-ona

El compuesto del título se sintetiza mediante la desprotección del **Intermediario 280.2**, de una manera análoga a la preparación del Ejemplo **44**, como un aceite incoloro; ES-MS: M+H = 235.1: $_{C}t_{Ret}$ = 1.86 minutos.

Intermediario 280.2: Terbutil-éster del ácido [2-(2-oxo-4-piridin-3-il-metil-piperazin-1-il)-etil]-carbámico

El compuesto del título se sintetiza mediante el acoplamiento del Intermediario **280.3** y el terbutil-éster del ácido (2-bromo-etil)-carbámico, de una manera análoga a la preparación del Intermediario **269.2**, como un aceite incoloro; ES-MS: M+H = 335.2: $_{C}t_{Ret}$ = 4.06 minutos.

Intermediario 280.3: 4-piridin-3-il-metil-piperazin-2-ona

El compuesto del título se sintetiza mediante el acoplamiento de la piperazin-2-ona y clorhidrato de cloruro de picolilo, de una manera análoga a la preparación del Intermediario **269.2**, como un sólido blanco; ES-MS: M+H = 192.1: $_{C}t_{Ret}$ = 1.74 minutos.

Intermediario 281.1: Ácido 6-cloro-3-[3-(5-cloro-piridin-2-il-

metil)-5-fenil-3H-imidazol-4-il]-1H-indol-2-carboxílico (el cual también es un compuesto de la fórmula I de acuerdo con la invención)

El compuesto del título se sintetiza mediante la hidrólisis del Intermediario **281.2**, de una manera análoga a la preparación del Intermediario **2.1**, como un sólido incoloro; ES-MS: M+H = 462.8: $_{ct}t_{Ret}$ = 5.77 minutos.

Intermediario 281.2: Etil-éster del ácido 6-cloro-3-[3-(5-cloro-piridin-2-il-metil)-5-fenil-3H-imidazol-4-il]-1H-indol-2-carboxílico (el cual también es un compuesto de la fórmula I de acuerdo con la invención)

El compuesto del título se sintetiza mediante la condensación del **Intermediario 2.3**, el **Intermediario 281.3** y 1-[isociano-(toluen-4-sulfonil)-metil]-2-fluoro-benceno, de una manera análoga a la preparación del Intermediario **2.2**, como un sólido incoloro; ES-MS: M+H = 490.8: $_{ct}t_{Ret}$ = 6.14 minutos.

Intermediario 281.3: C-(5-cloro-piridin-2-il)-metil-amina

Una mezcla de la 5-cloro-2-ciano-piridina (1.5 gramos, 10.8 milimoles) y Pd/C al 10 por ciento (0.4 gramos) en EtOH (40 mililitros) y HCl concentrado (1.2 mililitros), se agita bajo una atmósfera de H_2 (1 bar). Después de 2 horas, la mezcla de reacción se filtra a través de Celite, y se lava cuidadosamente con tetrahidrofurano. La concentración al vacío y la cromatografía por evaporación instantánea en gel de sílice del residuo proporciona el compuesto del título como un sólido blanco; ES-MS: M+H = 143.0:

$_{C}t_{Ret}$ = 3.33 minutos.

Intermediario 282.1: 2-amino-1-(4-piridin-3-il-metil-piperazin-1-il)-etanona

El compuesto del título se sintetiza mediante la desprotección del **Intermediario 282.2**, de una manera análoga a la preparación del Ejemplo **44**, como un aceite incoloro; ES-MS: M+H = 235.2: $_{C}t_{Ret}$ = 1.62 minutos.

Intermediario 282.2: Terbutil-éster del ácido [2-oxo-2-(4-piridin-3-il-metil-piperazin-1-il)-etil]-carbámico

El compuesto del título se sintetiza mediante la condensación de la 1-piridin-3-il-metil-piperazina y N-Boc-glicina, de una manera análoga a la preparación del Ejemplo **2**, como un sólido incoloro; ES-MS: M+H = 335.3; HPLC: $_{A}t_{Ret}$ = 3.93 minutos.

Intermediario 283.1: [1-(2-amino-etil)-piperidin-4-il]-piridin-2-il-amina

El compuesto del título se sintetiza mediante la reducción del Intermediario **283.2**, de una manera análoga a la preparación del Intermediario **149.1**, como un aceite incoloro; ES-MS: M+H = 221.0: $_{A}t_{Ret}$ = 2.29 minutos.

Intermediario 283.2: [4-(piridin-2-il-amino)-piperidin-1-il]-acetonitrilo

El compuesto del título se sintetiza mediante el acoplamiento del Intermediario **283.3**, y bromo-acetonitrilo, de una manera análoga a la preparación del Intermediario **149.2**, como un aceite incoloro; ES-MS: M+H = 217.1: $_{A}t_{Ret}$ = 3.11 minutos.

Intermediario 283.3: Piperidin-4-il-piridin-2-il-amina • 3HCl

El compuesto del título se sintetiza mediante la desprotección del **Intermediario 283.4,** de una manera análoga a la preparación del Intermediario **193.1,** como un aceite incoloro; ES-MS: M+H = 178.0: $_{A}t_{Ret}$ = 2.48 minutos.

Intermediario 283.4: Terbutil-éster del ácido 4-(piridin-2-il-amino)-piperidin-1-carboxílico

Una mezcla de la 4-amino-1-Boc-piperidina (2.0 gramos, 9.7 milimoles), 2-bromo-piridina (1.93 mililitros, 19.4 milimoles), NaO^{t}Bu (2.7 gramos, 27.1 milimoles), 2-diciclohexil-fosfino-2'-(N,N-dimetil-amino)-bifenilo (472 miligramos, 1.16 milimoles) y complejo de tris-(dibenciliden-acetona)-dipaladio/cloroformo (620 miligramos, 0.58 milimoles) en dioxano (10 mililitros), se calienta a 90°C. Después de completarse, la mezcla de reacción se apaga mediante H_2O, se agrega dicloro-metano, y la capa orgánica se lava con salmuera, se seca sobre $MgSO_4$ y se evapora al vacio. La cromatografía por evaporación instantánea en gel de sílice del residuo proporciona el compuesto del título como un polvo blanco; ES-MS: M+H = 278.3: $_{A}t_{Ret}$ = 4.75 minutos.

Intermediario 284.1: [1-(2-amino-etil)-piperidin-4-il]-metil-piridin-2-il-amina

El compuesto del título se sintetiza mediante la reducción del Intermediario **284.2,** de una manera análoga a la preparación del Intermediario **149.1,** como un aceite incoloro; ES-MS: M+H = 253.3:

$_At_{Rel}$ = 2.31 minutos.

Intermediario 284.2: [4-(metil-piridin-2-il-amino)-piperidin-1-il]-acetonitrilo

El compuesto del título se sintetiza mediante el acoplamiento del Intermediario **284.3** y bromo-acetonitrilo, de una manera análoga a la preparación del Intermediario **149.2**, como un aceite incoloro; ES-MS: M+H = 231.3: $_At_{Rel}$ = 3.29 minutos.

Intermediario 284.3: Metil-piperidin-4-il-piridin-2-il-amina

El compuesto del título se sintetiza mediante la desprotección del **Intermediario 284.4**, de una manera análoga a la preparación del Intermediario **193.1**, como un aceite incoloro; ES-MS: M+H = 192.2: $_At_{Rel}$ = 2.62 minutos.

Intermediario 284.4: Terbutil-éster del ácido 4-(metil-piridin-2-il-amino)-piperidin-1-carboxílico

Una mezcla del Intermediario **283.4** (1.14 gramos, 4.0 milimoles) y MeI (0.37 mililitros, 6.0 milimoles) en dimetil-formamida (10 mililitros), se trata con NaH al 60 por ciento en aceite mineral (240 miligramos, 6.0 milimoles) a temperatura ambiente. Después de completarse, la mezcla de reacción se apaga mediante H_2O, se agrega EtOAc, y la capa orgánica se lava con salmuera, se seca sobre $MgSO_4$ y se evapora al vacío. La cromatografía por evaporación instantánea en gel de sílice del residuo proporciona el compuesto del título como un polvo blanco; ES-MS: M+H = 232.3: $_At_{Rel}$ = 4.87 minutos.

Intermediario 285.1: 2-[4-(piridin-2-iloxi)-piperidin-1-il]-etil-

amina

El compuesto del título se sintetiza mediante la reducción del Intermediario **285.2**, de una manera análoga a la preparación del Intermediario **149.1**, como un aceite incoloro; ES-MS: M+H = 222.3: $_Dt_{Ret}$ = 1.46 minutos.

Intermediario 285.2: [4-(piridin-2-iloxi)-piperidin-1-il]-acetonitrilo

El compuesto del título se sintetiza mediante el acoplamiento del Intermediario **285.3** y bromo-acetonitrilo, de una manera análoga a la preparación del Intermediario **149.2**, como un aceite incoloro; ES-MS: M+H = 218.3: $_Dt_{Ret}$ = 1.78 minutos.

Intermediario 285.3: 2-(Piperidin-4-iloxi)-piridina

El compuesto del título se sintetiza mediante la desprotección del **Intermediario 285.4**, de una manera análoga a la preparación del Intermediario **193.1**, como un aceite incoloro; ES-MS: M+ =179.1: $_Dt_{Ret}$ = 1.47 minutos.

Intermediario 285.4: Terbutil-éster del ácido 4-(piridin-2-iloxi)-piperidin-1-carboxílico

Una mezcla del 4-hidroxi-1-piperidin-carboxilato de terbutilo (2.0 gramos, 9.64 milimoles) y 2-fluoro-piridina (0.93 mililitros, 10.6 milimoles) en dimetil-formamida (10 mililitros), se trata con NaH al 60 por ciento en aceite mineral (600 miligramos, 12.5 milimoles) a temperatura ambiente. Después de completarse, la mezcla de reacción se apaga mediante H_2O, se agrega EtOAc, y la capa orgánica se lava con salmuera, se seca sobre $MgSO_4$ y se evapora al

vacío. La cromatografía por evaporación instantánea en gel de sílice del residuo proporciona el compuesto del título como un polvo blanco; ES-MS: M+H = 279.0: $_{D}t_{Ret}$ = 2.82 minutos.

El **Ejemplo 286** se sintetiza mediante la condensación del ácido (S)-3-amino-3-(4-cloro-fenil)-propiónico, el **Intermediario 10.1**, y 1-(isociano-fenil-metan-sulfonil)-4-metil-benceno, de una manera análoga a la preparación del Ejemplo **1**, como un sólido incoloro; ES-MS: M+H = 495.7; HPLC: $_{A}t_{Ret}$ = 4.28 minutos.

Ejemplo 287: (S)-3-[5-(6-cloro-5-fluoro-1H-indol-3-il)-4-fenil-imidazol-1-il]-3-(4-cloro-fenil)-N-metil-propionamida

El compuesto del título se sintetiza mediante la condensación del Ejemplo **286** y sal de metil-amina • HCl, en analogía a la preparación del Ejemplo **2**, como un sólido blanco.

Los **Ejemplos 288, 289 y 290** se preparan también en analogía al **Ejemplo 287**.

Ejemplo 291: {2-[4-(piridin-3-carbonil)-piperazin-1-il]-etil}-amida del ácido 6-cloro-3-[3-(4-cloro-bencil)-5-fenil-3H-imidazol-4-il]-1H-indol-2-carboxílico

Una solución del Ejemplo **44** (109 miligramos, 0.19 milimoles) en piridina (1.0 mililitros), se trata con sal de clorhidrato de cloruro de nicotinilo (41 miligramos, 0.23 milimoles) a temperatura ambiente. Después de completarse, la mezcla de reacción se apaga mediante H_2O, se agrega EtOAc, y la capa orgánica se lava con salmuera, se seca sobre $MgSO_4$ y se evapora al vacío. La cromatografía por evaporación instantánea en gel de sílice del residuo proporciona el

compuesto del título como un polvo blanco.

Los **Ejemplos 294, 295, 296, 298, 299, 305, 309, 310 y 312** se preparan también en analogía al **Ejemplo 291**.

Ejemplo 292: {2-[4-(1-piridin-2-il-etil)-piperazin-1-il]-etil}-amida del ácido 6-cloro-3-[3-(4-cloro-bencil)-5-fenil-3H-imidazol-4-il]-1H-indol-2-carboxílico

Una mezcla del Ejemplo **44** (80 miligramos, 0.14 milimoles), K_2CO_3 (39 miligramos, 0.28 milimoles), y el Intermediario **292.1** en tolueno (0.5 mililitros) y CH_3CN (0.5 mililitros), se calienta a 85°C. Después de completarse, la mezcla de reacción se apaga mediante H_2O, se agrega EtOAc, y la capa orgánica se lava con salmuera, se seca sobre $MgSO_4$ y se evapora al vacío. La cromatografía por evaporación instantánea en gel de sílice del residuo proporciona el compuesto del título como un polvo blanco.

Los **Ejemplos 297, 304 y 311** se preparan también en analogía al **Ejemplo 292**.

Intermediario 292.1: 1-piridin-2-il-etil-éster del ácido metan-sulfónico

Una mezcla del Intermediario **292.2** (1.0 gramos, 8.12 milimoles) y Et_3N (2.3 mililitros, 16.2 milimoles) en dicloro-metano (10 mililitros), se trata mediante cloruro de metan-sulfonilo (0.66 mililitros, 8.53 milimoles) a 0°C. Después de completarse, la mezcla de reacción se apaga mediante H_2O, se agrega dicloro-metano, y la capa orgánica se lava con salmuera, se seca sobre $MgSO_4$ y se evapora al vacío, para proporcionar el producto crudo, el cual se

somete al siguiente paso sin mayor purificación; ES-MS: M+ = 202.1; $_{A}t_{Rel}$ = 1.37 minutos.

Intermediario 292.2: 1-piridin-2-il-etanol

Una solución de la 2-acetil-piridina (2.0 gramos, 16.5 milimoles) en metanol (33 mililitros), se trata mediante $NaBH_4$ (624 miligramos, 16.5 milimoles) a 0°C. Después de completarse, la mezcla de reacción se apaga mediante H_2O, se agrega EtOAc, y la capa orgánica se lava con salmuera, se seca sobre $MgSO_4$ y se evapora al vacío para proporcionar el producto crudo, el cual se somete al siguiente paso sin mayor purificación; ES-MS: M+ = 124.0; ^{1}H-RMN (DMSO-d_6) 8.45 (d, 1H), 7.75 (td, 1H), 7.50 (d, 1H), 7.20 (dd, 1H), 5.30 (d, 1H), 4.70-4.60 (m, 1H), 1.30 (d, 3H).

Ejemplo 293: {2-[4-(6-fluoro-piridin-3-carbonil)-piperazin-1-il]-etil}-amida del ácido 6-cloro-3-[3-(4-cloro-bencil)-5-fenil-3H-imidazol-4-il]-1H-indol-2-carboxílico

El compuesto del título se sintetiza mediante la condensación del Ejemplo **44** (100 miligramos, 0.17 milimoles) y ácido 6-fluoro-nicotínico (37 miligramos, 0.26 milimoles) en analogía a la preparación del Ejemplo **2** como un sólido blanco.

Los **Ejemplos 300, 301, 302, 303, 306, 307, 308, 313, 314, 315, 316, 317, 329 y 330** se preparan también en analogía al **Ejemplo 293**.

Intermediario 297.1: 1-pirazin-2-il-etil-éster del ácido metan-sulfónico

El compuesto del título se sintetiza mediante la metan-

sulfonilación del Intermediario **297.2** de una manera análoga a la preparación del Intermediario **292.1,** como un aceite incoloro; ES-MS: M+ = 203.1: $_At_{Ret}$ = 1.77 minutos.

Intermediario 297.2: 1-pirazin-2-il-etanol

El compuesto del título se sintetiza mediante la reducción de la acetil-pirazina de una manera análoga a la preparación del Intermediario **292.2,** como un aceite incoloro; ES-MS: M+ = 125.0; ^{1}H-RMN (DMSO-d_6) 8.75 (s, 1H), 8.55-8.50 (m, 2H), 5.60 (d, 1H), 4.85-4.75 (m, 1H), 1.40 (d, 3H).

Intermediario 304.1:

El compuesto del título se sintetiza mediante la metan-sulfonilación del Intermediario **304.2** de una manera análoga a la preparación del Intermediario **292.1,** como un aceite incoloro; ES-MS: M+ = 202.1: $_At_{Ret}$ = 1.10 minutos.

Intermediario 304.2:

El compuesto del título se sintetiza mediante la reducción de la 3-acetil-piridina de una manera análoga a la preparación del Intermediario **292.2,** como un aceite incoloro; ES-MS: M+ = 124.0; ^{1}H-RMN (DMSO-d_6) 8.50 (d, 1H), 8.40 (dd, 1H), 7.70 (td, 1H), 7.30 (dd, 1H), 5.30 (d, 1H), 4.80-4.70 (m, 1H), 1.35 (d, 3H).

Ejemplo 318: 6-cloro-3-[3-(4-cloro-bencil)-5-fenil-3H-imidazol-4-il]-2-(4,5-dihidro -oxazol-2-il)-1H-indol

Una mezcla del Intermediario **2.1** (600 miligramos, 1.3 milimoles), CDI (260 miligramos, 1.56 milimoles), bromhidrato de 2-bromo-etil-amina (411 miligramos, 1.95 milimoles) y Et_3N (0.55

mililitros, 3.89 milimoles) en tetrahidrofurano (6 mililitros), se calienta a reflujo. Después de completarse, la mezcla de reacción se apaga mediante H_2O, se agrega EtOAc, y la capa orgánica se lava con salmuera, se seca sobre $MgSO_4$ y se evapora al vacío. La cromatografía por evaporación instantánea en gel de sílice del residuo proporciona el compuesto del título como un polvo blanco.

Ejemplo 319: 5-{6-cloro-3-[3-(4-cloro-bencil)-5-fenil-3H-imidazol-4-il]-1H-indol-2-il}-3H-[1,3,4]-oxadiazol-2-ona

Una mezcla del Intermediario **319.1** (200 miligramos, 0.42 milimoles), CDI (89 miligramos, 0.54 milimoles) y Et_3N (0.1 mililitros, 0.71 milimoles) en tetrahidrofurano (3.6 mililitros) y dimetil-formamida (0.4 mililitros), se calienta a reflujo. Después de completarse, la mezcla de reacción se apaga mediante H_2O, se agrega EtOAc, y la capa orgánica se lava con salmuera, se seca sobre $MgSO_4$ y se evapora al vacío. La cromatografía por evaporación instantánea en gel de sílice del residuo proporciona el compuesto del título como un polvo blanco.

Intermediario 319.1: Hidrazida del ácido 6-cloro-3-[3-(4-cloro-bencil)-5-fenil-3H-imidazol-4-il]-1H-indol-2-carboxílico (la cual también es un compuesto de la fórmula I de acuerdo con la invención)

Una mezcla del Intermediario **2.2** (1.0 gramos, 2.0 milimoles) e hidrazina (0.49 mililitros, 10.2 milimoles) en EtOH (50 mililitros), se calienta a reflujo. Después de completarse, la mezcla de reacción se concentra al vacío, se agrega dicloro-metano, y la capa orgánica se

lava con salmuera, se seca sobre $MgSO_4$ y se evapora al vacío. La cromatografía por evaporación instantánea en gel de sílice del residuo proporciona el compuesto del título como un polvo blanco. ES-MS: M+ = 476.1: ${}_At_{Ret}$ = 3.88 minutos.

Ejemplo 320: (5-{6-cloro-3-[3-(4-cloro-bencil)-5-fenil-3H-imidazol-4-il]-1H-indol-2-il}-[1,3,4]-oxadiazol-2-il)-piridin-3-il-amina

Una mezcla del Intermediario **319.1** (400 miligramos, 0.84 milimoles), 3-isotiocianato-piridina (94 microlitros, 0.84 milimoles) y piridina (0.14 mililitros, 1.76 milimoles) en tetrahidrofurano (2.8 mililitros), se calienta a 50°C. Después de 15 minutos, se agregan TsCl (198 miligramos, 1.0 milimoles) y piridina (0.14 mililitros, 1.76 milimoles), y se agita durante 16 horas a 70°C. Después de completarse, la mezcla de reacción se concentra al vacío, se agrega EtOAc, y la capa orgánica se lava con salmuera, se seca sobre $MgSO_4$ y se evapora al vacío. La cromatografía por evaporación instantánea en gel de sílice del residuo proporciona el compuesto del título como un polvo blanco.

Los **Ejemplo 321 y 322** se preparan también en analogía al **Ejemplo 320**.

Ejemplo 323: 5-{6-cloro-3-[3-(4-cloro-bencil)-5-fenil-3H-imidazol-4-il]-1H-indol-2-il}-3-piridin-3-il-metil-3H-[1,3,4]-oxadiazol-2-ona

El compuesto del título se sintetiza mediante el acoplamiento del Ejemplo **319** y sal de 3-cloro-metil-piridina • HCl, en analogía a la

preparación del Ejemplo **292** como un sólido blanco.

Ejemplo 324: 6-cloro-3-{3-[4-cloro-2-(4-metil-piperazin-1-il-metil)-bencil]-5-fenil-3H-imidazol-4-il}-5-fluoro-1H-indol

Una mezcla del Intermediario **324.1** (100 miligramos, 0.177 milimoles), 1-metil-piperazina (30 microlitros 0.266 milimoles) y K_2CO_3 (36.8 miligramos, 0.266 milimoles) en dimetil-formamida (2 mililitros), se agita a temperatura ambiente. Después de completarse, la mezcla de reacción se concentra al vacío, se agrega EtOAc, y la capa orgánica se lava con salmuera, se seca sobre $MgSO_4$ y se evapora al vacío. La cromatografía por evaporación instantánea en gel de sílice del residuo proporciona el compuesto del título como un polvo blanco.

Los **Ejemplos 325, 326 y 327** se preparan también en analogía al **Ejemplo 324**.

Intermediario 324.1: 6-cloro-3-[3-(4-cloro-2-cloro-metil-bencil)-5-fenil-3H-imidazol-4-il]-5-fluoro-1H-indol

Una mezcla del Ejemplo **148** (1.1 gramos, 2.36 milimoles) y Et_3N (0.49 mililitros, 3.53 milimoles) en dimetil-formamida (25 mililitros) se trata mediante MsCl (0.20 mililitros, 2.59 milimoles) a 0°C. Después de completarse, la mezcla de reacción se concentra al vacío, se agrega EtOAc, y la capa orgánica se lava con salmuera, se seca sobre $MgSO_4$ y se evapora al vacío. La cromatografía por evaporación instantánea en gel de sílice del residuo proporciona el compuesto del título como un polvo blanco. ES-MS: M+H = 485.9: $_{c}t_{Ret}$ = 6.52 minutos.

Ejemplo 328: [2-(2-oxo-3-piridin-2-il-metil-imidazolidin-1-il)-etil]-amida del ácido 6-cloro-3-[3-(4-cloro-bencil)-5-fenil-3H-imidazol-4-il]-1H-indol-2-carboxílico

Una mezcla del Intermediario **328.1** (24 miligramos, 0.038 milimoles) y CDI (6.7 miligramos, 0.041 milimoles) en dicloro-metano (0.5 mililitros) se agita a temperatura ambiente. Después de completarse, se agrega dicloro-metano a la mezcla de reacción, y la capa orgánica se lava con salmuera, se seca sobre $MgSO_4$ y se evapora al vacío. La cromatografía por evaporación instantánea en gel de sílice del residuo proporciona el compuesto del título como un polvo blanco. ES-MS: M+H = 664.0: $_{ct}t_{Ret}$ = 5.63 minutos.

Intermediario 328.1: (2-{2-[(piridin-2-il-metil)-amino]-etil-amino}-etil)-amida del ácido 6-cloro-3-[3-(4-cloro-bencil)-5-fenil-3H-imidazol-4-il]-1H-indol-2-carboxílico (la cual también es un compuesto de la fórmula I de acuerdo con la invención)

El compuesto del título se sintetiza mediante la aminación reductiva de **Intermediario 328.2** y piridin-2-carbaldehído, de una manera análoga a la preparación del Ejemplo **233**, como un sólido incoloro; ES-MS: M+H = 638.0; HPLC: $_{ct}t_{Ret}$ = 5.50 minutos.

Intermediario 328.2: [2-(2-amino-etil-amino)-etil]-amida del ácido 6-cloro-3-[3-(4-cloro-bencil)-5-fenil-3H-imidazol-4-il]-1H-indol-2-carboxílico (la cual también es un compuesto de la fórmula I de acuerdo con la invención)

El compuesto del título se sintetiza mediante la desprotección

del **Intermediario 328.3** de una manera análoga a la preparación del Ejemplo **44** como un sólido incoloro; ES-MS: M+H = 547.1; HPLC: $_{ct}t_{Ret}$ = 5.29 minutos.

Intermediario 328.3: Terbutil-éster del ácido {2-[2-({6-cloro-3-[3-(4-cloro-bencil)-5-fenil-3H-imidazol-4-il]-1H-indol-2-carbonil}-amino)-etil-amino]-etil}-carbámico (el cual también es un compuesto de la fórmula I de acuerdo con la invención)

El compuesto del título se sintetiza mediante la condensación del **Intermediario 2.1** y el terbutil-éster del ácido [2-(2-amino-etil-amino)-etil]-carbámico, de una manera análoga a la preparación del Ejemplo **2**, como un sólido incoloro; ES-MS: M+H = 647.0; HPLC: $_{ct}t_{Ret}$ = 6.02 minutos.

Intermediario 331.1: Sal de 2-((S)-pirrolidin-3-il-amino)-etil-éster del ácido acético • 2HBr

El compuesto del título se sintetiza de acuerdo con el procedimiento descrito para el **Intermediario 89.1** como la sal de HBr correspondiente; ES-MS: M+H = 173.1.

Ejemplo 332: {6-cloro-3-[3-(4-cloro-bencil)-5-fenil-3H-imidazol-4-il]-1H-indol-2-il}-[(S)-3-(2-hidroxi-etil-amino)-pirrolidin-1-il]-metanona

Se agrega K_2CO_3 (17 miligramos, 0.12 milimoles) a una solución del Ejemplo **331** (50 miligramos, 0.08 milimoles) en metanol (1 mililitro) a temperatura ambiente. Se agrega H_2O (0.5 mililitros), y la mezcla de reacción se agita bajo reflujo durante 3 horas. Se deja enfriar a temperatura ambiente y se neutraliza cuidadosamente

mediante la adición de una solución acuosa de HCl 0.1M, seguida por el procesamiento acuoso. El producto crudo se recristaliza a partir de $EtOAc/CH_2Cl_2$ para proporcionar el compuesto del título como un sólido blanco.

Intermediario 333.1: Sal de (S)-pirrolidin-3-il-(2-pirrolidin-1-il-etil)-amina • 3HBr

El compuesto del título se sintetiza de acuerdo con el procedimiento descrito para el **Intermediario 89.1** como la sal de HBr correspondiente; ES-MS: M+H = 184.2.

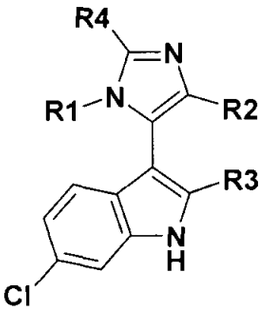
Intermediario 334.1: Sal de (S)-pirrolidin-3-il-(3-pirrolidin-1-il-propil)-amina • 3HBr

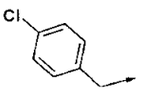
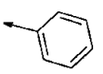
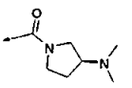
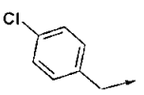
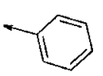
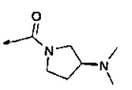
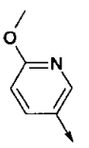
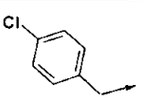
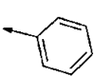
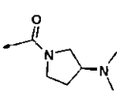
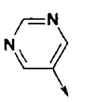
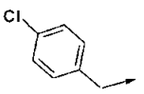
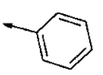
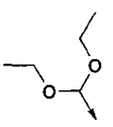
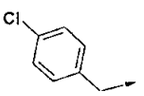
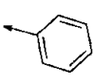
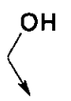
El compuesto del título se sintetiza de acuerdo con el procedimiento descrito para el **Intermediario 89.1** como la sal de HBr correspondiente; ES-MS: M+H = 198.3.

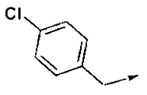
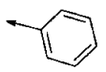
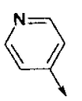
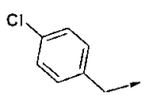
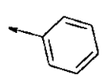
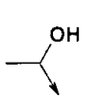
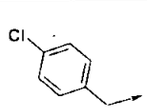
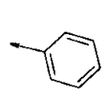
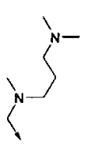
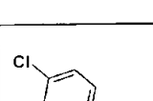
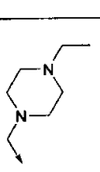
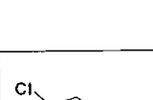
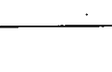
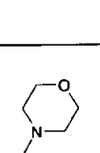
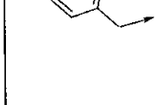
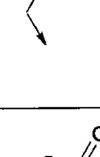
Intermediario 335.1: Sal de (2-metoxi-etil)-metil-(S)-pirrolidin-3-il-amina • 2HBr

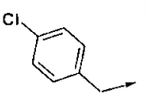
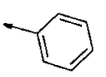
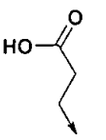
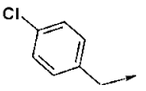
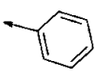
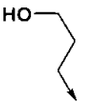
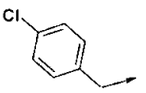
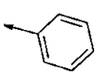
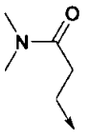
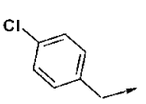
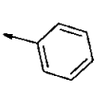
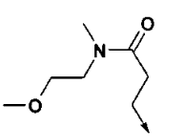
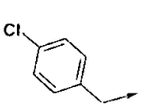
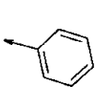
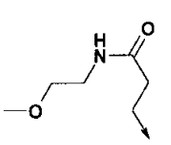
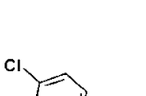
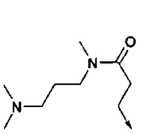
El compuesto del título se sintetiza de acuerdo con el procedimiento descrito para el **Intermediario 89.1** como la sal de HBr correspondiente; ES-MS: M+H = 159.2; ^{1}H-RMN ($CDCl_3$) 3.43 (t, 2H), 3.38 (s, 3H), 3.17-3.03 (m, 2H), 2.99-2.91 (m, 2H), 2.80 (dd, 1H), 2.67-2.57 (m, 3H), 2.24 (s, 3H).

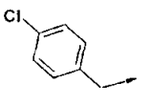
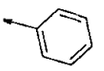
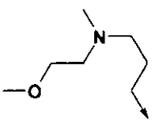
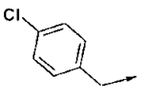
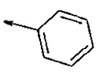
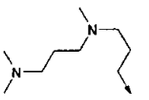
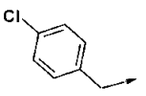
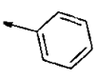
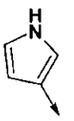
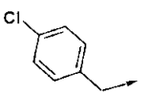
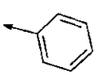
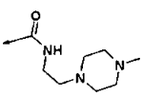
Tabla 3 para Ejemplos Adicionales:



Ejemplo	R^1	R^2	R^3	R^4	Análisis MS/HPLC/NMR
336					M+= 635.0 $_At_{Ret}$ = 3.83 min
337					M+= 665.0 $_At_{Ret}$ = 4.07 min
338					M+= 635.9 $_At_{Ret}$ = 3.97 min
339			H		M+H = 521.8 $_Et_{ret}$ = 5.16 min
340			H		M+H = 449.9 $_Et_{ret}$ = 4.53 min

Ejemplo	R^1	R^2	R^3	R^4	Análisis MS/HPLC/NMR
341			H		M-H = 493.1 $_Et_{ret}$ = 4.65 min
342			H		M+H = 463.9 $_Et_{ret}$ = 4.51 min
343			H		M-H = 545.2 $_Et_{ret}$ = 4.03 min
344			H		M-H = 542.2 $_Et_{ret}$ = 4.09 min
345			H		M-H = 519.0 $_Et_{ret}$ = 4.68 min
346			H		M-H = 473.1 $_Et_{ret}$ = 4.57 min
347			H		M-H = 516.0 $_Et_{ret}$ = 4.89 min

Ejemplo	R^1	R^2	R^3	R^4	Análisis MS/HPLC/NMR
348			H		M-H = 488.9 $_E t_{ret}$ = 4.55 min
349			H		M+H = 478.2 $_E t_{ret}$ = 4.51 min
350			H		M-H = 519.2 $_E t_{ret}$ = 4.61 min
351			H		M-H = 559.0 $_E t_{ret}$ = 4.67 min
352			H		M-H = 549.2 $_E t_{ret}$ = 4.55 min
353			H		M-H = 590.2 $_E t_{ret}$ = 4.11 min

Ejemplo	R^1	R^2	R^3	R^4	Análisis MS/HPLC/NMR
354			H		M-H = 545.1 $_{E}t_{Ret}$ = 4.13 min
355			H		M-H = 572.2 $_{E}t_{Ret}$ = 3.99 min
356			H		M-H = 481.1 ^{1}HNMR($CDCl_3$) δ 8.36 (bs 1H), 8.31 (bs, 1H), 7.61 (d, 2H), 7.39 (s, 1H), 7.21-7.12 (m, 7H), 6.99 (d, 1H), 6.89 (d, 1H), 6.86 (d, 2H), 6.80-6,76 (m, 1H), 6.49-6.46 (m, 1H), 5.07 (s, 2H).
357				Me	M-H = 599.0 $_{E}t_{Ret}$ = 3.88.min

Todos los compuestos sin los **Ejemplos 336, 337, 338** se obtienen mediante desprotección mediada por KOH o TBAF de los precursores protegidos por N-tosilo correspondientes.

Procedimiento típico para la desprotección mediada por TBAF:

El intermediario N-protegido (0.1 milimoles) se agrega a una solución de TBAF 3M en tetrahidrofurano a temperatura ambiente, y se agita hasta que se complete la reacción. El procesamiento acuoso y la cromatografía por evaporación instantánea en gel de sílice del material crudo proporciona los ejemplos finales.

Procedimiento típico para la desprotección mediada por KOH:

El intermediario N-protegido (0.1 milimoles, 1.0 equivalentes) se disuelve en metanol (5 mililitros) y se trata con KOH en polvo (0.15 milimoles, 1.5 equivalentes) a temperatura ambiente. La reacción se calienta entonces a 65°C y se agita hasta completarse. Se enfría en un baño de hielo y se neutraliza cuidadosamente mediante la adición de una solución acuosa de HCl 0.1M, seguida por el procesamiento acuoso y la cromatografía por evaporación instantánea en gel de sílice del material crudo, para proporcionar los ejemplos finales.

Ejemplo 336: {6-cloro-3-[3-(4-cloro-bencil)-5-fenil-2-piridin-3-il-3H-imidazol-4-il]-1H-indol-2-il}-((S)-3-dimetil-amino-pirrolidin-1-il)-metanona

Una mezcla del Intermediario **336.1** (100 miligramos, 0.15 milimoles), ácido piridin-3-borónico (38 miligramos, 0.31 milimoles), $Pd(PPh_3)_4$ (18 miligramos, 0.015 milimoles) y K_2CO_3 (85 miligramos,

0.62 milimoles) en dioxano (0.8 mililitros) y H_2O (0.4 mililitros), se calienta a 90°C. Después de completarse, la mezcla de reacción se apaga mediante H_2O, se agrega EtOAc, y la capa orgánica se lava con salmuera, se seca sobre $MgSO_4$ y se evapora al vacío. La cromatografía por evaporación instantánea en gel de sílice del residuo proporciona el compuesto del título como un polvo blanco.

Los **Ejemplos 337 y 338** se preparan también en analogía al **Ejemplo 336**.

Intermediario 336.1: {3-[2-bromo-3-(4-cloro-bencil)-5-fenil-3H-imidazol-4-il]-6-cloro-1H-indol-2-il}-((S)-3-dimetil-amino-pirrolidin-1-il)-metanona (el cual también es un compuesto de la fórmula I de acuerdo con la invención)

El compuesto del título se sintetiza mediante la condensación del **Intermediario 336.2** y dimetil-(S)-pirrolidin-3-il-amina de una manera análoga a la preparación del Ejemplo **2**, como un sólido incoloro; ES-MS: M+ = 637.7; HPLC: $_At_{Ret}$ = 4.67 minutos.

Intermediario 336.2: Ácido 3-[2-bromo-3-(4-cloro-bencil)-5-fenil-3H-imidazol-4-il]-6-cloro-1H-indol-2-carboxílico (el cual también es un compuesto de la fórmula I de acuerdo con la invención)

El compuesto del título se sintetiza mediante la hidrólisis del Ejemplo **145** de una manera análoga a la preparación del Intermediario **2.1** como un sólido incoloro; ES-MS: M+ = 541.7; HPLC: $_At_{Ret}$ = 5.10 minutos.

Intermediario 339.1: 6-cloro-3-[3-(4-cloro-bencil)-2-dietoxi-

metil-5-fenil-3H-imidazol-4-il]-1-(toluen-4-sulfonil)-1H-indol

Una solución del Intermediario **144.1** (1.7 gramos, 3.4 milimoles), el **intermediario 339.2** (1.8 gramos, 4.2 milimoles), $Pd(PPh_3)_4$ (410 miligramos, 0.34 milimoles), y K_3PO_4 (1.9 gramos, 8.7 milimoles) en dioxano/H_2O (3:1; 40 mililitros), se calienta a 100°C en un tubo sellado bajo una atmósfera de argón durante 30 minutos. Entonces se deja enfriar a temperatura ambiente, y se diluye en EtOAc. La capa orgánica se lava con H_2O, una solución acuosa de ácido cítrico (al 15 por ciento en peso) y salmuera, se seca y se concentra. La cromatografía por evaporación instantánea en gel de sílice del producto crudo proporciona el compuesto del título como un sólido verdoso. ES-MS: M+H = 677.2: $_{E}t_{Ret}$ = 5.91 minutos.

Intermediario 339.2: 1-(4-cloro-bencil)-2-dietoxi-metil-5-yodo-4-fenil-1H-imidazol

Se agrega NIS (5.5 gramos, 24 milimoles) a una solución del Intermediario **339.3** (5.9 gramos, 15.9 milimoles) en CH_3CN (60 mililitros) a temperatura ambiente. La mezcla de reacción se calienta entonces a 85°C y se agita durante 3 días. Después de completarse, se deja enfriar a temperatura ambiente y se diluye con EtOAc. La capa orgánica se lava repetidamente con una solución acuoso saturada de $NaHCO_3$, se seca y se concentra. La cromatografía por evaporación instantánea en gel de sílice del producto crudo proporciona el compuesto del título como un aceite amarillo. ES-MS: M+H = 498.3: $_{E}t_{Ret}$ = 5.40 minutos.

Intermediario 339.3: 1-(4-cloro-bencil)-2-dietoxi-metil-4-

fenil-1H-imidazol

Se agrega NaH al 60 por ciento en aceite mineral (0.83 gramos, 20.8 milimoles) a una solución del Intermediario **339.4** (3.9 gramos, 16.0 milimoles) en tetrahidrofurano (20 mililitros) a temperatura ambiente. La reacción se deja agitándose durante 20 minutos, seguido por la adición de bromuro de 4-cloro-bencilo (3.4 gramos, 16.0 milimoles). La agitación se continúa durante 1 hora a temperatura ambiente, y entonces la reacción se apaga mediante la adición de EtOAc y H_2O . La capa orgánica se separa, se lava con salmuera, se seca y se concentra, para dar el compuesto del título, el cual se sometió sin mayor purificación a la siguiente etapa. ES-MS: M+H = 371.2: $_{Et}t_{Ret}$ = 4.65 minutos.

Intermediario 339.4: 2-dietoxi-metil-4-fenil-1H-imidazol

Se agrega NaOMe (solución al 18 por ciento en MeOH; 2.83 gramos, 51 milimoles) a una solución de dietoxi-acetonitrilo (4.9 mililitros, 34.3 milimoles) en MeOH (60 mililitros), y se agita durante 1 hora a temperatura ambiente. Entonces se agrega clorhidrato de fenil-acil-amina (3.0 gramos, 17.1 milimoles) a la mezcla de reacción, seguida por NaOMe (solución al 18 por ciento en MeOH; 2.83 gramos, 51 milimoles). Después de 2 horas de agitación a temperatura ambiente, la mezcla de reacción se diluye con EtOAc, y la capa orgánica se lava con H_2O y salmuera. Entonces la capa orgánica se seca y se concentra. El producto crudo se purifica mediante trituración con EtOAc/hexanos. Sólido amarillo. ES-MS: M+H = 247.1: ^{1}H-RMN (DMSO d_6) δ 7.73 (d, 2H), 7.52 (s, 1H), 7.30

(dd, 2H), 7.27 (dd, 1H), 5.51 (s, 1H), 3.60 (q, 2H), 3.54 (q, 2H), 1.14 (t, 6H).

Intermediario 340.1: {1-(4-cloro-bencil)-5-[6-cloro-1-(toluen-4-sulfonil)-1H-indol-3-il]-4-fenil-1H-imidazol-2-il}-metanol

Una solución del Intermediario **340.2** (43 miligramos, 0.06 milimoles) en tetrahidrofurano (2 mililitros), se trata con una solución de LAH (solución 2M en tetrahidrofurano; 30 microlitros, 0.06 milimoles) a 0°C. La mezcla de reacción se deja calentar a temperatura ambiente, y se agita durante 15 minutos. Se apaga mediante la adición de EtOAc. La capa orgánica se lava con ácido cítrico acuoso (al 15 por ciento en peso) y salmuera, se seca y se concentra, para dar el compuesto del título como un sólido grisáceo. ES-MS: M-H = 600.4: $_{E}t_{Ret}$ = 5.31 minutos.

Intermediario 340.2: 1-(4-cloro-bencil)-5-[6-cloro-1-(toluen-4-sulfonil)-1H-indol-3-il]-4-fenil-1H-imidazol-2-carbaldehído

Una solución del Intermediario **339.1** (1.5 gramos, 2.2 milimoles) en tetrahidrofurano (30 mililitros) se trata con HCl (solución 1M en H_2O; 11 mililitros) a temperatura ambiente. La mezcla de reacción se calienta entonces a reflujo y se agita durante 1 hora. Después de enfriar a temperatura ambiente, se diluye con EtOAc, y la capa orgánica se lava con una solución acuosa saturada de $NaHCO_3$ y salmuera, se seca y se concentra, para dar el compuesto del título como un sólido blanco. ES-MS: M-H = 599.2: $_{E}t_{Ret}$ = 6.67 minutos.

El **Ejemplo 341** se sintetiza mediante el acoplamiento del

Intermediario **144.1** y ácido 4-piridin-borónico de una manera análoga a la preparación del Ejemplo **144** como un sólido blanco.

Intermediario 342.1: {1-(4-cloro-bencil)-5-[6-cloro-1-(toluen-4-sulfonil)-1H-indol-3-il]-4-fenil-1H-imidazol-2-il}-etanol

Una solución del Intermediario **340.2** (70 miligramos, 0.12 milimoles) en tetrahidrofurano (1 mililitro) se trata con MeMgBr (solución 3M en tetrahidrofurano; 120 microlitros) a temperatura ambiente. La mezcla de reacción se deja agitándose durante 1 hora y entonces s apaga mediante la adición de EtOAc. La capa orgánica se lava repetidamente con ácido cítrico acuoso (al 15 por ciento en peso) y salmuera, se seca y se concentra, para dar el compuesto del título como un sólido amarillo. ES-MS: M-CH_3 = 600.0: $_{Et}t_{Ret}$ = 5.33 minutos.

Intermediario 343.1: N-{1-(4-cloro-bencil)-5-[6-cloro-1-(toluen-4-sulfonil)-1H-indol-3-il]-4-fenil-1H-imidazol-2-il-metil}-N,N',N'-trimetil-propan-1,3-diamina

Se agregan AcOH (5 microlitros, 0.08 milimoles) y cianoborohidruro de sodio (8 miligramos, 0.12 milimoles) a una solución del Intermediario **340.2** (50 miligramos, 0.08 milimoles) y N,N,N-trimetil-propan-diamina (13 microlitros, 0.09 milimoles) en tetrahidrofurano (2 mililitros) a temperatura ambiente. La mezcla de reacción se agita durante 12 horas, y entonces se diluye con EtOAc. La capa orgánica se lava con una solución acuosa saturada de $NaHCO_3$, H_2O y salmuera, se seca y se concentra. La cromatografía por evaporación instantánea en gel de sílice del producto crudo

proporciona el compuesto del título como una espuma blanca. $_{E}t_{Ret}$ = 5.50 minutos.

Intermediario 344.1: 6-cloro-3-[3-(4-cloro-bencil)-4-etil-piperazin-1-il-metil-5-fenil-3H-imidazol-4-il]-1-(toluen-4-sulfonil)-1H-indol

El compuesto del título se sintetiza mediante aminación reductiva, de una manera análoga a la preparación del Intermediario **343.1**, como un sólido incoloro; ES-MS: M+H = 772.0: $_{E}t_{Ret}$ = 4.87 minutos.

Intermediario 345.1: 6-cloro-3-[3-(4-cloro-bencil)-2-morfolin-4-il-metil-5-fenil-3H-imidazol-4-il]-1-(toluen-4-sulfonil)-1H-indol

El compuesto del título se sintetiza mediante aminación reductiva, de una manera análoga a la preparación del Intermediario **343.1**, como un sólido incoloro; ES-MS: M+H = 773.2: $_{E}t_{Ret}$ = 5.40 minutos.

Intermediario 346.1: {1-(4-cloro-bencil)-5-[6-cloro-1-(toluen-4-sulfonil)-1H-indol-3-il]-4-fenil-1H-imidazol-2-il-metil}-dimetil-amina

El compuesto del título se sintetiza mediante aminación reductiva, de una manera análoga a la preparación del Intermediario **343.1**, como un sólido incoloro; ES-MS: M+H = 631.1: $_{E}t_{Ret}$ = 5.39 minutos.

Intermediario 347.1: Etil-éster del ácido 3-[1-(4-cloro-bencil)-5-[6-cloro-1-(toluen-4-sulfonil)-1H-indol-3-il]-4-fenil-1H-imidazol-2-il]-propiónico

Se agregan $ZnBr_2$ (280 miligramos, 1.2 milimoles) y Pd-C (al 5 por ciento, Engelhard 4709, 260 miligramos) a una solución del Intermediario **347.2** (910 miligramos, 1.2 milimoles) en EtOAc (20 mililitros) a temperatura ambiente. La mezcla de reacción se agita bajo una atmósfera de H_2 a temperatura ambiente durante 1 día. Entonces se diluye con EtOAc, y se filtra sobre un tapón de Celite y se concentra. La cromatografía por evaporación instantánea en gel de sílice del producto crudo proporciona el compuesto del título como un sólido amarillo. ES-MS: M+H = 674.2: $_{E}t_{Ret}$ = 5.57 minutos.

Intermediario 347.2: Etil-éster del ácido (E)-3-{1-(4-cloro-bencil)-5-[6-cloro-1-(toluen-4-sulfonil)-1H-indol-3-il]-4-fenil-1H-imidazol-2-il}-acrílico

Una solución de fosfono-acetato de trietilo (320 microlitros, 1.6 milimoles) en tetrahidrofurano (10 mililitros), se trata con NaH al 60 por ciento en aceite mineral (62 miligramos, 1.6 milimoles) a 0°C. La solución se agita durante 5 minutos, y entonces se agrega mediante una cánula a una solución del Intermediario **340.2** (845 miligramos, 1.4 milimoles) en tetrahidrofurano (10 mililitros) a temperatura ambiente. La mezcla de reacción resultante se agita durante 30 minutos a temperatura ambiente, y entonces se diluye con EtOAc. La capa orgánica se lava con H_2O y salmuera, se seca y se concentra para dar el compuesto del título como un sólido amarillo. ES-MS: M-H = 669.9: $_{E}t_{Ret}$ = 6.27 minutos.

Ejemplo 348: Ácido 3-[1-(4-cloro-bencil)-5-(6-cloro-1H-indol-3-il)-4-fenil-1H-imidazol-2-il]—N-(2-metoxi-etil)-carboxílico

Se agrega KOH en polvo (140 miligramos, 2.2 milimoles) a una solución del Intermediario **347.1** (583 miligramos, 0.87 milimoles) en EtOH (10 mililitros) a temperatura ambiente. La mezcla de reacción se calienta entonces a 80°C durante 20 horas. Después de enfriar a temperatura ambiente, se transfiere a un baño de hielo y se acidifica mediante la adición cuidadosa de una solución acuosa de HCl (5M). La agitación se continúa durante 30 minutos a 0°C, y el precipitado resultante del compuesto del título se aísla mediante filtración, y se seca bajo presión reducida para dar un sólido amarillo.

Intermediario 349.1: 3-[1-(4-cloro-bencil)-5-[6-cloro-1-(toluen-4-sulfonil)-1H-indol-3-il]-4-fenil-1H-imidazol-2-il]-propan-1-ol

Una solución del Intermediario **347.1** (150 miligramos, 0.22 milimoles) en tetrahidrofurano (5 mililitros), se trata con LAH (solución 2M en tetrahidrofurano; 224 microlitros, 0.44 milimoles) a 0°C. La mezcla de reacción se deja calentar a temperatura ambiente, y se agita durante 30 minutos. Se apaga mediante la adición de EtOAc. La capa orgánica se lava con ácido citrico acuoso (al 15 por ciento en peso) y salmuera, se seca y se concentra para dar el compuesto del título como un sólido grisáceo. ES-MS: M-H = 628.0: $_{ET}t_{Ret}$ = 5.27 minutos.

Ejemplo 350: 3-[1-(4-cloro-bencil)-5-(6-cloro-1H-indol-3-il)-4-fenil-1H-imidazol-2-il]-N,N-dimetil-propionamida

Se agregan N-metil-morfolina (67 microlitros, 0.61 milimoles)

y HATU (93 miligramos, 0.24 milimoles) a una solución del Ejemplo **348** (100 miligramos, 0.2 milimoles) en tetrahidrofurano (5 mililitros) a temperatura ambiente .La mezcla de reacción se agita durante 5 minutos, seguido por la adición de N,N dimetil-amina (solución 2M en tetrahidrofurano, 310 microlitros, 0.62 milimoles). La agitación se continúa a temperatura ambiente y, después de 1 hora, la mezcla de reacción se diluye con EtOAc. La capa orgánica se lava con una solución acuosa saturado de $NaHCO_3$ y salmuera, se seca y se concentra. El producto crudo restante se purifica mediante cromatografía por evaporación instantánea (SiO_2; DCM/MeOH, gradiente del 0 al 10 por ciento de MeOH), para dar el compuesto del título como un sólido blanco.

Los **Ejemplos 351, 352 y 353** se preparan también en analogía al **Ejemplo 350**.

Ejemplo 354: {3-[1-(4-cloro-bencil)-5-(6-cloro-1H-indol-3-il)-4-fenil-1H-imidazol-2-il]-propil}-(2-metoxi-etil)-metil-amina

Una solución del Ejemplo **351** (40 miligramos, 0.07 milimoles) en tetrahidrofurano (3 mililitros) se trata con LAH (solución 2M en tetrahidrofurano; 36 microlitros) a 0°C. La reacción se deja calentar a temperatura ambiente, y se agita durante 3 horas. Entonces se apaga mediante la adición de EtOAc y H_2O. La capa orgánica se separa y se lava con salmuera, se seca y se concentra. La cromatografía por evaporación instantánea en gel de sílice del producto crudo proporciona el compuesto del título como un sólido amarillo.

El **Ejemplo 355** también se prepara en analogía al **Ejemplo 354**.

Intermediario 356.1: 6-cloro-3-[3-(4-cloro-bencil)-5-fenil-2-(tri-isopropil-silanil-1H-pirrol-3-il)-3H-imidazol-4-il]-6-cloro-1-(toluen-4-sulfonil)-1H-indol

El compuesto del título se sintetiza mediante el acoplamiento del Intermediario **356.2** y ácido 2-(tri-isopropil-silanil-1H-pirrol-3-il)-borónico, de una manera análoga a la preparación del Ejemplo **341** como un sólido incoloro; ES-MS: M+H = 792.7; ^{1}H-RMN ($CDCl_3$) δ 8.02 (s, 1H), 7.61 (d, 2H), 7.47 (d, 2H), 7.40 (s, 1H), 7.19 (dd, 4H), 7.09-7.04 (m, 4H), 7.00 (d, 1H), 6.91 (s, 1H), 6.59 (s, 1H), 5.01 (s, 2H), 2.39 (s, 3H), 1.37-1.31 (m, 3H), 1.03 (d, 18H).

Intermediario 356.2: 3-[2-bromo-3-(4-cloro-bencil)-5-fenil-3H-imidazol-4-il]-6-cloro-1-(toluen-4-sulfonil)-1H-indol

Se agrega NBS (728 miligramos, 4.1 milimoles) a una solución del Intermediario **356.3** (1.9 gramos, 3.4 milimoles) en tetrahidrofurano (100 mililitros) a 0°C. La mezcla de reacción se deja alcanzar la temperatura ambiente, y se agita durante 4 horas. El producto se aisla mediante el procesamiento acuoso, y se purifica mediante cromatografía por evaporación instantánea en gel de sílice, para dar el compuesto del título. ES-MS: M-H = 649.7: $_{Et}t_{Ret}$ = 6.71 minutos.

Intermediario 356.3: 6-cloro-3-[3-(4-cloro-bencil)-5-fenil-3H-imidazol-4-il]-1-(toluen-4-sulfonil)-1H-indol

Se agrega NaH al 50 por ciento en aceite mineral (284

miligramos, 5.9 milimoles) a una solución del Ejemplo **1** (1.65 gramos, 3.9 milimoles) en tetrahidrofurano (40 mililitros) a 0°C. La mezcla de reacción se deja calentar a temperatura ambiente, y se agita durante 15 minutos. Se agrega TsCl (902 miligramos, 4.7 milimoles) y se continúa la agitación durante 1 hora. La reacción se apaga mediante la adición de EtOAc y H_2O. La capa orgánica se separa, se lava con salmuera, se seca y se concentra. El producto crudo se purifica mediante trituración con EtOAc/hexanos, para dar el compuesto del título como un sólido blanco. ES-MS: M+H = 573.7: ${}_{E}t_{Rel}$ = 5.33 minutos.

Intermediario 357.1: Ácido 6-cloro-3-3-(4-cloro-bencil)-2-metil-5-fenil-3H-imidazol-4-il]-1H-indol-2-carboxílico (el cual también es un compuesto de la fórmula I de acuerdo con la invención)

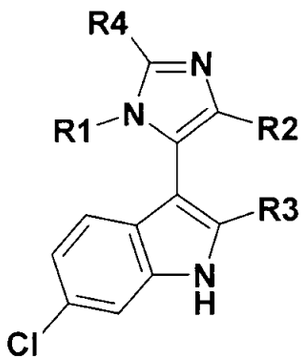
Una solución del Intermediario **357.2** (36 miligramos, 0.07 milimoles) en EtOH (5 mililitros) se trata con KOH en polvo (7 miligramos, 0.11 milimoles), y se calienta con agitación a 90°C durante 16 horas. Después de completarse, la reacción se deja enfriar a temperatura ambiente, y se neutraliza mediante la adición cuidadosa de HCl 1N en EtOH. Se concentra, y el producto crudo restante se absorbe en EtOAc. La capa orgánica se lava repetidamente con H_2O, se seca y se concentra, para dar el compuesto del título como un sólido blanco. ES-MS: M-H = 474.0: ${}_{E}t_{Rel}$ = 4.45 minutos

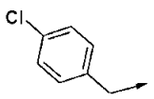
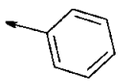
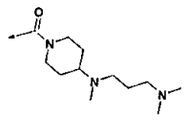
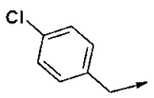
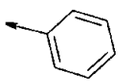
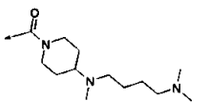
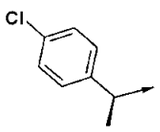
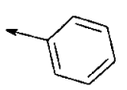
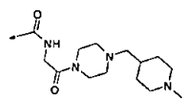
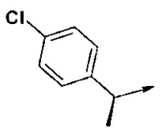
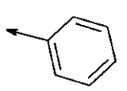
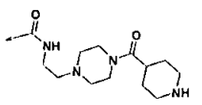
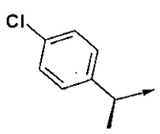
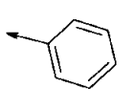
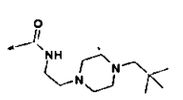
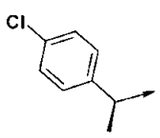
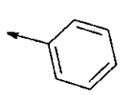
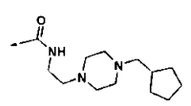
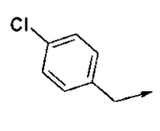
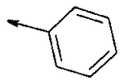
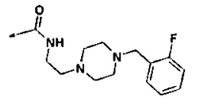
Intermediario 357.2: Etil-éster del ácido 6-cloro-3-3-(4-

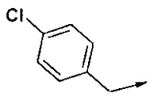
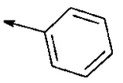
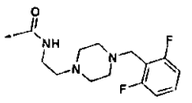
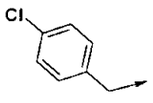
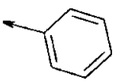
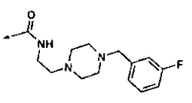
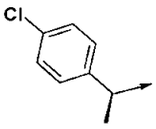
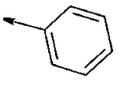
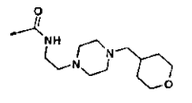
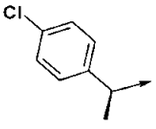
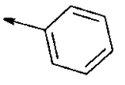
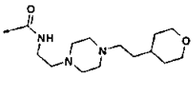
cloro-bencil)-2-metil-5-fenil-3H-imidazol-4-il]-1H-indol-2-carboxílico (el cual también es un compuesto de la fórmula I de acuerdo con la invención)

Una mezcla del Ejemplo **145** (125 miligramos, 0.19 milimoles), trimetil-boroxina (110 microlitros, 0.78 milimoles), $Pd(PPh_3)_4$ (23 miligramos, 0.02 milimoles), K_3PO_4 (170 miligramos, 0.78 milimoles), H_2O (3 mililitros) y dioxano (3 mililitros), se coloca en un tubo sellado bajo una atmósfera de argón, y se calienta a 80°C durante 1 hora. Después de completarse, la mezcla de reacción se apaga mediante la adición de H_2O. Se agrega EtOAc, y la capa orgánica se lava con salmuera, se seca sobre $MgSO_4$ y se evapora al vacío. La cromatografía por evaporación instantánea en gel de sílice del residuo proporciona el compuesto del título como un polvo incoloro; ES-MS: M-H = 502.0: $_{E}t_{Ret}$ = 4.72 minutos.

Tabla 4 para Ejemplos Adicionales:



Ejemplo	R^1	R^2	R^3	R^4	Análisis MS/HPLC/NMR
358				H	M+H= 642.9 $_{D}t_{Ret}$ = 2.65 min
359				H	M+H= 657.0 $_{D}t_{Ret}$ = 2.65 min
360				H	M+H= 711.9 $_{C}t_{Ret}$ = 5.35 min
361				H	M+H= 697.8 $_{C}t_{Ret}$ = 5.32 min
362				H	M+H= 657.2 $_{A}t_{Ret}$ = 5.70 min
363				H	M+H= 668.9 $_{A}t_{Ret}$ = 5.72 min
364				H	M+H= 680.9 $_{D}t_{Ret}$ = 2.84 min

Ejemplo	R^1	R^2	R^3	R^4	Análisis MS/HPLC/NMR
365				H	M+H= 698.8 $_Dt_{Ret}$ = 2.87 min
366				H	M+H= 680.9 $_Dt_{Ret}$ = 2.85 min
367				H	M+H= 684.8 $_Ct_{Ret}$ = 5.54 min
368				H	M+H= 698.9 $_Ct_{Ret}$ = 5.43 min

Intermediario 358.1: N,N,N'-Trimetil-N'-piperidin-4-il-propan-1,3-diamina

El compuesto del título se sintetiza mediante hidrogenación del Intermediario **358.2** de una manera análoga a la preparación del Intermediario **347.1** como un sólido incoloro; ES-MS: M+H = 200.2; TLC: Rf = 0.14 (DCM/MeOH/NH_3 = 70:30:1).

Intermediario 358.2: Bencil-éster del ácido 4-[(3-dimetil-amino-propil)-metil-amino]-piperidin-1-carboxílico

El compuesto del título se sintetiza mediante la aminación reductiva de **Intermediario 358.3** y formaldehído, de una manera análoga a la preparación del Ejemplo **233** como un aceite incoloro; ES-MS: M+H = 334.3; $_Dt_{Ret}$ = 2.25 minutos.

Intermediario 358.3: Bencil-éster del ácido 4-(3-dimetil-amino-propil-amino)-piperidin-1-carboxílico

El compuesto del título se sintetiza mediante la aminación reductiva del bencil-éster del ácido 4-oxo-piperidin-1-carboxílico y N,N-dimetil-propil-amina, de una manera análoga a la preparación del Ejemplo **233** como un aceite incoloro; ES-MS: M+H = 320.2; $_Dt_{Ret}$ = 2.22 minutos.

Intermediario 359.1: N,N,N'-trimetil-N'-piperidin-4-il-butan-1,4-diamina

El compuesto del título se sintetiza mediante la hidrogenación del Intermediario **359.2** de una manera análoga a la preparación del Intermediario **347.1** como un sólido incoloro; ES-MS: M+H = 214.1; TLC: Rf = 0.05 (DCM/MeOH/NH_3 = 70:30:1).

Intermediario 359.2: Bencil-éster del ácido 4-[(4-dimetil-amino-butil)-metil-amino]-piperidin-1-carboxílico

El compuesto del título se sintetiza mediante la aminación reductiva de **Intermediario 359.3** y formaldehído de una manera análoga a la preparación del Ejemplo **233** como un aceite incoloro; ES-MS: M+H = 348.3; $_Dt_{Ret}$ = 2.27 minutos.

Intermediario 359.3: Bencil-éster del ácido 4-(4-dimetil-amino-butil-amino)-piperidin-1-carboxílico

El compuesto del título se sintetiza mediante la aminación reductiva del bencil-éster del ácido 4-oxo-piperidin-1-carboxílico y N,N-dimetil-butil-amina, de una manera análoga a la preparación del Ejemplo **233** como un aceite incoloro; ES-MS: M+H = 334.2; $_Dt_{Ret}$ = 2.23 minutos.

Intermediario 360.1: Sal de 2-amino-1-[4-(1-metil-piperidin-4-il-metil)-piperazin-1-il]-etanona • 3HCl

El compuesto del título se sintetiza mediante la desprotección del **Intermediario 360.2** de una manera análoga a la preparación del Ejemplo **44** como un aceite incoloro; ES-MS: M+H = 255.2.

Intermediario 360.2: Terbutil-éster del ácido {2-[4-(1-metil-piperidin-4-il-metil)-piperazin-1-il]-2-oxo-etil}-carbámico

El compuesto del título se sintetiza mediante la condensación de la 1-piridin-3-il-metil-piperazina y N-Boc-glicina, de una manera análoga a la preparación del Ejemplo **2** como un sólido incoloro; ES-MS: M+H = 355.2.

Intermediario 361.1: Terbutil-éster del ácido 4-(4-{2-[(6-cloro-3-{3-[(S)-1-(4-cloro-fenil)-etil]-5-fenil-3H-imidazol-4-il}-1H-indol-2-carbonil)-amino]-etil}-piperazin-1-carbonil)-piperidin-1-carboxílico

El **Intermediario 361.1** también se prepara en analogía al **Ejemplo 293**. ES-MS: M+H = 797.9; $_Ct_{Ret}$ = 6.10 minutos.

I

Intermediario 362.1: 2-[4-(2,2-dimetil-propil)-piperazin-1-il]-etil-amina

El compuesto del título se sintetiza mediante la reducción del Intermediario **362.2** de una manera análoga a la preparación del Intermediario **149.1** como un aceite incoloro; ES-MS: M+H = 200.2: TLC: Rf = 0.30 (DCM/MeOH/NH_3 = 40:10:1).

Intermediario 362.2: [4-(2,2-dimetil-propil)-piperazin-1-il]-acetonitrilo

El compuesto del título se sintetiza mediante el acoplamiento del Intermediario **362.3** y bromo-acetonitrilo de una manera análoga a la preparación del Intermediario **149.2** como un aceite incoloro; ES-MS: M+H = 196.2: TLC: Rf = 0.93 (DCM/MeOH/NH_3 = 40:10:1).

Intermediario 362.3: Sal de 1-(2,2-dimetil-propil)-piperazina • 2HCl

El compuesto del título se sintetiza mediante la desprotección del **Intermediario 362.4** de una manera análoga a la preparación del Intermediario **193.1,** como un aceite incoloro; ES-MS: M+H =157.2: TLC: Rf = 0.60 (DCM/MeOH/NH_3 = 40:10:1).

Intermediario 362.4: Terbutil-éster del ácido 4-(2,2-dimetil-propil)-piperazin-1-carboxílico

El compuesto del título se sintetiza mediante aminación reductiva, de 1-Boc-piperazina y pivalaldehído, de una manera análoga a la preparación del Ejemplo **233,** como un aceite incoloro; ES-MS: M+H = 257.3; TLC: Rf = 0.82 (DCM/EtOAc = 4:1).

Intermediario 363.1: 2-(4-ciclopentil-metil-piperazin-1-il)-etil-amina

El compuesto del título se sintetiza mediante la reducción del Intermediario **363.2** de una manera análoga a la preparación del Intermediario **149.1**, como un aceite incoloro; ES-MS: M+H = 212.2: TLC: Rf = 0.17 (DCM/MeOH/NH_3 = 40:10:1).

Intermediario 363.2: (4-ciclopentil-metil-piperazin-1-il)-acetonitrilo

El compuesto del título se sintetiza mediante el acoplamiento del Intermediario **363.3** y bromo-acetonitrilo de una manera análoga a la preparación del Intermediario **149.2** como un aceite incoloro; ES-MS: M+H = 208.2: TLC: Rf = 0.70 (DCM/MeOH/NH_3 = 80:10:1).

Intermediario 363.3: Sal de 1-ciclopentil-metil-piperazina • 2HCl

El compuesto del título se sintetiza mediante la desprotección del **Intermediario 363.4** de una manera análoga a la preparación del Intermediario **193.1**, como un aceite incoloro; ES-MS: M+H =169.2: TLC: Rf = 0.16 (DCM/MeOH/NH_3 = 80:10:1).

Intermediario 362.4: Terbutil-éster del ácido 4-ciclopentil-metil-piperazin-1-carboxílico

El compuesto del título se sintetiza mediante la aminación reductiva de 1-Boc-piperazina y ciclopentan-carbaldehído, de una manera análoga a la preparación del Ejemplo **233**, como un aceite incoloro; ES-MS: M+H = 269.2; TLC: Rf = 0.45 (DCM/EtOAc = 1:1).

Ejemplo 364: {2-[4-(2-fluoro-bencil)-piperazin-1-il]-etil}-amida del ácido 6-cloro-3-[3-(4-cloro-bencil)-5-fenil-3H-imidazol-4-il]-1H-indol-2-carboxílico

El compuesto del título se sintetiza mediante la aminación reductiva del Ejemplo **44** y 2-fluoro-benzaldehído, de una manera análoga a la preparación del Ejemplo **233**, como un sólido incoloro.

Los **Ejemplos 365 y 366** se preparan también en analogía al **Ejemplo 364**.

Tabla 5 - Actividad inhibidora de Mdm2 y Mdm4 de los compuestos representativos de la presente invención

Compuesto	IC_{50} (μM) de inhibición de p53-Hdm2 Ensayo de polarización de fluorescencia	IC_{50} (μM) de inhibición de p53-Hdm4 Ensayo (TR-FRET)
42	0.30	10.4
101	0.015	1.32
135	7.2	68.3
142	0.64	43.4
148	0.11	55.3
271	0.30	54.9
328	0.19	63.7

Ejemplo 369: Tabletas que comprenden los compuestos de la fórmula I

Se preparan tabletas que comprenden, como ingrediente activo, 100 miligramos de cualquiera de los compuestos de la fórmula I de los Ejemplos 1 a 146, con la siguiente composición, siguiendo los procedimientos convencionales:

Composición

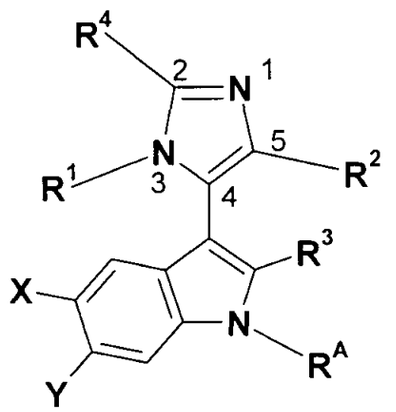
Ingrediente activo	100 mg
lactosa cristalina	240 mg
Avicel	80 mg
PVPPXL	20 mg
Aerosil	2 mg
estearato de magnesio	5 mg
	---
	447 mg

Fabricación: El ingrediente activo se mezcla con los materiales portadores, y se comprime por medio de una máquina formadora de tabletas (Korsch EKO, diámetro del troquel de 10 milímetros).

Avicel® es celulosa microcristalina (FMC, Filadelfia, EUA). PVPPXL es polivinil-polipirrolidona reticulada (BASF, Alemania). Aerosil® es dióxido de silicio (Degussa, Alemania).

REIVINDICACIONES

1. Un compuesto de la fórmula I:



(I)

en donde:

R^1 es alquilo insustituido o sustituido, alquenilo insustituido o sustituido o alquinilo insustituido o sustituido, arilo insustituido o sustituido o heterociclilo insustituido o sustituido;

R^2 es alquilo insustituido o sustituido, alquenilo insustituido o sustituido, alquinilo insustituido o sustituido, arilo insustituido o sustituido o heterociclilo insustituido o sustituido;

R^3 es hidrógeno, halógeno, alquilo insustituido o sustituido, alquenilo insustituido o sustituido, alquinilo insustituido o sustituido, arilo insustituido o sustituido, carboxilo, ciano, carboxilo esterificado, heterociclil-carbonilo insustituido o sustituido (heterociclil-C)=O)-), carbamoílo insustituido o sustituido o heterociclilo insustituido o sustituido;

R^4 es hidrógeno, halógeno, alquilo insustituido o

sustituido, alquenilo insustituido o sustituido, alquinilo insustituido o sustituido, arilo insustituido o sustituido, carboxilo, ciano, carboxilo esterificado, heterociclil-carbonilo insustituido o sustituido (heterociclil-C)=O)-), carbamoílo insustituido o sustituido o heterociclilo insustituido o sustituido;

R^A es hidrógeno o alquilo insustituido o sustituido o acilo;

X es hidrógeno, alquilo de 1 a 7 átomos de carbono, halo-alquilo de 1 a 7 átomos de carbono, alcoxilo de 1 a 7 átomos de carbono, halógeno o ciano; e

Y es alquilo de 1 a 7 átomos de carbono, halo-alquilo de 1 a 7 átomos de carbono, alcoxilo de 1 a 7 átomos de carbono, halógeno o ciano;

y/o un tautómero, un N-óxido, y/o una sal del mismo.

2. Un compuesto de la fórmula I de acuerdo con la reivindicación 1, en donde:

R^1 es alquilo insustituido o sustituido, alquenilo insustituido o sustituido o alquinilo insustituido o sustituido;

R^2 es arilo insustituido o sustituido;

R^3 es hidrógeno, alquilo insustituido o sustituido, carboxilo, ciano, carboxilo esterificado, heterociclil-carbonilo insustituido o sustituido (heterociclil-C)=O)-), carbamoílo insustituido o sustituido, heterociclilo insustituido o sustituido o ciano,

R^4 es hidrógeno, alquilo insustituido o sustituido, halógeno o heterociclilo insustituido o sustituido,

R^A es hidrógeno o alquilo insustituido o sustituido o acilo;

X es hidrógeno, alquilo de 1 a 7 átomos de carbono, halo-alquilo de 1 a 7 átomos de carbono, alcoxilo de 1 a 7 átomos de carbono, halógeno o ciano; e

Y es alquilo de 1 a 7 átomos de carbono, halo-alquilo de 1 a 7 átomos de carbono, alcoxilo de 1 a 7 átomos de carbono, halógeno o ciano;

y/o un tautómero, un N-óxido, y/o una sal del mismo.

3. Un compuesto de la fórmula I de acuerdo con la reivindicación 1, o con la reivindicación 2, en donde, para los sustituyentes R^1, R^2, R^3, R^4, R^A, X e Y,

en alquilo insustituido o sustituido, alquilo de preferencia tiene hasta 20, más preferiblemente hasta 12 átomos de carbono y está insustituido o sustituido por uno o más sustituyentes seleccionados independientemente a partir del grupo que consiste en alquilo de 1 a 7 átomos de carbono, hidroxi-alquilo de 1 a 7 átomos de carbono, alcoxilo de 1 a 7 átomos de carbono-alquilo de 1 a 7 átomos de carbono, N-mono- o N,N-di-[alquilo de 1 a 7 átomos de carbono, fenilo, alcanoílo de 1 a 7 átomos de carbono y/o fenil-alquilo de 1 a 7 átomos de carbono]-amino-alquilo de 1 a 7 átomos de carbono, halo-alquilo de 1 a 7 átomos de carbono, hidroxilo, alcoxilo de 1 a 7 átomos de carbono, alcoxilo de 1 a 7 átomos de carbono-alcoxilo de 1 a 7 átomos de carbono, (alcoxilo de 1 a 7 átomos de carbono)-alcoxilo de 1 a 7 átomos de carbono-alcoxilo de

1 a 7 átomos de carbono, halo-alcoxilo de 1 a 7 átomos de carbono, halógeno, fenoxilo, naftiloxilo, fenil- o naftil-alcoxilo de 1 a 7 átomos de carbono; amino-alcoxilo de 1 a 7 átomos de carbono, alcanoiloxilo de 1 a 7 átomos de carbono, benzoiloxilo, naftoiloxilo, oxo que no está en el átomo de carbono de enlace, amino, amino-alquilo de 1 a 7 átomos de carbono, N-mono- o N,N-di-[alquilo de 1 a 7 átomos de carbono, fenilo, alcanoílo de 1 a 7 átomos de carbono y/o fenil-alquilo de 1 a 7 átomos de carbono]-amino, N-(heterociclil-alquilo de 1 a 7 átomos de carbono)- o N-(heterociclil-alquilo de 1 a 7 átomos de carbono-)-N-(alquilo de 1 a 7 átomos de carbono)-amino, en donde el heterociclilo de preferencia tiene de 3 a 14 átomos del anillo, respectivamente, de los cuales de 1 a 4 son un heteroátomo independientemente seleccionado a partir de N, S, S(=O), $S(=O)_2$ y O, y está saturado, formilo (CHO), carboxilo, alcoxilo de 1 a 7 átomos de carbono-carbonilo, fenil- o naftil-alcoxilo de 1 a 7 átomos de carbono-carbonilo, alcanoílo de 2 a 7 átomos de carbono, benzoílo, naftoílo, carbamoílo, carbamoílo N-mono- o N,N-disustituido, en donde los sustituyentes se seleccionan a partir de alquilo inferior e hidroxi-alquilo inferior; amidino, guanidino, ureido, mercapto, tioalquilo de 1 a 7 átomos de carbono, tiofenilo o tionaftilo, fenil- o naftil-tioalquilo de 1 a 7 átomos de carbono, alquilo de 1 a 7 átomos de carbono-tiofenilo, alquilo de 1 a 7 átomos de carbono-tionaftilo, halo-alquilo de 1 a 7 átomos de carbono-mercapto, sulfonamido, benzo-sulfonamido, azido, azido-alquilo de 1 a 7 átomos de carbono, en especial azido-metilo, nitro, ciano;

heterociclilo insustituido o sustituido, el cual es heteociclilo mono- a tri-cíclico que está insaturado o saturado, tiene de 3 a 14 átomos del anillo, de los cuales de 1 a 4 son un heteroátomo independientemente seleccionado a partir de N, S, S(=O), $S(=O)_2$ y O, de preferencia N, y está insustituido o sustituido con una o más, de preferencia hasta tres, fracciones independientemente seleccionadas a partir del grupo que consiste en alquilo de 1 a 7 átomos de carbono, hidroxi-alquilo de 1 a 7 átomos de carbono, hidroxilo, oxo, amino o N-mono- o N,N-di-(alquilo de 1 a 7 átomos de carbono, {amino o mono- o di-(alquilo de 1 a 7 átomos de carbono)-amino}-alquilo de 1 a 7 átomos de carbono, alcanoílo de 1 a 7 átomos de carbono y/o alcoxilo de 1 a 7 átomos de carbono-carbonil)-amino, alcanoílo de 1 a 7 átomos de carbono, alquilo de 1 a 7 átomos de carbono-sulfonilo y heterociclilo saturado con 3 a 14 átomos del anillo y con 1 a 4 heteroátomos independientemente seleccionados a partir de N, S, S(=O), $S(=O)_2$ y O, de preferencia N, en donde este heterociclilo saturado está insustituido o sustituido por una o más, en especial hasta tres, fracciones independientemente seleccionadas a partir de alquilo de 1 a 7 átomos de carbono, hidroxi-alquilo de 1 a 7 átomos de carbono, alcoxilo de 1 a 7 átomos de carbono-alquilo de 1 a 7 átomos de carbono, oxo, amino, mono- o di-(alquilo de 1 a 7 átomos de carbono)-amino), alcanoílo de 1 a 7 átomos de carbono y alcoxilo de 1 a 7 átomos de carbono-carbonilo; naftilo o fenilo, cada uno de los cuales está insustituido o sustituido por una o más fracciones independientemente seleccionadas a partir

de alquilo de 1 a 7 átomos de carbono, halo-alquilo de 1 a 7 átomos de carbono, hidroxilo, alcoxilo de 1 a 7 átomos de carbono, hidroxi-alcoxilo de 1 a 7 átomos de carbono, alcoxilo de 1 a 7 átomos de carbono-alcoxilo de 1 a 7 átomos de carbono, (alcoxilo de 1 a 7 átomos de carbono-alcoxilo de 1 a 7 átomos de carbono)-alcoxilo de 1 a 7 átomos de carbono, [amino, mono- o di-(alquilo de 1 a 7 átomos de carbono)-amino]-alcoxilo de 1 a 7 átomos de carbono, amino, mono- o di-[(alquilo de 1 a 7 átomos de carbono, alcanoílo de 1 a 7 átomos de carbono, alcoxilo de 1 a 7 átomos de carbono-carbonilo, hidroxi-alquilo de 1 a 7 átomos de carbono, alcoxilo de 1 a 7 átomos de carbono-alquilo de 1 a 7 átomos de carbono y/o (amino, mono- o di-(alquilo de 1 a 7 átomos de carbono)-amino)-alquilo de 1 a 7 átomos de carbono]-amino, halógeno y heterociclilo saturado, heterociclilo saturado-alquilo de 1 a 7 átomos de carbono o heterociclilo saturado-alcoxilo de 1 a 7 átomos de carbono, en donde el heterociclilo saturado, respectivamente, tiene de 3 a 14 átomos del anillo, de los cuales de 1 a 4 son un heteroátomo independientemente seleccionado a partir de N, S, S(=O), $S(=O)_2$ y O, y está insustituido o sustituido con una o más, en especial hasta tres, fracciones independientemente seleccionadas a partir de alquilo de 1 a 7 átomos de carbono, hidroxi-alquilo de 1 a 7 átomos de carbono, alcoxilo de 1 a 7 átomos de carbono-alquilo de 1 a 7 átomos de carbono, hidroxilo, oxo, amino, mono- o di-(alquilo de 1 a 7 átomos de carbono)-amino), alcanoílo de 1 a 7 átomos de carbono y alcoxilo de 1 a 7 átomos de carbono-carbonilo, nitro o ciano; y

cicloalquilo de 3 a 8 átomos de carbono, que está insustituido o sustituido por uno o más, en especial hasta tres, sustituyentes seleccionados independientemente a partir de los sustituyentes para arilo sustituido más adelante;

en donde cada fenilo o naftilo (también en fenoxilo o naftoxilo) mencionado anteriormente como sustituyente o parte de un sustituyente de alquilo sustituido (o también de arilo sustituido, heterociclilo etc. mencionados en la presente) está él mismo insustituido o sustituido por uno o más, por ejemplo, hasta tres, de preferencia 1 ó 2 sustituyentes seleccionados independientemente a partir de alquilo de 1 a 7 átomos de carbono, halo-alquilo de 1 a 7 átomos de carbono, hidroxilo, alcoxilo de 1 a 7 átomos de carbono, alcoxilo de 1 a 7 átomos de carbono-alcoxilo de 1 a 7 átomos de carbono, halógeno, en especial flúor, cloro, bromo o yodo, halo-alquilo de 1 a 7 átomos de carbono, tal como trifluoro-metilo, azido, amino, N-mono- o N,N-di-(alquilo de 1 a 7 átomos de carbono, fenilo, naftilo, alcanoílo de 1 a 7 átomos de carbono, fenil-alquilo de 1 a 7 átomos de carbono y/o naftil-alquilo de 1 a 7 átomos de carbono)-amino, carboxilo, alcoxilo de 1 a 7 átomos de carbono-carbonilo carbamoílo, sulfamoílo, nitro y ciano;

alquenilo insustituido o sustituido es alquenilo de 2 a 20 átomos de carbono, el cual es lineal o ramificado e incluye uno o más dobles enlaces, en dónde los sustituyentes son uno o más sustituyentes seleccionados independientemente a partir de aquéllos mencionados para alquilo sustituido;

alquinilo insustituido o sustituido es alquinilo de 2 a 20 átomos de carbono, el cual es lineal o ramificado, e incluye uno o más triples enlaces, en donde los sustituyentes son uno o más sustituyentes seleccionados independientemente a partir de aquéllos mencionados para alquilo sustituido;

en arilo insustituido o sustituido, arilo de preferencia tiene de 6 a 18 átomos de carbono y es una fracción carbocíclica insaturada mono-, di-, o poli-cíclica con dobles enlaces conjugados en el anillo, que está insustituida o sustituida por uno o más sustituyentes seleccionados independientemente a partir del grupo que consiste en alquilo de 1 a 7 átomos de carbono, alquenilo de 2 a 7 átomos de carbono; alquinilo de 2 a 7 átomos de carbono; arilo de 6 a 18 átomos de carbono-alquilo de 1 a 7 átomos de carbono, en donde arilo está insustituido o sustituido por alquilo de 1 a 7 átomos de carbono, por pirrolidinilo, por pirazolidinilo, por imidazolidinilo, por piperidinilo, por azepanilo, por piperazinilo, por amino, por N-mono- y/o N,N-di-alquilo de 1 a 7 átomos de carbono-amino, por halógeno, por hidroxilo, por alcoxilo de 1 a 7 átomos de carbono, y/o por halo-alquilo de 1 a 7 átomos de carbono; (pirrolidinilo, piridazolidinilo, imidazolidinilo, piperidinilo, azepanilo, piperazinilo, morfolino, tiomorfolino, piridinilo, pirimidinilo, pirazinilo, piridazinilo, oxazolilo o tiazolil)-alquilo de 1 a 7 átomos de carbono, en donde pirrolidinilo, pirazolidinilo, imidazolidinilo, piperidinilo, azepanilo, piperazinilo, piridinilo, pirimidinilo, pirazinilo, piridazinilo, oxazolilo o tiazolilo están insustituidos o sustituidos por alquilo de 1 a 7 átomos

de carbono, por pirrolidinilo, por pirazolidinilo, por imidazolidinilo, por azepanilo, por piperazinilo, por amino, por N-mono- y/o N,N-di-alquilo de 1 a 7 átomos de carbono-amino, por halógeno, por alcoxilo de 1 a 7 átomos de carbono, y/o por halo-alquilo de 1 a 7 átomos de carbono; (pirrolidinilo, pirazolidinilo, imidazolidinilo, piperidinilo, azepanilo, piperazinilo, piridinilo, pirimidinilo, pirazinilo, piridazinilo, oxazolilo o tiazolil)-oxi-alquilo de 1 a 7 átomos de carbono, en donde pirrolidinilo, pirazolidinilo, imidazolidinilo, piperidinilo, azepanilo, piperazinilo, piridinilo, pirimidinilo, pirazinilo, piridazinilo, oxazolilo y tiazolilo están insustituidos o sustituidos por alquilo de 1 a 7 átomos de carbono, por pirrolidinilo, por pirazolidinilo, por imidazolidinilo, por piperidinilo, por azepanilo, por piperazinilo, por amino, por N-mono- y/o N,N-di-alquilo de 1 a 7 átomos de carbono-amino, por halógeno, por alcoxilo de 1 a 7 átomos de carbono, y/o por halo-alquilo de 1 a 7 átomos de carbono; (pirrolidina, pirazolidinilo, imidazolidinilo, piperidina, azepano, piperazina, piridina, pirimidina, pirazina, piridazina, oxazolil o tiazol)-carbonil-alquilo de 1 a 7 átomos de carbono, en donde pirrolidina, pirazolidina, imidazolidina, piperidina, azepano, piperazina, piridina, pirimidina, piridazina, oxazol o piridazina están insustituidos o sustituidos por alquilo de 1 a 7 átomos de carbono, por pirrolidinilo, por pirazolidinilo, por imidazolidinilo, por azepanilo, por piperazinilo, por amino, por N-mono- y/o N,N-di-alquilo de 1 a 7 átomos de carbono-amino, por halógeno, por alcoxilo de 1 a 7 átomos de carbono, y/o por halo-alquilo de 1 a 7 átomos de carbono; halo-alquilo de 1 a 7 átomos de

carbono, hidroxi-alquilo de 1 a 7 átomos de carbono; alcoxilo de 1 a 7 átomos de carbono-alquilo de 1 a 7 átomos de carbono; alcoxilo de 1 a 7 átomos de carbono-alcoxilo de 1 a 7 átomos de carbono-alquilo de 1 a 7 átomos de carbono; feniloxi- o naftiloxi-alquilo de 1 a 7 átomos de carbono; fenil-alcoxilo de 1 a 7 átomos de carbono- o naftil-alcoxilo de 1 a 7 átomos de carbono-alquilo de 1 a 7 átomos de carbono; amino-alquilo de 1 a 7 átomos de carbono; N-mono- o N,N-di-(alquilo de 1 a 7 átomos de carbono, alcoxilo de 1 a 7 átomos de carbono-alquilo de 1 a 7 átomos de carbono y/o (mono- o di-(alquilo de 1 a 7 átomos de carbono)-amino)-alquilo de 1 a 7 átomos de carbono)-amino-alquilo de 1 a 7 átomos de carbono; alcoxilo de 1 a 7 átomos de carbono-alquilo de 1 a 7 átomos de carbono-amino-alquilo de 1 a 7 átomos de carbono; mono- o di-[arilo de 6 a 18 átomos de carbono-alquilo de 1 a 7 átomos de carbono, en donde arilo está insustituido o sustituido por alquilo de 1 a 7 átomos de carbono, por pirrolidinilo, por pirazolidinilo, por imidazolidinilo, por piperidinilo, por azepanilo, por piperazinilo, por amino, por N-mono- y/o N,N-di-alquilo de 1 a 7 átomos de carbono-amino, por halógeno, por hidroxilo, por alcoxilo de 1 a 7 átomos de carbono, y/o por halo-alquilo de 1 a 7 átomos de carbono; naftil- o fenil-alquilo de 1 a 7 átomos de carbono]-amino-alquilo de 1 a 7 átomos de carbono; alcanoílo de 1 a 7 átomos de carbono-amino-alquilo de 1 a 7 átomos de carbono; carboxi-alquilo de 1 a 7 átomos de carbono; benzoil- o naftoil-amino-alquilo de 1 a 7 átomos de carbono; alquilo de 1 a 7 átomos de carbono-sulfonil-amino-alquilo de 1 a 7 átomos de

carbono; fenil- o naftil-sulfonil-amino-alquilo de 1 a 7 átomos de carbono, en donde fenilo o naftilo está insustituido o sustituido por una o más fracciones de alquilo de 1 a 7 átomos de carbono; fenil- o naftil-alquilo de 1 a 7 átomos de carbono-sulfonil-amino-alquilo de 1 a 7 átomos de carbono; halógeno; hidroxilo; alcoxilo de 1 a 7 átomos de carbono; arilo de 6 a 18 átomos de carbono-alcoxilo de 1 a 7 átomos de carbono, en donde arilo está insustituido o sustituido por alquilo de 1 a 7 átomos de carbono, por alcoxilo de 1 a 7 átomos de carbono, por pirrolidinilo, por pirazolidinilo, por imidazolidinilo, por piperidinilo, por azepanilo, por piperazinilo, por amino, por N-mono- y/o N,N-di-alquilo de 1 a 7 átomos de carbono-amino, por halógeno, por hidroxilo, por alcoxilo de 1 a 7 átomos de carbono, y/o por halo-alquilo de 1 a 7 átomos de carbono; halo-alcoxilo de 1 a 7 átomos de carbono; hidroxi-alcoxilo de 1 a 7 átomos de carbono; alcoxilo de 1 a 7 átomos de carbono-alcoxilo de 1 a 7 átomos de carbono; (alcoxilo de 1 a 7 átomos de carbono-alcoxilo de 1 a 7 átomos de carbono)-alcoxilo de 1 a 7 átomos de carbono; [amino, mono- o di-(alquilo de 1 a 7 átomos de carbono)-amino]-alcoxilo de 1 a 7 átomos de carbono, N-alcanoílo de 1 a 7 átomos de carbono-amino-alcoxilo de 1 a 7 átomos de carbono; N-insustituido-, N-mono- o N,N-di-(alquilo de 1 a 7 átomos de carbono)-carbamoil-alcoxilo de 1 a 7 átomos de carbono; fenil- o naftiloxilo; fenil- o naftil-alquiloxilo de 1 a 7 átomos de carbono; (pirrolidinilo, pirazolidinilo, imidazolidinilo, piperidinilo, azepanilo, piperazinilo, piridinilo, pirimidinilo, pirazinilo, piridazinilo, oxazolilo o tiazolil)-alcoxilo de 1 a 7 átomos de carbono, en donde

pirrolidinilo, pirazolidinilo, imidazolidinilo, piperidinilo, azepanilo, piperazinilo, piridinilo, pirimidinilo, pirazinilo, piridazinilo, oxazolilo y tiazolilo están insustituidos o sustituidos por alquilo de 1 a 7 átomos de carbono, por pirrolidinilo, por pirazolidinilo, por imidazolidinilo, por piperidinilo, por azepanilo, por piperazinilo, por amino, por N-mono- y/o N,N-di-alquilo de 1 a 7 átomos de carbono-amino, por halógeno, por alcoxilo de 1 a 7 átomos de carbono, y/o por halo-alquilo de 1 a 7 átomos de carbono; (pirrolidinilo, pirazolidinilo, imidazolidinilo, piperidinilo, azepanilo, piperazinilo, piridinilo, pirimidinilo, pirazinilo, piridazinilo, oxazolilo o tiazolil)-oxi-alcoxilo de 1 a 7 átomos de carbono, en donde pirrolidinilo, pirazolidinilo, imidazolidinilo, piperidinilo, azepanilo, piperazinilo, piridinilo, pirimidinilo, pirazinilo, piridazinilo, oxazolilo y tiazolilo están insustituidos o sustituidos por alquilo de 1 a 7 átomos de carbono, por pirrolidinilo, por pirazolidinilo, por imidazolidinilo, por piperidinilo, por azepanilo, por piperazinilo, por amino, por N-mono- y/o N,N-di-alquilo de 1 a 7 átomos de carbono-amino, por halógeno, por alcoxilo de 1 a 7 átomos de carbono, y/o por halo-alquilo de 1 a 7 átomos de carbono; alcanoiloxilo de 1 a 7 átomos de carbono; benzoil- o naftoiloxilo; tioalquilo de 1 a 7 átomos de carbono; halo-tioalquilo de 1 a 7 átomos de carbono; alcoxilo de 1 a 7 átomos de carbono-tioalquilo de 1 a 7 átomos de carbono; tiofenilo o tionaftilo; fenil- o naftil-tioalquilo de 1 a 7 átomos de carbono; tioalcanoílo de 1 a 7 átomos de carbono; tiobenzoílo o tionaftoílo; nitro; amino; mono- o di-[(alquilo de 1 a 7 átomos de carbono, alcanoílo de 1 a 7 átomos

de carbono, alcoxilo de 1 a 7 átomos de carbono-carbonilo, hidroxi-alquilo de 1 a 7 átomos de carbono, alcoxilo de 1 a 7 átomos de carbono-alquilo de 1 a 7 átomos de carbono y/o (amino, mono- o di-(alquilo de 1 a 7 átomos de carbono)-amino)-alquilo de 1 a 7 átomos de carbono]-amino; mono- o di-(naftil- o fenil-alquilo de 1 a 7 átomos de carbono)-amino; alcanoílo de 1 a 7 átomos de carbono-amino; benzoil- o naftoil-amino insustituido o sustituido por amino-, N-mono- o N,N-di-(alquilo de 1 a 7 átomos de carbono y/o fenil- o naftil-alquilo de 1 a 7 átomos de carbono)-amino; alcoxilo de 1 a 7 átomos de carbono-carbonil-amino; (fenil o naftil)-alcoxilo de 1 a 7 átomos de carbono-carbonil-amino; alquilo de 1 a 7 átomos de carbono-sulfonil-amino; fenil- o naftil-sulfonil-amino, en donde fenilo o naftilo está insustituido o sustituido por una o más fracciones de alquilo de 1 a 7 átomos de carbono; fenil- o naftil-alquilo de 1 a 7 átomos de carbono-sulfonil-amino; alcanoílo de 1 a 7 átomos de carbono; alcoxilo de 1 a 7 átomos de carbono-alcanoílo de 1 a 7 átomos de carbono; carboxilo; alcoxilo de 1 a 7 átomos de carbono-carbonilo; fenoxi- o naftoxi-carbonilo; fenil- o naftil-alcoxilo de 1 a 7 átomos de carbono-carbonilo; alquilendioxilo de 1 a 10 átomos de carbono, en especial de 1 a 4 átomos de carbono, tal como metilendioxilo o 1,2-etilendioxilo; carbamoílo; N-mono- o N,N-di-[alquilo de 1 a 7 átomos de carbono, naftil-alquilo de 1 a 7 átomos de carbono, fenil-alquilo de 1 a 7 átomos de carbono, N'-mono- o N',N'-di-(alquilo de 1 a 7 átomos de carbono)-amino-alquilo de 1 a 7 átomos de carbono, pirrolidinil-alquilo de 1 a 7 átomos de carbono, pirazolidinil-alquilo de

1 a 7 átomos de carbono, imidazolidinil-alquilo de 1 a 7 átomos de carbono, piperidinil-alquilo de 1 a 7 átomos de carbono, azepanil-alquilo de 1 a 7 átomos de carbono, piperazinil- o N-(alquilo de 1 a 7 átomos de carbono)-piperazinil-alquilo de 1 a 7 átomos de carbono, mono-alcoxilo de 1 a 7 átomos de carbono-alquilo de 1 a 7 átomos de carbono, (N'-mono- o N',N'-di-(alquilo de 1 a 7 átomos de carbono)-amino); fenilo, piridinilo, oxazolilo o tiazolilo, cada uno de los cuales está insustituido o sustituido por alcoxilo de 1 a 7 átomos de carbono, por halógeno, por pirrolidino, por pirazolidino, por imidazolidino, por piperidino, por azepan-1-ilo, por piperazino, por hidroxi-alquilo de 1 a 7 átomos de carbono-amino, por hidroxi-alquilo de 1 a 7 átomos de carbono, por amino o por N-mono- o N,N-di-(alquilo de 1 a 7 átomos de carbono)-amino; pirrolidinilo, pirazolidinilo, imidazolidinilo, piperidinilo, azepanilo, piperazinilo, pirimidinilo, pirazinilo y/o piridazinil]-amino-carbonilo, tal como N-mono- o N,N-di-(alquilo de 1 a 7 átomos de carbono)-amino-carbonilo; N-alcoxilo de 1 a 7 átomos de carbono-alquilo de 1 a 7 átomos de carbono-carbamoílo; pirrolidin-1-carbonilo; amino-N-pirrolidin-1-carbonilo; N-mono- o N,N-di-(alquilo de 1 a 7 átomos de carbono)-amino-pirrolidin-1-carbonilo; imidazolidin-1-carbonilo; piperidin-1-carbonil-morfolin-4-carbonilo; tiomorfolin-4-carbonilo; S-oxo-tiomorfolin-4-carbonilo; S,S-dioxo-tiomorfolin-4-carbonilo; piperazin-1-carbonilo; N-alquilo de 1 a 7 átomos de carbono-piperazin-1-carbonilo; N-alcoxilo de 1 a 7 átomos de carbono-carbonil-piperazin-1-carbonilo; pirrolidinil-alquilo de 1 a 7 átomos de

carbono sustituido por N-mono- o N,N-di-(alquilo de 1 a 7 átomos de carbono)-amino o insustituido; ciano; alquenileno de 1 a 7 átomos de carbono, o -alquinileno; alquilo de 1 a 7 átomos de carbono-sulfonilo; fenil- o naftil-sulfonilo, en donde fenilo o naftilo está insustituido o sustituido por una o más, en especial una a tres, fracciones de alquilo de 1 a 7 átomos de carbono; fenil- o naftil-alquilo de 1 a 7 átomos de carbono-sulfonilo; sulfamoílo; N-mono- o N,N-di-(alquilo de 1 a 7 átomos de carbono, fenil-, naftil-, fenil-alquilo de 1 a 7 átomos de carbono-, pirrolidinil-alquilo de 1 a 7 átomos de carbono, pirazolidinil-alquilo de 1 a 7 átomos de carbono, imidazolil-alquilo de 1 a 7 átomos de carbono, piperidinil-alquilo de 1 a 7 átomos de carbono, azepanil-alquilo de 1 a 7 átomos de carbono, piperazinil-alquilo de 1 a 7 átomos de carbono, N-alquilo de 1 a 7 átomos de carbono-piperazinil-alquilo de 1 a 7 átomos de carbono, naftil-alquilo de 1 a 7 átomos de carbono, fenilo que está insustituido o sustituido por alcoxilo de 1 a 7 átomos de carbono, por halógeno, en especial flúor, por pirrolidino, por pirazolidino, por imidazolidino, por azepan-1-ilo, por piperidino, por piperazino, por hidroxi-alquilo de 1 a 7 átomos de carbono o por N-mono- o N,N-di-(alquilo de 1 a 7 átomos de carbono)-alquilo de 1 a 7 átomos de carbono; pirrolidinilo, pirazolidinilo, imidazolidinilo, piperidinilo, azepanilo, piperazinilo, piridinilo, pirimidinilo, pirazinilo, piridazinilo, oxazolilo y/o tiazolil)-amino-sulfonilo, pirazolilo, pirazolidinilo, pirrolilo, pirrolidinilo, piridilo que está insustituido o sustituido por alcoxilo de 1 a 7 átomos de carbono y/o por halo-alquilo de 1 a 7 átomos de carbono,

pirrolidinilo, pirazolidinilo, imidazolidinilo, piperidinilo, azepanilo, piperazinilo, morfolinilo, tiomorfolinilo, S-oxo-tiomorfolinilo, S,S-dioxo-tiomorfolinilo, piperazinilo, N-alquilo de 1 a 7 átomos de carbono-piperazinilo, 4-(fenil-alquilo de 1 a 7 átomos de carbono)-piperazinilo, 4-(naftil-alquilo de 1 a 7 átomos de carbono)-piperazinilo, 4-(alcoxilo de 1 a 7 átomos de carbono-carbonil)-piperazinilo, 4-(fenil-alcoxilo de 1 a 7 átomos de carbono-carbonil)-piperazinilo, 4-(naftil-alcoxilo de 1 a 7 átomos de carbono-carbonil)-piperazinilo, oxazolilo y tiazolilo;

heterociclilo insustituido o sustituido es un radical heterocíclico que está insaturado (entonces también denominado como hetero-arilo), saturado o parcialmente saturado, y es un anillo monocíclico o bicíclico o triciclico; tiene de 3 a 24 átomos del anillo; en donde uno a cuatro átomos de carbono del anillo son reemplazados por un heteroátomo seleccionado a partir del grupo que consiste en nitrógeno, oxigeno, azufre S(=O) o $S(=O)_2$, teniendo el alilo de enlace de 4 a 12 átomos del anillo; cuyo heterociclilo está insustituido o sustituido por uno o más sustituyentes seleccionados independientemente a partir del grupo que consiste en los sustituyentes definidos anteriormente para alquilo sustituido o para arilo sustituido;

cicloalquilo insustituido o sustituido es cicloalquilo de 3 a 8 átomos de carbono y está insustituido o sustituido por uno o más sustituyentes seleccionados independientemente a partir de los sustituyentes para arilo sustituido anteriores;

carboxilo esterificado es alquiloxi-carbonilo insustituido o sustituido, ariloxi-carbonilo insustituido o sustituido, cicloalquiloxi-carbonilo insustituido o sustituido, o heterociclil-carbonilo insustituido o sustituido, en donde alquilo, arilo, cicloalquilo y heterociclilo y sus formas sustituidas son como se definen anteriormente;

en heterociclil-carbonilo insustituido o sustituido, heterociclilo es de preferencia una fracción seleccionada a partir de heterociclilo como se define anteriormente, y está insustituido o sustituido por uno o más sustituyentes seleccionados independientemente a partir de aquéllos para alquilo sustituido y arilo sustituido, y a partir de oxo;

en carbamoílo insustituido o sustituido, los sustituyentes de nitrógeno se seleccionan a partir de uno o dos sustituyentes seleccionados independientemente a partir de alquilo de 1 a 7 átomos de carbono insustituido o sustituido como se define anteriormente, arilo insustituido o sustituido como se define anteriormente, cicloalquilo insustituido o sustituido como se define anteriormente y a partir de heterociclilo insustituido o sustituido como se define anteriormente, en donde de preferencia solamente está presente un sustituyente de nitrógeno de carbamoílo, o bien, un sustituyente de nitrógeno es alquilo de 1 a 7 átomos de carbono, el otro se selecciona a partir del grupo de sustituyentes justamente mencionados;

acilo es aril-carbonil-sulfonilo insustituido o sustituido,

heterociclil-carbonilo o -sulfonilo insustituido o sustituido, cicloalquil-carbonilo o -sulfonilo insustituido o sustituido, formilo o alquil-carbonilo o -sulfonilo insustituido o sustituido, alquil-oxicarbonilo u -oxisulfonilo insustituido o sustituido, aril-oxi-carbonilo u -oxisulfonilo insustituido o sustituido, heterociclil-oxicarbonilo u -oxisulfonilo insustituido o sustituido, cicloalquiloxi-carbonilo u -oxisulfonilo insustituido o sustituido, o N-mono- o N,N-di-(arilo insustituido o sustituido, heterociclilo insustituido o sustituido, cicloalquilo insustituido o sustituido o alquilo insustituido o sustituido)-amino-carbonilo; en donde arilo insustituido o sustituido, heterociclilo insustituido o sustituido, cicloalquilo insustituido o sustituido y alquilo insustituido o sustituido son como se describen anteriormente;

y/o un tautómero, un N-óxido, y/o una sal del mismo.

4. Un compuesto de la fórmula I de acuerdo con la reivindicación 1, o con la reivindicación 2, en donde:

R^1 es alquilo de 1 a 7 átomos de carbono que es lineal o ramificado y está insustituido o sustituido por una o más, en especial hasta tres, fracciones independientemente seleccionadas a partir del grupo que consiste en alquilo de 1 a 7 átomos de carbono, en especial metilo, de hidroxilo, de hidroxi-alquilo de 1 a 7 átomos de carbono, en especial hidroxi-metilo, de alcoxilo de 1 a 7 átomos de carbono-alquilo de 1 a 7 átomos de carbono, en especial 2-metoxi-etoxilo o metoxi-etoxilo o etoxi-metoxilo, de arilo de 6 a 14 átomos de carbono, en especial fenilo, en donde arilo está

insustituido o sustituido por una o más, en especial hasta tres, fracciones independientemente seleccionadas a partir del grupo que consiste en alquilo de 1 a 7 átomos de carbono, en especial metilo, halo-alquilo de 1 a 7 átomos de carbono, en especial trifluoro-metilo, hidroxilo, alcoxilo de 1 a 7 átomos de carbono, alcoxilo de 1 a 7 átomos de carbono-alcoxilo de 1 a 7 átomos de carbono, en especial 2-metoxi-etoxilo ó 3-metoxi-propoxilo, [amino, mono- o di-(alquilo de 1 a 7 átomos de carbono)-amino]-alcoxilo de 1 a 7 átomos de carbono, amino, mono- o di-[alquilo de 1 a 7 átomos de carbono, hidroxi-alquilo de 1 a 7 átomos de carbono, alcoxilo de 1 a 7 átomos de carbono-alquilo de 1 a 7 átomos de carbono, amino-alquilo de 1 a 7 átomos de carbono, amino y/o mono- o di-(alquilo de 1 a 7 átomos de carbono)-amino-alquilo de 1 a 7 átomos de carbono]-amino, halógeno, en especial flúor, cloro o bromo, y heterociclilo saturado-alcoxilo de 1 a 7 átomos de carbono, en donde heterociclilo saturado tiene de 3 a 14 átomos del anillo, de los cuales de 1 a 4 son un heteroátomo independientemente seleccionado a partir de N, S, S(=O), $S(=O)_2$ y O, y está insustituido o sustituido con alquilo de 1 a 7 átomos de carbono, en especial pirrolidinil-, piperidinil-, piperazinil- o N-(alquilo de 1 a 7 átomos de carbono)-piperazinil-alcoxilo de 1 a 7 átomos de carbono, y de heterociclilo de 3 a 14 átomos de carbono mono- o bi-cíclico con 3 a 14 átomos del anillo, de los cuales de 1 a 4 son un heteroátomo independientemente seleccionado a partir de N, S, S(=O), $S(=O)_2$ y O, y está insustituido o sustituido con alquilo de 1 a 7 átomos de carbono, en especial el hetero-arilo

correspondiente, más especialmente indolilo, isoindolilo, indazolilo, quinolinilo, isoquinolinilo, ftalazinilo, quinoxalinilo, quinazolinilo, cinolinilo, benzo-furanilo, isobenzo-furanilo, cromenilo, isocromenilo, benzo-tiofenilo, tiocromenilo o isotiocromenilo,

R^2 es arilo de 6 a 14 átomos de carbono (en especial fenilo) que está insustituido o sustituido por una o más, en especial hasta tres, fracciones independientemente seleccionadas a partir del grupo que consiste en alquilo de 1 a 7 átomos de carbono-fenilo, en especial metilo, hidroxilo, y halógeno, en especial flúor o cloro,

R^3 es hidrógeno o de preferencia,

alquilo de 1 a 7 átomos de carbono que está insustituido por una o más, en especial hasta tres, fracciones independientemente seleccionadas a partir del grupo que consiste en hidroxilo, amino y heterociclil-alquilo de 1 a 7 átomos de carbono-amino, en donde el heterociclilo tiene de 3 a 14 átomos del anillo, de los cuales de 1 a 4 son un heteroátomo independientemente seleccionado a partir de N, S, S(=O), $S(=O)_2$ y O, y está saturado, en especial (morfolinilo, tiomorfolinilo, S-oxo-tiomorfolinilo o S,S-dioxo-tiomorfolinil)-alquilo de 1 a 7 átomos de carbono-amino,

ciano, carboxilo, alcoxilo de 1 a 7 átomos de carbono-carbonilo o arilo de 6 a 14 átomos de carbono-alcoxilo de 1 a 7 átomos de carbono-carbonilo;

heterociclil-carbonilo (heterociclil-C(=O)) en donde el heterociclilo está insaturado o de preferencia saturado, tiene de 3 a 14 átomos del anillo, de los cuales de 1 a 4 son un heteroátomo

independientemente seleccionado a partir de N, S, S(=O), $S(=O)_2$ y O, de preferencia N, tal como pirrolidinilo, piperidinilo, piperazinilo, morfolinilo, tiomorfolinilo, S-oxo-tiomorfolinilo o S,S-dioxo-tiomorfolinilo, y está insustituido o sustituido con una o más, en especial una a tres, fracciones independientemente seleccionadas a partir del grupo que consiste en alquilo de 1 a 7 átomos de carbono, hidroxi-alquilo de 1 a 7 átomos de carbono, hidroxilo, oxo, amino o N-mono- o N,N-di-(alquilo de 1 a 7 átomos de carbono, {amino o mono- o di-alquilo de 1 a 7 átomos de carbono-amino}-alquilo de 1 a 7 átomos de carbono, alcanoílo de 1 a 7 átomos de carbono y/o alcoxilo de 1 a 7 átomos de carbono-carbonil)-amino, alcanoílo de 1 a 7 átomos de carbono, alquilo de 1 a 7 átomos de carbono-sulfonilo y heterociclilo saturado con 3 a 14 átomos del anillo y con 1 a 4 heteroátomos independientemente seleccionados a partir de N, S, S(=O), $S(=O)_2$ y O, de preferencia N, por ejemplo, pirrolidinilo, imidazolidinilo, piperidinilo, piperazinilo, morfolinilo, tiomorfolinilo, S-oxo-tiomorfolinilo o S,S-dioxo-tiomorfolinilo, en donde este heterociclilo saturado está insustituido o sustituido por una o más, en especial hasta tres, fracciones independientemente seleccionadas a partir de alquilo de 1 a 7 átomos de carbono, hidroxi-alquilo de 1 a 7 átomos de carbono-alcóxilo de 1 a 7 átomos de carbono-alquilo de 1 a 7 átomos de carbono, oxo, amino y mono- o di-(alquilo de 1 a 7 átomos de carbono)-amino),

carbamoílo, N-mono- o N,N-di-[alquilo de 1 a 7 átomos de carbono, hidroxi-alquilo de 1 a 7 átomos de carbono, alcoxilo de 1

a 7 átomos de carbono-alquilo de 1 a 7 átomos de carbono, amino-alquilo de 1 a 7 átomos de carbono, mono- o di-(alquilo de 1 a 7 átomos de carbono)-amino-alquilo de 1 a 7 átomos de carbono, arilo de 6 a 14 átomos de carbono, en donde arilo está insustituido o sustituido por una o más, en especial hasta tres, fracciones independientemente seleccionadas a partir del grupo que consiste en alquilo de 1 a 7 átomos de carbono, alcoxilo de 1 a 7 átomos de carbono, heterociclilo saturado con 3 a 14 átomos del anillo y con 1 a 4 heteroátomos independientemente seleccionados a partir de N, S, S(=O), $S(=O)_2$ y O, de preferencia N, por ejemplo, pirrolidinilo, imidazolidinilo, piperidinilo, piperazinilo, azepanilo, morfolinilo, tiomorfolinilo, S-oxo-tiomorfolinilo o S,S-dioxo-tiomorfolinilo, en donde este heterociclilo saturado está insustituido o sustituido con una o más, en especial hasta tres, fracciones independientemente seleccionadas a partir de alquilo de 1 a 7 átomos de carbono, hidroxi-alquilo de 1 a 7 átomos de carbono, hidroxilo, oxo, y alcoxilo de 1 a 7 átomos de carbono-carbonilo, arilo de 6 a 14 átomos de carbono-alquilo de 1 a 7 átomos de carbono, y heterociclilo saturado o (heterociclilo saturado)-alquilo de 1 a 7 átomos de carbono, en donde heterociclilo saturado en ambos casos tiene de 3 a 14 átomos del anillo y de 1 a 4 heteroátomos independientemente seleccionados a partir de N, S, S(=O), $S(=O)_2$ y O, de preferencia N, por ejemplo, pirrolidinilo, imidazolidinilo, piperidinilo, piperazinilo, azepanilo, morfolinilo, tiomorfolinilo, S-oxo-tiomorfolinilo, S,S-dioxo-tiomorfolinilo, indolilo o isoindolilo o (pirrolidinilo, imidazolidinilo,

piperidinilo, piperazinilo, azepanilo, morfolinilo, tiomorfolinilo, S-oxo-tiomorfolinilo, S,S-dioxo-tiomorfolinilo, indolilo o isoindolil)-alquilo de 1 a 7 átomos de carbono, en donde este heterociclilo saturado está insustituido o sustituido con una o más, en especial hasta tres, fracciones independientemente seleccionadas a partir de alquilo de 1 a 7 átomos de carbono, hidroxi-alquilo de 1 a 7 átomos de carbono, alcoxilo de 1 a 7 átomos de carbono-alquilo de 1 a 7 átomos de carbono, oxo, alcanoílo de 1 a 7 átomos de carbono y alcoxilo de 1 a 7 átomos de carbono-carbonil]-carbamoílo,

hetero-arilo con 3 a 14 átomos del anillo y con 1 a 5 heteroátomos del anillo independientemente seleccionados a partir del grupo que consiste en N, S, S(=O), $S(=O)_2$ y O, en especial N, S y O, tal como triazolilo o en especial tetrazolilo,

o ciano,

R^4 es hidrógeno, alquilo de 1 a 7 átomos de carbono, halógeno o hetero-arilo con 3 a 14 átomos del anillo y con 1 a 5 heteroátomos independientemente seleccionados a partir del grupo que consiste en N, S, S(=O), $S(=O)_2$ y O, en especial N, tal como piridilo,

R^A es hidrógeno o alquilo de 1 a 7 átomos de carbono, de preferencia hidrógeno;

X es hidrógeno, alquilo de 1 a 7 átomos de carbono, halógeno o ciano, en especial hidrógeno o flúor, e

Y es alquilo de 1 a 7 átomos de carbono, halógeno o ciano, en especial metilo, flúor, cloro, bromo o ciano,

y/o un tautómero, un N-óxido y/o una sal farmacéuticamente aceptable del mismo.

5. Un compuesto de la fórmula I de acuerdo con la reivindicación 1 o con la reivindicación 2, en donde:

R^1 es alquilo de 1 a 7 átomos de carbono, en especial 3,3-dimetil-butilo, alquilo de 1 a 7 átomos de carbono-bencilo, en especial metil-bencilo, más especialmente 4-metil-bencilo, (halo-alquilo de 1 a 7 átomos de carbono)-bencilo, en especial trifluoro-metil-bencilo, más especialmente 4-trifluoro-metil-bencilo, hidroxi-halo-bencilo, en especial cloro-hidroxi-bencilo, más especialmente 4-cloro-2-hidroxi-bencilo, halo-bencilo, en especial bromo-bencilo, más especialmente 4-bromo-bencilo, cloro-bencilo, más especialmente 4-cloro-bencilo, fluoro-bencilo, más especialmente 4-fluoro-bencilo, dicloro-bencilo, más especialmente 3,4- ó 2,4-dicloro-bencilo, cloro-fluoro-bencilo, más especialmente 4-cloro-3-fluoro-bencilo, 3-cloro-4-fluoro-bencilo o 4-cloro-2-fluoro-bencilo, (R,S)- o de preferencia (R)- o (S)-1-(halo-fenil)-1-(alquilo de 1 a 7 átomos de carbono o hidroxi)-alquilo de 1 a 7 átomos de carbono, en especial (R,S)- o de preferencia (R)- o (S)-1-(fluoro-fenilo, cloro-fenilo o bromo-fenil)-1-(metil o hidroxi)-metilo, más especialmente (R,S)- o de preferencia (R)- o (S)-1-(4-fluoro-fenilo, 4-cloro-fenil o 4-bromo-fenil)-1-(metil o hidroxi)-metilo, (R,S)- o de preferencia (R)- o (S)-1-(halo-fenil)-1-[(hidroxilo o alcoxilo de 1 a 7 átomos de carbono)-alquilo de 1 a 7 átomos de carbono]-alquilo de 1 a 7 átomos de carbono, en especial (R,S)- o de preferencia (R)- o (S)-1-(cloro-fenil)-1-(hidroxi-metil o

metoxi-metil)-metilo, más especialmente (R,S)- o de preferencia (R)- o (S)-1-(4-cloro-fenil)-1-(hidroxi-metil o metoxi-metil)-metilo, alquilo de 1 a 7 átomos de carbono-halo-bencilo, en especial metil-halo-bencilo, más especialmente 4-cloro-2-metil-bencilo, hidroxi-halo-bencilo, en especial hidroxi-cloro-bencilo, más especialmente 4-cloro-2-hidroxi-bencilo, alcoxilo de 1 a 7 átomos de carbono-halo-bencilo, en especial metoxi-cloro-bencilo, tal como 4-cloro-2-metoxi-bencilo, (hidroxi-alcoxilo de 1 a 7 átomos de carbono, o alcoxilo de 1 a 7 átomos de carbono-alcoxilo de 1 a 7 átomos de carbono)-halo-bencilo, en especial (2-hidroxi-etoxilo, 3-hidroxi-propoxilo o 2-metoxi-etoxi)-cloro-bencilo, más especialmente 4-cloro-2-(2-hidroxi-etoxilo, 3-hidroxi-propoxi o 2-metoxi-etoxi)-bencilo, [amino, N-mono- o N,N-di-(alquilo de 1 a 7 átomos de carbono-amino)-alcoxilo de 1 a 7 átomos de carbono]-halo-bencilo, en especial [2-(N,N-dimetil-amino)-etoxi]-cloro-bencilo, más especialmente 2-[2-(N,N-dimetil-amino)-etoxi]-4-cloro-bencilo, (hidroxi-alquilo de 1 a 7 átomos de carbono-amino)-halo-bencilo, en especial [(2-hidroxi-metil- ó 3-hidroxi-propil)-amino]-cloro-bencilo, más especialmente 2-[(2-hidroxi-metil- ó 3-hidroxi-propil)-amino]-4-cloro-bencilo, (alcoxilo de 1 a 7 átomos de carbono-alquilo de 1 a 7 átomos de carbono-amino)-halo-bencilo, en especial [(2-metoxi-metil- ó 3-metoxi-propil)-amino]-cloro-bencilo, más especialmente 2-[(2-metoxi-metil- ó 3-metoxi-propil)-amino]-4-cloro-bencilo, [{amino, N-mono- o N,N-di-(alquilo de 1 a 7 átomos de carbono)-amino}-alquilo de 1 a 7 átomos de carbono-amino]-halo-bencilo, en especial [(2-dimetil-amino-etil-amino]-cloro-bencilo, más

especialmente 2-(2-dimetil-amino-etil-amino)-4-cloro-bencilo, (pirrolidinil-, piperidinil-, piperazinil- o N-(alquilo de 1 a 7 átomos de carbono)-piperazinil-alcoxilo de 1 a 7 átomos de carbono)-halo-bencilo, en especial (pirrolidino-, piperidino-, piperazino- o 4-(alquilo de 1 a 7 átomos de carbono)-piperazin-1-il-alcoxilo de 1 a 7 átomos de carbono)-halo-bencilo, más especialmente 4-cloro-2-[2-(pirrolidino-, piperidino-, piperazino- o 4-(alquilo de 1 a 7 átomos de carbono)-piperazin-1-il)-etoxi]-bencilo, indolil-alquilo de 1 a 7 átomos de carbono, en especial indolil-metilo, más especialmente indol-6-il-metilo, benzo-furanil-alquilo de 1 a 7 átomos de carbono, en especial benzo-furanil-metilo, más especialmente benzo-furan-6-il-metilo, o benzo-tiofenil-alquilo de 1 a 7 átomos de carbono, en especial benzo-tiofenil-metilo, más especialmente benzo-tiofen-6-il-metilo;

R^2 es fenilo, alquilo de 1 a 7 átomos de carbono-fenilo, en especial metil-fenilo, más especialmente 2-metil-fenilo, hidroxi-fenilo, en especial 3-hidroxi-fenilo, o halofenilo, en especial fenilo o fluoro-, cloro- o fluoro-cloro-fenilo, más especialmente fenilo, 2-fluoro-fenilo, 3-fluoro-fenilo o 3-cloro-2-fluoro-fenilo,

R^3 es hidrógeno o de preferencia hidroxi-alquilo de 1 a 7 átomos de carbono, en especial hidroxi-metilo, amino-alquilo de 1 a 7 átomos de carbono, en especial 2-amino-etilo, (morfolinilo, tiomorfolinilo, S-oxo-tiomorfolinilo o S,S-dioxo-tiomorfolinil)-alquilo de 1 a 7 átomos de carbono-amino-alquilo de 1 a 7 átomos de carbono, en especial N-(2-morfolino-etil)-amino-metilo,

ciano, carboxilo, alcoxilo de 1 a 7 átomos de carbono-

carbonilo, en especial metoxi-carbonilo o etoxi-carbonilo,

azetidin-carbonilo, en especial azetidin-1-il-carbonilo, pirrolidin-carbonilo, en especial pirrolidin-1-carbonilo, (R,S)- o de preferencia (R)- o (S)-[amino o N'-mono- o N',N'-di-(alquilo de 1 a 7 átomos de carbono y/o {amino o mono- o di-alquilo de 1 a 7 átomos de carbono-amino}-alquilo de 1 a 7 átomos de carbono)-amino]-pirrolidin-carbonilo o aquiral, en especial (R,S)- o de preferencia (R)- o (S)-3-(dimetil-amino)-pirrolidin-1-carbonilo, (R,S)- o de preferencia (R)- o (S)-3-(dietil-amino)-pirrolidin-1-carbonilo, (R,S)- o de preferencia (R)- o (S)-3-[N-2-(dimetil-amino)-etil-amino]-pirrolidin-1-carbonilo, (R,S)- o de preferencia (R)- o (S)-3-[N-3-(dimetil-amino)-propil-amino]-pirrolidin-1-carbonilo, (R,S)- o de preferencia (R)- o (S)-3-[N-2-(dimetil-amino)-etil-N-metil-amino]-pirrolidin-1-carbonilo, o (R,S)- o de preferencia (R)- o (S)-3-[N-3-(dimetil-amino)-propil-N-metil-amino]-pirrolidin-1-carbonilo o (R,S)-, (R,S)- o de preferencia (R)- o (S)-pirrolidinil-pirrolidin-carbonilo, en especial (R,S)- o de preferencia (R)- o (S)-3-(pirrolidin-1-il)-pirrolidin-carbonilo, (R,S)- o de preferencia (R)- o (S)-[(amino, mono- o di-(alquilo de 1 a 7 átomos de carbono)-amino)-piperidinil]-pirrolidin-carbonilo, en especial (R,S)- o de preferencia (R)- o (S)-3-(4-dimetil-amino-piperidin-1-il)-pirrolidin-1-carbonilo, (R,S)- o de preferencia (R)- o (S)-[hidroxi-alquilo de 1 a 7 átomos de carbono, hidroxilo, amino o mono- o di-(alquilo de 1 a 7 átomos de carbono, alcanoílo de 1 a 7 átomos de carbono, alcoxilo de 1 a 7 átomos de carbono-carbonil)-amino]-pirrolidin-carbonilo, en especial (R,S)- o de preferencia (R)- o

(S)-3-hidroxi-pirrolidin-1-carbonilo, en especial (R,S)- o de preferencia (R)- o (S)-3-hidroxi-metil-pirrolidin-1-carbonilo, (R,S)- o de preferencia (R)- o (S)-3-amino-pirrolidin-1-carbonilo, (R,S)- o de preferencia (R)- o (S)-3-etil-amino-pirrolidin-1-carbonilo, (R,S)- o de preferencia (R)- o (S)-3-terbutoxi-carbonil-amino-pirrolidin-1-carbonilo, (R,S)- o de preferencia (R)- o (S)-3-(N-metil-N-acetil-amino)-pirrolidin-1-carbonilo, (R,S)- o de preferencia (R)- o (S)-(piperazinilo, alquilo de 1 a 7 átomos de carbono-piperazinilo, (hidroxi-alquilo de 1 a 7 átomos de carbono)-piperazinilo, morfolinilo, tiomorfolinilo, S-oxo-tiomorfolinilo o S,S-dioxo-tiomorfolinil)-pirrolidin-carbonilo, en especial (R,S)- o de preferencia (R)- o (S)-3-(4-metil-piperazino)-pirrolidin-1-carbonilo, (R,S)- o de preferencia (R)- o (S)-3-(4-(2-hidroxi-etil)-piperazino)-pirrolidin-1-carbonilo, (R,S)- o de preferencia (R)- o (S)-3-morfolino-pirrolidin-1-carbonilo o (R,S)- o de preferencia (R)- o (S)-3-dioxo-tiomorfolino-pirrolidin-1-carbonilo,

piperidinil-carbonilo, en especial piperidin-1-carbonilo (piperidin-1-il-C(=O)-), (hidroxilo, hidroxi-alquilo de 1 a 7 átomos de carbono, amino o mono- o di-(alquilo de 1 a 7 átomos de carbono)-amino)-piperidin-carbonilo, en especial 4-hidroxi-metil-piperidin-1-carbonilo o 4-dimetil-amino-piperidin-1-carbonilo, oxoimidazolidinil-piperidin-carbonilo, en especial 4-(2-oxo-imidazolidin-1-il)-piperidin-1-carbonilo, (fenil-oxoimidazolidinil)-piperidin-carbonilo, en especial 4-(3-fenil-2-oxo-imidazolidin-1-il)-piperidin-1-carbonilo, pirrolidinil- u oxo-pirrolidinil-piperidin-carbonilo, en especial 4-(pirrolidin-1-il)-

piperidin-1-carbonilo o 4-(2-oxo-pirrolidin-1-il)-piperidin-1-carbonilo, piperazinil- o N-(alquilo de 1 a 7 átomos de carbono)-piperazinil-piperidin-carbonilo, en especial 4-(4-metil-piperazin-1-il)-piperidin-1-carbonilo, (morfolinilo, tiomorfolinilo, S-oxo-tiomorfolinilo o S,S-dioxo-tiomorfolinil)-piperidin-carbonilo, en especial 4-morfolino-piperidin-1-carbonilo, (oxo-benzo-imidazolidinil)-piperidin-carbonilo, en especial (2-oxo-1,3-benzo-imidazolidin-1-il)-piperidin-carbonilo, piperazin-carbonilo, en especial piperazin-1-carbonilo, (alquilo de 1 a 7 átomos de carbono o hidroxi-alquilo de 1 a 7 átomos de carbono)-piperazin-carbonilo, en especial 4-metil-, 4-(2-hidroxi-etil)- o 4-(3-hidroxi-propil)-piperazin-1-carbonilo, oxopiperazin-carbonilo, en especial 2-oxo-piperazin-4-carbonilo, alcanoílo de 1 a 7 átomos de carbono-piperazin-carbonilo, en especial 1-acetil-piperazin-4-carbonilo, alquilo de 1 a 7 átomos de carbono-sulfonil-piperazin-carbonilo, en especial 4-metan-sulfonil-piperazin-1-carbonilo,

morfolin-carbonilo (morfolinil-C(=O)-), en especial morfolin-1-carbonilo, (tiomorfolin, S-oxo-tiomorfolin o S,S-dioxo-tiomorfolin)-carbonilo, en especial S,S-dioxo-tiomorfolin-1-carbonilo,

carbamoílo (sinónimo: amino-carbonilo, -C(=O)-NH_2),

N-mono- o N,N-di-(alquilo de 1 a 7 átomos de carbono)-carbamoílo, en especial N-metil-, N,N-dimetil-, N-etil- o N-terbutil-carbamoílo,

N-[(hidroxi- o alcoxilo de 1 a 7 átomos de carbono)-alquilo de 1 a 7 átomos de carbono]-carbamoílo, en especial N-(2-hidroxi-etil)-carbamoílo, N-(3-hidroxi-propil)-carbamoílo, N-(2-metoxi-

etil)-carbamoílo o N-(3-metoxi-propil)-carbamoílo, N-[(amino, mono- o di-(alquilo de 1 a 7 átomos de carbono)-amino)-alquilo de 1 a 7 átomos de carbono]-carbamoílo, en especial N-(2-amino-etil)-carbamoílo, N-(2-(metil-amino)-etil-carbamoílo, 2-(N,N-di-(metil)-amino)-etil-carbamoílo, 3-(N,N-di-(metil)-amino)-propil-carbamoílo, N-[2-(N,N-di-(metil)-amino)-etil]-N-metil-carbamoílo, N-[3-(N,N-di-(metil)-amino)-propil]-N-metil-carbamoílo, 2-(N,N-di-(etil)-amino)-etil-carbamoílo, 3-(N,N-di-(etil)-amino)-propil-carbamoílo, N-[2-(N,N-di-(etil)-amino)-etil]-N-metil-carbamoílo, N-[3-(N,N-di-(etil)-amino)-propil]-N-metil-carbamoílo, N-fenil-carbamoílo, N-(alcoxilo de 1 a 7 átomos de carbono-fenil)-carbamoílo, en especial N-(metoxi-fenil)-carbamoílo, [(pirrolidinilo, piperidinilo, piperazinilo o 1-(alquilo de 1 a 7 átomos de carbono)-piperazinil)-fenil]-carbamoílo, en especial N-[3-(piperazin-4-ilo o 1-metil-piperazin-4-il)-fenil]-carbamoílo, N-(fenil-alquilo de 1 a 7 átomos de carbono)-carbamoílo, en especial N-bencil-carbamoílo, N-(oxoimidazolidinil-alquilo de 1 a 7 átomos de carbono)-carbamoílo, en especial N-[2-(2-oxoimidazol-1-il)-etil]-carbamoílo, N-(pirrolidinil-alquilo de 1 a 7 átomos de carbono)-carbamoílo, en especial N-(pirrolidino-metil)-carbamoílo, N-(2-pirrolidino-etil)-carbamoílo o N-(3-pirrolidino-propil)-carbamoílo, N-(oxo-pirrolidinil-alquilo de 1 a 7 átomos de carbono)-carbamoílo, en especial N-(2-oxo-pirrolidino-metil)-carbamoílo, N-[2-(2-oxo-pirrolidino)-etil]-carbamoílo o N-[3-(2-oxo-pirrolidino)-propil]-carbamoílo,

N-piperidinil-carbamoílo, en especial N-piperidin-4-il-carbamoílo, N-[(alquilo de 1 a 7 átomos de carbono)-piperidinil]-

carbamoílo, en especial N-(1-metil-piperidin-4-il)-carbamoílo, N-[(hidroxi-alquilo de 1 a 7 átomos de carbono)-piperidinil]-carbamoílo, en especial N-[1-(2-hidroxi-etil)-piperidin-4-il]-carbamoílo, N-[N-(alcoxilo de 1 a 7 átomos de carbono-carbonil)-piperidinil]-carbamoílo, en especial N-[1-(terbutoxi-carbonil)-piperidin-4-il]-carbamoílo, N-(piperidinil-alquilo de 1 a 7 átomos de carbono)-carbamoílo, en especial N-(piperidin-1-il-metil)-, N-[2-(piperidin-1-il)-etil]- o N-[3-(piperidin-1-il)-propil]-carbamoílo, N-(azepan-alquilo de 1 a 7 átomos de carbono)-carbamoílo, en especial N-(azepan-1-il-metil)-, N-[2-(piperidin-1-il)-etil]- o N-[3-(piperidin-1-il)-propil]-carbamoílo, N-(piperazinil-alquilo de 1 a 7 átomos de carbono)-carbamoílo, en especial N-(piperazin-1-il-metil)-, N-[2-(piperazin-1-il)-etil]- o N-[3-(piperazin-1-il)-propil]-carbamoílo, N-(oxopiperazinil-alquilo de 1 a 7 átomos de carbono)-carbamoílo, en especial N-[(2-oxo-piperazin-4-il)-metil]-, N-[2-(2-oxo-piperazin-4-il)-etil]- o N-[3-(2-oxo-piperazin-4-il)-propil]-carbamoílo, N-((alquilo de 1 a 7 átomos de carbono)-piperazinil-alquilo de 1 a 7 átomos de carbono)-carbamoílo, en especial N-[(1-metil-piperazin-4-il)-metil]-, N-[2-(1-metil-piperazin-4-il)-etil]- o N-[3-(1-metil-piperazin-1-il)-propil]-carbamoílo, N-(1-(hidroxi-alquilo de 1 a 7 átomos de carbono)-piperazinil-alquilo de 1 a 7 átomos de carbono)-carbamoílo, en especial N-[(1-(2-hidroxi-etil)-piperazin-4-il)-metil]-, N-[2-(1-(2-hidroxi-etil)-piperazin-4-il)-etil]- o N-[3-(1-(2-hidroxi-etil)-piperazin-1-il)-propil]-carbamoílo, N-(1-(alcanoílo de 1 a 7 átomos de carbono)-piperazinil-alquilo de 1 a 7 átomos de carbono)-carbamoílo, en especial N-[(1-acetil-piperazin-4-

il)-metil]-, N-[2-(1-acetil-piperazin-4-il)-etil]- o N-[3-(1-acetil-piperazin-1-il)-propil]-carbamoílo, N-(1-(alcoxilo de 1 a 7 átomos de carbono-carbonil)-piperazinil-alquilo de 1 a 7 átomos de carbono)-carbamoílo, en especial N-[(1-(terbutoxi-carbonil)-piperazin-4-il)-metil]-, N-[2-(1-(terbutoxi-carbonil)-piperazin-4-il)-etil]- o N-[3-(1-(terbutoxi-carbonil)-piperazin-1-il)-propil]-carbamoílo, N-[(morfolinilo, tiomorfolinilo, S-oxo-tiomorfolinilo o S,S-dioxo-tiomorfolinil)-alquilo de 1 a 7 átomos de carbono]-carbamoílo, en especial N-morfolino-metil-, N-(2-morfolino-etil)-, N-(3-morfolino-propil)-carbamoílo, N-(S,S-dioxo-tiomorfolino)-metil-, N-[2-(S,S-dioxo-tiomorfolino)-etil]- o N-[3-(S,S-dioxo-tiomorfolino)-propil]-carbamoílo, N-[dioxo-1H, 3H-isoindolil)-alquilo de 1 a 7 átomos de carbono)-carbamoílo, en especial N-(1,7-dioxo-1H, 7H-isoindolin-2-il-metil)-, N-[2-(1,7-dioxo-1H, 7H-isoindolin-2-il)-etil]- o N-[3-(1,7-dioxo-1H, 7H-isoindolin-2-il)-propil]-carbamoílo,

triazolilo o tetrazolilo, en especial tetrazol-5-ilo,

o ciano,

R^4 es hidrógeno, alquilo de 1 a 7 átomos de carbono, en especial metilo, halógeno, en especial bromo o cloro, o piridilo, en especial piridin-3-, -4- ó -2-ilo,

R^A es hidrógeno o alquilo de 1 a 7 átomos de carbono, de preferencia hidrógeno;

X es hidrógeno, alquilo de 1 a 7 átomos de carbono, halógeno o ciano, en especial hidrógeno o flúor, e

Y es alquilo de 1 a 7 átomos de carbono, halógeno o

ciano, en especial metilo, flúor, cloro, bromo o ciano,

y/o un tautómero, un N-óxido y/o una sal farmacéuticamente aceptable del mismo.

6. Un compuesto de la fórmula I de acuerdo con la reivindicación 1 o con la reivindicación 2, en donde:

R^1 es halo-bencilo, en especial bromo-bencilo, más especialmente 4-bromo-bencilo, cloro-bencilo, más especialmente 4-cloro-bencilo, o fluoro-bencilo, más especialmente 4-fluoro-bencilo,

R^2 es fenilo,

R^3 es hidroxi-alquilo de 1 a 7 átomos de carbono, en especial hidroxi-metilo, carboxilo, (R,S)- o de preferencia (R)- o (S)-[amino o N'-mono- o N',N'-di-(alquilo de 1 a 7 átomos de carbono y/o {amino o mono- o di-alquilo de 1 a 7 átomos de carbono-amino}-alquilo de 1 a 7 átomos de carbono)-amino]-pirrolidin-carbonilo o aquiral, en especial (R,S)- o de preferencia (R)- o (S)-3-[N-2-(dimetil-amino)-etil-N-metil-amino]-pirrolidin-1-carbonilo, amino o mono- o di-(alquilo de 1 a 7 átomos de carbono)-amino-piperidin-carbonilo, en especial 4-dimetil-amino-piperidin-1-carbonilo, carbamoílo, N-alquilo de 1 a 7 átomos de carbono-carbamoílo, en especial N-metil- o N-etil-carbamoílo, N-((alquilo de 1 a 7 átomos de carbono)-piperazinil-alquilo de 1 a 7 átomos de carbono)-carbamoílo, en especial N-[(1-metil-piperazin-4-il)-metil]-, N-[2-(1-metil-piperazin-4-il)-etil]- o N-[3-(1-metil-piperazin-1-il)-propil]-carbamoílo, o N-[(morfolinil o tiomorfolinil)-alquilo de 1 a 7 átomos de carbono]-carbamoílo, en especial N-morfolino-metil-, N-(2-morfolino-etil)-, N-(3-morfolino-

propil)-carbamoílo,

R^4 es hidrógeno o alquilo de 1 a 7 átomos de carbono, en especial metilo, o halógeno, en especial bromo o cloro, más preferiblemente hidrógeno,

R^A es hidrógeno;

X es halógeno o flúor, e

Y es halógeno o ciano, en especial cloro o ciano;

y/o un tautómero, un N-óxido y/o una sal farmacéuticamente aceptable del mismo,.

7. Un compuesto de la fórmula I de acuerdo con la reivindicación 1 o con la reivindicación 2, seleccionado a partir del grupo de compuestos con los siguientes nombres:

6-cloro-3-[3-(4-cloro-bencil)-5-fenil-3H-imidazol-4-il]-1H-indol;

(2-morfolin-4-il-etil)-amida del ácido 6-cloro-3-[3-(4-cloro-bencil)-5-fenil-3H-imidazol-4-il]-1H-indol-2-carboxílico;

ácido 6-cloro-3-[3-(4-cloro-bencil)-5-fenil-3H-imidazol-4-il]-1H-indol-2-carboxílico;

etil-éster del ácido 6-cloro-3-[3-(4-cloro-bencil)-5-fenil-3H-imidazol-4-il]-1H-indol-2-carboxílico;

[2-(1,3-dioxo-1,3-dihidro-isoindol-2-il)-etil]-amida del ácido 6-cloro-3-[3-(4-cloro-bencil)-5-fenil-3H-imidazol-4-il]-1H-indol-2-carboxílico;

terbutil-éster del ácido 4-[2-({6-cloro-3-[3-(4-cloro-bencil)-

5-fenil-3H-imidazol-4-il]-1H-indol-2-carbonil}-amino)-etil]-piperazin-1-carboxílico;

terbutil-éster del ácido 4-[3-({6-cloro-3-[3-(4-cloro-bencil)-5-fenil-3H-imidazol-4-il]-1H-indol-2-carbonil}-amino)-propil]-piperazin-1-carboxílico;

terbutil-éster del ácido 4-({6-cloro-3-[3-(4-cloro-bencil)-5-fenil-3H-imidazol-4-il]-1H-indol-2-carbonil}-amino)-piperidin-1-carboxílico;

[2-(terbutil-dimetil-silaniloxi)-etil]-amida del ácido 6-cloro-3-[3-(4-cloro-bencil)-5-fenil-3H-imidazol-4-il]-1H-indol-2-carboxílico;

[3-(terbutil-dimetil-silaniloxi)-propil]-amida del ácido 6-cloro-3-[3-(4-cloro-bencil)-5-fenil-3H-imidazol-4-il]-1H-indol-2-carboxílico;

terbutil-éster del ácido ((S)-1-{6-cloro-3-[3-(4-cloro-bencil)-5-fenil-3H-imidazol-4-il]-1H-indol-2-carbonil}-pirrolidin-3-il)-carbámico;

ácido 6-cloro-3-[3-(4-cloro-bencil)-5-fenil-3H-imidazol-4-il]-5-fluoro-1H-indol-2-carboxílico;

metil-éster del ácido 6-cloro-3-[3-(4-cloro-bencil)-5-fenil-3H-imidazol-4-il]-5-fluoro-1H-indol-2-carboxílico;

terbutil-éster del ácido ((R)-1-{6-cloro-3-[3-(4-cloro-bencil)-5-fenil-3H-imidazol-4-il]-1H-indol-2-carbonil}-pirrolidin-3-il)-carbámico;

ácido 3-[3-(4-bromo-bencil)-5-fenil-3H-imidazol-4-il]-6-cloro-1H-indol-2-carboxílico;

etil-éster del ácido 3-[3-(4-bromo-bencil)-5-fenil-3H-imidazol-4-il]-6-cloro-1H-indol-2-carboxílico;

3-[3-(2-terbutoxi-4-cloro-bencil)-5-fenil-3H-imidazol-4-il]-6-cloro-5-fluoro-1H-indol;

ácido 3-[3-(4-cloro-bencil)-5-fenil-3H-imidazol-4-il]-6-ciano-1H-indol-2-carboxílico;

metil-éster del ácido 3-[3-(4-cloro-bencil)-5-fenil-3H-imidazol-4-il]-6-ciano-1H-indol-2-carboxílico;

ácido 6-cloro-3-{3-[(S)-1-(4-cloro-fenil)-etil]-5-fenil-3H-imidazol-4-il}-1H-indol-2-carboxílico;

etil-éster del ácido 6-cloro-3-{3-[(S)-1-(4-cloro-fenil)-etil]-5-fenil-3H-imidazol-4-il}-1H-indol-2-carboxílico;

amida del ácido 6-cloro-3-[3-(3,3-dimetil-butil)-5-fenil-3H-imidazol-4-il]-1H-indol-2-carboxílico;

etil-éster del ácido 6-cloro-3-[3-(3,3-dimetil-butil)-5-fenil-3H-imidazol-4-il]-1H-indol-2-carboxílico;

amida del ácido 6-cloro-3-[3-(3,3-dimetil-butil)-5-fenil-3H-imidazol-4-il]-1H-indol-2-carboxílico;

6-cloro-3-[3-(4-cloro-bencil)-5-fenil-3H-imidazol-4-il]-2-(1H-tetrazol-5-il)-1H-indol;

6-cloro-3-[3-(4-cloro-bencil)-5-fenil-3H-imidazol-4-il]-1H-indol-2-carbonitrilo;

{6-cloro-3-[3-(4-cloro-bencil)-5-fenil-3H-imidazol-4-il]-1H-indol-2-il}-metanol;

{6-cloro-3-[3-(4-cloro-bencil)-5-fenil-3H-imidazol-4-il]-1H-

indol-2-il-metil}-(2-morfolin-4-il-etil)-amina;

3-[1-(4-cloro-bencil)-5-(6-cloro-5-fluoro-1H-indol-3-il)-1H-imidazol-4-il]-fenol;

6-cloro-3-[3-(4-cloro-bencil)-5-(3-metoxi-fenil)-3H-imidazol-4-il]-5-fluoro-1H-indol;

{6-cloro-3-[3-(4-cloro-bencil)-5-(3-hidroxi-fenil)-3H-imidazol-4-il]-1H-indol-2-il}-((S)-3-dimetil-amino-pirrolidin-1-il)-metanona;

{6-cloro-3-[3-(4-cloro-bencil)-5-(3-metoxi-fenil)-3H-imidazol-4-il]-1H-indol-2-il}-((S)-3-dimetil-amino-pirrolidin-1-il)-metanona;

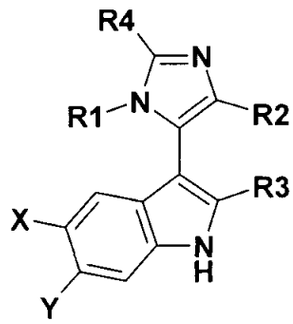
6-cloro-3-[3-(4-cloro-bencil)-2-metil-5-fenil-3H-imidazol-4-il]-1H-indol;

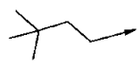
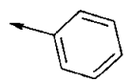
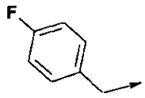
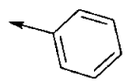
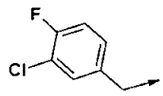
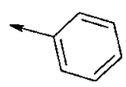
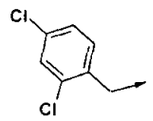
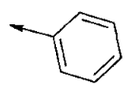
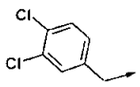
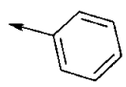
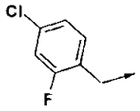
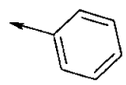
etil-éster del ácido 6-bromo-3-[2-cloro-3-(4-cloro-bencil)-5-fenil-3H-imidazol-4-il]-1H-indol-2-carboxílico; y

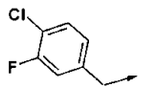
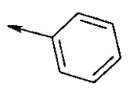
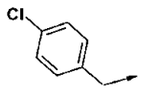
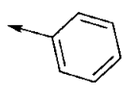
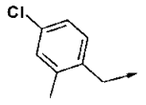
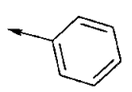
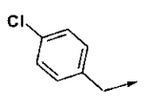
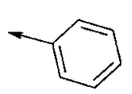
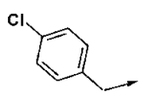
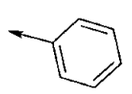
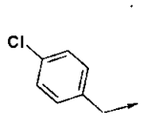
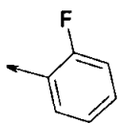
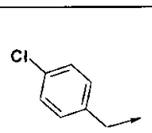
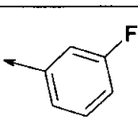
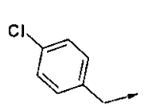
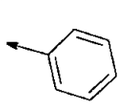
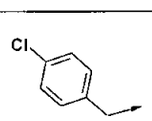
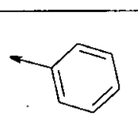
etil-éster del ácido 6-cloro-3-[2-cloro-3-(4-cloro-bencil)-5-fenil-3H-imidazol-4-il]-1H-indol-2-carboxílico;

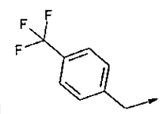
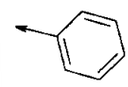
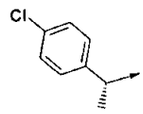
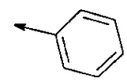
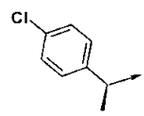
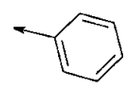
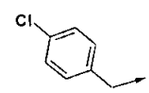
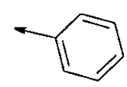
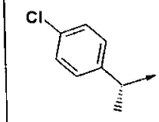
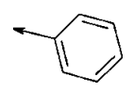
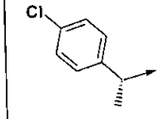
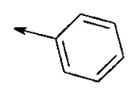
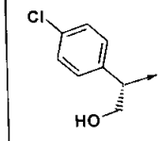
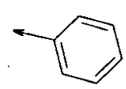
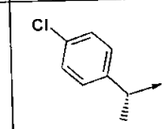
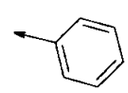
y/o un tautómero, un N-óxido y/o una sal farmacéuticamente aceptable del mismo.

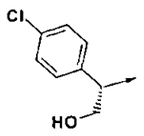
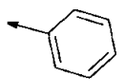
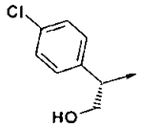
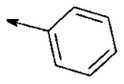
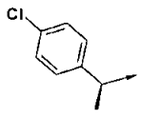
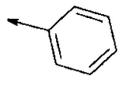
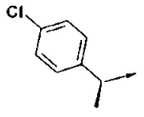
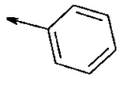
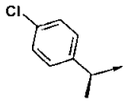
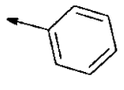
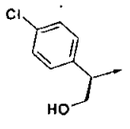
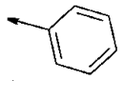
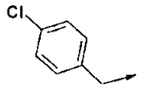
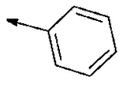
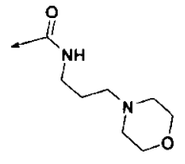
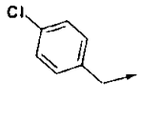
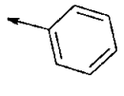
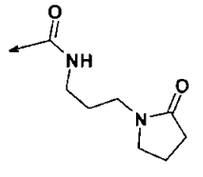
8. Un compuesto de la fórmula I de acuerdo con la reivindicación 1 o con la reivindicación 2, seleccionado a partir del grupo de compuestos dados en las siguientes tablas y mediante la siguiente fórmula:

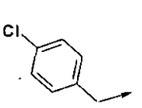
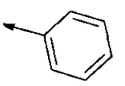
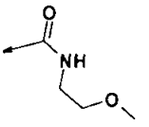
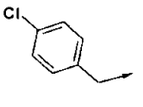
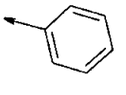
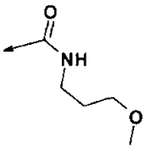
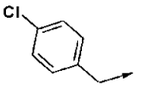
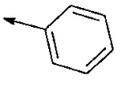
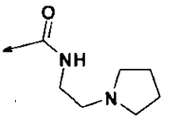
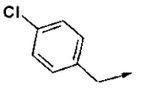
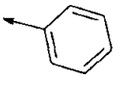
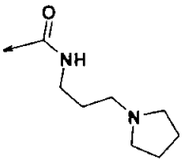
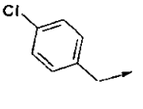
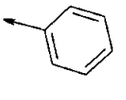
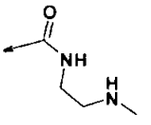
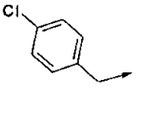
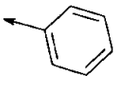
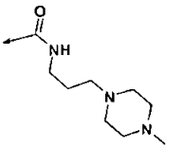
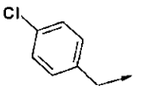
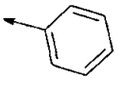
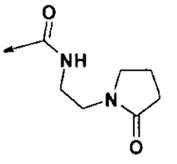


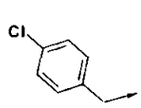
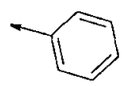
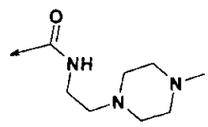
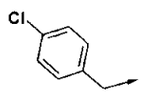
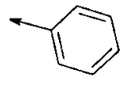
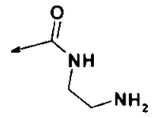
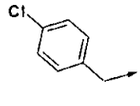
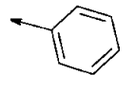
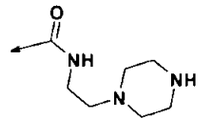
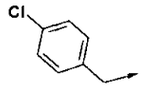
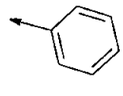
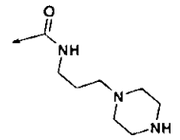
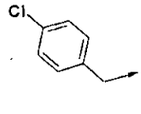
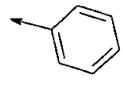
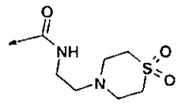
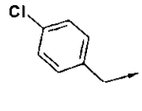
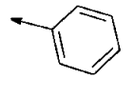
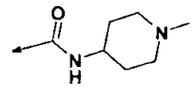
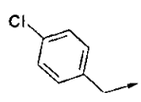
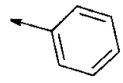
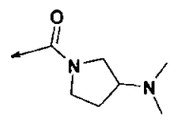
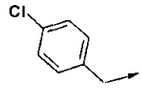
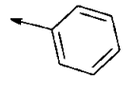
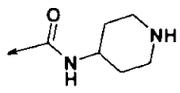
Compuesto	X e Y	R^1	R^2	R^3	R^4
AA	X=H Y=Cl			H	H
AB	X=H Y=Cl			H	H
AC	X=H Y=Cl			H	H
AD	X=H Y=Cl			H	H
AE	X=H Y=Cl			H	H
AF	X=H Y=Cl			H	H

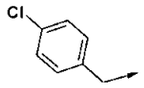
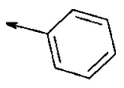
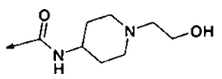
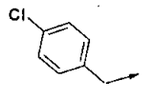
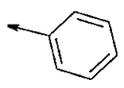
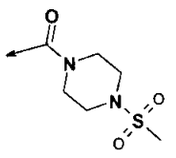
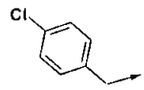
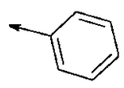
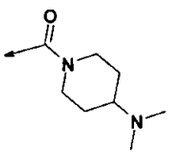
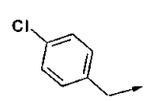
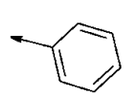
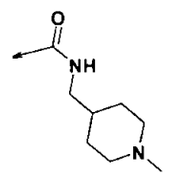
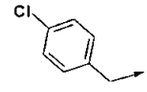
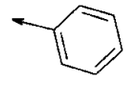
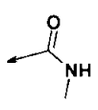
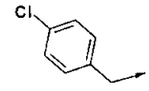
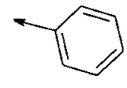
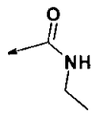
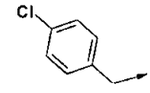
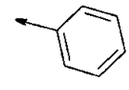
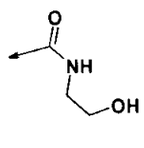
Compuesto	X e Y	R^1	R^2	R^3	R^4
AG	X=H Y=Cl			H	H
AH	X=F Y=Cl			H	H
AI	X=H Y=Cl			H	H
AJ	X=H Y=Br			H	H
AK	X=H Y=Me			H	H
AL	X=H Y=Cl			H	H
AM	X=H Y=Cl			H	H
AO	X=H Y=CN			H	H
AP	X=F Y=F			H	H

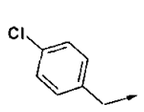
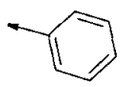
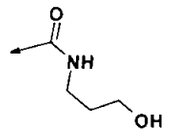
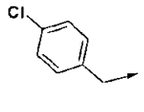
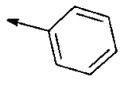
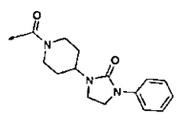
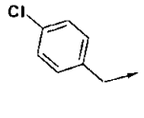
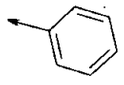
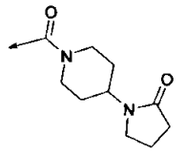
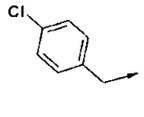
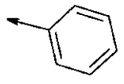
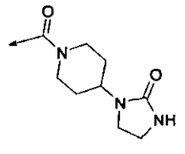
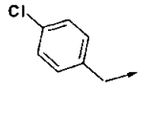
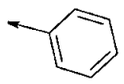
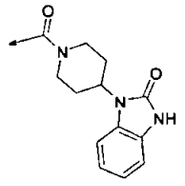
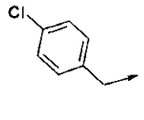
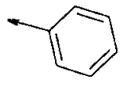
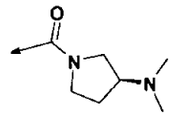
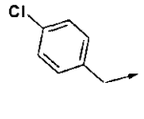
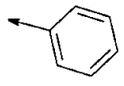
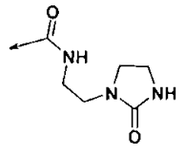
Compuesto	X e Y	R^1	R^2	R^3	R^4
AQ	X=H Y=Cl			H	H
AR	X=H Y=Cl			H	H
AS	X=H Y=Cl			H	H
AT	X=H Y=Cl			H	H
AU	X=F Y=Cl			H	H
AV	X=F Y=F			H	H
AX	X=H Y=Cl			H	H
AY	X=H Y=CN			H	H

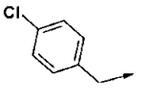
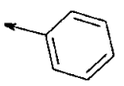
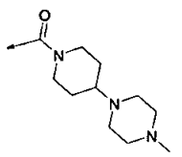
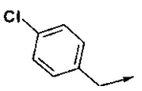
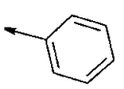
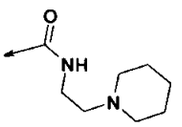
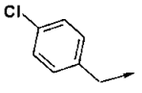
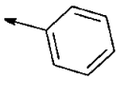
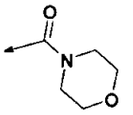
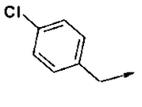
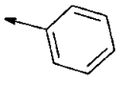
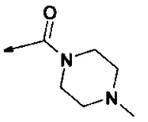
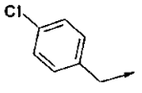
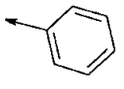
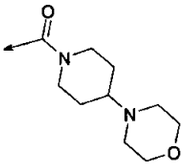
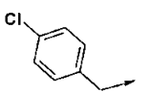
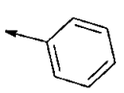
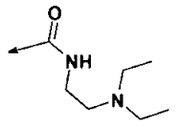
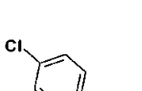
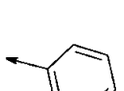
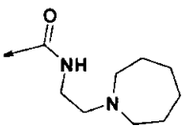
Compuesto	X e Y	R^1	R^2	R^3	R^4
AZ	X=F Y=Cl			H	H
BA	X=H Y=CN			H	H
BB	X=F Y=Cl			H	H
BC	X=H Y=CN			H	H
BD	X=F Y=F			H	H
BE	X=F Y=Cl			H	H
BF	X=H Y=Cl				H
BG	X=H Y=Cl				H

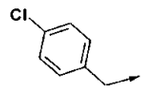
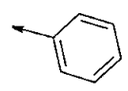
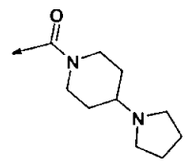
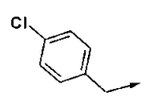
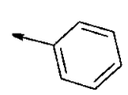
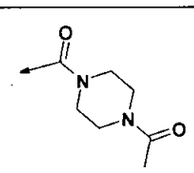
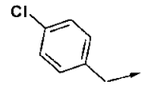
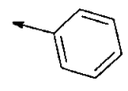
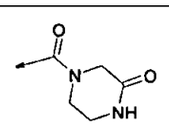
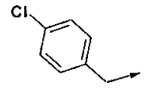
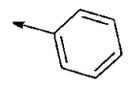
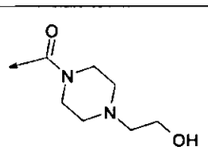
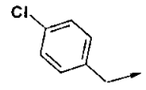
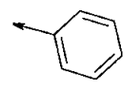
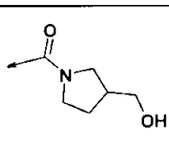
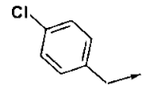
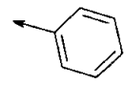
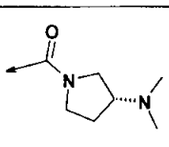
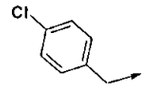
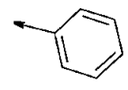
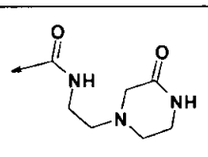
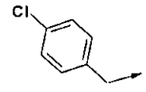
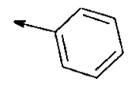
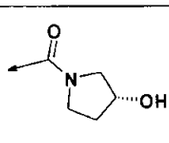
Compuesto	X e Y	R^1	R^2	R^3	R^4
BH	X=H Y=Cl				H
BI	X=H Y=Cl				H
BJ	X=H Y=Cl				H
BK	X=H Y=Cl				H
BL	X=H Y=Cl				H
BM	X=H Y=Cl				H
BN	X=H Y=Cl				H

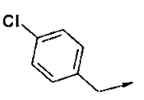
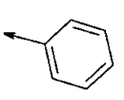
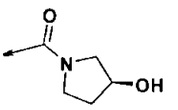
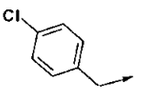
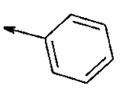
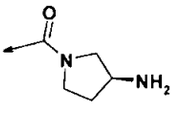
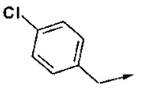
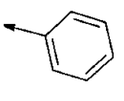
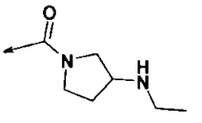
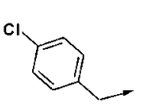
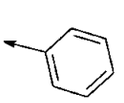
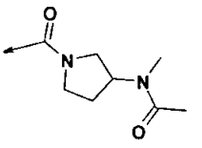
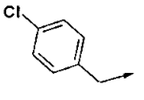
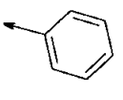
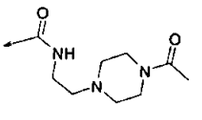
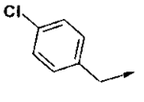
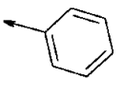
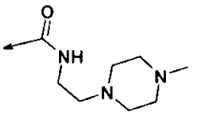
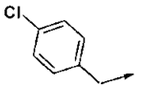
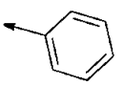
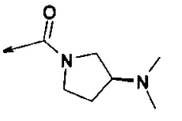
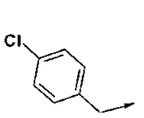
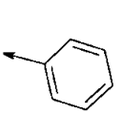
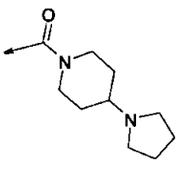
Compuesto	X e Y	R^1	R^2	R^3	R^4
BO	X=H Y=Cl				H
BP	X=H Y=Cl				H
BQ	X=H Y=Cl				H
BR	X=H Y=Cl				H
BS	X=H Y=Cl				H
BT	X=H Y=Cl				H
BU	X=H Y=Cl				H
BV	X=H Y=Cl				H

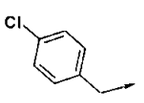
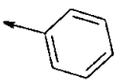
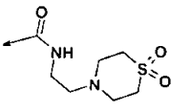
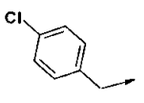
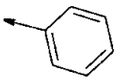
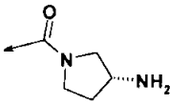
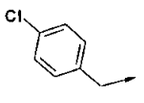
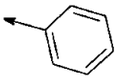
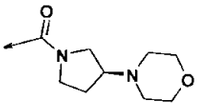
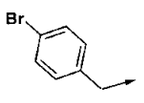
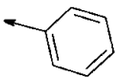
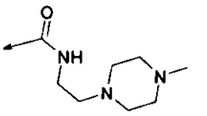
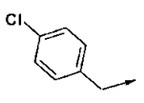
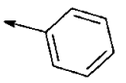
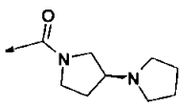
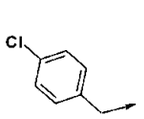
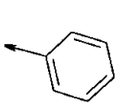
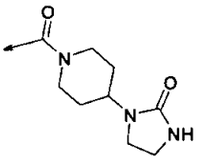
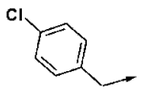
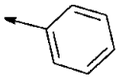
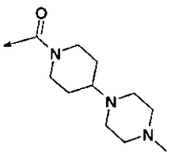
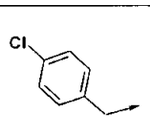
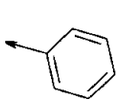
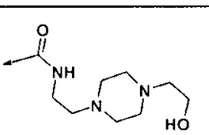
Compuesto	X e Y	R^1	R^2	R^3	R^4
BX	X=H Y=Cl				H
BY	X=H Y=Cl				H
BZ	X=H Y=Cl				H
CA	X=H Y=Cl				H
CB	X=H Y=Cl				H
CC	X=H Y=Cl				H
CD	X=H Y=Cl				H

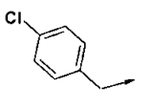
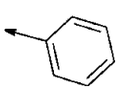
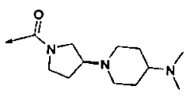
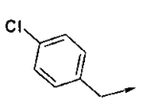
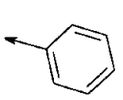
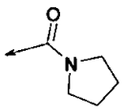
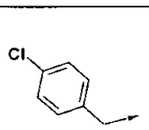
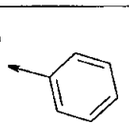
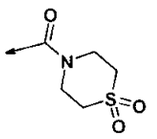
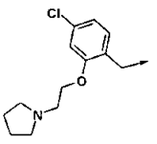
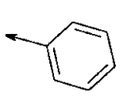
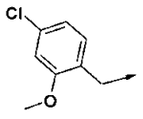
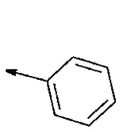
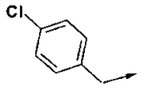
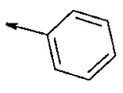
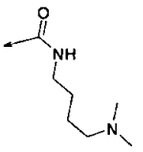
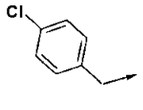
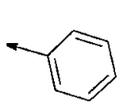
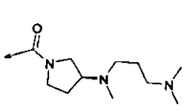
Compuesto	X e Y	R^1	R^2	R^3	R^4
CE	X=H Y=Cl				H
CF	X=H Y=Cl				H
CG	X=H Y=Cl				H
CH	X=H Y=Cl				H
CI	X=H Y=Cl				H
CJ	X=H Y=Cl				H
CK	X=H Y=Cl				H

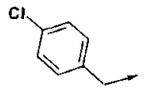
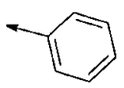
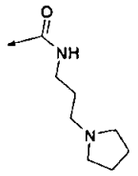
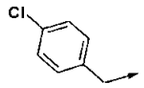
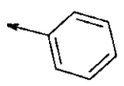
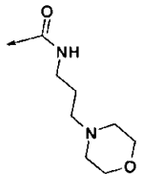
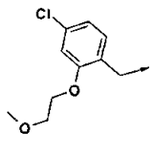
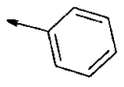
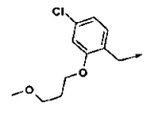
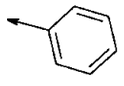
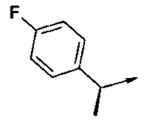
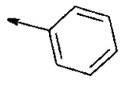
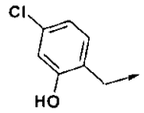
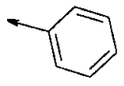
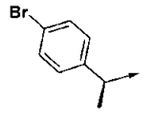
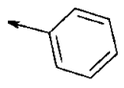
Compuesto	X e Y	R^1	R^2	R^3	R^4
CL	X=H Y=Cl				H
CM	X=H Y=Cl				H
CN	X=H Y=Cl				H
CO	X=H Y=Cl				H
CP	X=H Y=Cl				H
CQ	X=H Y=Cl				H
CR	X=H Y=Cl				H

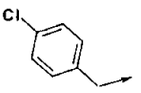
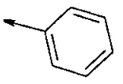
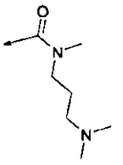
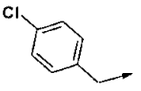
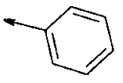
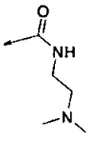
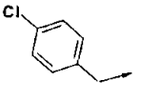
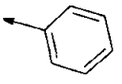
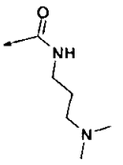
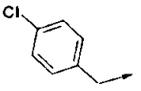
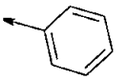
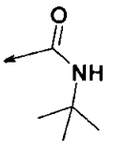
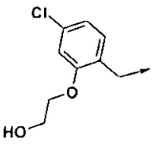
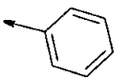
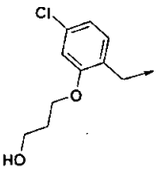
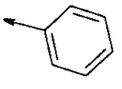
Compuesto	X e Y	R^1	R^2	R^3	R^4
CS	X=H Y=Cl				H
CT	X=H Y=Cl				H
CU	X=H Y=Cl				H
CV	X=H Y=Cl				H
CW	X=H Y=Cl				H
CX	X=H Y=Cl				H
CY	X=H Y=Cl				H
CZ	X=H Y=Cl				H

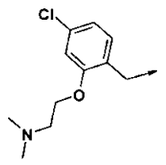
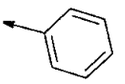
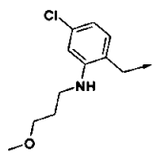
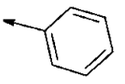
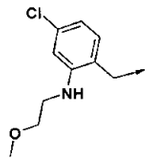
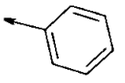
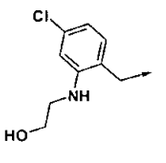
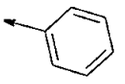
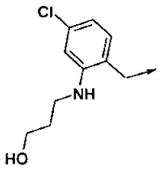
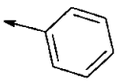
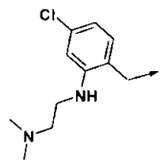
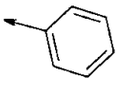
Compuesto	X e Y	R^1	R^2	R^3	R^4
DA	X=H Y=Cl				H
DB	X=H Y=Cl				H
DC	X=H Y=Cl				H
DD	X=H Y=Cl				H
DE	X=H Y=Cl				H
DF	X=F Y=Cl				H
DG	X=F Y=Cl				H
DH	X=F Y=Cl				H

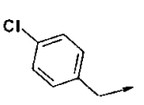
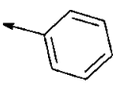
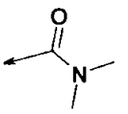
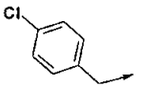
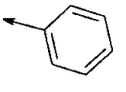
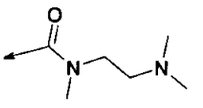
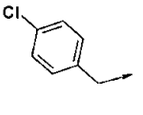
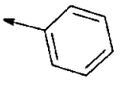
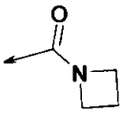
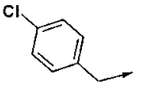
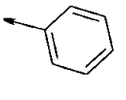
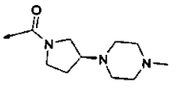
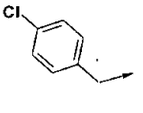
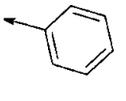
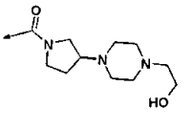
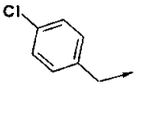
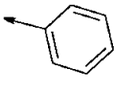
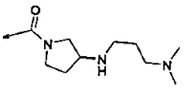
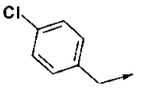
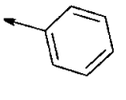
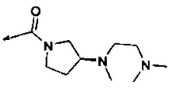
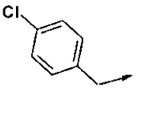
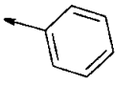
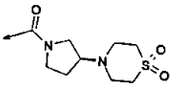
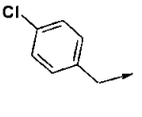
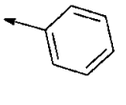
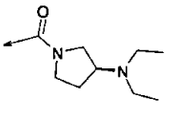
Compuesto	X e Y	R^1	R^2	R^3	R^4
DI	X=F Y=Cl				H
DJ	X=H Y=Cl				H
DK	X=H Y=Cl				H
DL	X=H Y=Cl				H
DM	X=H Y=Cl				H
DN	X=F Y=Cl				H
DO	X=F Y=Cl				H
DP	X=H Y=Cl				H

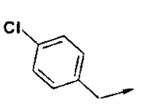
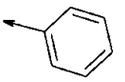
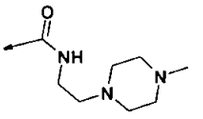
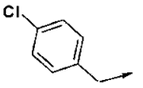
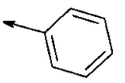
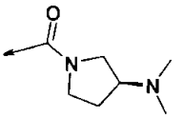
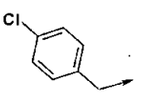
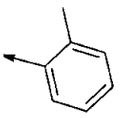
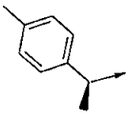
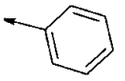
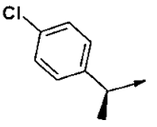
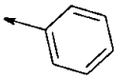
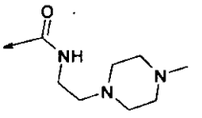
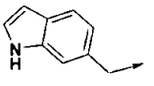
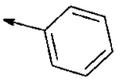
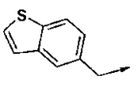
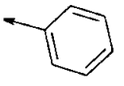
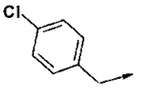
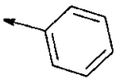
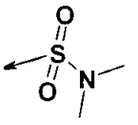
Compuesto	X e Y	R^1	R^2	R^3	R^4
DQ	X=H Y=Cl				H
DR	X=H Y=Cl				H
DS	X=H Y=Cl				H
DT	X=F Y=Cl			H	H
DU	X=F Y=Cl			H	H
DV	X=H Y=Cl				H
DW	X=H Y=Cl				H

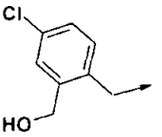
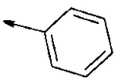
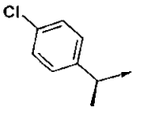
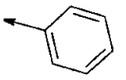
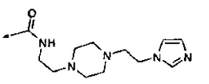
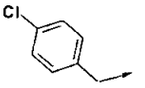
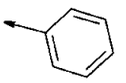
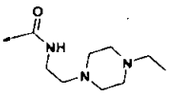
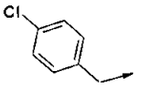
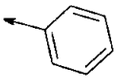
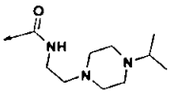
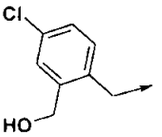
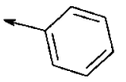
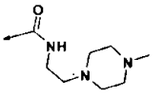
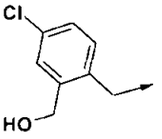
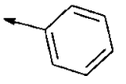
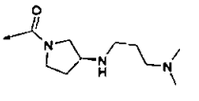
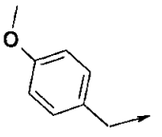
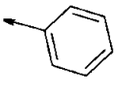
Compuesto	X e Y	R^1	R^2	R^3	R^4
DX	X=F Y=Cl				H
DY	X=F Y=Cl				H
DZ	X=F Y=Cl			H	H
EA	X=F Y=Cl			H	H
EB	X=F Y=Cl			H	H
EC	X=F Y=Cl			H	H
ED	X=F Y=Cl			H	H

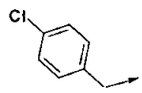
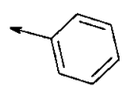
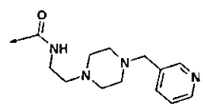
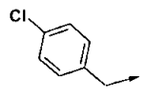
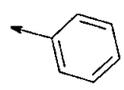
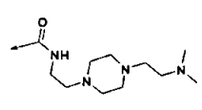
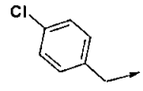
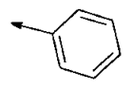
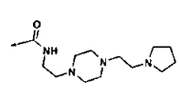
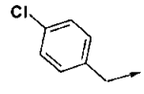
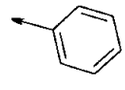
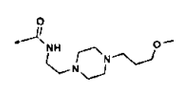
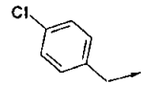
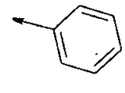
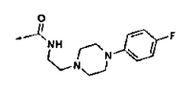
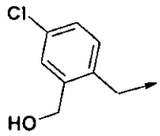
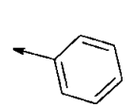
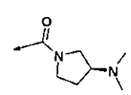
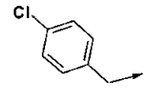
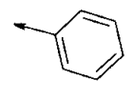
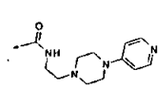
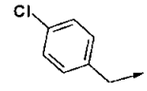
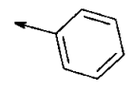
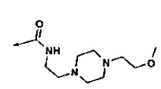
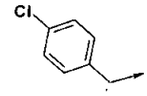
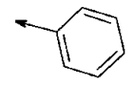
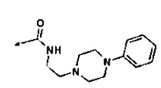
Compuesto	X e Y	R^1	R^2	R^3	R^4
EF	X=H Y=Cl				H
EG	X=H Y=Cl				H
EH	X=H Y=Cl				H
EI	X=H Y=Cl				H
EJ	X=F Y=Cl			H	H
EK	X=F Y=Cl			H	H

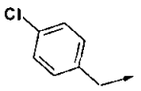
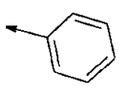
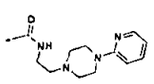
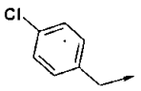
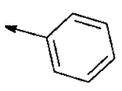
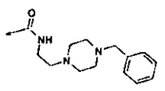
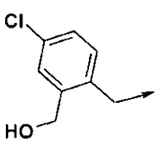
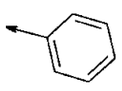
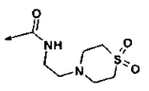
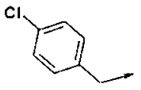
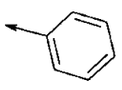
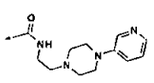
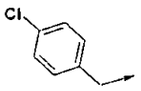
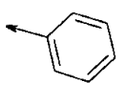
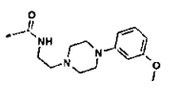
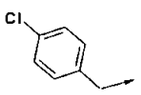
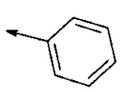
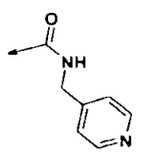
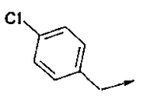
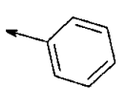
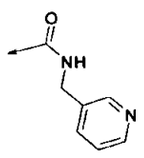
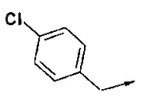
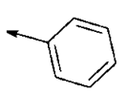
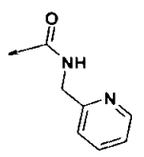
Compuesto	X e Y	R^1	R^2	R^3	R^4
EL	X=F Y=Cl			H	H
EM	X=F Y=Cl			H	H
EN	X=F Y=Cl			H	H
EO	X=F Y=Cl			H	H
EP	X=F Y=Cl			H	H
EQ	X=F Y=Cl			H	H

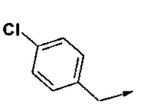
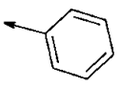
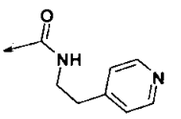
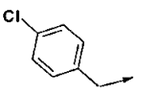
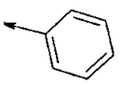
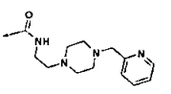
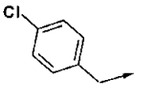
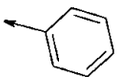
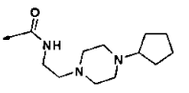
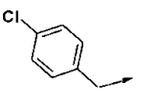
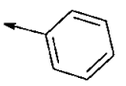
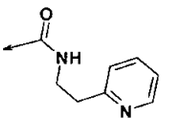
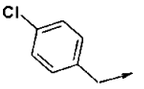
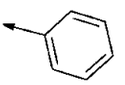
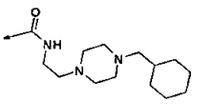
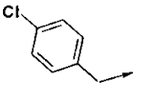
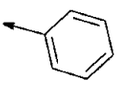
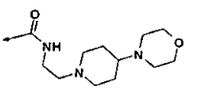
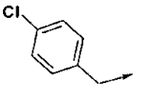
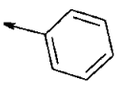
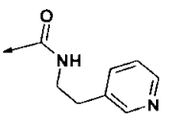
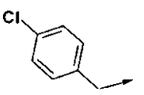
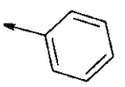
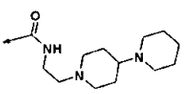
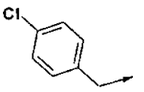
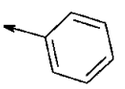
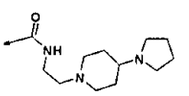
Compuesto	X e Y	R^1	R^2	R^3	R^4
ER	X=H Y=Cl				H
ES	X=H Y=Cl				H
ET	X=H Y=Cl				H
EU	X=H Y=Cl				H
EV	X=H Y=Cl				H
EW	X=H Y=Cl				H
EX	X=H Y=Cl				H
EY	X=H Y=Cl				H
EZ	X=H Y=Cl				H

Compuesto	X e Y	R^1	R^2	R^3	R^4
FA	X=H Y=CN				H
FB	X=H Y=CN				H
FC	X=F Y=Cl			H	H
FD	X=F Y=Cl			H	H
FE	X=H Y=Cl				H
FF	X=F Y=Cl			H	H
FG	X=F Y=Cl			H	H
FH	X=H Y=Cl				H

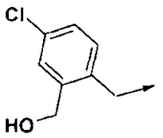
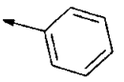
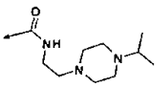
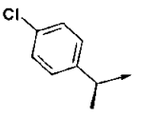
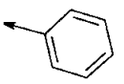
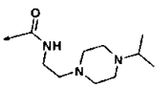
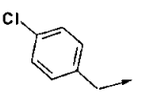
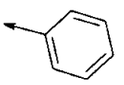
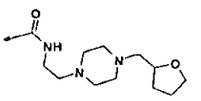
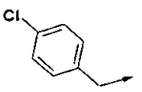
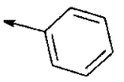
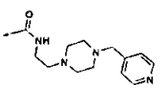
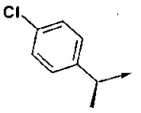
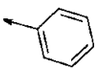
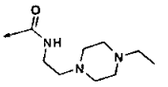
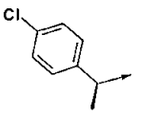
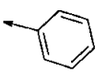
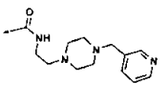
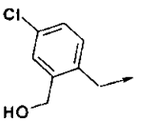
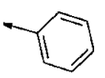
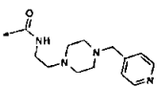
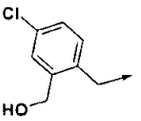
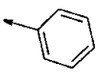
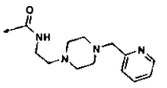
Compuesto	X e Y	R^1	R^2	R^3	R^4
FI	X=F Y=Cl			H	H
FJ	X=H Y=Cl				H
FK	X=H Y=Cl				H
FL	X=H Y=Cl				H
FM	X=H Y=Cl				H
FN	X=H Y=Cl				H
FO	X=F Y=Cl			H	H

Compuesto	X e Y	R^1	R^2	R^3	R^4
FP	X=H Y=Cl				H
FQ	X=H Y=Cl				H
FR	X=H Y=Cl				H
FS	X=H Y=Cl				H
FT	X=H Y=Cl				H
FU	X=H Y=Cl				H
FV	X=H Y=Cl				H
FW	X=H Y=Cl				H
FX	X=H Y=Cl				H

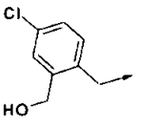
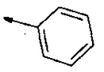
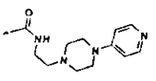
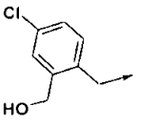
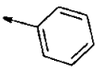
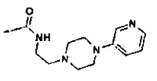
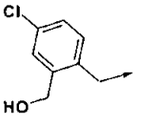
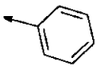
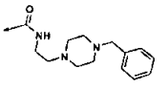
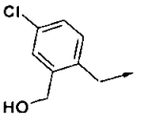
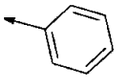
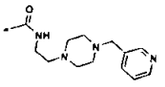
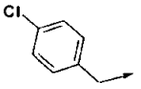
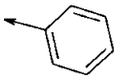
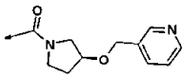
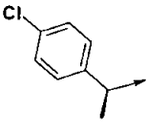
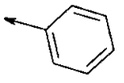
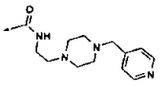
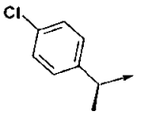
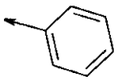
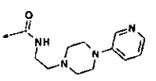
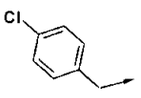
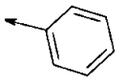
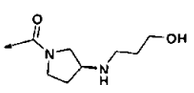
Compuesto	X e Y	R^1	R^2	R^3	R^4
FY	X=H Y=Cl				H
FZ	X=H Y=Cl				H
GA	X=H Y=Cl				H
GB	X=H Y=Cl				H
GC	X=H Y=Cl				H
GD	X=H Y=Cl				H
GE	X=H Y=Cl				H
GF	X=H Y=Cl				H

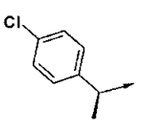
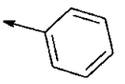
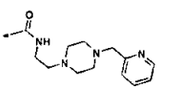
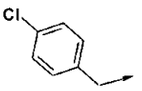
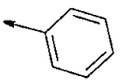
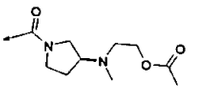
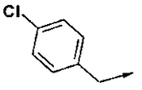
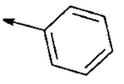
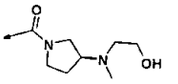
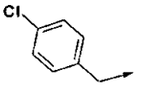
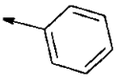
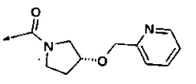
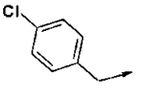
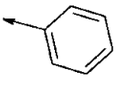
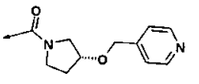
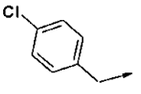
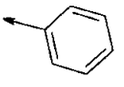
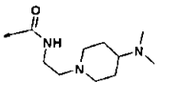
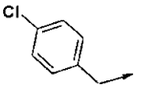
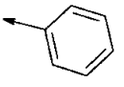
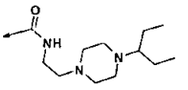
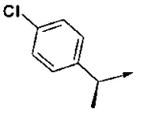
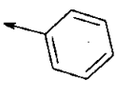
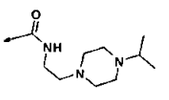
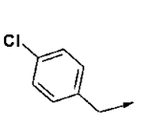
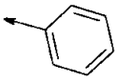
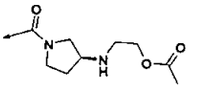
Compuesto	X e Y	R^1	R^2	R^3	R^4
GG	X=H Y=Cl				H
GH	X=H Y=Cl				H
GI	X=H Y=Cl				H
GJ	X=H Y=Cl				H
GK	X=H Y=Cl				H
GL	X=H Y=Cl				H
GM	X=H Y=Cl				H
GN	X=H Y=Cl				H
GO	X=H Y=Cl				H

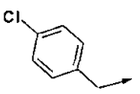
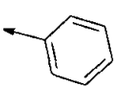
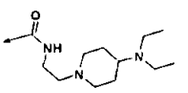
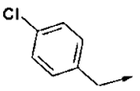
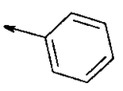
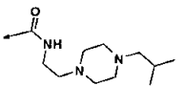
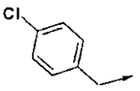
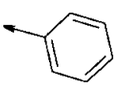
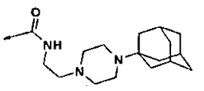
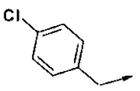
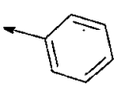
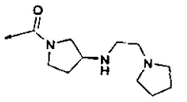
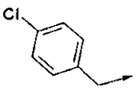
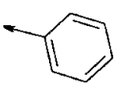
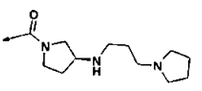
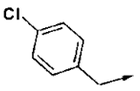
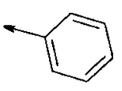
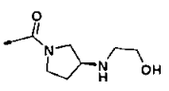
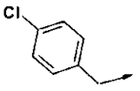
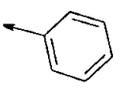
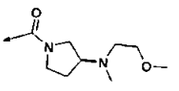
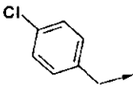
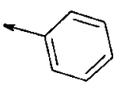
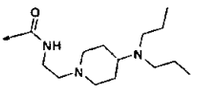
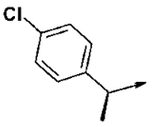
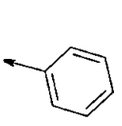
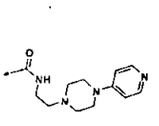
650

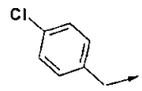
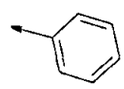
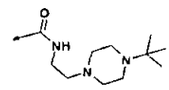
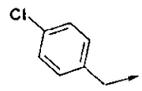
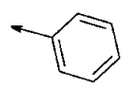
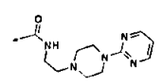
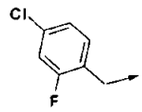
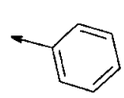
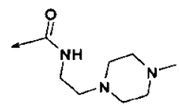
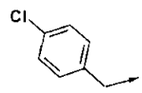
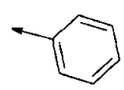
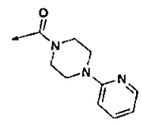
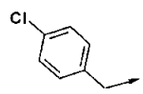
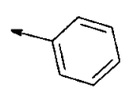
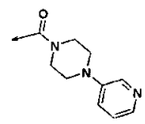
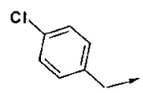
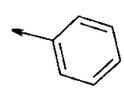
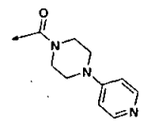
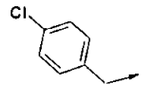
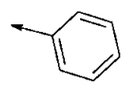
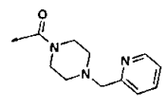
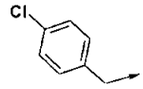
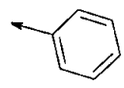
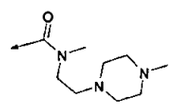
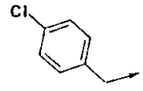
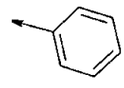
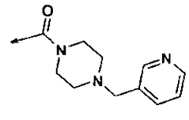
Compuesto	X e Y	R^1	R^2	R^3	R^4
GP	X=H Y=Cl				H
GQ	X=H Y=Cl				H
GR	X=H Y=Cl				H
GS	X=H Y=Cl				H
GT	X=H Y=Cl				H
GU	X=H Y=Cl				H
GV	X=H Y=Cl				H
GW	X=H Y=Cl				H

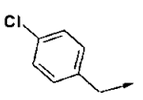
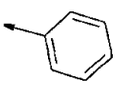
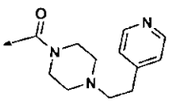
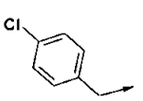
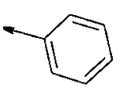
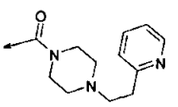
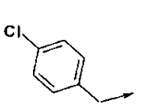
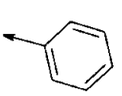
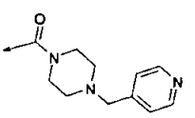
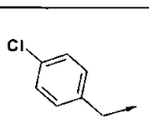
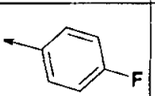
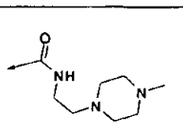
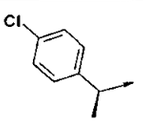
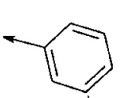
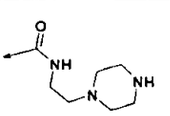
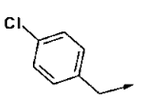
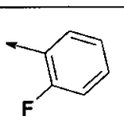
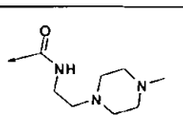
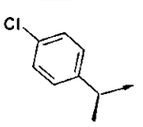
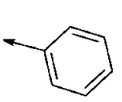
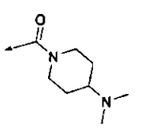
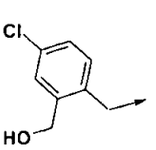
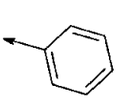
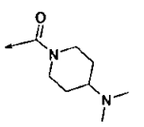
651

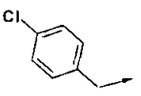
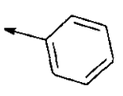
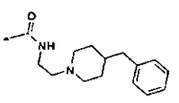
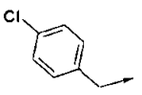
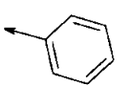
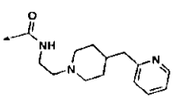
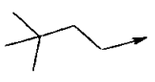
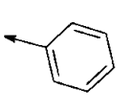
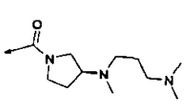
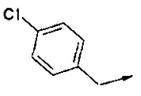
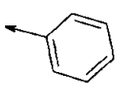
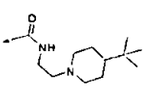
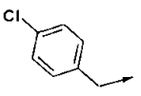
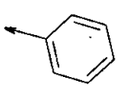
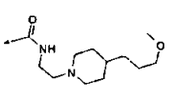
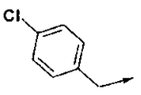
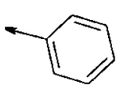
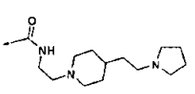
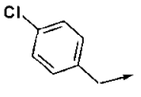
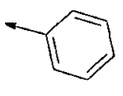
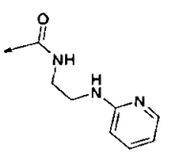
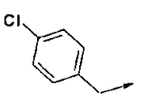
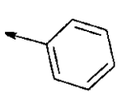
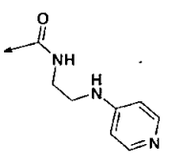
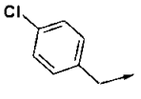
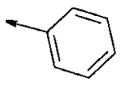
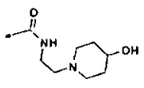
Compuesto	X e Y	R^1	R^2	R^3	R^4
GX	X=H Y=Cl				H
GY	X=H Y=Cl				H
GZ	X=H Y=Cl				H
HA	X=H Y=Cl				H
HB	X=H Y=Cl				H
HC	X=H Y=Cl				H
HD	X=H Y=Cl				H
HE	X=H Y=Cl				H

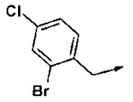
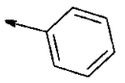
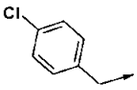
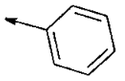
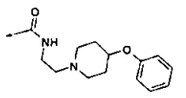
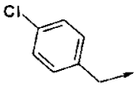
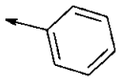
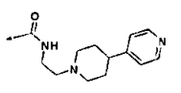
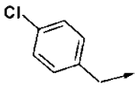
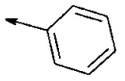
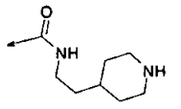
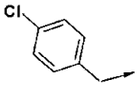
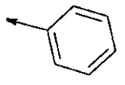
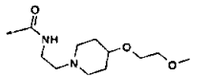
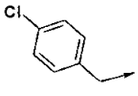
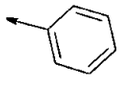
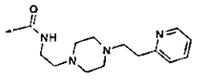
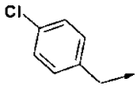
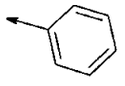
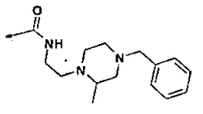
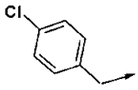
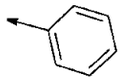
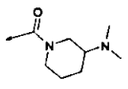
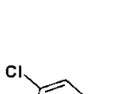
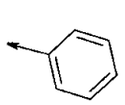
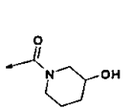
Compuesto	X e Y	R^1	R^2	R^3	R^4
HF	X=H Y=Cl				H
HG	X=H Y=Cl				H
HH	X=H Y=Cl				H
HI	X=H Y=Cl				H
HJ	X=H Y=Cl				H
HK	X=H Y=Cl				H
HL	X=H Y=Cl				H
HM	X=H Y=Cl				H
HN	X=H Y=Cl				H

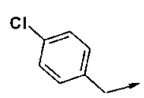
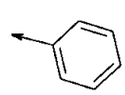
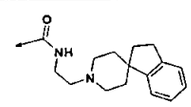
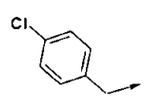
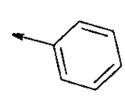
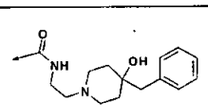
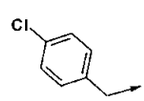
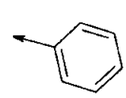
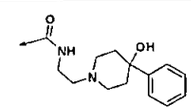
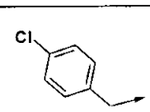
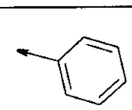
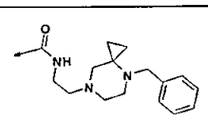
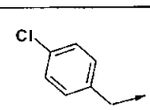
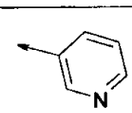
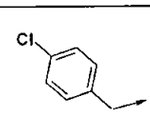
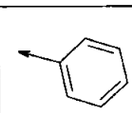
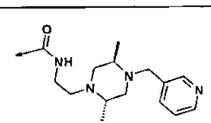
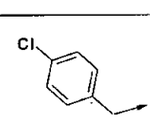
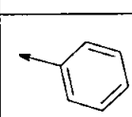
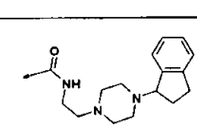
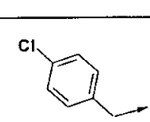
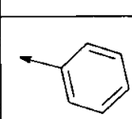
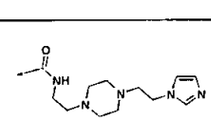
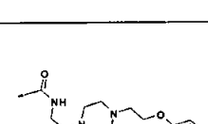
Compuesto	X e Y	R^1	R^2	R^3	R^4
HO	X=H Y=Cl				H
HP	X=H Y=Cl				H
HQ	X=H Y=Cl				H
HR	X=H Y=Cl				H
HS	X=H Y=Cl				H
HT	X=H Y=Cl				H
HU	X=H Y=Cl				H
HV	X=H Y=Cl				H
HW	X=H Y=Cl				H

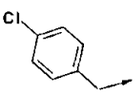
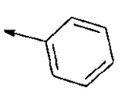
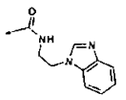
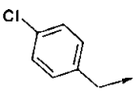
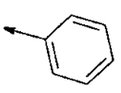
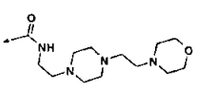
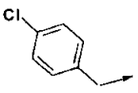
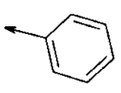
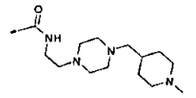
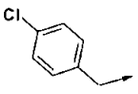
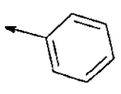
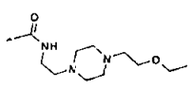
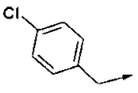
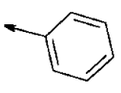
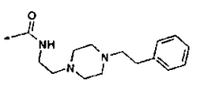
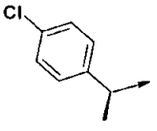
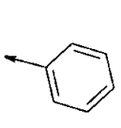
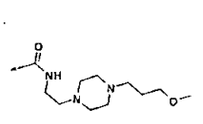
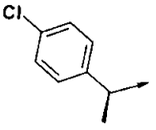
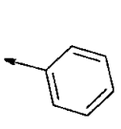
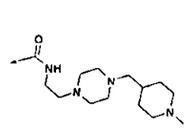
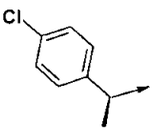
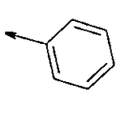
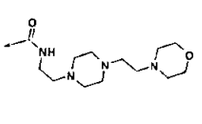
Compuesto	X e Y	R^1	R^2	R^3	R^4
HX	X=H Y=Cl				H
HY	X=H Y=Cl				H
HZ	X=H Y=Cl				H
IA	X=H Y=Cl				H
IB	X=H Y=Cl				H
IC	X=H Y=Cl				H
ID	X=H Y=Cl				H
IE	X=H Y=Cl				H
IF	X=H Y=Cl				H

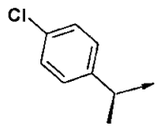
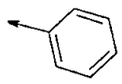
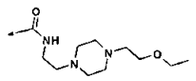
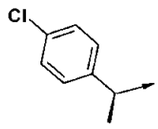
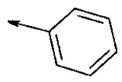
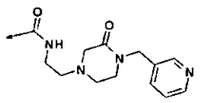
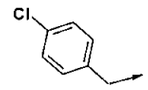
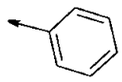
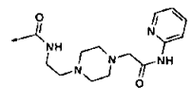
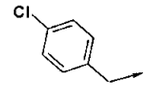
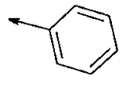
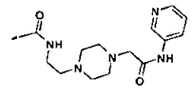
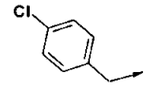
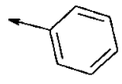
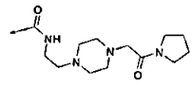
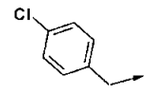
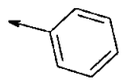
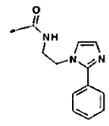
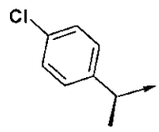
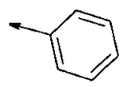
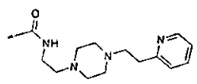
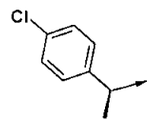
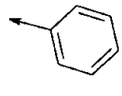
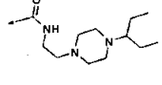
Compuesto	X e Y	R^1	R^2	R^3	R^4
IG	X=H Y=Cl				H
IH	X=H Y=Cl				H
II	X=H Y=Cl				H
IJ	X=H Y=Cl				H
IK	X=H Y=Cl				H
IL	X=H Y=Cl				H
IM	X=H Y=Cl				H
IN	X=H Y=Cl				H

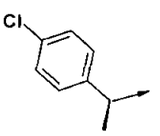
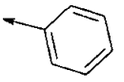
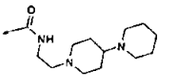
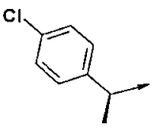
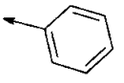
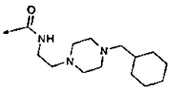
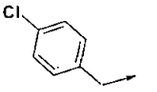
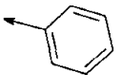
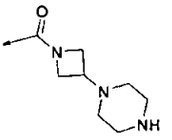
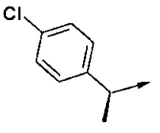
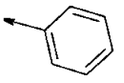
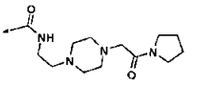
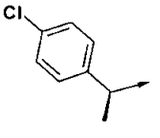
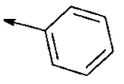
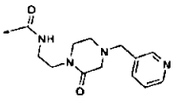
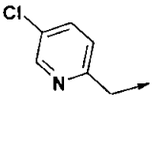
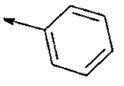
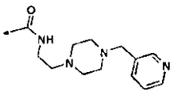
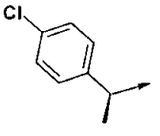
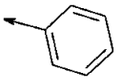
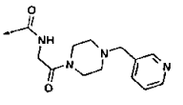
Compuesto	X e Y	R^1	R^2	R^3	R^4
IO	X=H Y=Cl				H
IP	X=H Y=Cl				H
IQ	X=H Y=Cl				H
IR	X=H Y=Cl				H
IS	X=H Y=Cl				H
IT	X=H Y=Cl				H
IU	X=H Y=Cl				H
IV	X=H Y=Cl				H
IW	X=H Y=Cl				H

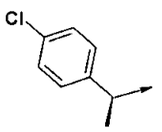
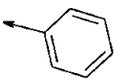
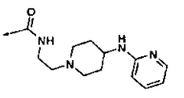
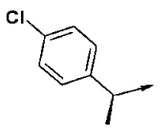
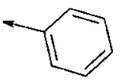
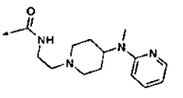
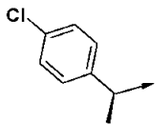
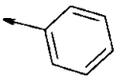
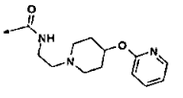
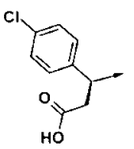
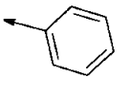
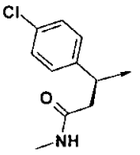
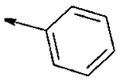
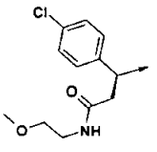
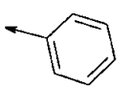
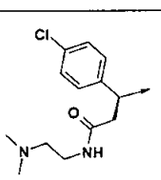
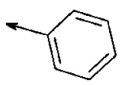
Compuesto	X e Y	R^1	R^2	R^3	R^4
IX	X=F Y=Cl			H	H
IY	X=H Y=Cl				H
IZ	X=H Y=Cl				H
JA	X=H Y=Cl				H
JB	X=H Y=Cl				H
JC	X=H Y=Cl				H
JD	X=H Y=Cl				H
JE	X=H Y=Cl				H
JF	X=H Y=Cl				H

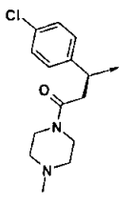
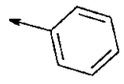
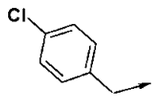
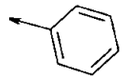
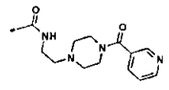
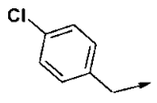
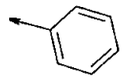
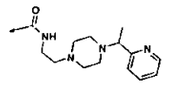
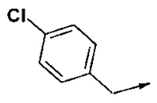
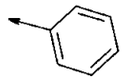
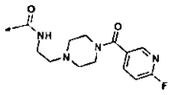
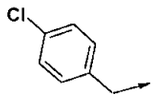
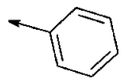
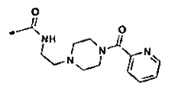
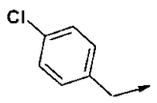
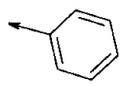
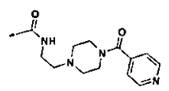
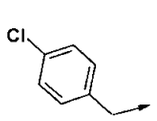
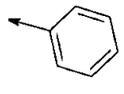
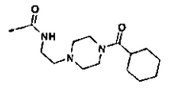
Compuesto	X e Y	R^1	R^2	R^3	R^4
JG	X=H Y=Cl				H
JH	X=H Y=Cl				H
JI	X=H Y=Cl				H
JJ	X=H Y=Cl				H
JK	X=F Y=Cl			H	H
JL	X=H Y=Cl				H
JM	X=H Y=Cl				H
JN	X=H Y=Cl				H
JO	X=H Y=Cl				H

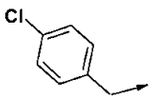
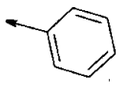
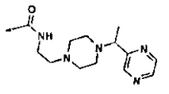
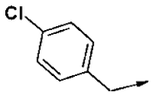
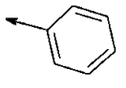
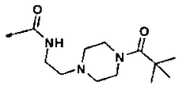
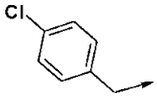
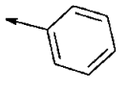
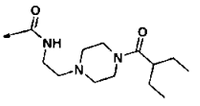
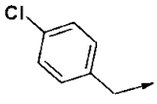
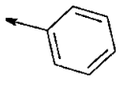
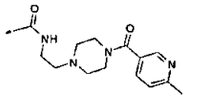
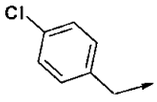
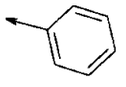
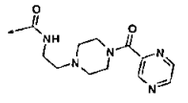
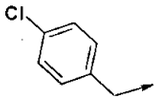
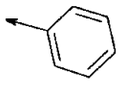
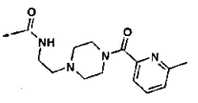
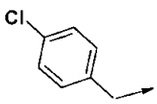
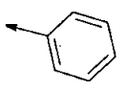
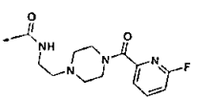
Compuesto	X e Y	R^1	R^2	R^3	R^4
JP	X=H Y=Cl				H
JQ	X=H Y=Cl				H
JR	X=H Y=Cl				H
JS	X=H Y=Cl				H
JT	X=H Y=Cl				H
JU	X=H Y=Cl				H
JV	X=H Y=Cl				H
JW	X=H Y=Cl				H

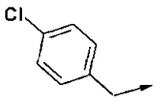
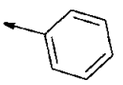
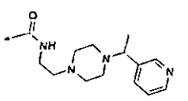
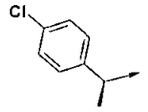
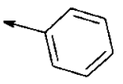
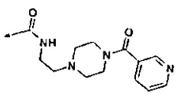
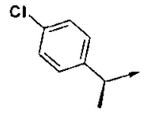
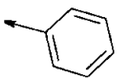
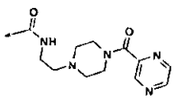
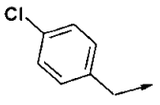
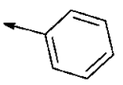
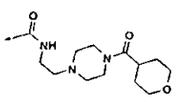
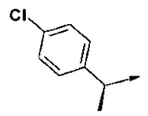
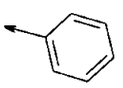
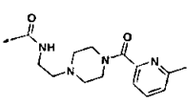
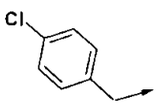
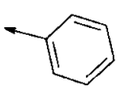
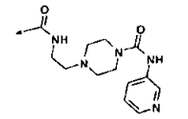
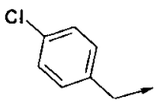
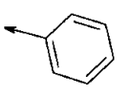
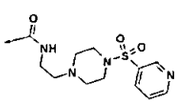
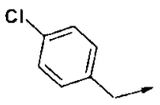
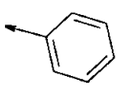
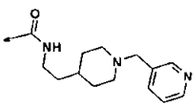
Compuesto	X e Y	R^1	R^2	R^3	R^4
JX	X=H Y=Cl				H
JY	X=H Y=Cl				H
JZ	X=H Y=Cl				H
KA	X=H Y=Cl				H
KB	X=H Y=Cl				H
KC	X=H Y=Cl				H
KD	X=H Y=Cl				H
KE	X=H Y=Cl				H

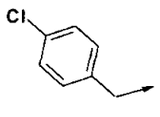
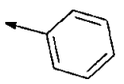
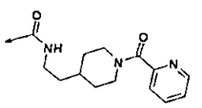
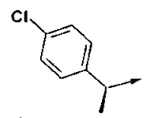
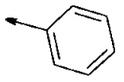
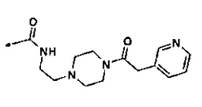
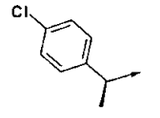
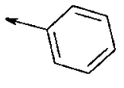
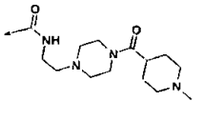
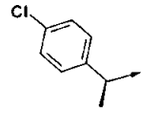
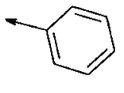
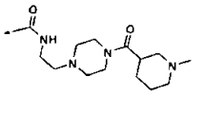
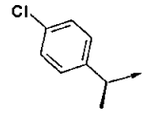
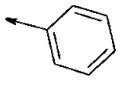
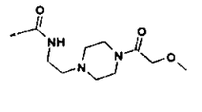
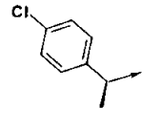
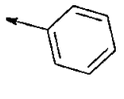
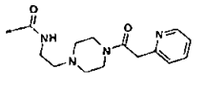
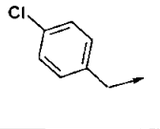
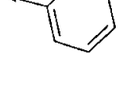
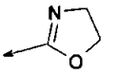
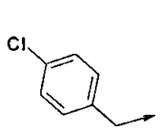
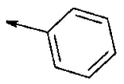
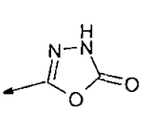
Compuesto	X e Y	R^1	R^2	R^3	R^4
KF	X=H Y=Cl				H
KG	X=H Y=Cl				H
KH	X=H Y=Cl				H
KI	X=H Y=Cl				H
KJ	X=H Y=Cl				H
KK	X=H Y=Cl				H
KL	X=H Y=Cl				H

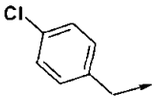
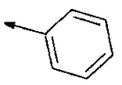
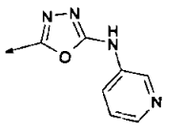
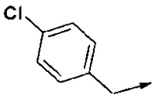
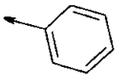
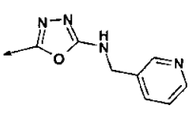
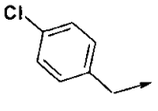
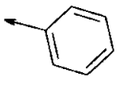
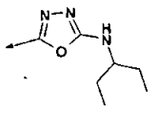
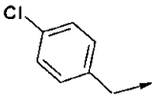
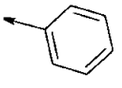
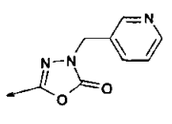
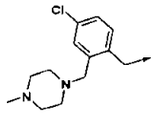
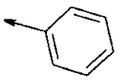
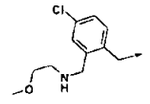
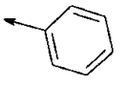
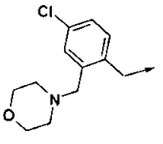
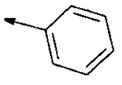
Compuesto	X e Y	R^1	R^2	R^3	R^4
KM	X=H Y=Cl				H
KN	X=H Y=Cl				H
KO	X=H Y=Cl				H
KP	X=F Y=Cl			H	H
KQ	X=F Y=Cl			H	H
KR	X=F Y=Cl			H	H
KS	X=F Y=Cl			H	H

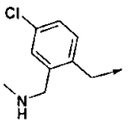
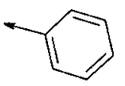
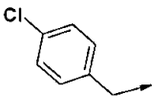
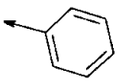
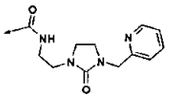
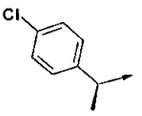
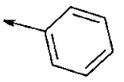
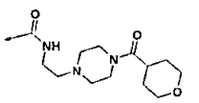
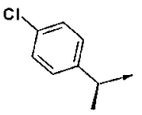
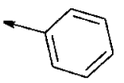
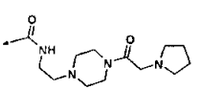
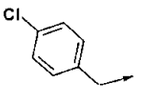
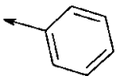
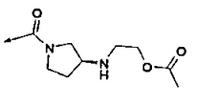
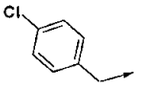
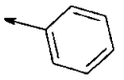
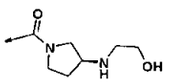
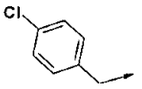
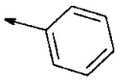
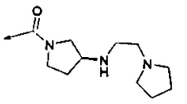
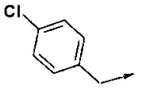
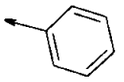
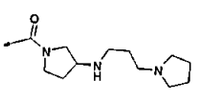
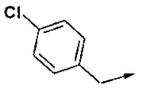
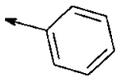
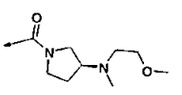
Compuesto	X e Y	R^1	R^2	R^3	R^4
KT	X=F Y=Cl			H	H
KU	X=H Y=Cl				H
KV	X=H Y=Cl				H
KW	X=H Y=Cl				H
KX	X=H Y=Cl				H
KY	X=H Y=Cl				H
KZ	X=H Y=Cl				H

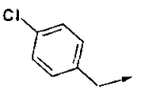
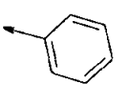
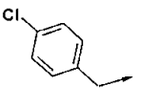
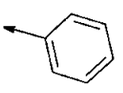
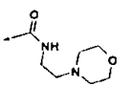
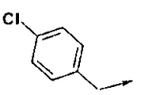
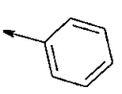
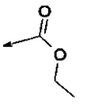
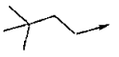
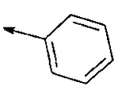
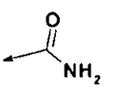
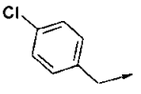
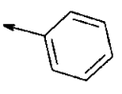
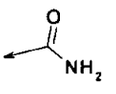
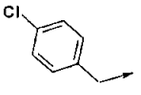
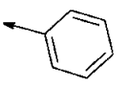
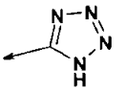
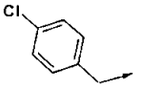
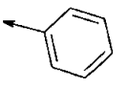
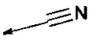
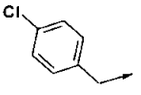
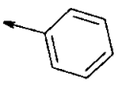
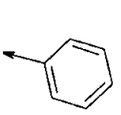
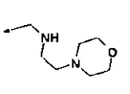
Compuesto	X e Y	R^1	R^2	R^3	R^4
LA	X=H Y=Cl				H
LB	X=H Y=Cl				H
LC	X=H Y=Cl				H
LD	X=H Y=Cl				H
LE	X=H Y=Cl				H
LF	X=H Y=Cl				H
LG	X=H Y=Cl				H

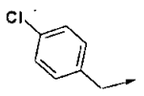
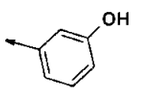
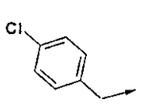
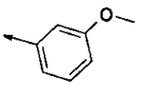
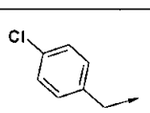
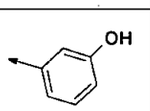
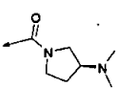
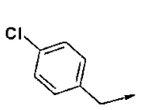
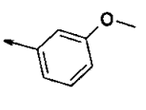
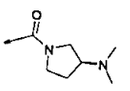
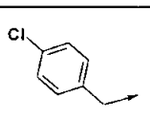
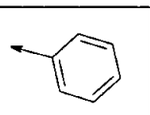
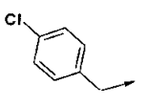
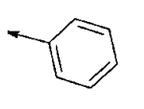
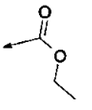
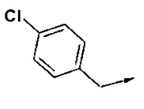
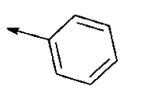
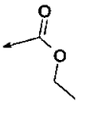
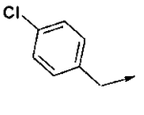
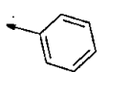
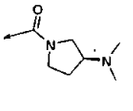
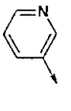
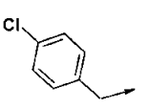
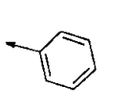
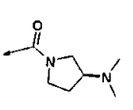
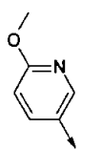
Compuesto	X e Y	R^1	R^2	R^3	R^4
LH	X=H Y=Cl				H
LI	X=H Y=Cl				H
LJ	X=H Y=Cl				H
LK	X=H Y=Cl				H
LL	X=H Y=Cl				H
LM	X=H Y=Cl				H
LN	X=H Y=Cl				H
LO	X=H Y=Cl				H

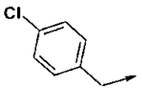
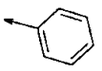
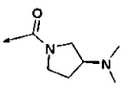
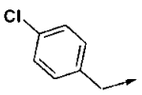
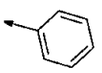
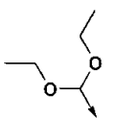
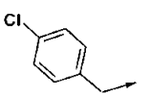
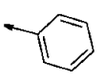
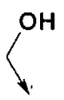
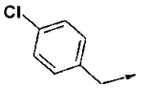
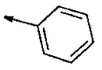
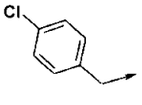
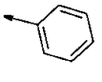
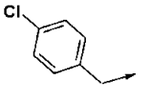
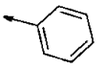
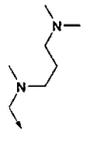
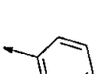
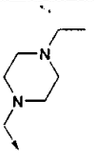
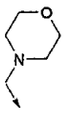
Compuesto	X e Y	R^1	R^2	R^3	R^4
LP	X=H Y=Cl				H
LQ	X=H Y=Cl				H
LR	X=H Y=Cl				H
LS	X=H Y=Cl				H
LT	X=H Y=Cl				H
LU	X=H Y=Cl				H
LV	X=H Y=Cl				H
LW	X=H Y=Cl				H

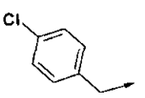
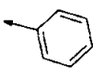
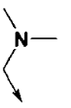
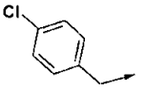
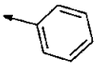
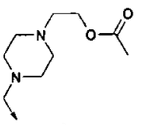
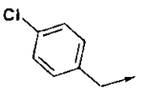
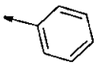
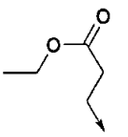
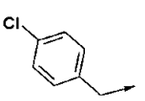
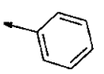
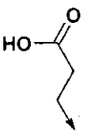
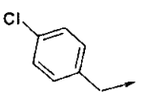
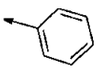
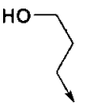
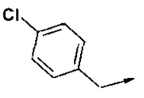
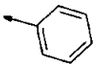
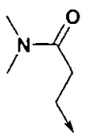
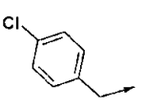
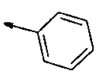
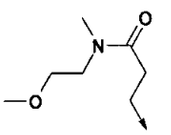
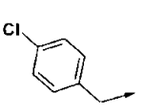
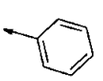
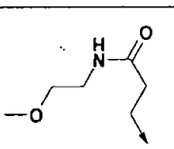
Compuesto	X e Y	R^1	R^2	R^3	R^4
LX	X=H Y=Cl				H
LY	X=H Y=Cl				H
LZ	X=H Y=Cl				H
MA	X=H Y=Cl				H
MB	X=F Y=Cl			H	H
MC	X=F Y=Cl			H	H
MD	X=F Y=Cl			H	H

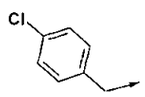
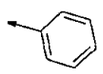
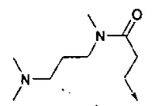
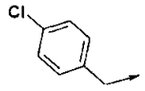
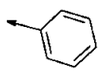
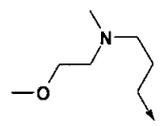
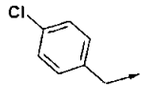
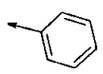
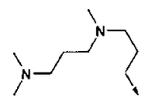
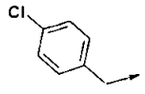
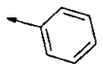
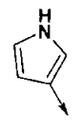
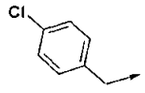
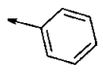
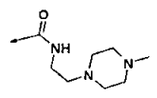
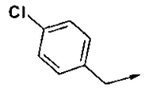
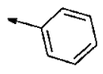
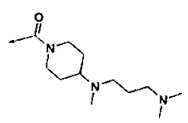
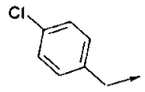
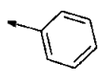
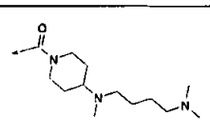
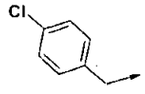
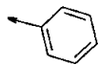
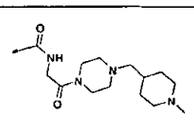
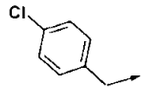
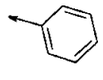
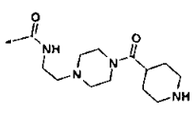
Compuesto	X e Y	R^1	R^2	R^3	R^4
ME	X=F Y=Cl			H	H
MF	X=H Y=Cl				H
MG	X=H Y=Cl				H
MH	X=H Y=Cl				H
MI	X=H Y=Cl				H
MJ	X=H Y=Cl				H
MK	X=H Y=Cl				H
ML	X=H Y=Cl				H
MM	X=H Y=Cl				H

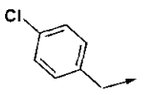
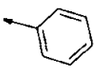
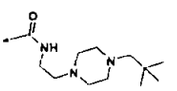
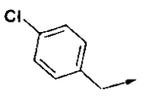
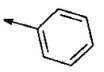
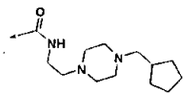
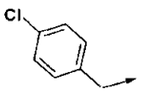
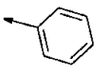
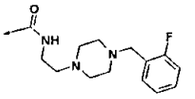
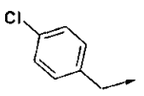
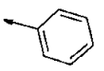
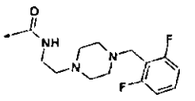
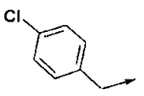
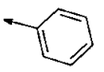
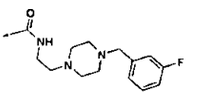
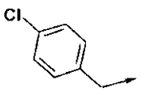
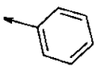
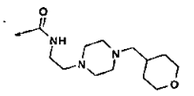
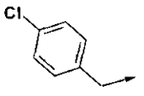
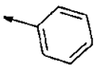
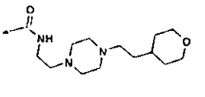
Compuesto	X e Y	R^1	R^2	R^3	R^4
MN	X=H Y=Cl			H	H
MO	X=H Y=Cl				H
MP	X=H Y=Cl				H
MQ	X=H Y=Cl				H
MR	X=H Y=Cl				H
MS	X=H Y=Cl				H
MT	X=H Y=Cl				H
MU	X=H Y=Cl				H
MV	X=H Y=Cl				H

Compuesto	X e Y	R^1	R^2	R^3	R^4
MW	X=F Y=Cl			H	H
MX	X=F Y=Cl			H	H
MY	X=H Y=Cl				H
MZ	X=H Y=Cl				H
NA	X=H Y=Cl			H	Me
NB	X=H Y=Cl				Br
NC	X=H Y=Cl				Cl
ND	X=H Y=Cl				
NE	X=H Y=Cl				

Compuesto	X e Y	R^1	R^2	R^3	R^4
NF	X=H Y=Cl				
NG	X=H Y=Cl			H	
NH	X=H Y=Cl			H	
NI	X=H Y=Cl			H	
NJ	X=H Y=Cl			H	
NK	X=H Y=Cl			H	
NL	X=H Y=Cl			H	
NM	X=H Y=Cl			H	

Compuesto	X e Y	R^1	R^2	R^3	R^4
NN	X=H Y=Cl			H	
NO	X=H Y=Cl			H	
NP	X=H Y=Cl			H	
NQ	X=H Y=Cl			H	
NR	X=H Y=Cl			H	
NS	X=H Y=Cl			H	
NT	X=H Y=Cl			H	
NU	X=H Y=Cl			H	

Compuesto	X e Y	R^1	R^2	R^3	R^4
NV	X=H Y=Cl			H	
NW	X=H Y=Cl			H	
NX	X=H Y=Cl			H	
NY	X=H Y=Cl			H	
NZ	X=H Y=Cl				Me
OA	X=H Y=Cl				H
OB	X=H Y=Cl				H
OC	X=H Y=Cl				H
OD	X=H Y=Cl				H

Compuesto	X e Y	R^1	R^2	R^3	R^4
OE	X=H Y=Cl				H
OF	X=H Y=Cl				H
OG	X=H Y=Cl				H
OH	X=H Y=Cl				H
OI	X=H Y=Cl				H
OJ	X=H Y=Cl				H
OK	X=H Y=Cl				H

y/o un tautómero, un N-óxido y/o una sal farmacéuticamente aceptable del mismo.

9. Una composición farmacéutica, la cual comprende un compuesto de la fórmula I, y/o un tautómero, un N-óxido y/o una sal

farmacéuticamente aceptable del mismo, de acuerdo con cualquiera de las reivindicaciones 1 a 8, y cuando menos un material de vehículo farmacéuticamente aceptable.

10. Una composición farmacéutica de acuerdo con la reivindicación 9, para utilizarse en el tratamiento de un trastorno o enfermedad que sea mediada por la actividad de MDM2 y/o MDM4, o variantes de los mismos.

11. Un compuesto de la fórmula I, y/o un tautómero, un N-óxido y/o una sal farmacéuticamente aceptable del mismo, de acuerdo con cualquiera de las reivindicaciones 1 a 8, para utilizarse como un medicamento.

12. El uso de un compuesto de la fórmula I, y/o un tautómero, un N-óxido y/o una sal farmacéuticamente aceptable del mismo, de acuerdo con cualquiera de las reivindicaciones 1 a 8, para la preparación de una composición farmacéutica para el tratamiento de un trastorno o enfermedad que sea mediada por la actividad de MDM2 y/o MDM4, o variantes de los mismos.

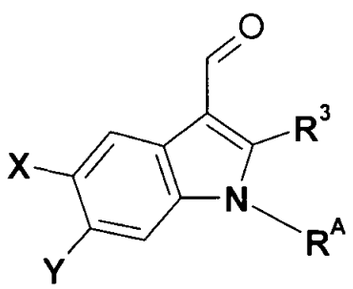
13. Un compuesto de la fórmula I, y/o un N-óxido, un tautómero y/o una sal farmacéuticamente aceptable del mismo, de acuerdo con cualquiera de las reivindicaciones 1 a 8, para el tratamiento de un trastorno o enfermedad que sea mediada por la actividad de MDM2 y/o MDM4, o variantes de los mismos.

14. Un método de tratamiento, el cual comprende administrar un compuesto de la fórmula I, y/o un tautómero, un N-óxido y/o una sal farmacéuticamente aceptable del mismo, de

acuerdo con cualquiera de las reivindicaciones 1 a 8, a una persona que necesite dicho tratamiento, en una cantidad efectiva para el tratamiento profiláctico y/o terapéutico de una enfermedad o trastorno que sea mediado por la actividad de MDM2 y/o MDM4, o variantes de los mismos.

15. Un método para la fabricación de un compuesto de la fórmula I, el cual comprende:

a) para la fabricación de un compuesto de la fórmula I, en donde R^4 es hidrógeno y R^1, R^2, R^3, R^A, X e Y son como se definen para un compuesto de la fórmula I en cualquiera de las reivindicaciones 1 a 8, hacer reaccionar un derivado de formil-indol de la fórmula II:



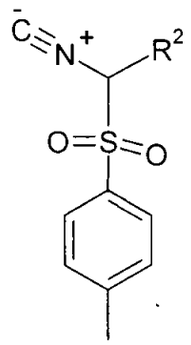
(II)

en donde R^3, R^A, X e Y son como se definen para un compuesto de la fórmula I en cualquiera de las reivindicaciones 1 a 8, con un compuesto de amino de la fórmula III:

$$R^1\text{-}NH_2 \qquad \text{(III)}$$

en donde R^1 es como se define para un compuesto de la fórmula I en cualquiera de las reivindicaciones 1 a 8, en la

presencia de un isocianuro de tosil-metilo de la fórmula IV:

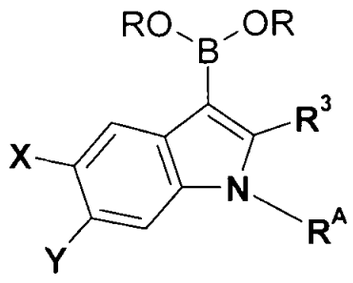


(IV)

en donde R^2 es como se define para un compuesto de la fórmula I en cualquiera de las reivindicaciones 1 a 8;

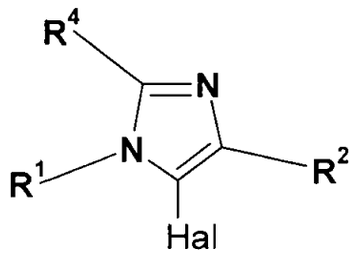
o

b) acoplar un ácido indol-borónico de la fórmula V:



(V)

en donde R^3, R^A, X e Y son como se definen para un compuesto de la fórmula I en cualquiera de las reivindicaciones 1 a 8, y cada R es arilo, alquenilo o en especial alquilo, o en donde los dos R forman un puente, en especial R es H, alquilo inferior, o R y R forman juntos 1,1,2,2-tetrametil-1,2-etileno, con un halo-imidazol de la fórmula VI:



(VI)

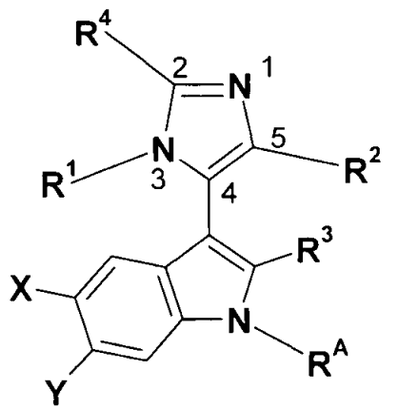
en donde R^1, R^2 y R^4 son como se definen para un compuesto de la fórmula I en cualquiera de las reivindicaciones 1 a 8, y Hal es halógeno, en especial bromo o más especialmente yodo,

en donde, en la reacción, los grupos funcionales de los materiales de partida pueden estar presentes en una forma protegida, y en donde se puedan obtener compuestos de la fórmula I que lleven uno o más grupos protectores, se remueven estos grupos protectores;

y, si se desea, un compuesto de la fórmula I que se pueda obtener de acuerdo con la reacción dada anteriormente, se convierte en un compuesto diferente de la fórmula I, una sal que se pueda obtener de un compuesto de la fórmula I se convierte en una sal diferente del mismo, un compuesto libre de la fórmula I que se pueda obtener se convierte en una sal del mismo, y/o un isómero que se pueda obtener de un compuesto de la fórmula I se separa en uno o más isómeros diferentes que se puedan obtener de la fórmula I.

RESUMEN

La invención se refiere a compuestos de 3-heterociclil-indolilo capaces de inhibir la interacción entre p53, o variantes del mismo, y MDM2 y/o MDM4, o variantes de los mismos, respectivamente, teniendo estos compuestos la fórmula I:



(I)

en donde:

R^1, R^2, R^3, R^4, R^A, e Y son como se definen en la memoria descriptiva. Debido a su actividad, los compuestos son útiles en el tratamiento de diferentes trastornos y enfermedades mediadas por la actividad de MDM2 y/o MDM4, o variantes de los mismos, tales como enfermedades inflamatorias o proliferativas, o en la protección de las células.

* * * * *

PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

NOVARTIS PHARMA AG
Patent Department
Postfach
4002 Basel
SUISSE

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(PCT Rule 71.1)

	Date of mailing *(day/month/year)* 06.07.2009
Applicant's or agent's file reference 50849-WO-PCT	**IMPORTANT NOTIFICATION**

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP2008/053667	27.03.2008	29.03.2007

Applicant
NOVARTIS AG et al

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary report on patentability and its annexes, if any, established on the international application.

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. **REMINDER**

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary report on patentability. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

The applicant's attention is drawn to Article 33(5), which provides that the criteria of novelty, inventive step and industrial applicability described in Article 33(2) to (4) merely serve the purposes of international preliminary examination and that "any Contracting State may apply additional or different criteria for the purposes of deciding whether, in that State, the claimed inventions is patentable or not" (see also Article 27(5)). Such additional criteria may relate, for example, to exemptions from patentability, requirements for enabling disclosure, clarity and support for the claims.

Name and mailing address of the international preliminary examining authority:	Authorized Officer
European Patent Office P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk - Pays Bas Tel. +31 70 340 - 2040 Fax: +31 70 340 - 3016	Lafitte-de Jong, S Tel. +31 70 340-4827

Form PCT/IPEA/416 (January 2004)

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Form PCT/IPEA/416
50849-WO-PCT		

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP2008/053667	27.03.2008	29.03.2007

International Patent Classification (IPC) or national classification and IPC
INV. C07D403/04

Applicant
NOVARTIS AG et al

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 7 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☐ *sent to the applicant and to the International Bureau)* a total of sheets, as follows:
      ☐ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in electronic form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

- ☒ Box No. I Basis of the report
- ☐ Box No. II Priority
- ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☒ Box No. VIII Certain observations on the international application

Date of submission of the demand	Date of completion of this report
2008-12-17	06.07.2009

Name and mailing address of the international preliminary examining authority:

European Patent Office P.B. 5818 Patentlaan 2
NL-2280 HV Rijswijk - Pays Bas
Tel. +31 70 340 - 2040
Fax: +31 70 340 - 3016

Authorized officer

Bourghida, E

Telephone No. +31 70 340-9517

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/EP2008/053667

Box No. I Basis of the report

1. With regard to the **language**, this report is based on

   ☒ the international application in the language in which it was filed

   ☐ a translation of the international application into , which is the language of a translation furnished for the purposes of:
   - ☐ international search (under Rules 12.3(a) and 23.1(b))
   - ☐ publication of the international application (under Rule 12.4(a))
   - ☐ international preliminary examination (under Rules 55.2(a) and/or 55.3(a))

2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

   Description, Pages

   1-192 as originally filed

   Claims, Numbers

   1-15 as originally filed

   ☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☐ The amendments have resulted in the cancellation of:
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

5. ☐ This opinion has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 70.2 (e)).

6. ☐ Supplementary international search report(s) from Authority(ies) have been received and taken into account in drawing up this report (Rule 45bis.8(b) and (c)).

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-15
	No:	Claims	
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-15
Industrial applicability (IA)	Yes:	Claims	1-15
	No:	Claims	

2. Citations and explanations (Rule 70.7):

see separate sheet

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1.1 Reference is made to the following document:

D1: US-B1-6 699 883 (DOEMLING ALEXANDER [DE] ET AL) 2 March 2004 (2004-03-02)

Methods of treatment:

2.1 Claim 14 relates to subject-matter considered by this Authority to be covered by the provisions of Rule 39.1(iv)/67.1(iv) PCT.

2.2 The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

Novelty:

3.1 D1 disloses the compound 3-(4-benzylpiperidin-1H-imidazol-5-yl)-1H-indole used as antitumour agents (see D1: column 1; example 3 column 16).

3.2 The compounds of formula (I) differ deom D1 in that their indole ring is substituted in position 6 by a group Y which is different from a hydrogen, whereas in D1 the corresponding indole ring is unsubstituted at the said position.

3.3 Thus, the subject-matter of claims 1-15 is novel in the sense of Article 33(2) PCT.

Inventive step:

4.1 D1 is regarded as the closest prior art for the inventive step assessment of the subject-matter of claims 1-15 and discloses a disloses the compound 3-(4-benzylpiperidin-1H-imidazol-5-yl)-1H-indole used as antitumour agents (see D1: column 1; example 3 column 16).

4.2 The compounds of formula (I) differ deom D1 in that their indole ring is substituted in position 6 by a group Y which is different from a hydrogen, whereas in D1 the corresponding indole ring is unsubstituted at the said position.

4.3 The problem to be solved can be regarded as the provision of further compounds to be used as antitumour agents.

4.5 The solution proposed by the subject-matter of claims 1-15 is not regarded as involving an inventive step in the sense of Article 33(3) PCT because the compounds of formula (I) only consist of obvious variations of substituents on the imidazol-4-yl-1H-indole moiety which is already known in the prior art for its use as antitumour agent.
Such variations can only be regarded as inventive if they present unexpected effects or properties in relation to the compound disclosed in D1 (in terms of comparative tests). However, no such effects or properties are indicated in the application.

4.6 Hence, an inventive step cannot be acknowledged for the subject-matter of claims 1-15.

Industrial Applicability:

5.1 Claims 1-15 relate to a subject-matter which is considered to have an industrial applicability, and therefore the subject-matter of such claims meets the criteria of Article 33(4) PCT.

Re Item VIII

Certain observations on the international application

6.1 The Applicant is entitled to claim all obvious modifications of what was described; alternative variations have to be supported by a certain number of examples so that the breadth of the main claim represents a reasonable generalisation of what has been exemplified, and it can be assumed that every compound falling within its scope actually provides a sol-tion to the problem underlying the invention.
Non-limiting terms like "**substituted**" (not being followed by a list of specific substituents) as used in the product claims of the present application are, however, speculative in the sense of Article 33(3) PCT: They include a great variety of structural possibilities not yet explored by the applicant, the effect of which cannot be foreseen having regard to the problem underlying the present invention.

Non-limititing terms as cited above include
- chemical groups which are structurally so remote from those of the examples that the activity of molecules comprising them cannot be predicted within the li-mits of qualitative structure-activity-relationship considerations
- mutagenic and/or toxic groups
and also
- known pharmacophoric groups with the same or a completely different activity which leads to hybrid molecules or bioconjugates the actual biological activities of which are unpredictable,
i.e. it cannot be foreseen, whether all molecules claimed provide a solution to the problem at all.

The applicant could, in order to overcome this objection, introduce the definition of

the substituents, and the definition of the substitutents of the substituents (if any) provided in the description and which are meant for the compounds claims 1-6 or alternatively, restrict the claims concerned appropriately.

6.2 The expression "disorder or disease which is mediated by the activity of MDM2 and/or MDM4 or variants thereof" used in claims 10-13 is a functional definition and do not provide the skilled person with the necessary teaching for assessing what subject-matter is actually comprised in this definition, i.e. a definition of this kind does not let this skilled person immediately be aware of which diseases can be treated by applying a medicament having this specific activity.
In consequence, the subject-matter of claims 10-13 does not fulfil the requirements of Article 6 PCT.

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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
9 October 2008 (09.10.2008)

PCT

(10) International Publication Number
WO 2008/119741 A3

(51) International Patent Classification:
C07D 403/04 (2006.01) *A61P 35/00* (2006.01)
A61K 31/4164 (2006.01)

(21) International Application Number:
PCT/EP2008/053667

(22) International Filing Date: 27 March 2008 (27.03.2008)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
07105269.0 29 March 2007 (29.03.2007) EP

(71) Applicant *(for all designated States except US)*: **NOVARTIS AG** [CH/CH]; Lichtstrasse 35, CH-4056 Basel (CH).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **BOETTCHER, Andreas** [DE/CH]; Röttelerstr. 15, CH-4058 Basel (CH). **BUSCHMANN, Nicole** [DE/CH]; Horburgstrasse 19, CH-4057 Basel (CH). **FURET, Pascal** [FR/FR]; 19, rue de la Forêt, F-68800 Thann (FR). **GROELL, Jean-Marc** [FR/FR]; Rue de Muespach 4a, F-68640 Steinsoultz (FR). **KALLEN, Jörg** [CH/CH]; Kaltbrunnenstrasse 41, CH-4054 Basel (CH). **HERGOVICH LISZTWAN, Joanna** [CA/FR]; 11b rue de Delle, F-68640 Muespach Le Haut (FR). **MASUYA, Keiichi** [JP/CH]; Gemeindeholzweg 30, CH-4103 Bottmingen (CH). **MAYR, Lorenz** [DE/DE]; Fritz-Schülin-Weg 16, 79589 Binzen (DE). **VAUPEL, Andrea** [DE/CH]; Rütiring 23, CH-4125 Riehen (CH).

(74) Agent: **DYER, James**; Novartis Pharma Ag, Patent Department, CH-4002 Basel (CH).

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

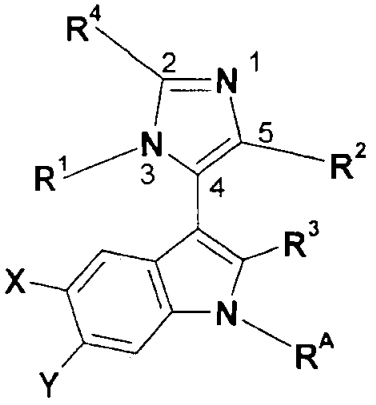
(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS,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

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

Published:
— *with international search report*
— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

(88) Date of publication of the international search report:
4 December 2008

(54) Title: 3-IMIDAZOLYL-INDOLES FOR THE TREATMENT OF PROLIFERATIVE DISEASES



(I)

(57) Abstract: The invention relates to 3-heterocyclyl indolyl compounds capable of inhibiting the interaction between p53, or variants thereof, and MDM2 and/or MDM4, or variants thereof, respectively, said compounds having the formula (I) wherein R^1, R^2, R^3, R^4, R^A, Y and Y are as defined in the specification. Due to their activity, the compounds are useful in the treatment of various disorders and diseases mediated by the activity of MDM2 and/or MDM4, or variants thereof, such as inflammatory or proliferative diseases or in the protection of cells.

WO 2008/119741 A3

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2008/053667

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D403/04 A61K31/4164 A61P35/00

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, WPI Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 6 699 883 B1 (DOEMLING ALEXANDER [DE] ET AL) 2 March 2004 (2004-03-02) column 1; examples 2,3,7-10	1-15
X	SISKO, JOSEPH ET AL: "An investigation of imidazole and oxazole syntheses using aryl-substituted TosMIC reagents" JOURNAL OF ORGANIC CHEMISTRY , 65(5), 1516-1524 CODEN: JOCEAH; ISSN: 0022-3263, 2000, XP002446642 table 1; compound 10	1-5,9-11

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents :

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

"E" earlier 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
19 September 2008	29/09/2008

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	Bourghida, E

Form PCT/ISA/210 (second sheet) (April 2005)

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2008/053667

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 6699883 B1	02-03-2004	AU 1853101 A	10-05-2001
		CA 2386795 A1	12-04-2001
		DE 19948417 A1	19-04-2001
		WO 0125213 A2	12-04-2001
		EP 1228044 A2	07-08-2002
		JP 2003511373 T	25-03-2003

691

Industria y Comercio
SUPERINTENDENCIA

REQUISITOS MÍNIMOS PARA ADMISIÓN A TRAMITE PCT

PATENTE DE INVENCIÓN [✓] MODELO DE UTILIDAD [ ]

- Indicación de que se solicita la concesión de una patente [✓]
- Datos de identificación del solicitante o de la persona que presenta la solicitud [✓]
- Descripción de la invención [✓]
- Dibujos de ser estos pertinentes [✓]
- Comprobante de pago de las tasas establecidas [✓]

COMPLETA [✓] INCOMPLETA [ ]

DISEÑO INDUSTRIAL [ ]

- Indicación de que se solicita el registro de Diseño Industrial [ ]
- Datos de identificación del solicitante o de la persona que presenta la solicitud [ ]
- Representación gráfica y fotográfica del Diseño Industrial o muestra del material que incorpora el diseño [ ]
- Comprobante de pago de las tasas establecidas [ ]

COMPLETA [ ] INCOMPLETA [ ]

ESQUEMA DE TRAZADO [ ]

- Indicación de que se solicita el registro de un Esquema de Trazado [ ]
- Datos de identificación del solicitante o de la persona que presenta la solicitud [ ]
- Representación gráfica del esquema trazado [ ]
- Comprobante de pago de las tasas establecidas [ ]

COMPLETA [ ] INCOMPLETA [ ]

Firma Responsable

Fe

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 09-106551- -00000-0000
Fecha: 2009-09-29 16:03:55 Dep. 2020 NUECREACIONE
Tra. 11 PATENTEIYII Eve: 379 FASENACIONALII
Act. 411 PRESENTACION Folios: 690

Carrera 13 No. 27-00 Piso 5,7y10
Conmutador: 3 82 0840
Fax: 3505220
E-mail: info@sic.gov.co
www.sic.gov.co
Bogotá D.C. - Colombia

Folio 692

2020
Bogotá D.C.,

Doctor(a)
OLARTE GARCIA CARLOS REYNALDO
Apoderado(a) y/o Representante de
NOVARTIS A.G.

REFERENCIA	Radicación No.	9 106551
	Solicitud internacional	PCT/EP2008/053667
	Fecha inicio fase nacional	29/10/2009
	Trámite	11
	Evento	379
	Actuación	416
	Oficio No.	9334
	Folios	1

Teniendo en cuenta que la solicitud de privilegio de patente que se tramita bajo el expediente indicado en la referencia, reúne los requisitos de forma establecidos en la Decisión 486 de la Comisión de la Comunidad Andina, el Tratado de Cooperación en Materia de Patentes (PCT), el Reglamento y la Circular Única de la Superintendencia de Industria y Comercio, se envía el extracto de la solicitud a la Oficina de Comunicaciones para efecto de su publicación en la Gaceta de Propiedad Industrial.

Cúmplase
Dado en Bogotá DC, 23 NOV. 2009

ALIX CARMENZA CESPEDES DE VERGEL
Directora de Nuevas Creaciones (c)

adpa11

OLARTERAISBECK
OLARTE RAISBECK MOURE & CASTRO LTDA.

SEÑORES
SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIRECCIÓN DE NUEVAS CREACIONES
E. S.

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 09-106551- -00001-0000
Fecha: 2010-08-12 16:23:35 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 379 FASENACIONALII
Act. 538 PETICION Folios: 2

Re.: Expediente No. 09-106.551
Solicitud de Patente de Invención titulada: "3-IMIDAZOLIL-INDOLES PARA EL TRATAMIENTO DE ENFERMEDADES PROLIFERATIVAS".
Solicitante: NOVARTIS AG
Nuestra Ref.: P2009/000162

SOLICITUD DE EXAMEN DE PATENTABILIDAD SEGÚN EL ARTÍCULO 44 DE LA DECISION 486, GACETA No. 613

CARLOS R. OLARTE, mayor de edad y vecino de Bogotá, D.C., identificado tal como aparece al pie de mi firma, en mi condición de apoderado, respetuosamente me permito solicitar que se examine si la invención reúne los requisitos de patentabilidad previstos en la misma, dando cumplimiento a lo establecido en el articulo 44 de la Decisión 486 de la comisión de la Comunidad Andina. Adjunto recibo por el monto de $470.000 pesos para cubrir la tasa correspondiente, según la Resolución 69699 del año 2009.

Atentamente,

CARLOS R. OLARTE
C. C. Nº 79.782.747 de Bogotá
T.P. 74.295

Anexo: Recibo por $470.000 pesos