PCT

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
INVENTAR

Industria y Comercio

SUPERINTE

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 10-160879- -00000-0000
Fecha: 2010-12-22 12:59:22 Dep: 2020 DIR.NUEVASCR
Tra: 11 PATENTEIYII Eve: 378 FASENACIONALI
Act: 411 PRESENTACION. Folios: 350

DELEGATURA DE PROPIEDAD INDUSTRIAL

DIRECCIÓN DE NUEVAS CREACIONES

10-160879

SOLICITUD DE PATENTE DE

INVENCIÓN

TITULO: COMPUESTOS ORGANICOS

SOLICITANTE: NOVARTIS AG

DIRECCIÓN: Lichtstrasse 35, CH- 4056 Basel, Suiza

APODERADO: CARLOS R. OLARTE

BOGOTÁ: 22 Diciembre de 2010

P2010/000189

27-01-2011

OLARTE RAISBECK

OLARTE RAISBECK MOUR

Industria y Comercio
SUPERINTENDENCIA

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PETITORIO - FORMULARIO ÚNICO DE SOLICITUD
PATENTE PCT
ENTRADA EN FASE NACIONAL **P2010/000189**

SOLICITUD DE:

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

[X] Capítulo I. [ ] 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

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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/EP2009/057947 Fecha Junio 25, 2009

Publicación Internacional No. WO 2009/156462 Fecha Diciembre 30, 2009

(6) **Título (54)** COMPUESTOS ORGANICOS (Folio 355)

Clasificación Internacional (51) C07D 213/61, C07D 401/04, C07D 401/06, C07D 401/12, C07D 401/14, A61K 31/4439, A61P 9/00

Prioridad **SI** [X] **NO** [ ]

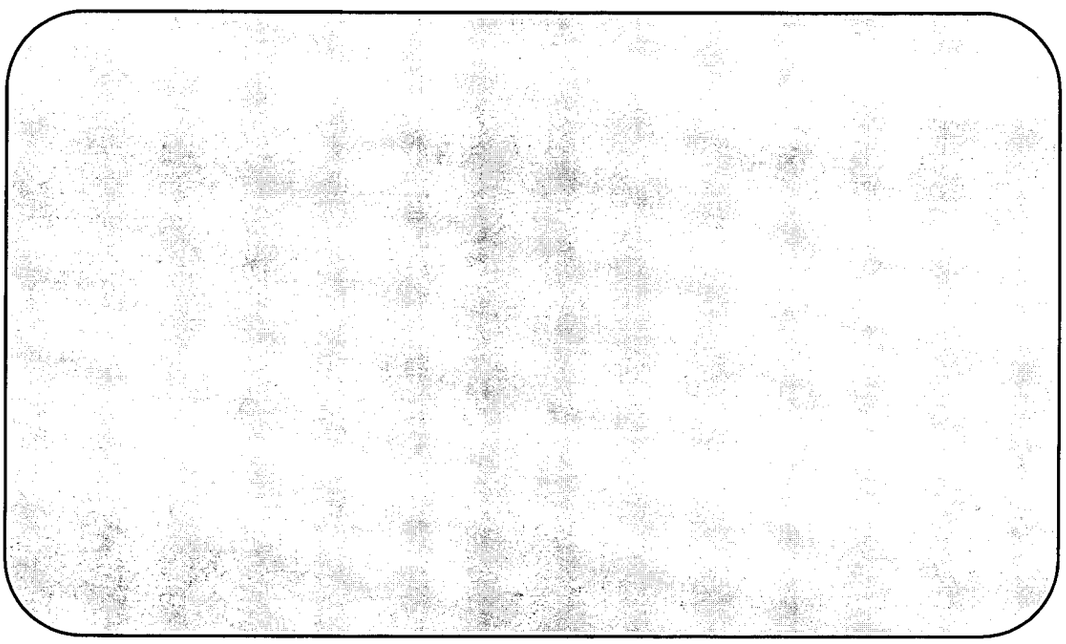
(33) País de Origen	(32) Fecha	(31) Número de Solicitud
US	Junio 27, 2008	61/076,452

(9) **Comprobante de pago No.** 10- **Fecha** Diciembre de 2010

ANEXOS

- [x] Comprobante de pago de la tasa de presentación de la solicitud.
- [x] Documento que acredita la existencia y representación legal cuando el solicitante sea persona jurídica.
- [x] Poderes, si fuere el caso. Adjunto copia simple ver expediente No. 08-102832.
- [ ] 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.

LISTA DE INVENTORES

PCT/EP2009/057947

3

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4

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 10 - 109,372
FECHA : DICIEMBRE 22 DE 2010

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

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
OLARTE RAISBEK	CONSIGNACION	BANCO DE BOGOTA	062754387	387590405	22/12/2010	4,996,000.00

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

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-01 SOLICITUDES	1 TRAMITES DE SOL. DE PATENTE DE IN	554,000.00
		TOTAL : $	554,000.00

SON: QUINIENTOS CINCUENTA Y CUATRO MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No._____

TRADUCCIÓN OFICIAL DE UN DOCUMENTO QUE ESTÁ ORIGINALMENTE EN INGLÉS

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 Oficial
JORGE E. SIERRA REYES
Licencia 376 - 1993 Miniusticia

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 Oficial
JORGE E. SIERRA REYES
Licencia 376 - 1993 Miniusticia

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.

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OLARTERAISBECK
OLARTE RAISBECK & FRIERI LTDA.

Carlos R. Olarte
J. Ian Raisbeck
Ana María Frieri
Juan Guillermo Moure
Natalia Castro

Zayde Chahin
Jacqueline Chaparro
José Luis Londoño
Felipe Mendoza
Simón Salinas

Of Counsel
Guillermo Chahin
Graciela Melo

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 Canonica 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

10

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. 2006

5. in Basel (Bâle) 6. on .....
7. by the State Chancery of the Canton of Basel-Stadt .....
8. no. 2'049'13'3/54
9. Seal / stamp: 10. Signature:

Heidi Fischer

STATE CHANCERY * BASLE-CITY *

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

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International Bureau

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C07D 401/04 (2006.01) *A61K 31/4439* (2006.01)
C07D 413/04 (2006.01) *A61P 9/00* (2006.01)
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25 June 2009 (25.06.2009)

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61/076,452 27 June 2008 (27.06.2008) US

(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)*: **ADAMS, Christopher** [US/US]; Novartis Institutes for BioMedical Research, Inc., 400 Technology Square, Cambridge, Massachusetts 02139 (US). **HU, Qi-Ying** [CN/US]; Novartis Institutes for BioMedical Research, Inc., 400 Technology Square, Cambridge, Massachusetts 02139 (US). **MCQUIRE, Leslie Wighton** [GB/US]; Novartis Institutes for BioMedical Research, Inc., 400 Technology Square, Cambridge, MA 02139 (US). **PAPILLON, Julien** [FR/US]; Novartis Institutes for BioMedical Research, Inc., 400 Technology Square, Cambridge, Massachusetts 02139 (US).

(74) Agent: **VOEGELI-LANGE, Regina**; 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, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PE, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, 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, MK, 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).

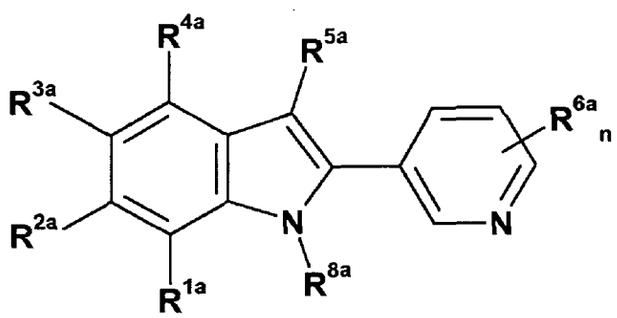
Declarations under Rule 4.17:

— *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 (Rule 48.2(g))*

(54) **Title**: ORGANIC COMPOUNDS



(I)

(57) **Abstract**: The present invention provides novel organic compounds of Formula (I): methods of use, and pharmaceutical compositions thereof.

WO 2009/156462 A2

ORGANIC COMPOUNDS

The mineralocorticoid hormone aldosterone is produced by the adrenal gland and acts on the distal tubules and collecting ducts of the kidney to increase reabsorption of ions and water in the kidney. Aldosterone causes conservation of sodium, secretion of potassium, increased water retention, and increased blood pressure.

Aldosterone has been implicated in the pathogenesis of cardiovascular diseases such as hypertension and heart failure. In clinical trials, treatment with the nonselective mineralocorticoid receptor antagonist (MRA) spironolactone or the selective MRA eplerenone significantly reduced morbidity and mortality among patients with heart failure or myocardial infarction already taking an angiotensin-converting enzyme inhibitor or a β-blocker. However, significant side effects such as gynecomastia and impotence were observed in male patients receiving spironolactone while hyperkalemia was seen in patients taking either drug.

The invention pertains to the compounds and methods for using them as described herein. Examples of compounds of the invention include the compounds of Formulae I-IV, and the compounds of the examples.

In another embodiment, the invention pertains, at least in part, to a method for treating an aldosterone synthase-mediated disorder or disease in a subject by administering to the subject a therapeutically effective amount of a compound of Formulae I-IV, such that the aldosterone synthase-mediated disorder or disease in the subject is treated.

In yet another embodiment, the invention pertains, at least in part, to a method for treating a subject for hypokalemia, hypertension, Conn's disease, renal failure, in particular, chronic renal failure, restenosis, atherosclerosis, syndrome X, obesity, nephropathy, post-myocardial infarction, coronary heart diseases, increased formation of collagen, fibrosis and remodeling following hypertension and endothelial dysfunction, cardiovascular diseases, renal dysfunction, liver diseases, cerebrovascular diseases, vascular diseases, retinopathy, neuropathy, insulinopathy, edema, endothelial dysfunction, baroreceptor dysfunction, migraine headaches, heart failure such as congestive heart failure, arrhythmia, diastolic dysfunction, left ventricular diastolic dysfunction, diastolic heart failure, impaired diastolic filling, systolic dysfunction, ischemia, hypertropic cardiomyopathy, sudden cardiac death, myocardial and vascular fibrosis, impaired arterial compliance, myocardial necrotic lesions, vascular damage,

myocardial infarction, left ventricular hypertrophy, decreased ejection fraction, cardiac lesions, vascular wall hypertrophy, endothelial thickening, or fibrinoid necrosis of coronary arteries, comprising administering to the subject a therapeutically effective amount of a compound of Formulae I-IV, such that the subject is treated.

In yet another embodiment, the invention pertains, at least in part, to pharmaceutical compositions, comprising an effective amount of a compound of Formulae 1, II, III or IV, wherein said effective amount is effective to treat an aldosterone synthase associated state.

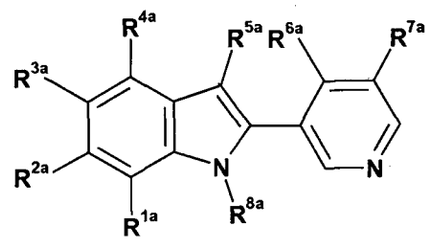
An alternative approach to ameliorate the deleterious effects of aldosterone is to suppress its production by inhibitors of aldosterone synthase, an enzyme responsible for the final steps of the biosynthesis of aldosterone from deoxycorticosterone, via conversion of corticosterone to form 18-OH-corticosterone, which is then converted to aldosterone.

The invention pertains, at least in part, to compounds, pharmaceutical compositions containing the compound and methods of use thereof. The present invention also relates to novel compounds which may be used, for example, as modulators of aldosterone synthase, or inhibitors of aldosterone synthesis.

The compounds of the present invention may, for example, be used to treat various aldosterone synthase associated states such as hypokalemia, hypertension, Conn's disease, renal failure, in particular, chronic renal failure, restenosis, atherosclerosis, syndrome X, obesity, nephropathy, post-myocardial infarction, coronary heart diseases, increased formation of collagen, fibrosis and remodeling following hypertension and endothelial dysfunction, cardiovascular diseases, renal dysfunction, liver diseases, cerebrovascular diseases, vascular diseases, retinopathy, neuropathy, insulinopathy, edema, endothelial dysfunction, baroreceptor dysfunction, migraine headaches, heart failure such as congestive heart failure, arrhythmia, diastolic dysfunction, left ventricular diastolic dysfunction, diastolic heart failure, impaired diastolic filling, systolic dysfunction, ischemia, hypertropic cardiomyopathy, sudden cardiac death, myocardial and vascular fibrosis, impaired arterial compliance, myocardial necrotic lesions, vascular damage, myocardial infarction, left ventricular hypertrophy, decreased ejection fraction, cardiac lesions, vascular wall hypertrophy, endothelial thickening, and fibrinoid necrosis of coronary arteries.

Compounds of the Invention

The present invention pertains, at least in part, to compounds of Formula I:



(I)

wherein:

R^{1a}, R^{2a}, R^{3a}, and R^{4a} are each independently hydrogen, halogen, cyano, hydroxy, alkoxy, alkyl, alkenyl, or alkoxycarbonyl;

R^{5a} is hydrogen halogen, cyano, alkyl, alkenyl, arylalkyl, heteroarylalkyl, aminocarbonyl, alkylaminocarbonyl, carboxylate, alkoxycarbonyl, heterocyclylcarbonyl, aryl, or heteroaryl;

R^{6a} and R^{7a} are each independently hydrogen, halogen, hydroxy, alkoxy, amino, alkyl, sulfonyl, -O-sulfonyl, alkylamino, heterocyclyl, aminocarbonyl, carboxylate, or alkoxycarbonyl;

R^{8a} is hydrogen, alkyl, arylalkyl, heteroarylalkyl, alkoxycarbonyl, sulfonyl, aroyl, aryl, or heteroaryl; and pharmaceutically acceptable salts, polymorphs, rotamers, prodrugs, enantiomers, hydrates, and solvates thereof;

with the proviso that at least one of R^{1a}-R^{8a} is other than hydrogen; and when R^{3a} is lower alkyl or halogen, then at least one of R^{1a}, R^{2a} and R^{4a}-R^{8a} is other than hydrogen; and when R^{5a} is cyano or lower alkyl optionally substituted with cyano, -C(O)-piperidine, amino, alkylamino, dialkylamino, carboxylate, alkoxycarbonyl, aminocarbonyl, or heterocyclyl, then at least one of R^{1a}-R^{4a} and R^{6a}-R^{8a} is other than hydrogen; and when R^{7a} is imidazolyl, then at least one of R^{1a}-R^{6a} and R^{8a} is other than hydrogen; and when R^{8a} is lower alkyl, arylalkyl or alkoxycarbonyl, then at least one of R^{1a}-R^{7a} is other than hydrogen; and when R^{5a} is lower alkyl and R^{8a} is alkyl substituted with carboxylate or $PO_3R^{21}R^{22}$ wherein R^{21} and R^{22} are each independently hydrogen or lower alkyl, then at least one of R^{1a}-R^{4a} and R^{6a} and R^{7a} is other than hydrogen; and when R^{3a} is halogen and R^{5a} and R^{8a} are independently lower alkyl optionally substituted with carboxylate, alkoxycarbonyl, or -C(O)-piperidine, then at least one of R^{1a}, R^{2a}, R^{4a}, R^{6a} and R^{7a} is other than hydrogen; and when R^{5a} is lower alkenyl substituted with heteroaryl and R^{8a} is lower alkyl, then at least one of R^{1a}-R^{4a}, R^{6a} and R^{7a} is other than hydrogen; and when R^{3a} is halogen or lower alkyl and R^{5a} is lower alkyl substituted with dialkylamino,

myocardial infarction, left ventricular hypertrophy, decreased ejection fraction, cardiac lesions, vascular wall hypertrophy, endothelial thickening, or fibrinoid necrosis of coronary arteries, comprising administering to the subject a therapeutically effective amount of a compound of Formulae I-IV, such that the subject is treated.

In yet another embodiment, the invention pertains, at least in part, to pharmaceutical compositions, comprising an effective amount of a compound of Formulae 1, II, III or IV, wherein said effective amount is effective to treat an aldosterone synthase associated state.

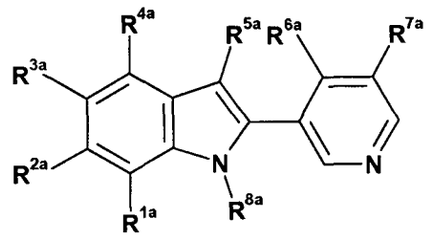
An alternative approach to ameliorate the deleterious effects of aldosterone is to suppress its production by inhibitors of aldosterone synthase, an enzyme responsible for the final steps of the biosynthesis of aldosterone from deoxycorticosterone, via conversion of corticosterone to form 18-OH-corticosterone, which is then converted to aldosterone.

The invention pertains, at least in part, to compounds, pharmaceutical compositions containing the compound and methods of use thereof. The present invention also relates to novel compounds which may be used, for example, as modulators of aldosterone synthase, or inhibitors of aldosterone synthesis.

The compounds of the present invention may, for example, be used to treat various aldosterone synthase associated states such as hypokalemia, hypertension, Conn's disease, renal failure, in particular, chronic renal failure, restenosis, atherosclerosis, syndrome X, obesity, nephropathy, post-myocardial infarction, coronary heart diseases, increased formation of collagen, fibrosis and remodeling following hypertension and endothelial dysfunction, cardiovascular diseases, renal dysfunction, liver diseases, cerebrovascular diseases, vascular diseases, retinopathy, neuropathy, insulinopathy, edema, endothelial dysfunction, baroreceptor dysfunction, migraine headaches, heart failure such as congestive heart failure, arrhythmia, diastolic dysfunction, left ventricular diastolic dysfunction, diastolic heart failure, impaired diastolic filling, systolic dysfunction, ischemia, hypertropic cardiomyopathy, sudden cardiac death, myocardial and vascular fibrosis, impaired arterial compliance, myocardial necrotic lesions, vascular damage, myocardial infarction, left ventricular hypertrophy, decreased ejection fraction, cardiac lesions, vascular wall hypertrophy, endothelial thickening, and fibrinoid necrosis of coronary arteries.

Compounds of the Invention

The present invention pertains, at least in part, to compounds of Formula I:



(I)

wherein:

R^{1a}, R^{2a}, R^{3a}, and R^{4a} are each independently hydrogen, halogen, cyano, hydroxy, alkoxy, alkyl, alkenyl, or alkoxycarbonyl;

R^{5a} is hydrogen halogen, cyano, alkyl, alkenyl, arylalkyl, heteroarylalkyl, aminocarbonyl, alkylaminocarbonyl, carboxylate, alkoxycarbonyl, heterocyclylcarbonyl, aryl, or heteroaryl;

R^{6a} and R^{7a} are each independently hydrogen, halogen, hydroxy, alkoxy, amino, alkyl, sulfonyl, -O-sulfonyl, alkylamino, heterocyclyl, aminocarbonyl, carboxylate, or alkoxycarbonyl;

R^{8a} is hydrogen, alkyl, arylalkyl, heteroarylalkyl, alkoxycarbonyl, sulfonyl, aroyl, aryl, or heteroaryl; and pharmaceutically acceptable salts, polymorphs, rotamers, prodrugs, enantiomers, hydrates, and solvates thereof;

with the proviso that at least one of R^{1a}-R^{8a} is other than hydrogen; and when R^{3a} is lower alkyl or halogen, then at least one of R^{1a}, R^{2a} and R^{4a}-R^{8a} is other than hydrogen; and when R^{5a} is cyano or lower alkyl optionally substituted with cyano, -C(O)-piperidine, amino, alkylamino, dialkylamino, carboxylate, alkoxycarbonyl, aminocarbonyl, or heterocyclyl, then at least one of R^{1a}-R^{4a} and R^{6a}-R^{8a} is other than hydrogen; and when R^{7a} is imidazolyl, then at least one of R^{1a}-R^{6a} and R^{8a} is other than hydrogen; and when R^{8a} is lower alkyl, arylalkyl or alkoxycarbonyl, then at least one of R^{1a}-R^{7a} is other than hydrogen; and when R^{5a} is lower alkyl and R^{8a} is alkyl substituted with carboxylate or $PO_3R^{21}R^{22}$ wherein R^{21} and R^{22} are each independently hydrogen or lower alkyl, then at least one of R^{1a}-R^{4a} and R^{6a} and R^{7a} is other than hydrogen; and when R^{3a} is halogen and R^{5a} and R^{8a} are independently lower alkyl optionally substituted with carboxylate, alkoxycarbonyl, or -C(O)-piperidine, then at least one of R^{1a}, R^{2a}, R^{4a}, R^{6a} and R^{7a} is other than hydrogen; and when R^{5a} is lower alkenyl substituted with heteroaryl and R^{8a} is lower alkyl, then at least one of R^{1a}-R^{4a}, R^{6a} and R^{7a} is other than hydrogen; and when R^{3a} is halogen or lower alkyl and R^{5a} is lower alkyl substituted with dialkylamino,

dialkylaminocarbonyl, carboxylate, alkoxycarbonyl or aminocarbonyl, then at least one of R^{1a}, R^{2a}, R^{4a}, and R^{6a}-R^{8a} is other than hydrogen; and when R^{3a} is –O-benzyl and R^{5a} is alkyl-NH_2, then at least one of R^{1a}, R^{2a}, R^{4a}, and R^{6a}-R^{8a} is other than hydrogen; and when R^{2a} and R^{3a} are each alkoxy and R^{5a} is cyano, then at least one of R^{1a}, R^{4a}, and R^{6a}-R^{8a} is other than hydrogen; and when R^{1a} and R^{3a} are each halogen and R^{5a} is alkyl–NH_2, then at least one of R^{2a}, R^{4a}, and R^{6a}-R^{8a} is other than hydrogen; and when R^{2a} is alkoxycarbonyl and R^{4a} is halogen, then at least one of R^{1a}, R^{3a}, R^{5a} and R^{6a}-R^{8a} is other than hydrogen; and when R^{5a} is alkyl and R^{7a} is –OCH_2-(N-methyl pyrrolidine), then at least one of R^{1a}-R^{4a}, R^{6a} and R^{8a} is other than hydrogen; and when R^{3a} is cycloalkyl and R^{5a} is alkyl–NH_2, then at least one of R^{1a}, R^{2a}, R^{4a}, and R^{6a}-R^{8a} is other than hydrogen; and when R^{3a} is alkyl substituted with aroyl, and R^5 and R^8 are each independently hydrogen or lower alkyl, then at least one of R^{1a}, R^{2a}, and R^{4a} is other than hydrogen.

Examples of R^{1a} include hydrogen, halogen (*e.g.*, chlorine or fluorine), hydroxy, and alkoxy (*e.g.*, methoxy).

In a further embodiment, R^{1a} is optionally substituted alkyl (*e.g.*, methyl, ethyl, or propyl), which may be substituted with groups such as carboxylate, hydroxy, alkylamino (*e.g.*, ethylamino) which may be further substituted with hydroxy, and aryl (*e.g.*, phenyl) which may be further substituted with carboxylate.

In yet a further embodiment, R^{1a} is optionally substituted alkenyl (*e.g.*, alkenyl is ethenyl or propenyl), which may be substituted with groups such as hydroxy, alkoxycarbonyl (*e.g.*, butoxycarbonyl), and aryl (*e.g.*, phenyl) which may be further substituted with alkoxycarbonyl (*e.g.*, methoxycarbonyl).

In one embodiment, R^{2a} includes hydrogen, halogen (*e.g.*, chlorine or fluorine), hydroxy, alkyl (*e.g.*, methyl), and alkoxy (*e.g.*, methoxy).

Examples of R^{3a} include, hydrogen, halogen (*e.g.*, chlorine or fluorine), alkoxy (*e.g.*, methoxy), cyano, and alkoxycarbonyl (*e.g.*, methoxycarbonyl).

In a further embodiment, R^{3a} is optionally substituted alkyl (*e.g.*, methyl or ethyl), which may be substituted with groups such as carboxylate, alkoxycarbonyl (*e.g.*, ethoxycarbonyl), hydroxy, and halogen. This optionally substituted alkyl may be, for example trifluoromethyl.

Examples of R^{4a} include, hydrogen, halogen (*e.g.*, fluorine), and cyano.

In one embodiment, R^{5a} includes hydrogen, halogen (*e.g.*, bromine), alkenyl (*e.g.*, propenyl), cyano, –$C(O)NH_2$, carboxylate, alkoxycarbonyl (*e.g.*, methoxycarbonyl or isopropoxycarbonyl), arylalkyl (*e.g.*, benzyl), heteroarylalkyl (*e.g.*, imidazolylmethyl),

heterocyclylcarbonyl (*e.g.*, pyrrolidinylcarbonyl), alkylaminocarbonyl (*e.g.*, ethylaminocarbonyl), and aryl (*e.g.*, phenyl).

In another embodiment, R^{5a} includes optionally substituted alkyl (*e.g.*, methyl, ethyl, propyl or butyl), which may be substituted with groups such as hydroxy, alkoxy (*e.g.*, ethoxy), and carboxylate.

In yet another embodiment, R^{5a} includes optionally substituted heteroaryl (*e.g.*, 1,2,4-oxadiazolyl), which may be substituted with groups such as alkyl (*e.g.*, methyl).

Examples of R^{6a} and R^{7a} include alkoxy (*e.g.*, methoxy, ethoxy, or benzyloxy), which may be substituted with hydroxy or aryl (*e.g.*, phenyl); halogen (*e.g.*, chlorine or fluorine); hydroxy; sulfonyl, which may be substituted with aryl (*e.g.*, phenylsulfonyl) or alkyl (*e.g.*, butylsulfonyl); alkylamino (*e.g.*, ethylamino); carboxylate; alkoxycarbonyl (*e.g.*, ethoxycarbonyl); aminocarbonyl; and amino (*e.g.*, $-NH(S(O)_2(CH_3)_2$, $-NR'-S(O)_2$-alkyl, -NR'-C(O)-alkyl, -NR'-C(O)-NR'-alkyl, and -NR'-C(O)-O-alkyl, wherein each R' is independently hydrogen, C_1-C_4-alkyl, or C_3-C_6-cycloalkyl). In another embodiment, R^{6a} is $-NH-S(O)_2-CH_3$.

In one embodiment, R^{6a} and R^{7a} includes optionally substituted heterocyclyl (*e.g.*, piperazinyl), which may be substituted with groups such as alkyl (*e.g.*, methyl).

In another embodiment, R^{6a} and R^{7a} includes optionally substituted alkyl (*e.g.*, methyl or ethyl), which may be substituted with groups such as heterocyclyl (*e.g.*, morpholinyl, piperazinyl, pyrrolidinyl, or thiomorpholinyl dioxide), which may itself be substituted with alkyl (*e.g.*, methyl) or $-NH_2$; hydroxy; alkoxy (*e.g.*, methoxy); or halogen. This optionally substituted alkyl may be, for example, trifluoromethyl.

In another embodiment, R^{6a} and R^{7a} includes optionally substituted alkyl (*e.g.*, methyl or ethyl), which may be substituted with amino (*e.g.*, $-NR^{30b}R^{31b}$). Examples of R^{30b} include hydrogen and methyl. Examples of R^{31b} include alkoxycarbonyl (*e.g.*, ethoxycarbonyl); alkylaminocarbonyl (*e.g.*, ethylaminocarbonyl); heterocyclylcarbonyl (*e.g.*, morpholinyl); acyl (*e.g.*, $-C(O)(CH_2)_2CH_3$); alkyl (*e.g.*, ethyl), which may optionally be substituted with hydroxy; sulfonyl, which may be substituted with benzyl; dialkylamino (*e.g.*, diethylaminosulfonyl); alkyl (*e.g.*, methylsulfonyl, ethylsulfonly, propylsulfonyl, butylsulfonyl, or trifluoromethylsulfonyl); or aryl (*e.g.*, phenylsulfonyl). This phenylsulfonyl may be, for example, further substituted with halogen (*e.g.*, fluorine).

In another embodiment, R^{6a} and R^{7a} includes optionally substituted –O-sulfonyl, which may be substituted with groups such as alkyl (*e.g.*, methyl); amino (*e.g.*,

dimethylamino, diethylamino, or –N(Et)(benzyl)); or heterocyclyl (*e.g.*, morpholinyl, piperazinyl, N-methyl piperazinyl, or pyrrolidinyl).

In one embodiment, R^{8a} includes hydrogen, heteroaryl (*e.g.*, 3-pyridinyl), and alkoxycarbonyl (*e.g.*, isopropoxycarbonyl or butoxycarbonyl).

In another embodiment, R^{8a} includes optionally substituted arylalkyl (*e.g.*, benzyl), which may be substituted with groups at the para position and/or at the meta position. Examples of such groups include alkoxycarbonyl (*e.g.*, methoxycarbonyl); carboxylate; alkyl (*e.g.*, methyl); cyano; alkoxy (*e.g.*, methoxy); halogen (*e.g.*, fluorine); sulfonyl, which is optionally substituted with alkyl (*e.g.*, methylsulfonyl); heteroaryl (*e.g.*, tetrazolyl); alkoxy (*e.g.*, methoxy or benzyloxy); or combinations thereof.

In yet another embodiment, R^{8a} includes optionally substituted heteroarylalkyl (*e.g.*, benzoimidizolyl methyl, 1,2,3-triazolylmethyl, or isoxazolyl methyl), which may be substituted with alkyl (*e.g.*, methyl), which may optionally be further substituted with aryl (*e.g.*, phenyl) such that R^{8a} is heteroarylalkyl substituted with benzyl.

In another embodiment, R^{8a} includes optionally substituted aroyl (*e.g.*, benzoyl), which may be substituted with groups at the para position and/or at the meta position. Examples of such groups include cyano, alkyl (*e.g.*, methyl or ethyl), alkoxy (*e.g.*, methoxy or dimethoxy), alkoxycarbonyl (*e.g.*, butoxycarbonyl), carboxylate, or combinations thereof.

In another embodiment, R^{8a} includes optionally substituted alkyl (*e.g.*, methyl, ethyl, propyl, isopropyl or butyl), which may be substituted with groups such as –$NHC(O)R^{20a}$ and –$OC(O)R^{20a}$, wherein R^{20a} is alkyl (*e.g.*, butyl).

In yet another embodiment, R^{8a} includes optionally substituted alkyl (*e.g.*, methyl, ethyl, propyl, isopropyl or butyl), which may be substituted with groups such as cycloalkyl (*e.g.*, cyclohexyl); carboxylate; hydroxy; alkoxycarbonyl (*e.g.*, butoxycarbonyl); and sulfonyl, which is optionally substituted with aryl (*e.g.*, phenylsulfonyl).

In still another embodiment, R^{8a} includes optionally substituted alkyl (*e.g.*, methyl, ethyl, propyl, isopropyl or butyl), which may be substituted with groups such as heterocyclyl (*e.g.*, piperazinyl or azetidyl), which may itself be substituted with groups such as alkyl, dialkyl (*e.g.*, dimethyl), and =O.

In yet another embodiment, R^{8a} includes optionally substituted alkyl (*e.g.*, methyl, ethyl, propyl, isopropyl or butyl), which may be substituted with groups such as heterocyclylcarbonyl (*e.g.*, piperazinylcarbonyl), which may itself be substituted with groups such as alkyl or dialkyl (*e.g.*, dimethyl); aryl (*e.g.*, phenyl), which may itself be

substituted with groups such as carboxylate; and alkoxy (*e.g.*, methoxy, ethoxy, propoxy, butoxy, pentoxy, or phenoxy), which may itself be substituted with groups such as alkoxycarbonyl (*e.g.*, methoxycarbonyl or ethoxycarbonyl), carboxylate, and hydroxy.

In one embodiment, R^{8a} is phenoxy substituted alkyl (*e.g.*, methyl, ethyl, propyl, isopropyl or butyl), and this phenoxy is optionally substituted at the para position and/or at the meta position with groups such as alkoxycarbonyl (*e.g.*, methoxycarbonyl or ethoxycarbonyl), carboxylate, and hydroxy.

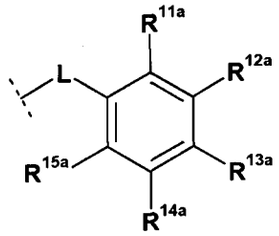
Another example of R^{8a} includes optionally substituted aryl (*e.g.*, phenyl), which may be substituted at the para position and/or at the meta position with groups such as cyano, alkoxy (*e.g.*, methoxy), or combinations thereof.

Another example of R^{8a} includes optionally substituted sulfonyl, which may be substituted with groups such as aryl (*e.g.*, phenyl), which may itself be substituted with groups such as alkyl (*e.g.*, methyl), carboxylate, or combinations thereof.

In one embodiment of the present invention R^{5a} is hydrogen, methyl, ethyl, cyano, carboxylate, or alkoxycarbonyl.

In another embodiment of the present invention R^{8a} is hydrogen, methyl, ethyl, benzyl-CO_2H, or benzyl-CO_2Me.

In yet another embodiment, R^{8a} is:



L is alkyl, carbonyl, sulfonyl, or $-(CH_2)_2-O-$; and

R^{11a}, R^{12a}, R^{13a}, R^{14a}, and R^{15a} are each independently hydrogen, alkyl, cyano, halogen, alkoxy, alkoxycarbonyl, carboxylate, heteroaryl, or sulfonyl.

Each of the aforementioned groups R^{1a}, R^{2a}, R^{3a}, R^{4a}, R^{5a}, R^{6a} and R^{8a} may be optionally substituted.

Another embodiment of Formual (I), wherein:

R^{1a} is hydrogen, halogen, hydroxy, alkoxy, alkyl, or alkenyl;

R^{2a} is hydrogen, halogen, alkyl, hydroxy, or alkoxy;

R^{3a} is hydrogen, halogen, cyano, alkoxy, alkyl, or alkoxycarbonyl;

R^{4a} is hydrogen, halogen, or cyano;

R^{5a} is hydrogen, halogen, cyano, alkyl, alkenyl, arylalkyl, heteroarylalkyl, aminocarbonyl, alkylaminocarbonyl, carboxylate, alkoxycarbonyl, heterocyclylcarbonyl, aryl, or heteroaryl;

R^{6a} and R^{7a} are each independently hydrogen, halogen, hydroxy, alkoxy, amino, alkyl, sulfonyl, -O-sulfonyl, alkylamino, heterocyclyl, aminocarbonyl, carboxylate, or alkoxycarbonyl; and

R^{8a} is hydrogen, alkyl, arylalkyl, heteroarylalkyl, alkoxycarbonyl, sulfonyl, aroyl, aryl, or heteroaryl.

Another embodiment of Formual (I), wherein:

R^{5a} is hydrogen, cyano, methyl, ethyl, carboxylate, or methoxycarbonyl.

Another embodiment of Formual (I), wherein:

R^{8a} is hydrogen, methyl, ethyl, benzyl-CO_2H, or benzyl-CO_2Me.

Another embodiment of Formual (I), wherein:

R^{1a} is hydrogen;

R^{2a} is hydrogen, halogen, or hydroxy;

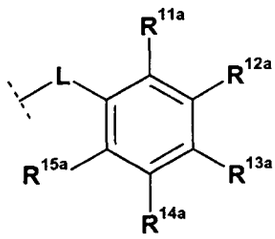
R^{3a} is hydrogen, halogen, cyano, or alkoxy;

R^{4a} is hydrogen or halogen;

R^{5a} is hydrogen or alkyl;

R^{6a} and R^{7a} are hydrogen;

R^{8a} is:



L is alkyl, carbonyl, sulfonyl, or -$(CH_2)_2$-O- ; and

R^{11a}, R^{12a}, R^{13a}, R^{14a}, and R^{15a} are each independently hydrogen, alkyl, cyano, halogen, alkoxy, alkoxycarbonyl, carboxylate, heteroaryl, or sulfonyl.

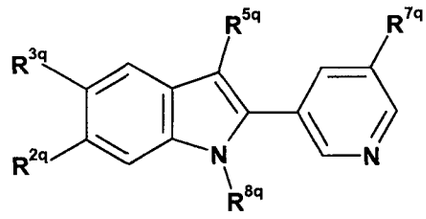
Another embodiment of Formual (I),, wherein:

R^{11a} and R^{15a} are each independently hydrogen, alkyl, cyano, halogen, or alkoxy;

R^{12a} and R^{14a} are each independently hydrogen, alkyl, cyano, halogen, alkoxy, alkoxycarbonyl, carboxylate, heteroaryl, or sulfonyl; and

R^{13a} is hydrogen, alkyl, cyano, alkoxy, alkoxycarbonyl, carboxylate, heteroaryl, or sulfonyl.

In yet another embodiment, the invention pertains, at least in part, to compounds of Formula II:



(II)

wherein:

R^{2q} is hydrogen or halogen;

R^{3q} is hydrogen, halogen, or cyano;

R^{5q} is hydrogen, alkyl, or cyano;

R^{7q} is hydrogen, halogen, alkoxy, -OSO_2-heterocyclyl, -O-arylalkyl, -NR'-SO_2-alkyl, -NR'-C(O)-alkyl, -NR'-C(O)-NR'-alkyl, -NR'-C(O)-O-alkyl, haloalkyl, or alkyl optionally substituted with heterocyclyl, –NR'-SO_2-alkyl, -NR'-SO_2-haloalkyl, NR'-C(O)-alkyl, NR'-C(O)-heterocyclyl, -NR'-C(O)-NR'-alkyl, or –NR'-C(O)-O-alkyl;

R^{8q} is hydrogen, alkyl, hydroxyalkyl, -alkyl-OC(O)-alkyl, carboxylate, alkoxycarbonyl, or arylalkyl substituted with alkyl, or aroyl substituted with cyano and/or alkyl, or -alkyl-O-aryl substituted with alkoxycarbonyl;

each R' is independently hydrogen, C_1-C_4-alkyl, or C_3-C_6-cycloalkyl; and pharmaceutically acceptable salts, polymorphs, rotamers, prodrugs, enantiomers, hydrates, and solvates thereof,

with the proviso that at least one of R^{2q}, R^{3q}, R^{5q}, R^{7q} and R^{8q} is other than hydrogen; and when R^{8q} is lower alkyl or alkoxycarbonyl, then at least one of R^{2q}, R^{3q}, R^{5q} and R^{7q} is other than hydrogen; and when R^{5q} is cyano, then at least one of R^{2q}, R^{3q}, and R^{8q} is other than hydrogen.

In another embodiment, R^{7q} is alkoxy or alkyl substituted with heterocyclyl and R^{8q} is alkyl.

Another embodiment of Formula (II), wherein R^{7q} is alkoxy or alkyl substituted with heterocyclyl and R^{8q} is alkyl.

Another embodiment of Formula (II), wherein

R^{2q} is hydrogen or halogen;

R^{3q} is hydrogen, or halogen;

R^{5q} is hydrogen or cyano;

R^{7q} is alkyl optionally substituted with heterocyclyl, –NR'-SO_2-alkyl, -NR'-SO_2-haloalkyl, NR'-C(O)-alkyl, NR'-C(O)-heterocyclyl, -NR'-C(O)-NR'-alkyl, or –NR'-C(O)-O-alkyl;

R' is independently hydrogen, C_1-C_4-alkyl, or C_3-C_6-cycloalkyl; and

R^{8q} is hydrogen, or C_{1-6}alkyl.

Another embodiment of Formula (II),, wherein

R^{2q} is hydrogen or halogen;

R^{3q} is hydrogen, or halogen;

R^{5q} is hydrogen or cyano;

R^{7q} is C_{1-4}alkyl optionally substituted with heterocyclyl, –NR'-SO_2-C_{1-4}alkyl, -NR'-SO_2-haloC_{1-4}alkyl, NR'-C(O)- C_{1-4}alkyl, NR'-C(O)-heterocyclyl, -NR'-C(O)-NR'-C_{1-4}alkyl, or –NR'-C(O)-O-C_{1-4}alkyl;

R' is independently hydrogen, or C_1-C_4-alkyl; and

R^{8q} is hydrogen, or C_{1-6}alkyl.

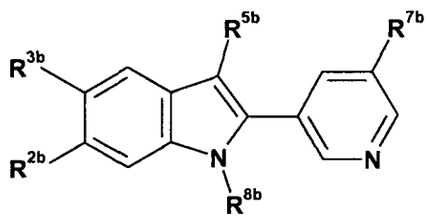
Another embodiment of Formula (II),, wherein

R^{7q} is C_{1-4}alkyl substituted with –NR'-SO_2-C_{1-4}alkyl, -NR'-SO_2-haloC_{1-4}alkyl, or NR'-C(O)- C_{1-4}alkyl;

R' is independently hydrogen, or C_1-C_4-alkyl; and

R^{8q} is hydrogen, methyl, or ethyl.

In yet another embodiment, the invention pertains, at least in part, to compounds of Formula III:



(III)

wherein:

R^{2b} is hydrogen or halogen;

R^{3b} is hydrogen, halogen, or cyano;

R^{5b} is alkyl;

R^{7b} is hydrogen, halogen, alkoxy, -OSO_2-heterocyclyl, -O-arylalkyl, -NR'-SO_2-alkyl, -NR'-C(O)-alkyl, -NR'-C(O)-NR'-alkyl, -NR'-C(O)-O-alkyl, haloalkyl, or alkyl

optionally substituted with heterocyclyl, –NR'-SO_2-alkyl, -NR'-SO_2-haloalkyl, NR'-C(O)-alkyl, -NR'-C(O)-NR'-alkyl, NR'-C(O)-heterocyclyl, or –NR'-C(O)-O-alkyl;

R^{8b} is hydrogen, alkyl, hydroxyalkyl, -alkyl-OC(O)-alkyl, carboxylate, alkoxycarbonyl, or arylalkyl substituted with alkyl, or aroyl substituted with cyano and/or alkyl, or -alkyl-O-aryl substituted with alkoxycarbonyl;

each R' is independently hydrogen, C_1-C_4-alkyl, or C_3-C_6-cycloalkyl; and pharmaceutically acceptable salts, polymorphs, rotamers, prodrugs, enantiomers, hydrates, and solvates thereof.

Another embodiment of Formaul (III), wherein

R^{2b} is hydrogen or halogen;

R^{3b} is hydrogen, halogen, or cyano;

R^{5b} is C_{1-4}alkyl;

R^{7b} is hydrogen, halogen, C_{1-4}alkoxy, -OSO_2-heterocyclyl, -O-arylalkyl, -NR'-SO_2-C_{1-4}alkyl, -NR'-C(O)- C_{1-4}alkyl, -NR'-C(O)-NR'- C_{1-4}alkyl, -NR'-C(O)-O-alkyl, haloalkyl, or C_{1-4}alkyl optionally substituted with heterocyclyl, –NR'-SO_2- C_{1-4}alkyl, -NR'-SO_2-halo C_{1-4}alkyl, NR'-C(O)- C_{1-4}alkyl, -NR'-C(O)-NR'- C_{1-4}alkyl, NR'-C(O)-heterocyclyl, or –NR'-C(O)-O- C_{1-4}alkyl;

R^{8b} is hydrogen, C_{1-4}alkyl, hydroxyalkyl, - C_{1-4}alkyl-OC(O)- C_{1-4}alkyl, carboxylate, alkoxycarbonyl, or arylalkyl substituted with C_{1-4}alkyl, or aroyl substituted with cyano and/or C_{1-4}alkyl, or - C_{1-4}alkyl-O-aryl substituted with alkoxycarbonyl;

each R' is independently hydrogen, C_1-C_4-alkyl, or C_3-C_6-cycloalkyl; and pharmaceutically acceptable salts, polymorphs, rotamers, prodrugs, enantiomers, hydrates, and solvates thereof.

Another embodiment of Formaul (III), wherein

R^{2b} is hydrogen or halogen;

R^{3b} is hydrogen, halogen, or cyano;

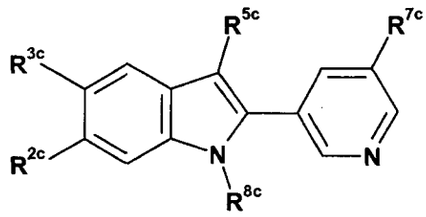
R^{5b} is methyl, ethyl or isopropyl;

R^{7b} is C_{1-4}alkyl substituted with –NR'-SO_2- C_{1-4}alkyl, -NR'-SO_2-haloC_{1-4}alkyl, NR'-C(O)- C_{1-4}alkyl, or -NR'-C(O)-NR'- C_{1-4}alkyl;

R^{8b} is hydrogen, methyl or ethyl;

each R' is independently hydrogen, or C_1-C_4-alkyl.

In yet another embodiment, the invention pertains, at least in part, to compounds of Formula IV:



(IV)

wherein:

R^{2c} is hydrogen or halogen;

R^{3c} is hydrogen, halogen, or cyano;

R^{5c} is cyano; and

R^{7c} is hydrogen, halogen alkoxy, -OSO_2-heterocyclyl, -O-arylalkyl, -NR'-SO_2-alkyl, -NR'-C(O)-alkyl, -NR'-C(O)-NR'-alkyl, -NR'-C(O)-O-alkyl or alkyl optionally substituted with heterocyclyl, –NR'-SO_2-alkyl, -NR'-SO_2-haloalkyl, NR'-C(O)-alkyl, NR'-C(O)-heterocyclyl, -NR'-C(O)-NR'-alkyl, or –NR'-C(O)-O-alkyl;

R^{8c} is alkyl;

each R' is independently hydrogen, C_1-C_4-alkyl, or C_3-C_6-cycloalkyl; and pharmaceutically acceptable salts, polymorphs, rotamers, prodrugs, enantiomers, hydrates, and solvates thereof.

Another embodiment of Formula (IV), wherein

R^{2c} is hydrogen or halogen;

R^{3c} is hydrogen, halogen, or cyano;

R^{5c} is cyano; and

R^{7c} is hydrogen, halogen, C_{1-4}alkoxy, -OSO_2-heterocyclyl, -O-arylalkyl, -NR'-SO_2-C_{1-4} alkyl, -NR'-C(O)- C_{1-4} alkyl, -NR'-C(O)-NR'- C_{1-4} alkyl, -NR'-C(O)-O- C_{1-4} alkyl or C_{1-4} alkyl optionally substituted with heterocyclyl, –NR'-SO_2- C_{1-4} alkyl, -NR'-SO_2-halo C_{1-4} alkyl, NR'-C(O)- C_{1-4} alkyl, NR'-C(O)-heterocyclyl, -NR'-C(O)-NR'- C_{1-4} alkyl, or –NR'-C(O)-O- C_{1-4} alkyl;

R^{8c} is C_{1-4} alkyl;

each R' is independently hydrogen, C_1-C_4-alkyl, or C_3-C_6-cycloalkyl; and pharmaceutically acceptable salts, polymorphs, rotamers, prodrugs, enantiomers, hydrates, and solvates thereof.

Another embodiment of Formula (IV),, wherein

R^{2c} is hydrogen or halogen;

R^{3c} is hydrogen, or halogen;

R^{5c} is cyano; and

R^{7c} is C_{1-4} alkyl optionally substituted with –NR'-SO_2- C_{1-4} alkyl, -NR'-SO_2-halo C_{1-4} alkyl, NR'-C(O)- C_{1-4} alkyl;

R^{8c} is C_{1-4} alkyl;

each R' is independently hydrogen or C_1-C_4-alkyl.

Another embodiment of Formula (IV),, wherein

R^{7c} is C_{1-4} alkyl substituted with –NR'-SO_2- C_{1-4} alkyl, -NR'-SO_2-halo C_{1-4} alkyl, NR'-C(O)- C_{1-4} alkyl; and

each R' is independently hydrogen, methyl, ethyl or propyl.

Definitions

The term "alkyl" includes saturated aliphatic groups, including straight-chain alkyl groups (*e.g.*, methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, nonyl, decyl, etc.), branched-chain alkyl groups (isopropyl, tert-butyl, isobutyl, etc.), cycloalkyl (alicyclic) groups (cyclopropyl, cyclopentyl, cyclohexyl, cycloheptyl, and cyclooctyl), alkyl substituted cycloalkyl groups, and cycloalkyl substituted alkyl groups. The term alkyl further includes alkyl groups, which can further include oxygen, nitrogen, sulfur or phosphorous atoms replacing one or more carbons of the hydrocarbon backbone. In certain embodiments, a straight chain or branched chain alkyl has 6 or fewer carbon atoms in its backbone (*e.g.*, C_1-C_6 for straight chain, C_3-C_6 for branched chain), and more preferably 4 or fewer. Likewise, preferred cycloalkyls have from 3-8 carbon atoms in their ring structure, and more preferably have 5 or 6 carbons in the ring structure. The term C_1-C_6 includes alkyl groups containing 1 to 6 carbon atoms.

Moreover, the term alkyl includes both "unsubstituted alkyls" and "substituted alkyls," the latter of which refers to alkyl moieties having substituents replacing a hydrogen on one or more carbons of the hydrocarbon backbone. Such substituents can include, for example, alkenyl, alkynyl, halogen, hydroxy, alkylcarbonyloxy, arylcarbonyloxy, alkoxycarbonyloxy, aryloxycarbonyloxy, carboxylate, alkylcarbonyl, arylcarbonyl, alkoxycarbonyl, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, alkylthiocarbonyl, alkoxy, phosphate, phosphonato, phosphinato, cyano, amino (including alkyl amino, dialkylamino, arylamino, diarylamino, and alkylarylamino), acylamino (including alkylcarbonylamino, arylcarbonylamino, carbamoyl and ureido), amidino, imino, sulfhydryl, alkylthio, arylthio, thiocarboxylate, sulfates, alkylsulfinyl, sulfonato, sulfamoyl, sulfonamido, nitro, trifluoromethyl, cyano, azido, heterocyclyl,

alkylaryl, or an aromatic or heteroaromatic moiety. Cycloalkyls can be further substituted, *e.g.*, with the substituents described above. An "alkylaryl" or an "arylalkyl" moiety is an alkyl substituted with an aryl (*e.g.*, phenylmethyl (benzyl)). The term "alkyl" also includes the side chains of natural and unnatural amino acids.

The term "aryl" includes groups, including 5- and 6-membered single-ring aromatic groups that may include from zero to four heteroatoms, for example, benzene, phenyl, pyrrole, furan, thiophene, thiazole, isothiaozole, imidazole, triazole, tetrazole, pyrazole, oxazole, isooxazole, pyridine, pyrazine, pyridazine, and pyrimidine, etc. Furthermore, the term "aryl" includes multicyclic aryl groups, *e.g.*, tricyclic, bicyclic, *e.g.*, naphthalene, benzoxazole, benzodioxazole, benzothiazole, benzoimidazole, benzothiophene, methylenedioxyphenyl, quinoline, isoquinoline, napthridine, indole, benzofuran, purine, benzofuran, deazapurine, or indolizine. Those aryl groups having heteroatoms in the ring structure may also be referred to as "aryl heterocycles," "heterocycles," "heteroaryls" or "heteroaromatics."

Typical heteroaryl groups include 2- or 3-thienyl, 2- or 3-furyl, 2- or 3-pyrrolyl, 2-, 4-, or 5-imidazolyl, 3-, 4-, or 5- pyrazolyl, 2-, 4-, or 5-thiazolyl, 3-, 4-, or 5-isothiazolyl, 2-, 4-, or 5-oxazolyl, 3-, 4-, or 5-isoxazolyl, 3- or 5-1,2,4-triazolyl, 4- or 5-1,2, 3-triazolyl, tetrazolyl, 2-, 3-, or 4-pyridyl, 3- or 4-pyridazinyl, 3-, 4-, or 5-pyrazinyl, 2-pyrazinyl, 2-, 4-, or 5-pyrimidinyl. A heteroaryl group may be mono-, bi-, tri-, or polycyclic.

The term "heteroaryl" also refers to a group in which a heteroaromatic ring is fused to one or more aryl, cycloaliphatic, or heterocyclyl rings, where the radical or point of attachment is on the heteroaromatic ring. Non-limiting examples include but are not limited to 1-, 2-, 3-, 5-, 6-, 7-, or 8- indolizinyl, 1-, 3-, 4-, 5-, 6-, or 7-isoindolyl, 2-, 3-, 4-, 5-, 6-, or 7-indolyl, 2-, 3-, 4-, 5-, 6-, or 7-indazolyl, 2-, 4-, 5-, 6-, 7-, or 8- purinyl, 1-, 2-, 3-, 4-, 6-, 7-, 8-, or 9-quinolizinyl, 2-, 3-, 4-, 5-, 6-, 7-, or 8-quinoliyl, 1-, 3-, 4-, 5-, 6-, 7-, or 8-isoquinoliyl, 1-, 4-, 5-, 6-, 7-, or 8-phthalazinyl, 2-, 3-, 4-, 5-, or 6-naphthyridinyl, 2-, 3- , 5- , 6-, 7-, or 8-quinazolinyl, 3-, 4-, 5-, 6-, 7-, or 8-cinnolinyl, 2-, 4-, 6-, or 7-pteridinyl, 1-, 2-, 3-, 4-, 5-, 6-, 7-, or 8-4aH carbazolyl, 1-, 2-, 3-, 4-, 5-, 6-, 7-, or 8-carbzaolyl, 1-, 3-, 4-, 5-, 6-, 7-, 8-, or 9-carbolinyl, 1-, 2-, 3-, 4-, 6-, 7-, 8-, 9-, or 10-phenanthridinyl, 1- , 2-, 3-, 4-, 5-, 6-, 7-, 8-, or 9-acridinyl, 1-, 2-, 4-, 5-, 6-, 7-, 8-, or 9-perimidinyl, 2-, 3-, 4-, 5-, 6-, 8-, 9- , or 10-phenathrolinyl, 1-, 2- , 3-, 4-, 6-, 7-, 8-, or 9-phenazinyl, 1-, 2-, 3-, 4-, 6-, 7-, 8-, 9-, or 10-phenothiazinyl, 1-, 2-, 3-, 4-, 6-, 7-, 8-, 9-, or 10-phenoxazinyl, 2-, 3-, 4-, 5-, 6-, or l- , 3-, 4-, 5-, 6-, 7-, 8-, 9-, or 10- benzisoqinolinyl, 2-, 3-, 4-, or thieno[2,3-b]furanyl, 2-, 3-, 5-, 6-, 7-, 8-, 9-, 10 -, or 11-7H-pyrazino[2,3-c]carbazolyl,2-, 3-, 5-, 6-, or 7-2H- furo[3,2-

b]-pyranyl, 2-, 3-, 4-, 5-, 7-, or 8-5H-pyrido[2,3-d]-o-oxazinyl, 1-, 3-, or 5-1H-pyrazolo[4,3-d]-oxazolyl, 2-, 4-, or 54H-imidazo[4,5-d] thiazolyl, 3-, 5-, or 8-pyrazino[2,3-d]pyridazinyl, 2-, 3-, 5-, or 6- imidazo[2,1-b] thiazolyl, 1-, 3-, 6-, 7-, 8-, or 9-furo[3,4-c]cinnolinyl, 1-, 2-, 3-, 4-, 5-, 6-, 8-, 9-, 10, or 11-4H-pyrido[2,3-c]carbazolyl, 2-, 3-, 6-, or 7-imidazo[1,2-b][1,2,4]triazinyl, 7-benzo[b]thienyl, 2-, 4-, 5- , 6-, or 7-benzoxazolyl, 2-, 4-, 5-, 6-, or 7-benzimidazolyl, 2-, 4-, 4-, 5-, 6-, or 7-benzothiazolyl, 1-, 2-, 4-, 5-, 6-, 7-, 8-, or 9-benzoxapinyl, 2-, 4-, 5-, 6-, 7-, or 8-benzoxazinyl, 1-, 2-, 3-, 5-, 6-, 7-, 8-, 9-, 10-, or 11-1H-pyrrolo[1,2-b][2]benzazapinyl. Typical fused heteroaryl groups include, but are not limited to 2-, 3-, 4-, 5-, 6-, 7-, or 8-quinolinyl, 1-, 3-, 4-, 5-, 6-, 7-, or 8-isoquinolinyl, 2-, 3-, 4-, 5-, 6-, or 7-indolyl, 2-, 3-, 4-, 5-, 6-, or 7-benzo[b]thienyl, 2-, 4-, 5- , 6-, or 7-benzoxazolyl, 2-, 4-, 5-, 6-, or 7-benzimidazolyl, 2-, 4-, 5-, 6-, or 7-benzothiazolyl.

The aromatic ring of an "aryl" or "heteroaryl" group can be substituted at one or more ring positions with such substituents as described above, as for example, halogen, hydroxy, alkoxy, alkylcarbonyloxy, arylcarbonyloxy, alkoxycarbonyloxy, aryloxycarbonyloxy, carboxylate, alkylcarbonyl, alkylaminoacarbonyl, arylalkyl aminocarbonyl, alkenylaminocarbonyl, alkylcarbonyl, arylcarbonyl, arylalkylcarbonyl, alkenylcarbonyl, alkoxycarbonyl, aminocarbonyl, alkylthiocarbonyl, phosphate, phosphonato, phosphinato, cyano, amino (including alkyl amino, dialkylamino, arylamino, diarylamino, and alkylarylamino), acylamino (including alkylcarbonylamino, arylcarbonylamino, carbamoyl and ureido), amidino, imino, sulfhydryl, alkylthio, arylthio, thiocarboxylate, sulfates, alkylsulfinyl, sulfonato, sulfamoyl, sulfonamido, nitro, trifluoromethyl, cyano, azido, heterocyclyl, alkylaryl, or an aromatic or heteroaromatic moiety. Aryl groups can also be fused or bridged with alicyclic or heterocyclic rings which are not aromatic so as to form a polycycle (*e.g.*, tetralin).

The term "alkenyl" includes unsaturated aliphatic groups analogous in length and possible substitution to the alkyls described above, but that contain at least one double bond.

For example, the term "alkenyl" includes straight-chain alkenyl groups (e.g., ethylenyl, propenyl, butenyl, pentenyl, hexenyl, heptenyl, octenyl, nonenyl, decenyl, etc.), branched-chain alkenyl groups, cycloalkenyl (alicyclic) groups (cyclopropenyl, cyclopentenyl, cyclohexenyl, cycloheptenyl, and cyclooctenyl), alkyl or alkenyl substituted cycloalkenyl groups, and cycloalkyl or cycloalkenyl substituted alkenyl groups. The term alkenyl further includes alkenyl groups which include oxygen, nitrogen, sulfur or phosphorous atoms replacing one or more carbons of the

hydrocarbon backbone. In certain embodiments, a straight chain or branched chain alkenyl group has 6 or fewer carbon atoms in its backbone (*e.g.*, C_2-C_6 or straight chain, C_3-C_6 for branched chain). Likewise, cycloalkenyl groups may have from 3-8 carbon atoms in their ring structure, and more preferably have 5 or 6 carbons in the ring structure. The term C_2-C_6 includes alkenyl groups containing 2 to 6 carbon atoms.

Moreover, the term alkenyl includes both "unsubstituted alkenyls" and "substituted alkenyls," the latter of which refers to alkenyl moieties having substituents replacing a hydrogen on one or more carbons of the hydrocarbon backbone. Such substituents can include, for example, alkyl groups, alkynyl groups, halogens, hydroxy, alkylcarbonyloxy, arylcarbonyloxy, alkoxycarbonyloxy, aryloxycarbonyloxy, carboxylate, alkylcarbonyl, arylcarbonyl, alkoxycarbonyl, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, alkylthiocarbonyl, alkoxy, phosphate, phosphonato, phosphinato, cyano, amino (including alkyl amino, dialkylamino, arylamino, diarylamino, and alkylarylamino), acylamino (including alkylcarbonylamino, arylcarbonylamino, carbamoyl and ureido), amidino, imino, sulfhydryl, alkylthio, arylthio, thiocarboxylate, sulfates, alkylsulfinyl, sulfonato, sulfamoyl, sulfonamido, nitro, trifluoromethyl, cyano, azido, heterocyclyl, alkylaryl, or an aromatic or heteroaromatic moiety.

The term "alkynyl" includes unsaturated aliphatic groups analogous in length and possible substitution to the alkyls described above, but which contain at least one triple bond.

For example, the term "alkynyl" includes straight-chain alkynyl groups (*e.g.*, ethynyl, propynyl, butynyl, pentynyl, hexynyl, heptynyl, octynyl, nonynyl, decynyl, etc.), branched-chain alkynyl groups, and cycloalkyl or cycloalkenyl substituted alkynyl groups. The term alkynyl further includes alkynyl groups which include oxygen, nitrogen, sulfur or phosphorous atoms replacing one or more carbons of the hydrocarbon backbone. In certain embodiments, a straight chain or branched chain alkynyl group has 6 or fewer carbon atoms in its backbone (*e.g.*, C_2-C_6 for straight chain, C_3-C_6 for branched chain). The term C_2-C_6 includes alkynyl groups containing 2 to 6 carbon atoms.

Moreover, the term alkynyl includes both "unsubstituted alkynyls" and "substituted alkynyls," the latter of which refers to alkynyl moieties having substituents replacing a hydrogen on one or more carbons of the hydrocarbon backbone. Such substituents can include, for example, alkyl groups, alkynyl groups, halogens, hydroxy, alkylcarbonyloxy, arylcarbonyloxy, alkoxycarbonyloxy, aryloxycarbonyloxy, carboxylate, alkylcarbonyl, arylcarbonyl, alkoxycarbonyl, aminocarbonyl, alkylaminocarbonyl,

dialkylaminocarbonyl, alkylthiocarbonyl, alkoxy, phosphate, phosphonato, phosphinato, cyano, amino (including alkyl amino, dialkylamino, arylamino, diarylamino, and alkylarylamino), acylamino (including alkylcarbonylamino, arylcarbonylamino, carbamoyl and ureido), amidino, imino, sulfhydryl, alkylthio, arylthio, thiocarboxylate, sulfates, alkylsulfinyl, sulfonato, sulfamoyl, sulfonamido, nitro, trifluoromethyl, cyano, azido, heterocyclyl, alkylaryl, or an aromatic or heteroaromatic moiety.

Unless the number of carbons is otherwise specified, the term "lower alkyl" means an alkyl group, as defined above, but having from one to five carbon atoms in its backbone structure. "Lower alkenyl" and "lower alkynyl" have chain lengths of, for example, 2-5 carbon atoms.

The term "alkoxy" includes substituted and unsubstituted alkyl, alkenyl, and alkynyl groups covalently linked to an oxygen atom. Examples of alkoxy groups include methoxy, ethoxy, isopropyloxy, propoxy, butoxy, and pentoxy groups. Examples of substituted alkoxy groups include halogenated alkoxy groups. The alkoxy groups can be substituted with groups such as alkenyl, alkynyl, halogen, hydroxy, alkylcarbonyloxy, arylcarbonyloxy, alkoxycarbonyloxy, aryloxycarbonyloxy, carboxylate, alkylcarbonyl, arylcarbonyl, alkoxycarbonyl, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, alkylthiocarbonyl, alkoxy, phosphate, phosphonato, phosphinato, cyano, amino (including alkyl amino, dialkylamino, arylamino, diarylamino, and alkylarylamino), acylamino (including alkylcarbonylamino, arylcarbonylamino, carbamoyl and ureido), amidino, imino, sulfhydryl, alkylthio, arylthio, thiocarboxylate, sulfates, alkylsulfinyl, sulfonato, sulfamoyl, sulfonamido, nitro, trifluoromethyl, cyano, azido, heterocyclyl, alkylaryl, or an aromatic or heteroaromatic moieties. Examples of halogen substituted alkoxy groups include, but are not limited to, fluoromethoxy, difluoromethoxy, trifluoromethoxy, chloromethoxy, dichloromethoxy, trichloromethoxy, etc.

The term "acyl" includes compounds and moieties which contain the acyl radical (CH_3CO-) or a carbonyl group. It includes substituted acyl moieties. The term "substituted acyl" includes acyl groups where one or more of the hydrogen atoms are replaced by for example, alkyl groups, alkynyl groups, halogens, hydroxy, alkylcarbonyloxy, arylcarbonyloxy, alkoxycarbonyloxy, aryloxycarbonyloxy, carboxylate, alkylcarbonyl, arylcarbonyl, alkoxycarbonyl, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, alkylthiocarbonyl, alkoxy, phosphate, phosphonato, phosphinato, cyano, amino (including alkyl amino, dialkylamino, arylamino, diarylamino, and alkylarylamino), acylamino (including alkylcarbonylamino, arylcarbonylamino, carbamoyl

and ureido), amidino, imino, sulfhydryl, alkylthio, arylthio, thiocarboxylate, sulfates, alkylsulfinyl, sulfonato, sulfamoyl, sulfonamido, nitro, trifluoromethyl, cyano, azido, heterocyclyl, alkylaryl, or an aromatic or heteroaromatic moiety.

The term "acylamino" includes moieties wherein an acyl moiety is bonded to an amino group. For example, the term includes alkylcarbonylamino, arylcarbonylamino, carbamoyl and ureido groups.

The term "aroyl" includes compounds and moieties with an aryl or heteroaromatic moiety bound to a carbonyl group. Examples of aroyl groups include phenylcarboxy, naphthyl carboxy, etc. It includes substituted aroyl moieties. The term "substituted aroyl" includes aroyl groups where one or more of the hydrogen atoms are replaced by for example, alkyl groups, alkynyl groups, halogens, hydroxy, alkylcarbonyloxy, arylcarbonyloxy, alkoxycarbonyloxy, aryloxycarbonyloxy, carboxylate, alkylcarbonyl, arylcarbonyl, alkoxycarbonyl, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, alkylthiocarbonyl, alkoxy, phosphate, phosphonato, phosphinato, cyano, amino (including alkyl amino, dialkylamino, arylamino, diarylamino, and alkylarylamino), acylamino (including alkylcarbonylamino, arylcarbonylamino, carbamoyl and ureido), amidino, imino, sulfhydryl, alkylthio, arylthio, thiocarboxylate, sulfates, alkylsulfinyl, sulfonato, sulfamoyl, sulfonamido, nitro, trifluoromethyl, cyano, azido, heterocyclyl, alkylaryl, or an aromatic or heteroaromatic moiety.

The terms "alkoxyalkyl," "alkylaminoalkyl" and "thioalkoxyalkyl" include alkyl groups, as described above, which further include oxygen, nitrogen or sulfur atoms replacing one or more carbons of the hydrocarbon backbone, *e.g.*, oxygen, nitrogen or sulfur atoms.

The term "carbamoyl" includes $H_2NC(O)$-, alkyl-NHC(O)-, $(alkyl)_2NC(O)$-, aryl-NHC(O)-, alkyl(aryl)-NC(O)-, heteroaryl-NHC(O)-, alkyl(heteroaryl)-NC(O)-, aryl-alkyl-NHC(O)-, alkyl(aryl-alkyl)-NC(O)-, etc. The term includes substituted carbamoyl moieties.

The term "sulfonyl" includes R-SO_2--, wherein R is hydrogen, alkyl, aryl, heteroaryl, aryl-alkyl, heteroaryl-alkyl, alkoxy, aryloxy, cycloalkyl, or heterocyclyl.

The term "sulfonamido" includes alkyl-$S(O)_2$-NH-, aryl-$S(O)_2$-NH-, aryl-alkyl-$S(O)_2$-NH-, heteroaryl-$S(O)_2$-NH-, heteroaryl-alkyl-$S(O)_2$-NH-, alkyl-$S(O)_2$-N(alkyl)-, aryl-$S(O)_2$-N(alkyl)-, aryl-alkyl-$S(O)_2$-N(alkyl)-, heteroaryl-$S(O)_2$-N(alkyl)-, heteroaryl-alkyl-$S(O)_2$-N(alkyl)-, etc. The term includes substituted carbamoyl moieties

The term "heterocyclyl" or "heterocyclo" includes an optionally substituted, saturated or unsaturated non-aromatic ring or ring system, *e.g.*, which is a 4-, 5-, 6-, or 7-membered monocyclic, 7-, 8-, 9-, 10-, 11-, or 12-membered bicyclic or 10-, 11-, 12-, 13-, 14- or 15-membered tricyclic ring system and contains at least one heteroatom selected from O, S and N, where the N and S can also optionally be oxidized to various oxidation states. The heterocyclic group can be attached at a heteroatom or a carbon atom. The heterocyclyl can include fused or bridged rings as well as spirocyclic rings. Examples of heterocycles include tetrahydrofuran (THF), dihydrofuran, 1, 4-dioxane, morpholine, 1,4-dithiane, piperazine, piperidine, 1,3-dioxolane, imidazolidine, imidazoline, pyrroline, pyrrolidine, tetrahydropyran, dihydropyran, oxathiolane, dithiolane, l,3-dioxane, 1,3-dithiane, oxathiane, thiomorpholine, etc.

The term "heterocyclyl" includes heterocyclic groups as defined herein substituted with 1, 2 or 3 substituents such as alkyl, hydroxy (or protected hydroxy), halo, oxo (*e.g.*, =O), amino, alkylamino or dialkylamino, alkoxy, cycloalkyl, carboxyl, heterocyclooxy, wherein heterocyclooxy denotes a heterocyclic group bonded through an oxygen bridge, alkyl-O-C(O)--, mercapto, nitro, cyano, sulfamoyl or sulfonamide, aryl, alkyl-C(O)-O--, aryl-C(O)-O--, aryl-S--, aryloxy, alkyl-S--, formyl (*e.g.*, HC(O)--), carbamoyl, aryl-alkyl--, and aryl substituted with alkyl, cycloalkyl, alkoxy, hydroxy, amino, alkyl-C(O)-NH--, alkylamino, dialkylamino or halogen.

The term "sulfamoyl" includes $H_2NS(O)_2$-, alkyl-$NHS(O)_2$-, $(alkyl)_2NS(O)_2$-, aryl-$NHS(O)_2$-, alkyl(aryl)-$NS(O)_2$-, $(aryl)_2NS(O)_2$-, heteroaryl-$NHS(O)_2$-, (aryl-alkyl)-$NHS(O)_2$-, (heteroaryl-alkyl)-$NHS(O)_2$- , etc. The term includes substituted sulfamoyl moieties.

The term "aryloxy" includes both an –O-aryl and an --O-heteroaryl group, wherein aryl and heteroaryl are defined herein. The term includes substituted aryloxy moieties.

The term "amine" or "amino" includes compounds where a nitrogen atom is covalently bonded to at least one carbon or heteroatom. The term includes "alkyl amino" which comprises groups and compounds wherein the nitrogen is bound to at least one additional alkyl group. The term "dialkyl amino" includes groups wherein the nitrogen atom is bound to at least two additional alkyl groups. The term "arylamino" and "diarylamino" include groups wherein the nitrogen is bound to at least one or two aryl groups, respectively. The term "alkylarylamino," "alkylaminoaryl" or "arylaminoalkyl" refers to an amino group which is bound to at least one alkyl group and at least one aryl group. The term "alkaminoalkyl" refers to an alkyl, alkenyl, or alkynyl group bound to a

nitrogen atom which is also bound to an alkyl group. The term "amine" or "amino" also includes substituted moieties.

The term "amide," "amido" or "aminocarbonyl" includes compounds or moieties which contain a nitrogen atom which is bound to the carbon of a carbonyl or a thiocarbonyl group. The term includes "alkaminocarbonyl" or "alkylaminocarbonyl" groups which include alkyl, alkenyl, aryl or alkynyl groups bound to an amino group bound to a carbonyl group. It includes arylaminocarbonyl and arylcarbonylamino groups which include aryl or heteroaryl moieties bound to an amino group which is bound to the carbon of a carbonyl or thiocarbonyl group. The terms "alkylaminocarbonyl," "alkenylaminocarbonyl," "alkynylaminocarbonyl," "arylaminocarbonyl," "alkylcarbonylamino," "alkenylcarbonylamino," "alkynylcarbonylamino," and "arylcarbonylamino" are included in term "amide." Amides also include urea groups (aminocarbonylamino) and carbamates (oxycarbonylamino). The term "amide," "amido" or "aminocarbonyl" also includes substituted moieties.

The term "carbonyl" or "carboxy" includes compounds and moieties which contain a carbon connected with a double bond to an oxygen atom. The carbonyl can be further substituted with any moiety which allows the compounds of the invention to perform its intended function. For example, carbonyl moieties may be substituted with alkyls, alkenyls, alkynyls, aryls, alkoxy, aminos, etc. Examples of moieties which contain a carbonyl include aldehydes, ketones, carboxylic acids, amides, esters, anhydrides, etc.

The term "thiocarbonyl" or "thiocarboxy" includes compounds and moieties which contain a carbon connected with a double bond to a sulfur atom. The term also includes substituted moieties.

The term "ether" includes compounds or moieties which contain an oxygen bonded to two different carbon atoms or heteroatoms. For example, the term includes "alkoxyalkyl" which refers to an alkyl, alkenyl, or alkynyl group covalently bonded to an oxygen atom which is covalently bonded to another alkyl group. The term also includes substituted moieties.

The term "ester" includes compounds and moieties which contain a carbon or a heteroatom bound to an oxygen atom which is bonded to the carbon of a carbonyl group. The term "ester" includes alkoxycarboxy groups such as methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, butoxycarbonyl, pentoxycarbonyl, etc. The alkyl, alkenyl, or alkynyl groups are as defined above. The term also includes substituted moieties.

The term "thioether" includes compounds and moieties which contain a sulfur atom bonded to two different carbon or hetero atoms. Examples of thioethers include, but are not limited to alkthioalkyls, alkthioalkenyls, and alkthioalkynyls. The term "alkthioalkyls" include compounds with an alkyl, alkenyl, or alkynyl group bonded to a sulfur atom which is bonded to an alkyl group. Similarly, the term "alkthioalkenyls" and alkthioalkynyls" refer to compounds or moieties wherein an alkyl, alkenyl, or alkynyl group is bonded to a sulfur atom which is covalently bonded to an alkynyl group. The term also includes substituted moieties.

The term "hydroxy" or "hydroxyl" includes groups with an –OH or $-O^-$.

The term "halogen" includes fluorine, bromine, chlorine, iodine, etc. The term "perhalogenated" generally refers to a moiety wherein all hydrogens are replaced by halogen atoms.

The terms "polycyclyl" or "polycyclic radical" refer to two or more cyclic rings (*e.g.*, cycloalkyls, cycloalkenyls, cycloalkynyls, aryls and/or heterocyclyls) in which two or more carbons are common to two adjoining rings, *e.g.*, the rings are "fused rings." Rings that are joined through non-adjacent atoms are termed "bridged" rings. Each of the rings of the polycycle can be substituted with such substituents as described above, as for example, halogen, hydroxy, alkylcarbonyloxy, arylcarbonyloxy, alkoxycarbonyloxy, aryloxycarbonyloxy, carboxylate, alkylcarbonyl, alkoxycarbonyl, alkylaminoacarbonyl, arylalkylaminocarbonyl, alkenylaminocarbonyl, alkylcarbonyl, arylcarbonyl, arylalkyl carbonyl, alkenylcarbonyl, aminocarbonyl, alkylthiocarbonyl, alkoxy, phosphate, phosphonato, phosphinato, cyano, amido, amino (including alkyl amino, dialkylamino, arylamino, diarylamino, and alkylarylamino), acylamino (including alkylcarbonylamino, arylcarbonylamino, carbamoyl and ureido), amidino, imino, sulfhydryl, alkylthio, arylthio, thiocarboxylate, sulfates, alkylsulfinyl, sulfonato, sulfamoyl, sulfonamido, nitro, trifluoromethyl, cyano, azido, heterocyclyl, alkyl, alkylaryl, or an aromatic or heteroaromatic moiety.

The term "heteroatom" includes atoms of any element other than carbon or hydrogen. Preferred heteroatoms are nitrogen, oxygen, sulfur and phosphorus.

It will be noted that the structure of some of the compounds of this invention includes asymmetric carbon atoms. It is to be understood accordingly that the isomers arising from such asymmetry (*e.g.*, all enantiomers and diastereomers) are included within the scope of this invention, unless indicated otherwise. Such isomers can be obtained in substantially pure form by classical separation techniques and by

stereochemically controlled synthesis. Furthermore, the structures and other compounds and moieties discussed in this application also include all tautomers thereof.

The term "isomers" refers to different compounds that have the same molecular formula but differ in arrangement and configuration of the atoms. Moreover, the term "an optical isomer" or "a stereoisomer" refers to any of the various stereo isomeric configurations which may exist for a given compound of the present invention and includes geometric isomers. It is understood that a substituent may be attached at a chiral center of a carbon atom. Therefore, the invention includes enantiomers, diastereomers or racemates of the compound. "Enantiomers" are a pair of stereoisomers that are non-superimposable mirror images of each other. A 1:1 mixture of a pair of enantiomers is a "racemic" mixture. The term is used to designate a racemic mixture where appropriate. "Diastereoisomers" are stereoisomers that have at least two asymmetric atoms, but which are not mirror-images of each other. The absolute stereochemistry is specified according to the Cahn- Ingold- Prelog R-S system. When a compound is a pure enantiomer the stereochemistry at each chiral carbon may be specified by either *R* or *S*. Resolved compounds whose absolute configuration is unknown can be designated (+) or (-) depending on the direction (dextro- or levorotatory) which they rotate plane polarized light at the wavelength of the sodium D line. Certain of the compounds described herein contain one or more asymmetric centers and may thus give rise to enantiomers, diastereomers, and other stereoisomeric forms that may be defined, in terms of absolute stereochemistry, as (*R*)-, or (*S*)-. The present invention is meant to include all such possible isomers, including racemic mixtures, optically pure forms and intermediate mixtures. Optically active (*R*)- and (*S*)- isomers may be prepared using chiral synthons or chiral reagents, or resolved using conventional techniques. If the compound contains a double bond, the substituent may be E or Z configuration. If the compound contains a disubstituted cycloalkyl, the cycloalkyl substituent may have a cis- or trans-configuration. All tautomeric forms are also intended to be included.

The recitation of ranges of values in the present application are merely intended to serve as a shorthand method of referring individually to each separate value falling within the range.

Any asymmetric carbon atom on the compounds of the present invention can be present in the (*R*)-, (*S*)- or (*R,S*)- configuration, preferably in the (*R*)- or (*S*)- configuration. Substituents at atoms with unsaturated bonds may, if possible, be present

in *cis*- (*Z*)- or *trans*- (*E*)- form. Therefore, the compounds of the present invention can be in the form of one of the possible isomers or mixtures thereof, for example, as substantially pure geometric (*cis* or *trans*) isomers, diastereomers, optical isomers (antipodes), racemates or mixtures thereof.

Any resulting mixtures of isomers can be separated on the basis of the physicochemical differences of the constituents, into the pure geometric or optical isomers, diastereomers, racemates, for example, by chromatography and/or fractional crystallization.

Any resulting racemates of final products or intermediates can be resolved into the optical antipodes by known methods, *e.g.*, by separation of the diastereomeric salts thereof, obtained with an optically active acid or base, and liberating the optically active acidic or basic compound. In particular, the imidazolyl moiety may thus be employed to resolve the compounds of the present invention into their optical antipodes, *e.g.*, by fractional crystallization of a salt formed with an optically active acid, *e.g.*, tartaric acid, dibenzoyl tartaric acid, diacetyl tartaric acid, di-*O,O'*-*p*-toluoyl tartaric acid, mandelic acid, malic acid or camphor-10-sulfonic acid. Racemic products can also be resolved by chiral chromatography, *e.g.*, high pressure liquid chromatography (HPLC) using a chiral adsorbent.

Compounds of the present invention are either obtained in the free form, as a salt thereof, or as prodrug derivatives thereof.

The term "pharmaceutically acceptable salts" includes salts that retain the biological effectiveness and properties of the compounds of this invention and, which are not biologically or otherwise undesirable. In many cases, the compounds of the present invention are capable of forming acid and/or base salts by virtue of the presence of amino and/or carboxyl groups or groups similar thereto. Pharmaceutically acceptable acid addition salts can be formed with inorganic acids and organic acids. Inorganic acids from which salts can be derived include, for example, hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, etc. Organic acids from which salts can be derived include, for example, acetic acid, propionic acid, glycolic acid, pyruvic acid, oxalic acid, maleic acid, malonic acid, succinic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, *p*- toluenesulfonic acid, salicylic acid, etc. Pharmaceutically acceptable base addition salts can be formed with inorganic and organic bases. Inorganic bases from which salts can be derived include, for example, sodium, potassium, lithium, ammonium, calcium,

magnesium, iron, zinc, copper, manganese, aluminum, etc.; particularly preferred are the ammonium, potassium, sodium, calcium and magnesium salts. Organic bases from which salts can be derived include, for example, primary, secondary, and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines, basic ion exchange resins, etc., specifically such as isopropylamine, trimethylamine, diethylamine, triethylamine, tripropylamine, and ethanolamine. The pharmaceutically acceptable salts of the present invention can be synthesized from a parent compound, a basic or acidic moiety, by conventional chemical methods. Generally, such salts can be prepared by reacting free acid forms of these compounds with a stoichiometric amount of the appropriate base (such as Na, Ca, Mg, or K hydroxide, carbonate, bicarbonate, or the like), or by reacting free base forms of these compounds with a stoichiometric amount of the appropriate acid. Such reactions are typically carried out in water or in an organic solvent, or in a mixture of the two. Generally, non-aqueous media like ether, ethyl acetate, ethanol, isopropanol, or acetonitrile are preferred, where practicable. Lists of additional suitable salts can be found, *e.g.*, in *Remington's Pharmaceutical Sciences,* 20th ed., Mack Publishing Company, Easton, Pa., (1985).

When a basic group is present in the compounds of the present invention, the compounds can be converted into acid addition salts thereof, in particular, acid addition salts with the pyridinyl moiety of the structure, preferably pharmaceutically acceptable salts thereof. These are formed, with inorganic acids or organic acids. Suitable inorganic acids include but are not limited to, hydrochloric acid, sulfuric acid, a phosphoric or hydrohalic acid. Suitable organic acids include but are not limited to, carboxylic acids, such as (C_1-C_4)alkanecarboxylic acids which, for example, are unsubstituted or substituted by halogen, *e.g.*, acetic acid, such as saturated or unsaturated dicarboxylic acids, *e.g.*, oxalic, succinic, maleic or fumaric acid, such as hydroxycarboxylic acids, *e.g.*, glycolic, lactic, malic, tartaric or citric acid, such as amino acids, *e.g.*, aspartic or glutamic acid, organic sulfonic acids, such as (C_1-C_4)alkylsulfonic acids, *e.g.*, methanesulfonic acid; or arylsulfonic acids which are unsubstituted or substituted, *e.g.*, by halogen. Preferred are salts formed with hydrochloric acid, methanesulfonic acid and maleic acid.

When an acidic group is present in the compounds of the present invention, the compounds can be converted into salts with pharmaceutically acceptable bases. Such salts include alkali metal salts, like sodium, lithium and potassium salts; alkaline earth

metal salts, like calcium and magnesium salts; ammonium salts with organic bases, *e.g.*, trimethylamine salts, diethylamine salts, *tris*(hydroxymethyl)methylamine salts, dicyclohexylamine salts and *N*-methyl-*D*-glucamine salts; salts with amino acids like arginine, lysine, etc. Salts may be formed using conventional methods, advantageously in the presence of an ethereal or alcoholic solvent, such as a lower alkanol. From the solutions of the latter, the salts may be precipitated with ethers, e.g., diethyl ether. Resulting salts may be converted into the free compounds by treatment with acids. These or other salts can also be used for purification of the compounds obtained.

When both a basic group and an acid group are present in the same molecule, the compounds of the present invention can also form internal salts.

Salts of compounds of the present invention having at least one salt-forming group may be prepared in a manner known per se. For example, salts of compounds of the present invention having acid groups may be formed, for example, by treating the compounds with metal compounds, such as alkali metal salts of suitable organic carboxylic acids, *e.g.* the sodium salt of 2-ethylhexanoic acid, with organic alkali metal or alkaline earth metal compounds, such as the corresponding hydroxides, carbonates or hydrogen carbonates, such as sodium or potassium hydroxide, carbonate or hydrogen carbonate, with corresponding calcium compounds or with ammonia or a suitable organic amine, stoichiometric amounts or only a small excess of the salt-forming agent preferably being used. Acid addition salts of compounds of the present invention are obtained in customary manner, *e.g.* by treating the compounds with an acid or a suitable anion exchange reagent. Internal salts of compounds of the present invention containing acid and basic salt-forming groups, *e.g.* a free carboxy group and a free amino group, may be formed, *e.g.* by the neutralisation of salts, such as acid addition salts, to the isoelectric point, *e.g.* with weak bases, or by treatment with ion exchangers.

Salts can be converted in customary manner into the free compounds; metal and ammonium salts can be converted, for example, by treatment with suitable acids, and acid addition salts, for example, by treatment with a suitable basic agent.

The present invention includes all pharmaceutically acceptable isotopically-labeled compounds of the invention, i.e. Agents of the Invention, wherein (1) one or more atoms are replaced by atoms having the same atomic number, but an atomic mass or mass number different from the atomic mass or mass number usually found in nature, and/or (2) the isotopic ratio of one or more atoms is different from the naturally occurring ratio.

Examples of isotopes suitable for inclusion in the compounds of the invention comprises isotopes of hydrogen, such as ^{2}H and ^{3}H, carbon, such as ^{11}C, ^{13}C and ^{14}C, chlorine, such as ^{36}Cl, fluorine, such as ^{18}F, iodine, such as ^{123}I and ^{125}I, nitrogen, such as ^{13}N and ^{15}N, oxygen, such as ^{15}O, ^{17}O and ^{18}O, phosphorus, such as ^{32}P, and sulphur, such as ^{35}S.

Certain isotopically-labeled Agents of the Invention, for example, those incorporating a radioactive isotope, are useful in drug and/or substrate tissue distribution studies. The radioactive isotopes tritium, *i.e.* ^{3}H, and carbon-14, *i.e.* ^{14}C, are particularly useful for this purpose in view of their ease of incorporation and ready means of detection.

Substitution with heavier isotopes such as deuterium, *i.e.* ^{2}H, may afford certain therapeutic advantages resulting from greater metabolic stability, for example, increased *in vivo* half-life or reduced dosage requirements, and hence may be preferred in some circumstances.

Substitution with positron emitting isotopes, such as ^{11}C, ^{18}F, ^{15}O and ^{13}N, can be useful in Positron Emission Topography (PET) studies for examining substrate receptor occupancy.

Isotopically-labeled Agents of the Invention can generally be prepared by conventional techniques known to those skilled in the art or by processes analogous to those described in the accompanying Examples and Preparations using an appropriate isotopically-labeled reagents in place of the non-labeled reagent previously employed.

The present invention also provides prodrug moieties of the compounds of the present invention that convert *in vivo* to the compounds of the present invention. A prodrug moiety is an active or inactive compound that is modified chemically through *in vivo* physiological action, such as hydrolysis, metabolism, etc., into a compound of this invention following administration of the prodrug to a subject. The term "prodrug moiety" includes moieties which can be metabolized *in vivo* to a hydroxy group and moieties which may advantageously remain esterified *in vivo*. Preferably, the prodrugs moieties are metabolized *in vivo* by esterases or by other mechanisms to hydroxy groups or other advantageous groups. Examples of prodrugs and their uses are well known in the art (See, *e.g.*, Berge et al. (1977) "Pharmaceutical Salts" *J. Pharm. Sci.* 66:1-19). The prodrugs can be prepared *in situ* during the final isolation and purification of the compounds, or by separately reacting the purified compound in its free acid form or hydroxy with a suitable esterifying agent. Hydroxy groups can be converted into esters

via treatment with a carboxylic acid. Examples of prodrug moieties include substituted and unsubstituted, branch or unbranched lower alkyl ester moieties, (*e.g.*, propionoic acid esters), lower alkenyl esters, di-lower alkyl-amino lower-alkyl esters (*e.g.*, dimethylaminoethyl ester), acylamino lower alkyl esters (*e.g.*, acetyloxymethyl ester), acyloxy lower alkyl esters (*e.g.*, pivaloyloxymethyl ester), aryl esters (phenyl ester), aryl-lower alkyl esters (*e.g.*, benzyl ester), substituted (*e.g.*, with methyl, halo, or methoxy substituents) aryl and aryl-lower alkyl esters, amides, lower-alkyl amides, di-lower alkyl amides, and hydroxy amides. Preferred prodrug moieties are propionoic acid esters and acyl esters.

The suitability and techniques involved in making and using prodrugs are well known by those skilled in the art. Prodrugs can be conceptually divided into two non-exclusive categories, bioprecursor prodrugs and carrier prodrugs. See *The Practice of Medicinal Chemistry*, Ch. 31-32 (Ed. Wermuth, Academic Press, San Diego, Calif., 2001). Generally, bioprecursor prodrugs are compounds are inactive or have low activity compared to the corresponding active drug compound that contains one or more protective groups and are converted to an active form by metabolism or solvolysis. Both the active drug form and any released metabolic products should have acceptably low toxicity. Typically, the formation of active drug compound involves a metabolic process or reaction that is one of the follow types:

1. Oxidative reactions, such as oxidation of alcohol, carbonyl, and acid functions, hydroxylation of aliphatic carbons, hydroxylation of alicyclic carbon atoms, oxidation of aromatic carbon atoms, oxidation of carbon-carbon double bonds, oxidation of nitrogen-containing functional groups, oxidation of silicon, phosphorus, arsenic, and sulfur, oxidative N-dealkylation, oxidative O- and S-dealkylation, oxidative deamination, as well as other oxidative reactions.

2. Reductive reactions, such as reduction of carbonyl groups, reduction of alcoholic groups and carbon-carbon double bonds, reduction of nitrogen-containing functions groups, and other reduction reactions.

3. Reactions without change in the state of oxidation, such as hydrolysis of esters and ethers, hydrolytic cleavage of carbon-nitrogen single bonds, hydrolytic cleavage of non-aromatic heterocycles, hydration and dehydration at multiple bonds, new atomic linkages resulting from dehydration reactions, hydrolytic dehalogenation, removal of hydrogen halide molecule, and other such reactions.

Carrier prodrugs are drug compounds that contain a transport moiety, *e.g.*, that improve uptake and/or localized delivery to a site(s) of action. Desirably for such a carrier prodrug, the linkage between the drug moiety and the transport moiety is a covalent bond, the prodrug is inactive or less active than the drug compound, and any released transport moiety is acceptably non-toxic. For prodrugs where the transport moiety is intended to enhance uptake, typically the release of the transport moiety should be rapid. In other cases, it is desirable to utilize a moiety that provides slow release, *e.g.*, certain polymers or other moieties, such as cyclodextrins. See, Cheng *et al.*, US20040077595, incorporated herein by reference. Such carrier prodrugs are often advantageous for orally administered drugs. Carrier prodrugs can, for example, be used to improve one or more of the following properties: increased lipophilicity, increased duration of pharmacological effects, increased site-specificity, decreased toxicity and adverse reactions, and/or improvement in drug formulation (*e.g.*, stability, water solubility, suppression of an undesirable organoleptic or physiochemical property). For example, lipophilicity can be increased by esterification of hydroxy groups with lipophilic carboxylic acids, or of carboxylic acid groups with alcohols, *e.g.*, aliphatic alcohols. Wermuth, *The Practice of Medicinal Chemistry*, Ch. 31-32, Ed. Werriuth, Academic Press, San Diego, Calif., 2001.

Exemplary prodrugs are, *e.g.*, esters of free carboxylic acids and *S*-acyl and *O*-acyl derivatives of thiols, alcohols or phenols, wherein acyl has a meaning as defined herein. Preferred are pharmaceutically acceptable ester derivatives convertible by solvolysis under physiological conditions to the parent carboxylic acid, *e.g.*, lower alkyl esters, cycloalkyl esters, lower alkenyl esters, benzyl esters, mono- or di-substituted lower alkyl esters, such as the ω-(amino, mono- or di-lower alkylamino, carboxy, lower alkoxycarbonyl)-lower alkyl esters, the α-(lower alkanoyloxy, lower alkoxycarbonyl or di-lower alkylaminocarbonyl)-lower alkyl esters, such as the pivaloyloxymethyl ester, etc. conventionally used in the art. In addition, amines have been masked as arylcarbonyloxymethyl substituted derivatives which are cleaved by esterases *in vivo* releasing the free drug and formaldehyde (Bundgaard, *J. Med. Chem.* 2503 (1989)). Moreover, drugs containing an acidic NH group, such as imidazole, imide, indole, etc., have been masked with N-acyloxymethyl groups (Bundgaard, *Design of Prodrugs*, Elsevier (1985)). Hydroxy groups have been masked as esters and ethers. EP 039,051 (Sloan and Little) discloses Mannich-base hydroxamic acid prodrugs, their preparation and use.

In view of the close relationship between the compounds, the compounds in the form of their salts and the prodrugs, any reference to the compounds of the present invention is to be understood as referring also to the corresponding prodrugs of the compounds of the present invention, as appropriate and expedient.

Furthermore, the compounds of the present invention, including their salts, can also be obtained in the form of their hydrates, or include other solvents used for their crystallization.

Compounds of the present invention are prepared from commonly available compounds using procedures known to those skilled in the art, including any one or more of the following conditions without limitation:

Within the scope of this text, only a readily removable group that is not a constituent of the particular desired end product of the compounds of the present invention is designated a "protecting group", unless the context indicates otherwise. The protection of functional groups by such protecting groups, the protecting groups themselves, and their cleavage 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 and P. G. M. Wuts, "Protective Groups in Organic Synthesis", Third edition, Wiley, New York 1999.

Mixtures of isomers obtainable according to the invention can be separated in a manner known per se into the individual isomers; diastereoisomers can be separated, for example, by partitioning between polyphasic solvent mixtures, recrystallisation and/or chromatographic separation, for example over silica gel or by *e.g.* medium pressure liquid chromatography over a reversed phase column, and racemates can be separated, for example, by the formation of salts with optically pure salt-forming reagents and separation of the mixture of diastereoisomers so obtainable, for example by means of fractional crystallisation, or by chromatography over optically active column materials.

Intermediates and final products can be worked up and/or purified according to standard methods, *e.g.* using chromatographic methods, distribution methods, (re-) crystallization, etc.

The following applies in general to all processes mentioned herein before and hereinafter.

All the above-mentioned process steps can be carried out under reaction conditions that are known per se, including those mentioned specifically, in the absence or, customarily, in the presence of solvents or diluents, including, for example, solvents

or diluents that are inert towards the reagents used and dissolve them, in the absence or presence of catalysts, condensation or neutralizing agents, for example ion exchangers, such as cation exchangers, *e.g.* in the H+ form, depending on the nature of the reaction and/or of the reactants at reduced, normal or elevated temperature, for example in a temperature range of from about -100 °C to about 190 °C, including, for example, from approximately -80 °C to approximately 150 °C, for example at from -80 to -60 °C, at room temperature, at from -20 to 40 °C or at reflux temperature, under atmospheric pressure or in a closed vessel, where appropriate under pressure, and/or in an inert atmosphere, for example under an argon or nitrogen atmosphere.

At all stages of the reactions, mixtures of isomers that are formed can be separated into the individual isomers, for example diastereoisomers or enantiomers, or into any desired mixtures of isomers, for example racemates or mixtures of diastereoisomers.

The solvents from which those solvents that are suitable for any particular reaction may be selected include those mentioned specifically or, for example, water, esters, such as lower alkyl-lower alkanoates, for example ethyl acetate, ethers, such as aliphatic ethers, for example diethyl ether, or cyclic ethers, for example tetrahydrofuran or dioxane, liquid aromatic hydrocarbons, such as benzene or toluene, alcohols, such as methanol, ethanol or 1- or 2-propanol, nitriles, such as acetonitrile, halogenated hydrocarbons, such as methylene chloride or chloroform, acid amides, such as dimethylformamide or dimethyl acetamide, bases, such as heterocyclic nitrogen bases, for example pyridine or *N*-methylpyrrolidin-2-one, carboxylic acid anhydrides, such as lower alkanoic acid anhydrides, for example acetic anhydride, cyclic, linear or branched hydrocarbons, such as cyclohexane, hexane or isopentane, or mixtures of those solvents, for example aqueous solutions, unless otherwise indicated in the description of the processes. Such solvent mixtures may also be used in working up, for example by chromatography or partitioning.

The compounds, including their salts, may also be obtained in the form of hydrates, or their crystals may, for example, include the solvent used for crystallization. Different crystalline forms may be present.

The invention relates also to those forms of the process in which a compound obtainable as an intermediate at any stage of the process is used as starting material and the remaining process steps are carried out, or in which a starting material is formed under the reaction conditions or is used in the form of a derivative, for example in a

protected form or in the form of a salt, or a compound obtainable by the process according to the invention is produced under the process conditions and processed further in situ.

All starting materials, building blocks, reagents, acids, bases, dehydrating agents, solvents and catalysts utilized to synthesize the compounds of the present invention are either commercially available or can be produced by organic synthesis methods known to one of ordinary skill in the art (Houben-Weyl 4th Ed. 1952, Methods of Organic Synthesis, Thieme, Volume 21).

Generally, enantiomers of the compounds of the present invention can be prepared by methods known to those skilled in the art to resolve racemic mixtures, such as by formation and recrystallization of diastereomeric salts or by chiral chromotagraphy or HPLC separation utilizing chiral stationery phases.

In starting compounds and intermediates which are converted to the compounds of the invention in a manner described herein, functional groups present, such as amino, thiol, carboxyl and hydroxy groups, are optionally protected by conventional protecting groups that are common in preparative organic chemistry. Protected amino, thiol, carboxyl and hydroxy groups are those that can be converted under mild conditions into free amino thiol, carboxyl and hydroxy groups without the molecular framework being destroyed or other undesired side reactions taking place.

The purpose of introducing protecting groups is to protect the functional groups from undesired reactions with reaction components under the conditions used for carrying out a desired chemical transformation. The need and choice of protecting groups for a particular reaction is known to those skilled in the art and depends on the nature of the functional group to be protected (hydroxy group, amino group, etc.), the structure and stability of the molecule of which the substituent is a part and the reaction conditions.

Well-known protecting groups that meet these conditions and their introduction and removal are described, *e.g.*, in McOmie, "Protective Groups in Organic Chemistry", Plenum Press, London, NY (1973); and Greene and Wuts, "Protective Groups in Organic Synthesis", John Wiley and Sons, Inc., NY (1999).

The above-mentioned reactions are carried out according to standard methods, in the presence or absence of diluent, preferably, such as are inert to the reagents and are solvents thereof, of catalysts, condensing or said other agents, respectively and/or inert atmospheres, at low temperatures, room temperature or elevated temperatures,

preferably at or near the boiling point of the solvents used, and at atmospheric or super-atmospheric pressure. The preferred solvents, catalysts and reaction conditions are set forth in the appended illustrative Examples.

The invention further includes any variant of the present processes, in which an intermediate product obtainable at any stage thereof is used as starting material and the remaining steps are carried out, or in which the starting materials are formed *in situ* under the reaction conditions, or in which the reaction components are used in the form of their salts or optically pure antipodes.

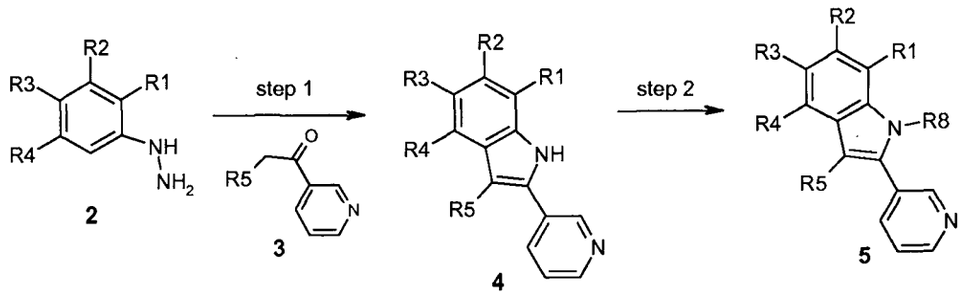
Abbreviations:

ATP: adenosine 5'-triphosphate	BINAP: racemic 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl
BOC: tertiary butyl carboxy	br: broad
bs: broad singlet	calcd: calculated
d: doublet	DAST: (diethylamino)sulfur trifluoride
dd: doublet of doublets	DCM: dichloromethane
DIEA: diethylisopropylamine	DME: 1,4-dimethoxyethane
DMF: *N,N*-dimethylformamide	DMSO: dimethylsulfoxide
DPPA: diphenylphosphorylazide	DTT: dithiothreitol
EDTA: ethylenediamine tetraacetic acid	ESI: electrospray ionization
EtOAc: ethyl acetate	h: hour(s)
HATU: *O*-(7-azobenzotriazol-1-yl)-1,1,3,3-tetramethyluroniumhexafluorophosphate	HOBt: 1-hydroxy-7-azabenzotriazole
HPLC: high pressure liquid chromatography	LCMS: liquid chromatography and mass spectrometry
MeOD: methanol-d4	MeOH: methanol
MS: mass spectrometry	m: multiplet
min: minutes	m/z: mass to charge ratio
n.d.: not determined	NMR: nuclear magnetic resonance
ppm: parts per million	Pr: propyl
PyBOP: benzotriazol-1-yloxy Tripyrrolidinophosphoniumhexafluorophosphate	rt: room temperature
s: singlet	t: triplet
TFA: trifluoroacetic acid	THF: tetrahydrofuran
TLC: thin layer chromatography	Tris·HCl: aminotris(hydroxymethyl) methane hydrochloride

Methods for Synthesizing Compounds of the Invention

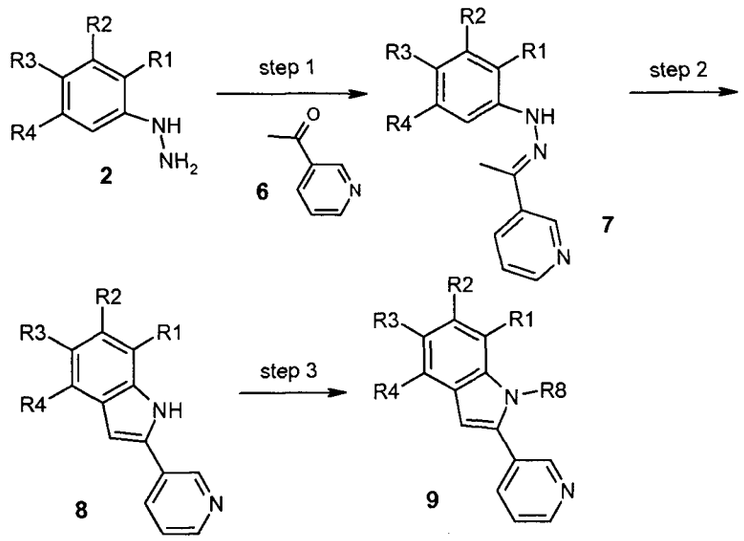
The compounds of the invention can be synthesized using the methods described in the following schemes, examples, and by using art recognized techniques. All compounds described herein are included in the invention as compounds. Compounds of the invention may be synthesized according to at least one of the methods described in schemes 1-7.

Scheme 1.



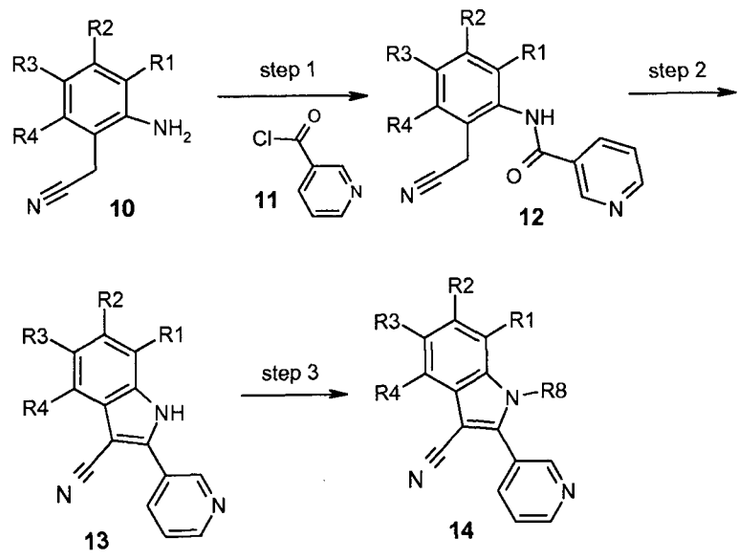
In step 1, the appropriate hydrazine derivative 2 is heated with 3-acetylpyridine derivative 3 in a solvent, *e.g.* ethanol, resulting in the formation of the corresponding hydrazone, which upon addition of an acid, *e.g.* hydrogen chloride, undergoes a Fisher reaction to give indole 4. Pyridine 3 can be conveniently prepared from nicotinic acid, via formation of the Weinreb amide and subsequent addition of the appropriate Grignard reagent, *e.g.* n-propyl magnesium bromide. In step 2, indole 4 is deprotonated with a strong base, such as potassium hexamethyldisilamide, and the resulting anion is trapped with the appropriate electrophilic reagent, *e.g.* an acid chloride, a chloroformate, an alkyl bromide, an alkyl chloride or an alkyl iodide, to give indole 5. Appropriate transformation of R8 in 5 leads to further analogs. For example, if R8 contains an ester, the ester can be hydrolyzed to the corresponding carboxylic acid. In another example, if R8 contains a nitrile, the nitrile can be reacted with azide to give the corresponding tetrazole.

Scheme 2.



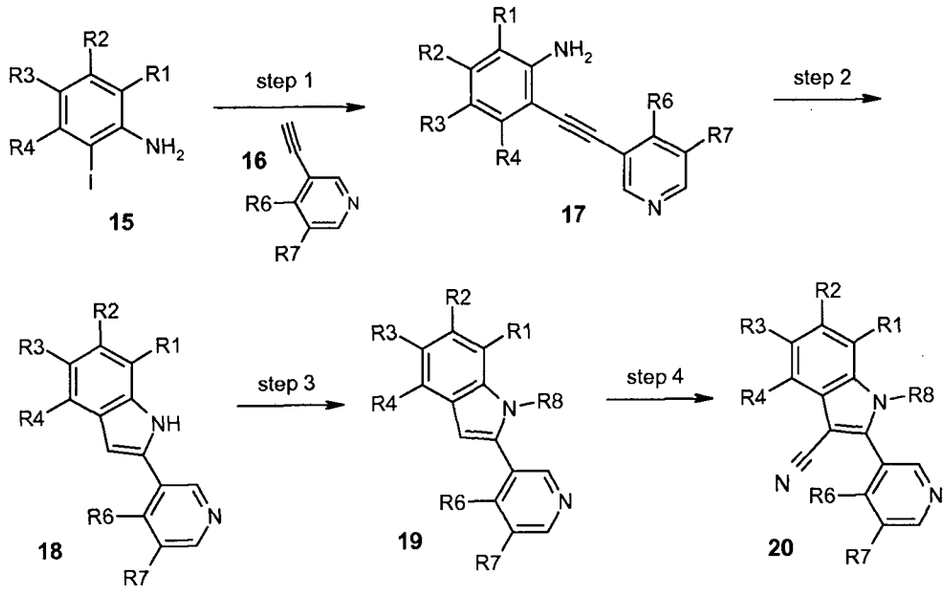
In step 1, the appropriate hydrazine derivative 2 is heated with 3-acetylpyridine 6 in a solvent, *e.g.* ethanol, resulting in the formation of the corresponding hydrazone 7. In step 2, 7 is heated, neat, with polyphosphoric acid, preferably between 160 °C and 220 °C, to give indole 8. In step 3, indole 4 is deprotonated with a strong base, *e.g.* potassium hexamethyldisilamide, and the resulting anion is trapped with the appropriate electrophilic reagent, *e.g.* an acid chloride, a chloroformate, an alpha,beta-unsturated ketone or ester, an alkyl bromide, an alkyl chloride or an alkyl iodide, to give indole 9. Appropriate transformation of R8 in 9 leads to further analogs. For example, if R8 contains an ester, the ester can be hydrolyzed to the corresponding carboxylic acid. In another example, if R8 contains a nitrile, the nitrile can be reacted with azide to give the corresponding tetrazole.

Scheme 3.



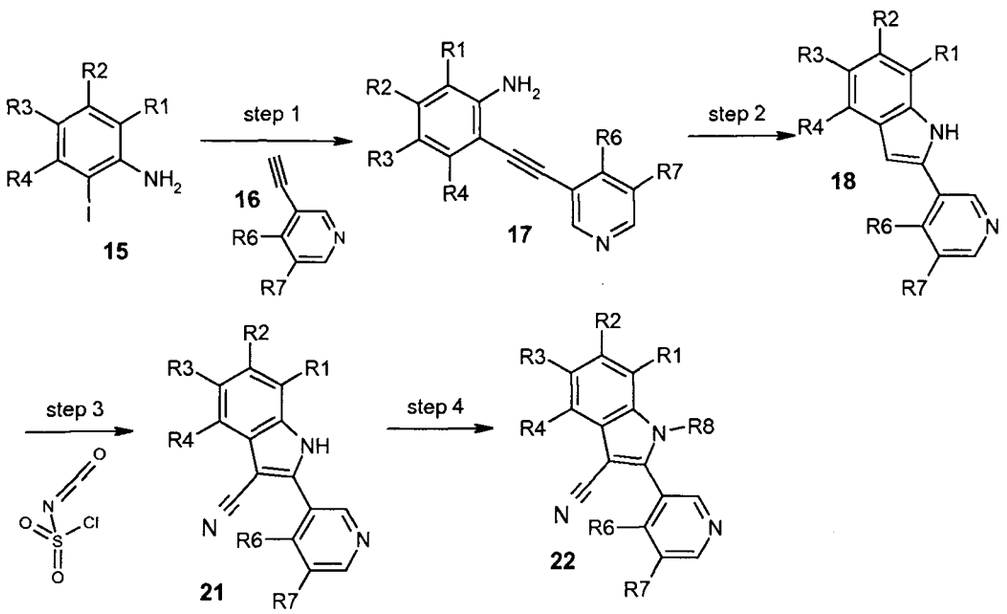
In step 1, the appropriate aniline derivative 10 is coupled with nicotinyl chloride in the presence of an amine base, *e.g.* diisopropylethylamine, to give amide 12. In step 2, heating of 12 in the presence of a strong base, *e.g.* sodium hydride, gives indole 13. In step 3, indole 13 is deprotonated with a strong base, *e.g.* sodium hydride, and the resulting anion is trapped with the appropriate electrophilic reagent, *e.g.* methyl iodide, to give indole 14.

Scheme 4.



Step 1 involves the reaction of an iodoaniline derivative 15 and acetylene derivative 16 in the presence of palladium salts, *e.g.* $PdCl_2(PPh_3)_2$, copper salts, preferably copper iodide, in an amine solvent, preferably triethylamine, to give alkyne 17. In step 2, treatment of aniline 17 with a base, *e.g.* potassium tert-butoxide, in a polar solvent, preferably N-methylpyrolidinone, gives indole 18. In step 3, indole 18 is deprotonated with a strong base, *e.g.* sodium hydride, and the resulting anion is trapped with the appropriate electrophilic reagent, *e.g.* an alkyl chloride, or an alpha,beta-unsturated ketone to give indole 19. Optionally, indole 19 can be reacted with chlorosulfonyl isocyanate, followed with dimethylformamide, as in step 4, to give indole 20. Appropriate transformations of R8 in 19 lead to further analogs. For example, if R8 contains an ester, the ester can be hydrolyzed to the corresponding carboxylic acid.

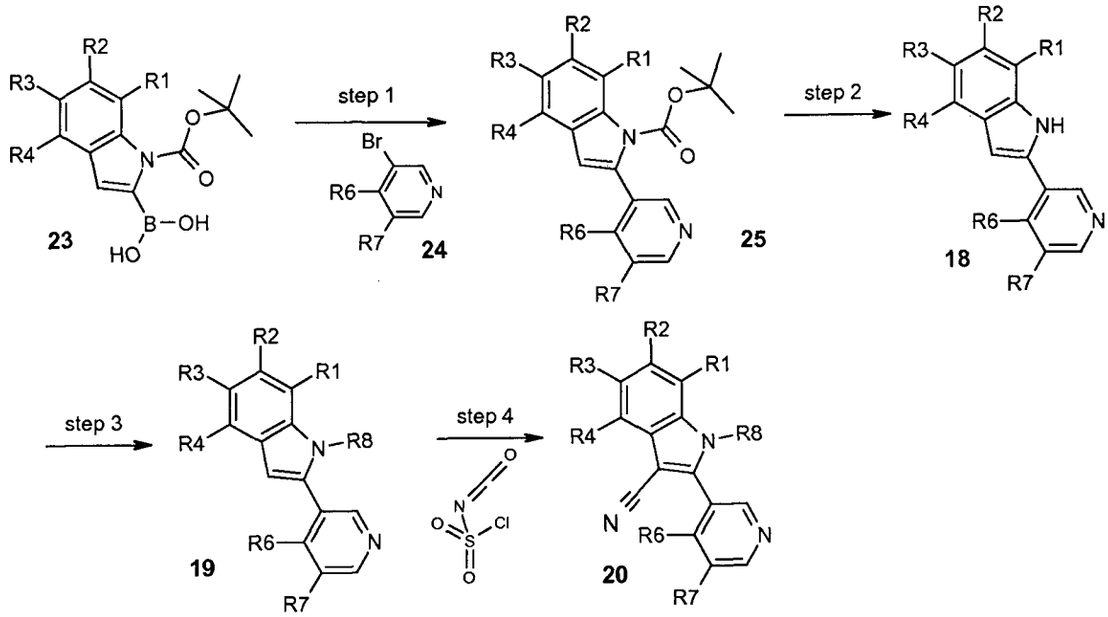
Scheme 5.



Step 1 involves the reaction of an iodoaniline derivative 15 and acetylene derivative 16 in the presence of palladium salts, *e.g.* $PdCl_2(PPh_3)_2$, copper salts, *e.g.* copper iodide, in an amine solvent, *e.g.* triethylamine, to give alkyne 17. In step 2, treatment of aniline 17 with a base, *e.g.* potassium tert-butoxide, in a polar solvent, *e.g.* N-methylpyrolidinone, gives indole 18. In step 3, indole 18 can be reacted with chlorosulfonyl isocyanate, followed with dimethylformamide, to give indole 21. In step 4, indole 21 is deprotonated with a strong base, *e.g.* sodium hydride, and the resulting

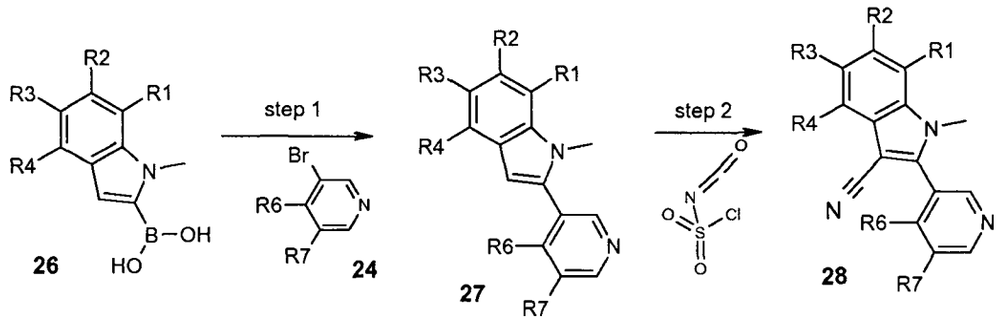
anion is trapped with the appropriate electrophilic reagent, *e.g.* methyl iodide to give indole 22.

Scheme 6.



In step 1, the appropriate N-Boc-2-indole boronic acid 23 is reacted with the appropriate 3-bromopyridine 24 in the presence of palladium salts, *e.g.* Pd_2dba_3, ligands, *e.g.* s-Phos, and a base, *e.g.* potassium phosphate, in an organic solvent, *e.g.* toluene, to give indole 25. In step 2, the carbamate is cleaved, *e.g.* using trifluoroacetic acid or silica gel. In step 3, indole 18 is deprotonated with a strong base, *e.g.* sodium hydride, and the resulting anion is trapped with the appropriate electrophilic reagent, *e.g.* methyl iodide to give indole 19. Alternatively, indole 18 can be heated with dimethylcarbonate in the presence of a base, *e.g.* potassium carbonate, to give indole 19, where R8 is methyl. Optionally, indole 19 can be reacted with chlorosulfonyl isocyanate, followed with dimethylformamide, as in step 4, to give indole 20. Appropriate transformations of R6 and R7 in 19 or 20 lead to further analogs.

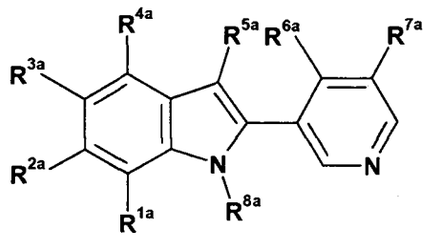
Scheme 7.



In step 1, the appropriate N-methyl-2-indole boronic acid 26 is reacted with the appropriate heterocycle 24 in the presence of palladium salts, *e.g.* Pd_2dba_3, ligands, *e.g.* s-Phos, and a base, *e.g.* potassium phosphate, in an organic solvent, *e.g.* toluene, to give indole 27. Optionally, indole 27 can be reacted with chlorosulfonyl isocyanate, followed with dimethylformamide, as in step 2, to give indole 28. Appropriate transformations of R6 and R7 in 27 or 28 lead to further analogs.

Methods of the Invention

The invention pertains, at least in part, to methods for treating a subject for a disorder or disease, by administering to a subject a therapeutically effective amount of a compound of Formula I:



(I)

wherein:

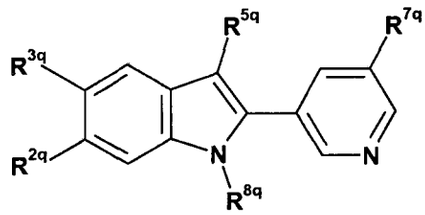
R^{1a}, R^{2a}, R^{3a}, and R^{4a} are each independently hydrogen, halogen, cyano, hydroxy, alkoxy, alkyl, alkenyl, or alkoxycarbonyl;

R^{5a} is hydrogen halogen, cyano, alkyl, alkenyl, arylalkyl, heteroarylalkyl, aminocarbonyl, alkylaminocarbonyl, carboxylate, alkoxycarbonyl, heterocyclylcarbonyl, aryl, or heteroaryl;

R^{6a} and R^{7a} are each independently hydrogen, halogen, hydroxy, alkoxy, amino, alkyl, sulfonyl, -O-sulfonyl, alkylamino, heterocyclyl, aminocarbonyl, carboxylate, or alkoxycarbonyl;

R^{8a} is hydrogen, alkyl, arylalkyl, heteroarylalkyl, alkoxycarbonyl, sulfonyl, aroyl, aryl, or heteroaryl; and pharmaceutically acceptable salts, polymorphs, rotamers, prodrugs, enantiomers, hydrates, and solvates thereof, with the proviso that at least one of R^{1a}-R^{8a} is other than hydrogen; and when R^{5a} is cyano or lower alkyl optionally substituted with cyano, -C(O)-piperidine, amino, alkylamino, dialkylamino, carboxylate, alkoxycarbonyl, aminocarbonyl, or heterocyclyl, then at least one of R^{1a}-R^{4a} and R^{6a}-R^{8a} is other than hydrogen; and when R^{7a} is imidazolyl, then at least one of R^{1a}-R^{6a} and R^{8a} is other than hydrogen; and when R^{8a} is alkyl, arylalkyl or alkoxycarbonyl, then at least one of R^{1a}-R^{7a} is other than hydrogen; and when R^{5a} is lower alkyl and R^{8a} is alkyl substituted with carboxylate or $PO_3R^{21}R^{22}$ wherein R^{21} and R^{22} are each independently hydrogen or lower alkyl, then at least one of R^{1a}-R^{4a} and R^{6a} and R^{7a} is other than hydrogen; and when R^{3a} is halogen and R^{5a} and R^{8a} are independently lower alkyl optionally substituted with carboxylate, alkoxycarbonyl, or -C(O)-piperidine, then at least one of R^{1a}, R^{2a}, R^{4a}, R^{6a} and R^{7a} is other than hydrogen; and when R^{3a} is halogen or lower alkyl and R^{5a} is lower alkyl substituted with dialkylamino, dialkylaminocarbonyl, carboxylate, alkoxycarbonyl or aminocarbonyl, then at least one of R^{1a}, R^{2a}, R^{4a}, and R^{6a}-R^{8a} is other than hydrogen; and when R^{2a} and R^{3a} are each alkoxy and R^{5a} is cyano, then at least one of R^{1a}, R^{4a}, and R^{6a}-R^{8a} is other than hydrogen; and when R^{3a} is alkyl substituted with aroyl, and R^5 and R^8 are each independently hydrogen or lower alkyl, then at least one of R^{1a}, R^{2a}, and R^{4a} is other than hydrogen, such that said disorder or disease in said subject is treated.

In one embodiment, the invention pertains, at least in part, to methods for treating a subject for a disorder or disease, by administering to a subject a therapeutically effective amount of a compound of Formula II:



(II)

wherein:

R^{2q} is hydrogen or halogen;

R^{3q} is hydrogen, halogen, or cyano;

R^{5q} is hydrogen, alkyl, or cyano;

R^{7q} is hydrogen, halogen, alkoxy, -OSO_2-heterocyclyl, -O-arylalkyl, -NR'-SO_2-alkyl, -NR'-C(O)-alkyl, -NR'-C(O)-NR'-alkyl, -NR'-C(O)-O-alkyl, haloalkyl, or alkyl optionally substituted with heterocyclyl, –NR'-SO_2-alkyl, -NR'-SO_2-haloalkyl, NR'-C(O)-alkyl, NR'-C(O)-heterocyclyl, -NR'-C(O)-NR'-alkyl, or –NR'-C(O)-O-alkyl;

R^{8q} is hydrogen, alkyl, hydroxyalkyl, -alkyl-OC(O)-alkyl, carboxylate, alkoxycarbonyl, or arylalkyl substituted with alkyl, or aroyl substituted with cyano and/or alkyl, or -alkyl-O-aryl substituted with alkoxycarbonyl;

each R' is independently hydrogen, C_1-C_4-alkyl, or C_3-C_6-cycloalkyl and pharmaceutically acceptable salts, polymorphs, rotamers, prodrugs, enantiomers, hydrates, and solvates thereof, with the proviso that at least one of R^{2q}, R^{3q}, R^{5q}, R^{7q} and R^{8q} is other than hydrogen, such that said disorder or disease in said subject is treated.

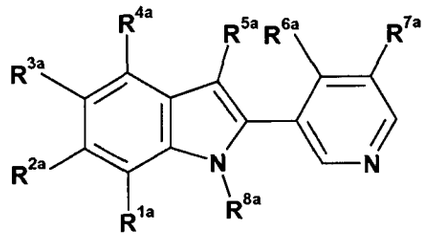
In another embodiment, the invention pertains, at least in part, to methods for treating a subject for a disorder or disease, by administering to a subject a therapeutically effective amount of a compound of Formulae III or IV, and pharmaceutically acceptable salts, polymorphs, rotamers, prodrugs, enantiomers, hydrates, and solvates thereof, such that said disorder or disease in said subject is treated.

The term "disorder" or "disease" includes any pathological condition, derangement, or abnormality of function of a part, organ, or system of an organism resulting from various causes, such as infection, genetic defect, or environmental stress, and characterized by an identifiable group of signs or symptoms; and any morbid physical or mental state. See *Dorland's Illustrated Medical Dictionary,* (W.B. Saunders Co. 27th ed. 1988).

In another embodiment, the disorder or disease is a disease selected from, hypokalemia, hypertension, Conn's disease, renal failure, in particular, chronic renal failure, restenosis, atherosclerosis, syndrome X, obesity, nephropathy, post-myocardial infarction, coronary heart diseases, increased formation of collagen, fibrosis and remodeling following hypertension and endothelial dysfunction, cardiovascular diseases, renal dysfunction, liver diseases, cerebrovascular diseases, vascular diseases, retinopathy, neuropathy, insulinopathy, edema, endothelial dysfunction, baroreceptor dysfunction, migraine headaches, heart failure such as congestive heart failure, arrhythmia, diastolic dysfunction, left ventricular diastolic dysfunction, diastolic heart failure, impaired diastolic filling, systolic dysfunction, ischemia, hypertropic cardiomyopathy, sudden cardiac death, myocardial and vascular fibrosis, impaired

arterial compliance, myocardial necrotic lesions, vascular damage, myocardial infarction, left ventricular hypertrophy, decreased ejection fraction, cardiac lesions, vascular wall hypertrophy, endothelial thickening, or fibrinoid necrosis of coronary arteries.

The invention also pertains, at least in part, to methods of inhibiting aldosterone synthase activity in a subject, by administering to a subject a therapeutically effective amount of a compound of Formula I:



(I)

wherein:

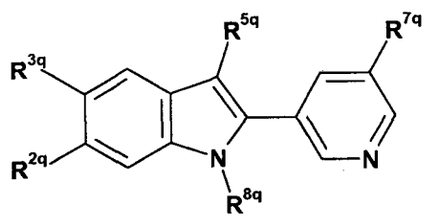
R^{1a}, R^{2a}, R^{3a}, and R^{4a} are each independently hydrogen, halogen, cyano, hydroxy, alkoxy, alkyl, alkenyl, or alkoxycarbonyl;

R^{5a} is hydrogen halogen, cyano, alkyl, alkenyl, arylalkyl, heteroarylalkyl, aminocarbonyl, alkylaminocarbonyl, carboxylate, alkoxycarbonyl, heterocyclylcarbonyl, aryl, or heteroaryl;

R^{6a} and R^{7a} are each independently hydrogen, halogen, hydroxy, alkoxy, amino, alkyl, sulfonyl, -O-sulfonyl, alkylamino, heterocyclyl, aminocarbonyl, carboxylate, or alkoxycarbonyl;

R^{8a} is hydrogen, alkyl, arylalkyl, heteroarylalkyl, alkoxycarbonyl, sulfonyl, aroyl, aryl, or heteroaryl; and pharmaceutically acceptable salts, polymorphs, rotamers, prodrugs, enantiomers, hydrates, and solvates thereof, such that aldosterone synthase activity is inhibited.

The invention also pertains, at least in part, to methods of inhibiting aldosterone synthase activity in a subject, by administering to a subject a therapeutically effective amount of a compound of Formula II:



(II)

wherein:

R^{2q} is hydrogen or halogen;

R^{3q} is hydrogen, halogen, or cyano;

R^{5q} is hydrogen, alkyl, or cyano;

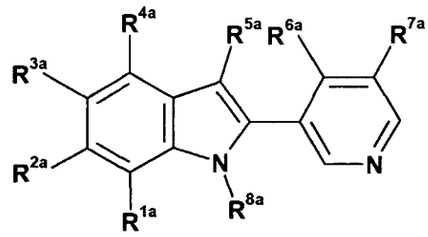
R^{7q} is hydrogen, halogen, alkoxy, -OSO_2-heterocyclyl, -O-arylalkyl, -NR'-SO_2-alkyl, -NR'-C(O)-alkyl, -NR'-C(O)-NR'-alkyl, -NR'-C(O)-O-alkyl, haloalkyl, or alkyl optionally substituted with heterocyclyl, –NR'-SO_2-alkyl, -NR'-SO_2-haloalkyl, NR'-C(O)-alkyl, NR'-C(O)-heterocyclyl, -NR'-C(O)-NR'-alkyl, or –NR'-C(O)-O-alkyl;

R^{8q} is hydrogen, alkyl, hydroxyalkyl, -alkyl-OC(O)-alkyl, carboxylate, alkoxycarbonyl, or arylalkyl substituted with alkyl, or aroyl substituted with cyano and/or alkyl, or -alkyl-O-aryl substituted with alkoxycarbonyl;

each R' is independently hydrogen, C_1-C_4-alkyl, or C_3-C_6-cycloalkyl, and pharmaceutically acceptable salts, polymorphs, rotamers, prodrugs, enantiomers, hydrates, and solvates thereof, such that aldosterone synthase activity is inhibited.

In one embodiment, the invention pertains, at least in part, to methods of inhibiting aldosterone synthase activity in a subject, by administering to a subject a therapeutically effective amount of a compound of Formulae III or IV, such that aldosterone synthase activity is inhibited.

Another embodiment of the present invention includes methods for treating an aldosterone synthase associated state, by administering to a subject a therapeutically effective amount of a compound of Formula I:



(I)

wherein:

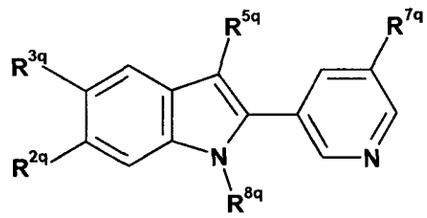
R^{1a}, R^{2a}, R^{3a}, and R^{4a} are each independently hydrogen, halogen, cyano, hydroxy, alkoxy, alkyl, alkenyl, or alkoxycarbonyl;

R^{5a} is hydrogen halogen, cyano, alkyl, alkenyl, arylalkyl, heteroarylalkyl, aminocarbonyl, alkylaminocarbonyl, carboxylate, alkoxycarbonyl, heterocyclylcarbonyl, aryl, or heteroaryl;

R^{6a} and R^{7a} are each independently hydrogen, halogen, hydroxy, alkoxy, amino, alkyl, sulfonyl, -O-sulfonyl, alkylamino, heterocyclyl, aminocarbonyl, carboxylate, or alkoxycarbonyl;

R^{8a} is hydrogen, alkyl, arylalkyl, heteroarylalkyl, alkoxycarbonyl, sulfonyl, aroyl, aryl, or heteroaryl; and pharmaceutically acceptable salts, polymorphs, rotamers, prodrugs, enantiomers, hydrates, and solvates thereof, such that said aldosterone synthase associated state in said subject is treated.

Yet another embodiment of the present invention includes methods of treating an aldosterone synthase associated state, by administering to a subject a therapeutically effective amount of a compound of Formula II:



(II)

wherein:

R^{2q} is hydrogen or halogen;

R^{3q} is hydrogen, halogen, or cyano;

R^{5q} is hydrogen, alkyl, or cyano;

R^{7q} is hydrogen, halogen, alkoxy, -OSO_2-heterocyclyl, -O-arylalkyl, -NR'-SO_2-alkyl, -NR'-C(O)-alkyl, -NR'-C(O)-NR'-alkyl, -NR'-C(O)-O-alkyl, haloalkyl, or alkyl optionally substituted with heterocyclyl, –NR'-SO_2-alkyl, -NR'-SO_2-haloalkyl, NR'-C(O)-alkyl, NR'-C(O)-heterocyclyl, -NR'-C(O)-NR'-alkyl, or –NR'-C(O)-O-alkyl;

R^{8q} is hydrogen, alkyl, hydroxyalkyl, -alkyl-OC(O)-alkyl, carboxylate, alkoxycarbonyl, or arylalkyl substituted with alkyl, or aroyl substituted with cyano and/or alkyl, or -alkyl-O-aryl substituted with alkoxycarbonyl;

each R' is independently hydrogen, C_1-C_4-alkyl, or C_3-C_6-cycloalkyl, and pharmaceutically acceptable salts, polymorphs, rotamers, prodrugs, enantiomers, hydrates, and solvates thereof, such that said aldosterone synthase associated state in said subject is treated.

Yet another embodiment of the present invention includes methods of treating an aldosterone synthase associated state, by administering to a subject a therapeutically

effective amount of a compound of Formula III or IV, such that said aldosterone synthase associated state in said subject is treated.

The term "aldosterone synthase associated state" refers to a state, disease, or disorder which can be treated by the modulation, (*e.g.*, inhibition) of aldosterone synthase. Aldosterone synthase is a mitcohcondrial cytochrome P450 enzyme catalyzing the last step of aldosterone production in the adrenal cortex, i.e., the conversion of 11-deoxycorticosterone to aldosterone. Aldosterone synthase has been demonstrated to be expressed in all cardiovascular tissues such as heart, umbilical cord, mesenteric and pulmonary arteries, aorta, endothelium and vascular cells. Moreover, the expression of aldosterone synthase is closely correlated with aldosterone production in cells. It has been observed that elevations of aldosterone activity induces different diseases such as congestive heart failure, myocardial fibrosis, ventricular arrhythmia and other adverse effects, etc.

Examples of aldosterone synthase associated states include hypokalemia, hypertension, Conn's disease, renal failure, in particular, chronic renal failure, restenosis, atherosclerosis, syndrome X, obesity, nephropathy, post-myocardial infarction, coronary heart diseases, increased formation of collagen, fibrosis and remodeling following hypertension and endothelial dysfunction, cardiovascular diseases, renal dysfunction, liver diseases, cerebrovascular diseases, vascular diseases, retinopathy, neuropathy, insulinopathy, edema, endothelial dysfunction, baroreceptor dysfunction, migraine headaches, heart failure such as congestive heart failure, arrhythmia, diastolic dysfunction, left ventricular diastolic dysfunction, diastolic heart failure, impaired diastolic filling, systolic dysfunction, ischemia, hypertropic cardiomyopathy, sudden cardiac death, myocardial and vascular fibrosis, impaired arterial compliance, myocardial necrotic lesions, vascular damage, myocardial infarction, left ventricular hypertrophy, decreased ejection fraction, cardiac lesions, vascular wall hypertrophy, endothelial thickening, and fibrinoid necrosis of coronary arteries.

In one embodiment, the aldosterone synthase associated state is characterized by abnormal activity of aldosterone synthase and/or abnormal expression of aldosterone synthase.

The term "abnormal" includes an activity or feature which differs from a normal activity or feature.

The term "abnormal activity" includes an activity which differs from the activity of the wild-type or native gene or protein, or which differs from the activity of the gene or

protein in a healthy subject. The abnormal activity can be stronger or weaker than the normal activity.

In one embodiment, the "abnormal activity" includes the abnormal (either over- or under-) production of mRNA transcribed from a gene. In another embodiment, the "abnormal activity" includes the abnormal (either over- or under-) production of polypeptide from a gene. In another embodiment, the abnormal activity refers to a level of a mRNA or polypeptide that is different from a normal level of said mRNA or polypeptide by about 15%, about 25%, about 35%, about 50%, about 65%, about 85%, about 100% or greater. Preferably, the abnormal level of the mRNA or polypeptide can be either higher or lower than the normal level of said mRNA or polypeptide. Yet in another embodiment, the abnormal activity refers to functional activity of a protein that is different from a normal activity of the wild-type protein. Preferably, the abnormal activity can be stronger or weaker than the normal activity. Preferably, the abnormal activity is due to the mutations in the corresponding gene, and the mutations can be in the coding region of the gene or non-coding regions such as transcriptional promoter regions. The mutations can be substitutions, deletions, insertions.

The compounds of the present invention, as aldosterone synthase inhibiting compounds, are useful for treatment of a disorder or disease mediated by aldosterone synthase or responsive to inhibition of aldosterone synthase. In particular, the compounds of the present invention are useful for treatment of a aldosterone synthase associated state including hypokalemia, hypertension, Conn's disease, renal failure, in particular, chronic renal failure, restenosis, atherosclerosis, syndrome X, obesity, nephropathy, post-myocardial infarction, coronary heart diseases, increased formation of collagen, fibrosis and remodeling following hypertension and endothelial dysfunction, cardiovascular diseases, renal dysfunction, liver diseases, cerebrovascular diseases, vascular diseases, retinopathy, neuropathy, insulinopathy, edema, endothelial dysfunction, baroreceptor dysfunction, migraine headaches, heart failure such as congestive heart failure, arrhythmia, diastolic dysfunction, left ventricular diastolic dysfunction, diastolic heart failure, impaired diastolic filling, systolic dysfunction, ischemia, hypertropic cardiomyopathy, sudden cardiac death, myocardial and vascular fibrosis, impaired arterial compliance, myocardial necrotic lesions, vascular damage, myocardial infarction, left ventricular hypertrophy, decreased ejection fraction, cardiac lesions, vascular wall hypertrophy, endothelial thickening, and fibrinoid necrosis of coronary arteries.

The term "aldosterone synthase inhibiting compound" includes compounds which reduce the activity of aldosterone synthase, *e.g.*, the ability of aldosterone synthase to synthesize aldosterone, *in vivo* or *in vitro*. In one embodiment, the aldosterone synthase inhibiting compounds are aldosterone synthesis inhibiting compounds.

The term "inhibition" or "inhibiting" includes the reduction or suppression of a given condition, symptom, or disorder, or disease, or a significant decrease in the baseline activity of a biological activity or process. In one embodiment, the condition or symptom or disorder or disease is mediated by aldosterone synthase activity. In another embodiment, the condition or symptom or disorder or disease is associated with the abnormal activity of aldosterone synthase, or the condition or symptom or disorder or disease is associated with the abnormal expression of aldosterone synthase.

The term "subject" includes animals (*e.g.*, mammals). A subject also refers to for example, primates (*e.g.*, humans, including males and females), cows, sheep, goats, horses, dogs, cats, rabbits, rats, mice, fish, birds, etc.

The term "a therapeutically effective amount" of a compound of the present invention refers to an amount of the compound of the present invention that will elicit the biological or medical response of a subject, for example, reduction or inhibition of an enzyme or a protein activity, or ameliorate symptoms, alleviate conditions, slow or delay disease progression, or prevent a disease, etc. In one non-limiting embodiment, the term "a therapeutically effective amount" refers to the amount of the compound of the present invention that, when administered to a subject, is effective to (1) at least partially alleviate, inhibit, prevent and/or ameliorate a condition, or a disorder or a disease (i) mediated by aldosterone synthase, or (ii) associated with aldosterone synthase activity, or (iii) characterized by abnormal activity of aldosterone synthase; or (2) reduce or inhibit the activity of aldosterone synthase; or (3) reduce or inhibit the expression of aldosterone synthase. In another non-limiting embodiment, the term "a therapeutically effective amount" refers to the amount of the compound of the present invention that, when administered to a cell, or a tissue, or a non-cellular biological material, or a medium, is effective to at least partially reduce or inhibit the activity of aldosterone synthase; or at least partially reduce or inhibit the expression of aldosterone synthase.

The effective amount can vary depending on such factors as the size and weight of the subject, the type of illness, or the particular organic compound. For example, the choice of the organic compound can affect what constitutes an "effective amount." One of ordinary skill in the art would be able to study the aforementioned factors and make

the determination regarding the effective amount of the organic compound without undue experimentation.

The term "treating" or "treatment" of any disease or disorder includes curing as well as ameliorating at least one symptom of the state, disease, or disorder (*e.g.*, the aldosterone synthase associated state). The term may also include alleviating or ameliorating at least one physical parameter including those which may not be discernible by the patient; or modulating the disease or disorder, either physically, (*e.g.*, stabilization of a discernible symptom), physiologically, (*e.g.*, stabilization of a physical parameter), or both. The terms may also include preventing or delaying the onset or development or progression of the disease or disorder.

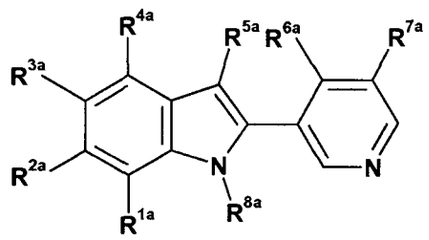
A further embodiment includes methods for treating an aldosterone synthase associated disorder or disease in a subject by administering to a subject an effective amount of a compound of the invention (*e.g.*, a compound of Formulae I-IV, or a compound otherwise described herein) in combination with a second agent, such that the subject is treated for said aldosterone synthase associated disorder.

The disorder or disease may be characterized by an abnormal activity of aldosterone synthase or abnormal expression of aldosterone synthase.

In one embodiment the disorder or disease includes but is not limited to hypokalemia, hypertension, Conn's disease, renal failure, in particular, chronic renal failure, restenosis, atherosclerosis, syndrome X, obesity, nephropathy, post-myocardial infarction, coronary heart diseases, increased formation of collagen, fibrosis and remodeling following hypertension and endothelial dysfunction, cardiovascular diseases, renal dysfunction, liver diseases, cerebrovascular diseases, vascular diseases, retinopathy, neuropathy, insulinopathy, edema, endothelial dysfunction, baroreceptor dysfunction, migraine headaches, heart failure such as congestive heart failure, arrhythmia, diastolic dysfunction, left ventricular diastolic dysfunction, diastolic heart failure, impaired diastolic filling, systolic dysfunction, ischemia, hypertropic cardiomyopathy, sudden cardiac death, myocardial and vascular fibrosis, impaired arterial compliance, myocardial necrotic lesions, vascular damage, myocardial infarction, left ventricular hypertrophy, decreased ejection fraction, cardiac lesions, vascular wall hypertrophy, endothelial thickening, and fibrinoid necrosis of coronary arteries.

In one embodiment, the invention pertains, at least in part, to methods for treating a subject for heart failure, congestive heart failure, arrhythmia, diastolic dysfunction, left ventricular diastolic dysfunction, diastolic heart failure, impaired diastolic

filling, systolic dysfunction, ischemia, hypertropic cardiomyopathy, sudden cardiac death, myocardial and vascular fibrosis, impaired arterial compliance, myocardial necrotic lesions, vascular damage, myocardial infarction, left ventricular hypertrophy, decreased ejection fraction, cardiac lesions, vascular wall hypertrophy, endothelial thickening, fibrinoid necrosis of coronary arteries, renal dysfunction, liver diseases, cerebrovascular diseases, vascular diseases, retinopathy, neuropathy, insulinopathy, edema, endothelial dysfunction, baroreceptor dysfunction, migraine headaches, or hypertension, comprising administering to said subject an effective amount of a compound of Formula I:



(I)

wherein:

R^{1a}, R^{2a}, R^{3a}, and R^{4a} are each independently hydrogen, halogen, cyano, hydroxy, alkoxy, alkyl, alkenyl, or alkoxycarbonyl;

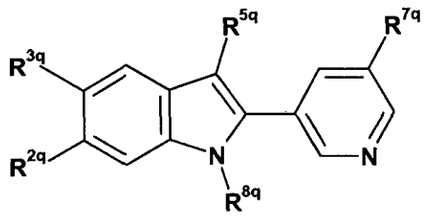
R^{5a} is hydrogen halogen, cyano, alkyl, alkenyl, arylalkyl, heteroarylalkyl, aminocarbonyl, alkylaminocarbonyl, carboxylate, alkoxycarbonyl, heterocyclylcarbonyl, aryl, or heteroaryl;

R^{6a} and R^{7a} are each independently hydrogen, halogen, hydroxy, alkoxy, amino, alkyl, sulfonyl, -O-sulfonyl, alkylamino, heterocyclyl, aminocarbonyl, carboxylate, or alkoxycarbonyl;

R^{8a} is hydrogen, alkyl, arylalkyl, heteroarylalkyl, alkoxycarbonyl, sulfonyl, aroyl, aryl, or heteroaryl; and pharmaceutically acceptable salts, polymorphs, rotamers, prodrugs, enantiomers, hydrates, and solvates thereof, such that said subject is treated.

In another embodiment, the invention pertains, at least in part, to methods for treating a subject for heart failure, congestive heart failure, arrhythmia, diastolic dysfunction, left ventricular diastolic dysfunction, diastolic heart failure, impaired diastolic filling, systolic dysfunction, ischemia, hypertropic cardiomyopathy, sudden cardiac death, myocardial and vascular fibrosis, impaired arterial compliance, myocardial necrotic lesions, vascular damage, myocardial infarction, left ventricular hypertrophy, decreased ejection fraction, cardiac lesions, vascular wall hypertrophy, endothelial thickening, fibrinoid necrosis of coronary arteries, renal dysfunction, liver diseases, cerebrovascular

diseases, vascular diseases, retinopathy, neuropathy, insulinopathy, edema, endothelial dysfunction, baroreceptor dysfunction, migraine headaches, or hypertension, comprising administering to said subject an effective amount of a compound of Formula II:



(II)

wherein:

R^{2q} is hydrogen or halogen;

R^{3q} is hydrogen, halogen, or cyano;

R^{5q} is hydrogen, alkyl, or cyano;

R^{7q} is hydrogen, halogen, alkoxy, -OSO_2-heterocyclyl, -O-arylalkyl, -NR'-SO_2-alkyl, -NR'-C(O)-alkyl, -NR'-C(O)-NR'-alkyl, -NR'-C(O)-O-alkyl, haloalkyl, or alkyl optionally substituted with heterocyclyl, –NR'-SO_2-alkyl, -NR'-SO_2-haloalkyl, NR'-C(O)-alkyl, NR'-C(O)-heterocyclyl, -NR'-C(O)-NR'-alkyl, or –NR'-C(O)-O-alkyl;

R^{8q} is hydrogen, alkyl, hydroxyalkyl, -alkyl-OC(O)-alkyl, carboxylate, alkoxycarbonyl, or arylalkyl substituted with alkyl, or aroyl substituted with cyano and/or alkyl, or -alkyl-O-aryl substituted with alkoxycarbonyl;

each R' is independently hydrogen, C_1-C_4-alkyl, or C_3-C_6-cycloalkyl, and pharmaceutically acceptable salts, polymorphs, rotamers, prodrugs, enantiomers, hydrates, and solvates thereof, such that said subject is treated.

In yet another embodiment, the invention pertains, at least in part, to methods for treating a subject for heart failure, congestive heart failure, arrhythmia, diastolic dysfunction, left ventricular diastolic dysfunction, diastolic heart failure, impaired diastolic filling, systolic dysfunction, ischemia, hypertropic cardiomyopathy, sudden cardiac death, myocardial and vascular fibrosis, impaired arterial compliance, myocardial necrotic lesions, vascular damage, myocardial infarction, left ventricular hypertrophy, decreased ejection fraction, cardiac lesions, vascular wall hypertrophy, endothelial thickening, fibrinoid necrosis of coronary arteries, renal dysfunction, liver diseases, cerebrovascular diseases, vascular diseases, retinopathy, neuropathy, insulinopathy, edema, endothelial dysfunction, baroreceptor dysfunction, migraine headaches, or hypertension, comprising administering to said subject an effective amount of a compound of Formula III or IV, and

pharmaceutically acceptable salts, polymorphs, rotamers, prodrugs, enantiomers, hydrates, and solvates thereof, such that said subject is treated.

In still another embodiment, the invention pertains, at least in part, to methods wherein the compound of the invention (*e.g.*, a compound of Formulae I-IV or a compound otherwise described herein) is administered in combination with a second agent.

The term "in combination with" a second agent or treatment includes co-administration of the compound of the invention (*e.g.*, a compound of Formulae I-IV or a compound otherwise described herein) with the second agent or treatment, administration of the compound of the invention first, followed by the second agent or treatment and administration of the second agent or treatment first, followed by the compound of the invention.

The term "second agent" includes any agent which is known in the art to treat, prevent, or reduce the symptoms of a disease or disorder described herein, *e.g.*, an aldosterone synthase associated disorder, such as, for example, hypokalemia, hypertension, Conn's disease, renal failure, in particular, chronic renal failure, restenosis, atherosclerosis, syndrome X, obesity, nephropathy, post-myocardial infarction, coronary heart diseases, increased formation of collagen, fibrosis and remodeling following hypertension and endothelial dysfunction, cardiovascular diseases, renal dysfunction, liver diseases, cerebrovascular diseases, vascular diseases, retinopathy, neuropathy, insulinopathy, edema, endothelial dysfunction, baroreceptor dysfunction, migraine headaches, heart failure such as congestive heart failure, arrhythmia, diastolic dysfunction, left ventricular diastolic dysfunction, diastolic heart failure, impaired diastolic filling, systolic dysfunction, ischemia, hypertropic cardiomyopathy, sudden cardiac death, myocardial and vascular fibrosis, impaired arterial compliance, myocardial necrotic lesions, vascular damage, myocardial infarction, left ventricular hypertrophy, decreased ejection fraction, cardiac lesions, vascular wall hypertrophy, endothelial thickening, and fibrinoid necrosis of coronary arteries. Furthermore, the second agent may be any agent of benefit to the patient when administered in combination with the administration of a compound of the invention.

Examples of second agents include HMG-Co-A reductase inhibitors, angiotensin II receptor antagonists, angiotensin converting enzyme (ACE) Inhibitors, calcium channel blockers (CCB), dual angiotensin converting enzyme/neutral endopeptidase (ACE/NEP) inhibitors, endothelin antagonists, renin inhibitors, diuretics, ApoA-I mimics, anti-diabetic

agents, obesity-reducing agents, aldosterone receptor blockers, endothelin receptor blockers, and CETP inhibitors.

The term "HMG-Co-A reductase inhibitor" (also called beta-hydroxy-beta-methylglutaryl-co-enzyme-A reductase inhibitors) includes active agents that may be used to lower the lipid levels including cholesterol in blood. Examples include atorvastatin, cerivastatin, compactin, dalvastatin, dihydrocompactin, fluindostatin, fluvastatin, lovastatin, pitavastatin, mevastatin, pravastatin, rivastatin, simvastatin, and velostatin, or, pharmaceutically acceptable salts thereof.

The term "ACE-inhibitor" (also called angiotensin converting enzyme inhibitors) includes molecules that interrupt the enzymatic degradation of angiotensin I to angiotensin II. Such compounds may be used for the regulation of blood pressure and for the treatment of congestive heart failure. Examples include alacepril, benazepril, benazeprilat, captopril, ceronapril, cilazapril, delapril, enalapril, enaprilat, fosinopril, imidapril, lisinopril, moveltopril, perindopril, quinapril, ramipril, spirapril, temocapril, and trandolapril, or, pharmaceutically acceptables salt thereof.

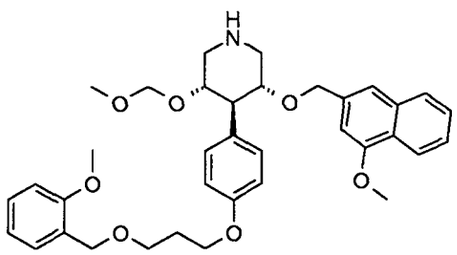
The term "calcium channel blocker (CCB)" includes dihydropyridines (DHPs) and non-DHPs (*e.g.*, diltiazem-type and verapamil-type CCBs). Examples include amlodipine, felodipine, ryosidine, isradipine, lacidipine, nicardipine, nifedipine, niguldipine, niludipine, nimodipine, nisoldipine, nitrendipine, and nivaldipine, and is preferably a non-DHP representative selected from the group consisting of flunarizine, prenylamine, diltiazem, fendiline, gallopamil, mibefradil, anipamil, tiapamil and verapamil, or, pharmaceutically acceptable salts thereof. CCBs may be used as anti-hypertensive, anti-angina pectoris, or anti-arrhythmic drugs.

The term "dual angiotensin converting enzyme/neutral endopetidase (ACE/NEP) inhibitor" includes omapatrilate (cf. EP 629627), fasidotril or fasidotrilate, or pharmaceutically acceptable salts thereof.

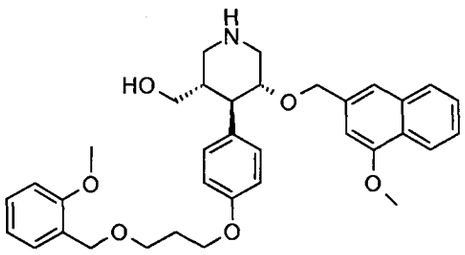
The term "endothelin antagonist" includes bosentan (cf. EP 526708 A), tezosentan (cf. WO 96/19459), or, pharmaceutically acceptable salts thereof.

The term "renin inhibitor" includes ditekiren (chemical name: [1*S*-[1*R**,2*R**,4*R**(1*R**,2*R**)]]-1-[(1,1-dimethylethoxy)carbonyl]-L-proly l-L-phenylalanyl-N-[2-hydroxy-5-methyl-1-(2-methylpropyl)-4-[[[2-methyl-1-[[(2-pyridinylmrthyl)amino]carbonyl]butyl]amino]carbonyl]hexyl]-*N*-alfa-methyl-L-histidinamide); terlakiren (chemical name: [*R*-(*R**,*S**)]-N-(4-morpholinylcarbonyl)-L-phenylalanyl-N-[1-(cyclohexylmethyl)-2-hydroxy-3-(1-methylethoxy)-3-oxopropyl]-S-

methyl-L-cysteineamide); and zankiren (chemical name: [1*S*-[1*R**[*R**(*R**)],2*S**,3*R**]]-*N*-[1-(cyclohexylmethyl)-2,3-dihydroxy-5-m ethylhexyl]-alfa-[[2-[[(4-methyl-1-piperazinyl)sulfonyl]methyl]-1-oxo-3-phenylpropyl]-amino]-4-thiazolepropanamide), or, hydrochloride salts thereof, or, SPP630, SPP635 and SPP800 as developed by Speedel, or RO 66-1132 and RO 66-1168 of Formula (A) and (B):



(A) and



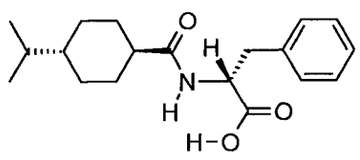
(B) , or,

pharmaceutically acceptable salts thereof.

The term "diuretic" includes thiazide derivatives (*e.g.*, chlorothiazide, hydrochlorothiazide, methylclothiazide, and chlorothalidon).

The term "ApoA-I mimic" includes D4F peptides (*e.g.*, formula D-W-F-K-A-F-Y-D-K-V-A-E-K-F-K-E-A-F)

The term "anti-diabetic agent" includes insulin secretion enhancers that promote the secretion of insulin from pancreatic β-cells. Examples include biguanide derivatives (*e.g.*, metformin), sulfonylureas (SU) (*e.g.*, tolbutamide, chlorpropamide, tolazamide, acetohexamide, 4-chloro-*N*-[(1-pyrolidinylamino)carbonyl]-benzensulfonamide (glycopyramide), glibenclamide (glyburide), gliclazide, 1-butyl-3-metanilylurea, carbutamide, glibonuride, glipizide, gliquidone, glisoxepid, glybuthiazole, glibuzole, glyhexamide, glymidine, glypinamide, phenbutamide, and tolylcyclamide), or pharmaceutically acceptable salts thereof. Further examples include phenylalanine derivatives (*e.g.*, nateglinide [*N*-(*trans*-4-isopropylcyclohexylcarbonyl)-*D*-phenylalanine] (cf. EP 196222 and EP 526171) of the formula



;

repaglinide [(*S*)-2-ethoxy-4-{2-[[3-methyl-1-[2-(1-piperidinyl)phenyl]butyl]amino]-2-oxoethyl}benzoic acid] (cf. EP 589874, EP 147850 A2, in particular Example 11 on page 61, and EP 207331 A1); calcium (2*S*)-2-benzyl-3-(*cis*-hexahydro-2-isoindolinlycarbonyl)-

propionate dihydrate (*e.g.*, mitiglinide (cf. EP 507534)); and glimepiride (cf. EP 31058). Further examples include DPP-IV inhibitors, GLP-1 and GLP-1 agonists.

DPP-IV is responsible for inactivating GLP-1. More particularly, DPP-IV generates a GLP-1 receptor antagonist and thereby shortens the physiological response to GLP-1. GLP-1 is a major stimulator of pancreatic insulin secretion and has direct beneficial effects on glucose disposal.

The DPP-IV inhibitor can be peptidic or, preferably, non-peptidic. DPP-IV inhibitors are in each case generically and specifically disclosed *e.g.* in WO 98/19998, DE 196 16 486 A1, WO 00/34241 and WO 95/15309, in each case in particular in the compound claims and the final products of the working examples, the subject-matter of the final products, the pharmaceutical preparations and the claims are hereby incorporated into the present application by reference to these publications. Preferred are those compounds that are specifically disclosed in Example 3 of WO 98/19998 and Example 1 of WO 00/34241, respectively.

GLP-1 is an insulinotropic protein which is described, *e.g.*, by W.E. Schmidt et al. in *Diabetologia*, 28, 1985, 704-707 and in US 5,705,483.

The term "GLP-1 agonists" includes variants and analogs of GLP-1(7-36)NH_2 which are disclosed in particular in US 5,120,712, US 5,118666, US 5,512,549, WO 91/11457 and by C. Orskov et al in J. Biol. Chem. 264 (1989) 12826. Further examples include GLP-1(7-37), in which compound the carboxy-terminal amide functionality of Arg^{36} is displaced with Gly at the 37th position of the GLP-1(7-36)NH_2 molecule and variants and analogs thereof including GLN^9-GLP-1(7-37), D-GLN^9-GLP-1(7-37), acetyl LYS^9-GLP-1(7-37), LYS^{18}-GLP-1(7-37) and, in particular, GLP-1(7-37)OH, VAL^8-GLP-1(7-37), GLY^8-GLP-1(7-37), THR^8-GLP-1(7-37), MET^8-GLP-1(7-37) and 4-imidazopropionyl-GLP-1. Special preference is also given to the GLP agonist analog exendin-4, described by Greig *et al.* in Diabetologia 1999, 42, 45-50.

Also included in the definition "anti-diabetic agent" are insulin sensitivity enhancers which restore impaired insulin receptor function to reduce insulin resistance and consequently enhance the insulin sensitivity. Examples include hypoglycemic thiazolidinedione derivatives (*e.g.*, glitazone, (*S*)-((3,4-dihydro-2-(phenyl-methyl)-2*H*-1-benzopyran-6-yl)methyl-thiazolidine-2,4-dione (englitazone), 5-{[4-(3-(5-methyl-2-phenyl-4-oxazolyl)-1-oxopropyl)-phenyl]-methyl}-thiazolidine-2,4-dione (darglitazone), 5-{[4-(1-methyl-cyclohexyl)methoxy)-phenyl]methyl}-thiazolidine-2,4-dione (ciglitazone), 5-{[4-(2-(1-indolyl)ethoxy)phenyl]methyl}-thiazolidine-2,4-dione (DRF2189), 5-{4-[2-(5-methyl-2-

phenyl-4-oxazolyl)-ethoxy)]benzyl}-thiazolidine-2,4-dione (BM-13.1246), 5-(2-naphthylsulfonyl)-thiazolidine-2,4-dione (AY-31637), bis{4-[(2,4-dioxo-5-thiazolidinyl)methyl]phenyl}methane (YM268), 5-{4-[2-(5-methyl-2-phenyl-4-oxazolyl)-2-hydroxyethoxy]benzyl}-thiazolidine-2,4-dione (AD-5075), 5-[4-(1-phenyl-1-cyclopropanecarbonylamino)-benzyl]-thiazolidine-2,4-dione (DN-108) 5-{[4-(2-(2,3-dihydroindol-1-yl)ethoxy)phenyl]methyl}-thiazolidine-2,4-dione, 5-[3-(4-chloro-phenyl])-2-propynyl]-5-phenylsulfonyl)thiazolidine-2,4-dione, 5-[3-(4-chlorophenyl])-2-propynyl]-5-(4-fluorophenyl-sulfonyl)thiazolidine-2,4-dione, 5-{[4-(2-(methyl-2-pyridinyl-amino)-ethoxy)phenyl]methyl}-thiazolidine-2,4-dione (rosiglitazone), 5-{[4-(2-(5-ethyl-2-pyridyl)ethoxy)phenyl]-methyl}thiazolidine-2,4-dione (pioglitazone), 5-{[4-((3,4-dihydro-6-hydroxy-2,5,7,8-tetramethyl-2H-1-benzopyran-2-yl)methoxy)-phenyl]-methyl}-thiazolidine-2,4-dione (troglitazone), 5-[6-(2-fluoro-benzyloxy)naphthalen-2-ylmethyl]-thiazolidine-2,4-dione (MCC555), 5-{[2-(2-naphthyl)-benzoxazol-5-yl]-methyl}thiazolidine-2,4-dione (T-174) and 5-(2,4-dioxothiazolidin-5-ylmethyl)-2-methoxy-N-(4-trifluoromethyl-benzyl)benzamide (KRP297)).

Further anti-diabetic agents include, insulin signalling pathway modulators, like inhibitors of protein tyrosine phosphatases (PTPases), antidiabetic non-small molecule mimetic compounds and inhibitors of glutamine-fructose-6-phosphate amidotransferase (GFAT); compounds influencing a dysregulated hepatic glucose production, like inhibitors of glucose-6-phosphatase (G6Pase), inhibitors of fructose-1,6-bisphosphatase (F-1,6-Bpase), inhibitors of glycogen phosphorylase (GP), glucagon receptor antagonists and inhibitors of phosphoenolpyruvate carboxykinase (PEPCK); pyruvate dehydrogenase kinase (PDHK) inhibitors; inhibitors of gastric emptying; insulin; inhibitors of GSK-3; retinoid X receptor (RXR) agonists; agonists of Beta-3 AR; agonists of uncoupling proteins (UCPs); non-glitazone type PPAR agonists; dual PPARα/ PPARγ agonists; antidiabetic vanadium containing compounds; incretin hormones, like glucagon-like peptide-1 (GLP-1) and GLP-1 agonists; beta-cell imidazoline receptor antagonists; miglitol; α_2-adrenergic antagonists; and pharmaceutically acceptable salts thereof.

The term "obesity-reducing agent" includes lipase inhibitors (*e.g.*, orlistat) and appetite suppressants (*e.g.*, sibutramine and phentermine).

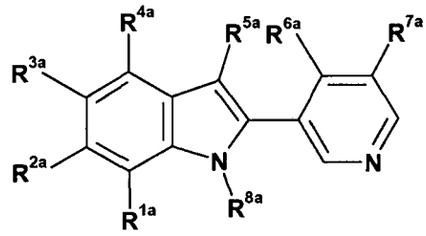
The term "aldosterone receptor blocker" includes spironolactone and eplerenone.

The term "endothelin receptor blocker" includes bosentan.

The term "CETP inhibitor" refers to a compound that inhibits the cholesteryl ester transfer protein (CETP) mediated transport of various cholesteryl esters and triglycerides from HDL to LDL and VLDL. Such CETP inhibition activity is readily determined by those skilled in the art according to standard assays (*e.g.*, U.S. Pat. No. 6,140,343). Examples include compounds disclosed in U.S. Pat. No. 6,140,343 and U. S. Pat. No. 6,197,786 (*e.g.*, [2R,4S]4-[(3,5-bis-trifluoromethyl-benzyl)-methoxycarbonyl- amino]-2-ethyl-6-trifluoromethyl-3,4-dihydro-2H-quinoline-1-carboxylic acid ethyl ester (torcetrapib); compounds disclosed in U.S. Pat. No. 6,723,752 (*e.g.*, (2R)-3-{[3-(4-Chloro-3-ethyl-phenoxy)-phenyl]-[[3-(1,1,2,2- tetrafluoro-ethoxy)-phenyl]-methyl]-amino}-1,1,1-trifluoro-2-propanol); compounds disclosed in U.S. patent application Ser. No. 10/807,838; polypeptide derivatives disclosed in U.S. Pat. No. 5,512,548; rosenonolactone derivatives and phosphate-containing analogs of cholesteryl ester disclosed in *J. Antibiot.,* 49(8): 815- 816 (1996), and *Bioorg. Med. Chem. Lett.;* 6:1951-1954 (1996), respectively. Furthermore, the CETP inhibitors also include those disclosed in WO2000/017165, WO2005/095409 and WO2005/097806.

Pharmaceutical Compositions of the Invention

The invention also pertains to pharmaceutical compositions comprising an effective amount of a compound of Formula I:



(I)

wherein:

R^{1a}, R^{2a}, R^{3a}, and R^{4a} are each independently hydrogen, halogen, cyano, hydroxy, alkoxy, alkyl, alkenyl, or alkoxycarbonyl;

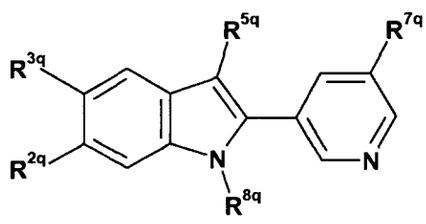
R^{5a} is hydrogen halogen, cyano, alkyl, alkenyl, arylalkyl, heteroarylalkyl, aminocarbonyl, alkylaminocarbonyl, carboxylate, alkoxycarbonyl, heterocyclylcarbonyl, aryl, or heteroaryl;

R^{6a} and R^{7a} are each independently hydrogen, halogen, hydroxy, alkoxy, amino, alkyl, sulfonyl, -O-sulfonyl, alkylamino, heterocyclyl, aminocarbonyl, carboxylate, or alkoxycarbonyl;

R^{8a} is hydrogen, alkyl, arylalkyl, heteroarylalkyl, alkoxycarbonyl, sulfonyl, aroyl, aryl, or heteroaryl; and pharmaceutically acceptable salts, polymorphs, rotamers, prodrugs, enantiomers, hydrates, and solvates thereof;

with the proviso that at least one of R^{1a}-R^{8a} is other than hydrogen; and when R^{5a} is cyano or lower alkyl optionally substituted with cyano, -C(O)-piperidine, amino, alkylamino, dialkylamino, carboxylate, alkoxycarbonyl, aminocarbonyl, or heterocyclyl, then at least one of R^{1a}-R^{4a} and R^{6a}-R^{8a} is other than hydrogen; and when R^{7a} is imidazolyl, then at least one of R^{1a}-R^{6a} and R^{8a} is other than hydrogen; and when R^{8a} is alkyl, arylalkyl or alkoxycarbonyl, then at least one of R^{1a}-R^{7a} is other than hydrogen; and when R^{5a} is lower alkyl and R^{8a} is alkyl substituted with carboxylate or $PO_3R^{21}R^{22}$ wherein R^{21} and R^{22} are each independently hydrogen or lower alkyl, then at least one of R^{1a}-R^{4a} and R^{6a} and R^{7a} is other than hydrogen; and when R^{3a} is halogen and R^{5a} and R^{8a} are independently lower alkyl optionally substituted with carboxylate, alkoxycarbonyl, or -C(O)-piperidine, then at least one of R^{1a}, R^{2a}, R^{4a}, R^{6a} and R^{7a} is other than hydrogen; and when R^{3a} is halogen or lower alkyl and R^{5a} is lower alkyl substituted with dialkylamino, dialkylaminocarbonyl, carboxylate, alkoxycarbonyl or aminocarbonyl, then at least one of R^{1a}, R^{2a}, R^{4a}, and R^{6a}-R^{8a} is other than hydrogen; and when R^{2a} and R^{3a} are each alkoxy and R^{5a} is cyano, then at least one of R^{1a}, R^{4a}, and R^{6a}-R^{8a} is other than hydrogen; and when R^{3a} is alkyl substituted with aroyl, and R^5 and R^8 are each independently hydrogen or lower alkyl, then at least one of R^{1a}, R^{2a}, and R^{4a} is other than hydrogen, wherein said effective amount is effective to treat an aldosterone synthase associated state.

In another embodiment, the invention pertains to pharmaceutical compositions comprising an effective amount of a compound of Formula II:



(II)

wherein:

R^{2q} is hydrogen or halogen;

R^{3q} is hydrogen, halogen, or cyano;

R^{5q} is hydrogen, alkyl, or cyano;

R^{7q} is hydrogen, halogen, alkoxy, -OSO_2-heterocyclyl, -O-arylalkyl, -NR'-SO_2-alkyl, -NR'-C(O)-alkyl, -NR'-C(O)-NR'-alkyl, -NR'-C(O)-O-alkyl, haloalkyl, or alkyl optionally substituted with heterocyclyl, –NR'-SO_2-alkyl, -NR'-SO_2-haloalkyl, NR'-C(O)-alkyl, NR'-C(O)-heterocyclyl, -NR'-C(O)-NR'-alkyl, or –NR'-C(O)-O-alkyl;

R^{8q} is hydrogen, alkyl, hydroxyalkyl, -alkyl-OC(O)-alkyl, carboxylate, alkoxycarbonyl, or arylalkyl substituted with alkyl, or aroyl substituted with cyano and/or alkyl, or -alkyl-O-aryl substituted with alkoxycarbonyl;

each R' is independently hydrogen, C_1-C_4-alkyl, or C_3-C_6-cycloalkyl,

with the proviso that at least one of R^{2q}, R^{3q}, R^{5q}, R^{7q} and R^{8q} is other than hydrogen, wherein said effective amount is effective to treat an aldosterone synthase associated state.

In still another embodiment, the invention pertains to pharmaceutical compositions comprising an effective amount of a compound of Formula III or IV, wherein said effective amount is effective to treat an aldosterone synthase associated state.

The pharmaceutical composition or combination of the present invention can be in unit dosage of about 1-1000 mg of active ingredients for a subject of about 50-70 kg, preferably about 1-500 mg or about 1-250 mg or about 1-150 mg or about 0.5-100 mg, or about 1-50 mg of active ingredients. The therapeutically effective dosage of a compound, the pharmaceutical composition, or the combinations thereof, is dependent on the species of the subject, the body weight, age and individual condition, the disorder or disease or the severity thereof being treated. A physician, clinician or veterinarian of ordinary skill can readily determine the effective amount of each of the active ingredients necessary to prevent, treat or inhibit the progress of the disorder or disease.

The above-cited dosage properties are demonstrable *in vitro* and *in vivo* tests using advantageously mammals, *e.g.*, mice, rats, dogs, monkeys or isolated organs, tissues and preparations thereof. The compounds of the present invention can be applied *in vitro* in the form of solutions, *e.g.*, preferably aqueous solutions, and *in vivo* either enterally, parenterally, advantageously intravenously, *e.g.*, as a suspension or in aqueous solution. The dosage *in vitro* may range between about 10^{-3} molar and about 10^{-9} molar concentrations, or between about 10^{-6} molar and about 10^{-9} molar concentrations.

The activities of a compound according to the present invention can be assessed by both *in vitro* and *in vivo* methods.

The term "pharmaceutically acceptable carrier" includes any and all solvents, dispersion media, coatings, surfactants, antioxidants, preservatives (*e.g.*, antibacterial agents, antifungal agents), isotonic agents, absorption delaying agents, salts, preservatives, drugs, drug stabilizers, binders, excipients, wetting agents, emulsifiers, buffers, disintegration agents, lubricants, coatings, sweetening agents, flavoring agents, dyes, such like materials and combinations thereof, as would be known to one of ordinary skill in the art (see, for example, Remington's Pharmaceutical Sciences, 18th Ed. Mack Printing Company, 1990, pp. 1289- 1329, incorporated herein by reference). Except insofar as any conventional carrier is incompatible with the active ingredient, its use in the therapeutic or pharmaceutical compositions is contemplated. Suitable pharmaceutically acceptable carriers include but are not limited to water, salt solutions, alcohol, vegetable oils, polyethylene glycols, gelatin, lactose, amylase, magnesium stearate, talc, silicic aid, viscous paraffin, perfume oil, fatty acid monoglycerides and diglycerides, petroethral fatty acid esters, hydroxymethyl-cellulose, polyvinylpyrrolidone, etc.

The pharmaceutical compositions of the invention can be formulated for particular routes of administration such as oral administration, parenteral administration, and rectal administration, etc. In addition, the pharmaceutical compositions of the present invention can be made up in a solid form including capsules, tablets, pills, granules, powders or suppositories, or in a liquid form including solutions, suspensions or emulsions. The pharmaceutical compositions can be subjected to conventional pharmaceutical operations such as sterilization and/or can contain conventional inert diluents, lubricating agents, or buffering agents, as well as adjuvants, such as preservatives, stabilizers, wetting agents, emulsifers and buffers, etc.

In certain embodiments, the pharmaceutical compositions are tablets and gelatin capsules comprising the active ingredient together with

a) diluents, *e.g.*, lactose, dextrose, sucrose, mannitol, sorbitol, cellulose and/or glycine;

b) lubricants, *e.g.*, silica, talcum, stearic acid, its magnesium or calcium salt and/or polyethyleneglycol; for tablets also

c) binders, *e.g.*, magnesium aluminum silicate, starch paste, gelatin, tragacanth, methylcellulose, sodium carboxymethylcellulose and/or polyvinylpyrrolidone; if desired

d) disintegrants, *e.g.*, starches, agar, alginic acid or its sodium salt, or effervescent mixtures; and/or

e) absorbents, colorants, flavors and sweeteners.

Tablets may be either film coated or enteric coated according to methods known in the art.

Suitable compositions for oral administration include an effective amount of a compound of the invention in the form of tablets, lozenges, aqueous or oily suspensions, dispersible powders or granules, emulsion, hard or soft capsules, or syrups or elixirs. Compositions intended for oral use are prepared according to any method known in the art for the manufacture of pharmaceutical compositions and such compositions can contain one or more agents selected from the group consisting of sweetening agents, flavoring agents, coloring agents and preserving agents in order to provide pharmaceutically elegant and palatable preparations. Tablets contain the active ingredient in admixture with nontoxic pharmaceutically acceptable excipients which are suitable for the manufacture of tablets. These excipients are, for example, inert diluents, such as calcium carbonate, sodium carbonate, lactose, calcium phosphate or sodium phosphate; granulating and disintegrating agents, for example, corn starch, or alginic acid; binding agents, for example, starch, gelatin or acacia; and lubricating agents, for example magnesium stearate, stearic acid or talc. The tablets are uncoated or coated by known techniques to delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such as glyceryl monostearate or glyceryl distearate can be employed. Formulations for oral use can be presented as hard gelatin capsules wherein the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules wherein the active ingredient is mixed with water or an oil medium, for example, peanut oil, liquid paraffin or olive oil.

Injectable compositions are preferably aqueous isotonic solutions or suspensions, and suppositories are advantageously prepared from fatty emulsions or suspensions. Said compositions may be sterilized and/or contain adjuvants, such as preserving, stabilizing, wetting or emulsifying agents, solution promoters, salts for regulating the osmotic pressure, and/or buffers. In addition, they may also contain other therapeutically valuable substances. Said compositions are prepared according to conventional mixing, granulating or coating methods, respectively, and contain about 0.1-75%, preferably about 1-50%, of the active ingredient.

Suitable compositions for transdermal application include an effective amount of a compound of the invention with carrier. Advantageous carriers include absorbable pharmacologically acceptable solvents to assist passage through the skin of the host. For example, transdermal devices are in the form of a bandage comprising a backing member, a reservoir containing the compound optionally with carriers, optionally a rate controlling barrier to deliver the compound of the skin of the host at a controlled and predetermined rate over a prolonged period of time, and means to secure the device to the skin.

Suitable compositions for topical application, *e.g.*, to the skin and eyes, include aqueous solutions, suspensions, ointments, creams, gels or sprayable formulations, *e.g.*, for delivery by aerosol or the like. Such topical delivery systems will in particular be appropriate for dermal application, *e.g.*, for the treatment of skin cancer, *e.g.*, for prophylactic use in sun creams, lotions, sprays, etc. They are thus particularly suited for use in topical, including cosmetic, formulations well-known in the art. Such may contain solubilizers, stabilizers, tonicity enhancing agents, buffers and preservatives.

The present invention further provides anhydrous pharmaceutical compositions and dosage forms comprising the compounds of the present invention as active ingredients, since water can facilitate the degradation of some compounds. For example, the addition of water (*e.g.*, 5%) is widely accepted in the pharmaceutical arts as a means of simulating long-term storage in order to determine characteristics such as shelf-life or the stability of formulations over time. See, *e.g.*, Jens T. Carstensen, *Drug Stability: Principles & Practice,* 2d. Ed., Marcel Dekker, NY, N.Y., 1995, pp. 379-80. In effect, water and heat accelerate the decomposition of some compounds. Thus, the effect of water on a formulation can be of great significance since moisture and/or humidity are commonly encountered during manufacture, handling, packaging, storage, shipment, and use of formulations.

Anhydrous pharmaceutical compositions and dosage forms of the invention can be prepared using anhydrous or low moisture containing ingredients and low moisture or low humidity conditions. Pharmaceutical compositions and dosage forms that comprise lactose and at least one active ingredient that comprises a primary or secondary amine are preferably anhydrous if substantial contact with moisture and/or humidity during manufacturing, packaging, and/or storage is expected.

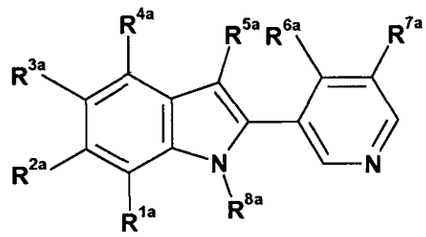
An anhydrous pharmaceutical composition should be prepared and stored such that its anhydrous nature is maintained. Accordingly, anhydrous compositions are

preferably packaged using materials known to prevent exposure to water such that they can be included in suitable formulary kits. Examples of suitable packaging include, but are not limited to, hermetically sealed foils, plastics, unit dose containers (*e. g.*, vials), blister packs, and strip packs.

The invention further provides pharmaceutical compositions and dosage forms that comprise one or more agents that reduce the rate by which the compound of the present invention as an active ingredient will decompose. Such agents, which are referred to herein as "stabilizers," include, but are not limited to, antioxidants such as ascorbic acid, pH buffers, or salt buffers, etc.

One embodiment of the invention includes a pharmaceutical composition as described above in combination with a second agent and a pharmaceutical carrier.

In yet another embodiment, the invention pertains, at least in part, to compounds of Formula I:



(I)

wherein:

R^{1a}, R^{2a}, R^{3a}, and R^{4a} are each independently hydrogen, halogen, cyano, hydroxy, alkoxy, alkyl, alkenyl, or alkoxycarbonyl;

R^{5a} is hydrogen halogen, cyano, alkyl, alkenyl, arylalkyl, heteroarylalkyl, aminocarbonyl, alkylaminocarbonyl, carboxylate, alkoxycarbonyl, heterocyclylcarbonyl, aryl, or heteroaryl;

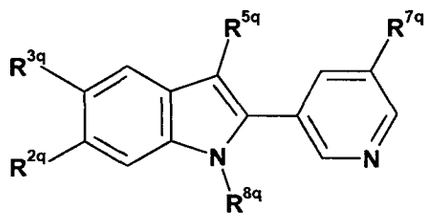
R^{6a} and R^{7a} are each independently hydrogen, halogen, hydroxy, alkoxy, amino, alkyl, sulfonyl, -O-sulfonyl, alkylamino, heterocyclyl, aminocarbonyl; carboxylate, or alkoxycarbonyl;

R^{8a} is hydrogen, alkyl, arylalkyl, heteroarylalkyl, alkoxycarbonyl, sulfonyl, aroyl, aryl, or heteroaryl; and pharmaceutically acceptable salts, polymorphs, rotamers, prodrugs, enantiomers, hydrates, and solvates thereof;

with the proviso that at least one of R^{1a}-R^{8a} is other than hydrogen; and when R^{5a} is cyano or lower alkyl optionally substituted with cyano, -C(O)-piperidine, amino, alkylamino, dialkylamino, carboxylate, alkoxycarbonyl, aminocarbonyl, or heterocyclyl,

then at least one of R^{1a}-R^{4a} and R^{6a}-R^{8a} is other than hydrogen; and when R^{7a} is imidazolyl, then at least one of R^{1a}-R^{6a} and R^{8a} is other than hydrogen; and when R^{8a} is alkyl, arylalkyl or alkoxycarbonyl, then at least one of R^{1a}-R^{7a} is other than hydrogen; and when R^{5a} is lower alkyl and R^{8a} is alkyl substituted with carboxylate or $PO_3R^{21}R^{22}$ wherein R^{21} and R^{22} are each independently hydrogen or lower alkyl, then at least one of R^{1a}-R^{4a} and R^{6a} and R^{7a} is other than hydrogen; and when R^{3a} is halogen and R^{5a} and R^{8a} are independently lower alkyl optionally substituted with carboxylate, alkoxycarbonyl, or -C(O)-piperidine, then at least one of R^{1a}, R^{2a}, R^{4a}, R^{6a} and R^{7a} is other than hydrogen; and when R^{3a} is halogen or lower alkyl and R^{5a} is lower alkyl substituted with dialkylamino, dialkylaminocarbonyl, carboxylate, alkoxycarbonyl or aminocarbonyl, then at least one of R^{1a}, R^{2a}, R^{4a}, and R^{6a}-R^{8a} is other than hydrogen; and when R^{2a} and R^{3a} are each alkoxy and R^{5a} is cyano, then at least one of R^{1a}, R^{4a}, and R^{6a}-R^{8a} is other than hydrogen; and when R^{3a} is alkyl substituted with aroyl, and R^5 and R^8 are each independently hydrogen or lower alkyl, then at least one of R^{1a}, R^{2a}, and R^{4a} is other than hydrogen, for use in therapy.

In still another embodiment, the invention pertains, at least in part, to compounds of Formula II:



(II)

wherein:

R^{2q} is hydrogen or halogen;

R^{3q} is hydrogen, halogen, or cyano;

R^{5q} is hydrogen, alkyl, or cyano;

R^{7q} is hydrogen, halogen, alkoxy, -OSO_2-heterocyclyl, -O-arylalkyl, -NR'-SO_2-alkyl, -NR'-C(O)-alkyl, -NR'-C(O)-NR'-alkyl, -NR'-C(O)-O-alkyl, haloalkyl, or alkyl optionally substituted with heterocyclyl, –NR'-SO_2-alkyl, -NR'-SO_2-haloalkyl, NR'-C(O)-alkyl, NR'-C(O)-heterocyclyl, -NR'-C(O)-NR'-alkyl, or –NR'-C(O)-O-alkyl;

R^{8q} is hydrogen, alkyl, hydroxyalkyl, -alkyl-OC(O)-alkyl, carboxylate, alkoxycarbonyl, or arylalkyl substituted with alkyl, or aroyl substituted with cyano and/or alkyl, or -alkyl-O-aryl substituted with alkoxycarbonyl;

each R' is independently hydrogen, C_1-C_4-alkyl, or C_3-C_6-cycloalkyl,

with the proviso that at least one of R^{2q}, R^{3q}, R^{5q}, R^{7q} and R^{8q} is other than hydrogen, for use in therapy.

Another embodiment of the invention pertains, at least in part, to compounds of Formula III or IV, for use in therapy.

Still another embodiment of the invention pertains, at least in part, to the use of compounds of Formula (I), (II), (III) or (IV), as described above, and the compounds of the examples, for the preparation of a pharmaceutical composition for the treatment of a disorder or disease in a subject mediated by the inhibition of aldosterone synthase.

In yet another embodiment, the invention pertains, at least in part, to compounds of Formula (I), (II), (III) or (IV), as described above, and the compounds of the examples, for use as a medicament.

Another embodiment of the invention pertains, at least in part, to pharmaceutical compositions, as described above, for use as a medicament.

In another embodiment, the invention pertains, at least in part, to the use of pharmaceutical compositions, as described above, for the preparation of a medicament for the treatment of a disorder or disease in a subject mediated by the inhibition of aldosterone synthase.

Another embodiment of the invention pertains, at least in part, to methods of treating a disorder or disease mediated by aldosterone synthase in a mammal, by administering to the mammal in need thereof a therapeutically effective amount of a compound of Formula (I), (II), (III) or (IV), as described above and in the examples.

Another embodiment of the invention pertains to kits comprising, a pharmaceutical composition as described above, packaged with instructions for use of the pharmaceutical composition in the treatment of an aldosterone synthase associated state in a subject in need thereof.

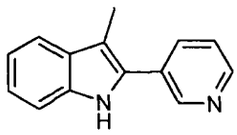
Exemplification of the Invention

The following examples are intended to illustrate the invention and are not to be construed as being limitations thereon. Temperatures are given in degrees centrigrade. If not mentioned otherwise, all evaporations are performed under reduced pressure, preferably between about 15 mm Hg and 100 mm Hg (= 20-133 mbar). The structure of final products, intermediates and starting materials is confirmed by standard analytical

methods, *e.g.*, microanalysis and spectroscopic characteristics, *e.g.*, MS, IR, NMR. Abbreviations used are those conventional in the art.

Example 1

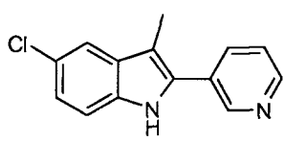
3-Methyl-2-pyridin-3-yl-1H-indole hydrochloride



3-Methyl-2-pyridin-3-yl-1H-indole hydrochloride is synthesized based on the method described in patent US3468894. A flask is charged with 3-propionylpyridine (1.004 g, 7.279 mmol), phenylhydrazine hydrochloride (1.010 g, 6.915 mmol) and ethanol (15 mL). The mixture is heated to reflux for 1 h and cooled to room temperature. To a portion of the reaction mixture (2.5 mL) is added HCl (4M in dioxane, 1 mL, 4 mmol) and the mixture is heated to reflux. After 3 h, the mixture is concentrated *in vacuo*. The solid is dissolved in the minimum amount of boiling methanol (17 mL) and allowed to cool slowly to room temperature. A solid precipitates and after cooling to 0 °C for 30 min, the yellow solid is filtered off, washed with portions of cold methanol and dried under high vacuum to give 3-methyl-2-pyridin-3-yl-1H-indole hydrochloride as yellow needles. ^{1}H NMR (400 MHz, MeOD) δ ppm (HCl salt) 2.56 (s, 3 H), 7.09 - 7.13 (m, 1 H), 7.23 - 7.26 (m, 1 H), 7.43 (d, *J*=8.1 Hz, 1 H), 7.63 (d, *J*=8.1 Hz, 1 H), 8.14 - 8.18 (m, 1 H), 8.74 (d, *J*=5.8 Hz, 1 H), 8.83-8.85 (m, 1 H), 9.08 (s, 1 H).

Example 2

5-Chloro-3-methyl-2-pyridin-3-yl-1H-indole hydrochloride

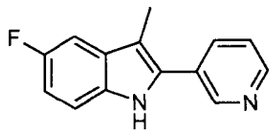


5-Chloro-3-methyl-2-pyridin-3-yl-1H-indole hydrochloride is synthesized based on the method described in patent US3468894. (4-Chloro-phenyl)-hydrazine hydrochloride (3.0 g, 16.8 mmol) and 3-propionylpyridine (2.4 g, 17.6 mmol) in ethanol (45 mL) is heated to reflux for 6 h. The mixture is then cooled to room temperature and added to HCl (4M in 1,4-dioxane, 17.6 mL). The resulting mixture is heated to reflux for 24 h. The mixture is then cooled to room temperature and the yellow precipitate is filtered and washed with

methanol (10 mL) three times to give 5-chloro-3-methyl-2-pyridin-3-yl-1H-indole hydrochloride as a yellow solid. MS (ESI) *m/z* 243.0 and 244.9 $(M+H)^+$.

Example 3

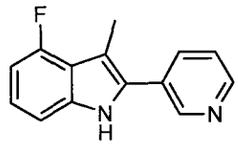
5-Fluoro-3-methyl-2-pyridin-3-yl-1H-indole hydrochloride

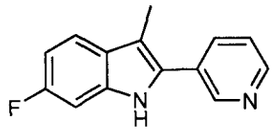


(4-Fluoro-phenyl)-hydrazine hydrochloride is processed according to the procedure described in Example 2 to give 5-fluoro-3-methyl-2-pyridin-3-yl-1H-indole hydrochloride. MS (ESI) *m/z* 227.0 $(M+H)^+$.

Example 4

4- and 6-Fluoro-3-methyl-2-pyridin-3-yl-1H-indole hydrochloride

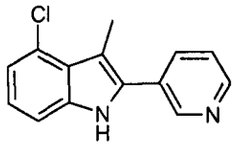


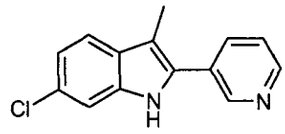


(3-Fluoro-phenyl)-hydrazine hydrochloride is processed according to the procedure described in Example 2 to give a mixture of 4-fluoro-3-methyl-2-pyridin-3-yl-1H-indole hydrochloride and 6-fluoro-3-methyl-2-pyridin-3-yl-1H-indole hydrochloride. MS (ESI) *m/z* 227.0 $(M+H)^+$.

Example 5

4- and 6-Chloro-3-methyl-2-pyridin-3-yl-1H-indole hydrochloride

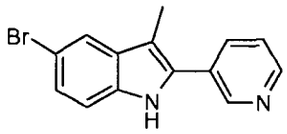




(3-Chloro-phenyl)-hydrazine hydrochloride is processed according to the procedure described in Example 2 to give a mixture of 4-chloro-3-methyl-2-pyridin-3-yl-1H-indole hydrochloride and 6-chloro-3-methyl-2-pyridin-3-yl-1H-indole hydrochloride. MS (ESI) *m/z* 242.96 and 244.98 $(M+H)^+$.

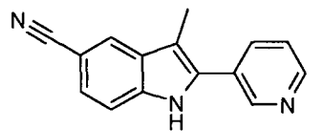
Example 6

(a) 5-Bromo-3-methyl-2-pyridin-3-yl-1H-indole



To a suspension of 4-bromophenylhydrazine hydrochloride (10.00 g, 42.95 mmol) in anhydrous ethanol (200 mL) is added 3-propionylpyridine (7.51 g, 42.95 mmol) and the mixture is stirred at reflux for 30 min. 4M HCl in 1,4-dioxane (42.9 mL) is added to the yellow solution and stirring is continued at reflux overnight. The reaction mixture is cooled with an ice-water bath and the yellow precipitate is filtered through a sintered funnel to give 5-bromo-3-methyl-2-pyridin-3-yl-1H-indole hydrochloride as a yellow solid. The product is dissolved in methanol (100 mL) and treated with sodium methoxide to give the free base, which is used in the next step without further purification.

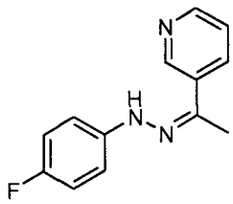
(b) 3-Methyl-2-pyridin-3-yl-1H-indole-5-carbonitrile



5-Bromo-3-methyl-2-pyridin-3-yl-1H-indole (5.0 g, 16.7 mmol) and copper (I) cyanide (1.9 g, 20.1 mmol) are placed in a round bottom flask which is flushed with N_2. *N*-Methylpyrrolidinone (40 mL) is added via syringe. The resulting mixture is heated to 200 °C under N_2 with vigorous stirring overnight. The mixture is cooled to room temperature and dichloromethane (200 mL) is added. The mixture is filtered through a pad of celite. The filtrate is washed with 10% aqueous ammonia in saturated aqueous ammonium chloride. The aqueous phase is extracted with dichloromethane. The combined organic phase is dried over sodium sulfate and concentrated. The residue is purified by silica gel flash chromatography (ethyl acetate-heptane, 0:1 to 1:0) to give 3-methyl-2-pyridin-3-yl-1H-indole-5-carbonitrile. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.45 (s, 3 H), 7.45 - 7.60 (m, 3 H), 8.06 - 8.11 (m, 1 H), 8.15 (s, 1 H), 8.60 (dd, *J*=4.8, 1.5 Hz, 1 H), 8.91 (d, *J*=1.5 Hz, 1 H), 11.94 (br. s., 1 H). HRMS (ESI) m/z 234.1031 [$(M+H)^+$ Calcd for $C_{15}H_{11}N_3$, 234.1031].

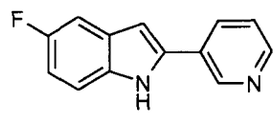
Example 7

(a) *N*-(4-Fluoro-phenyl)-*N'*-[1-pyridin-3-yl-eth-(Z)-ylidene]-hydrazine



3-Acetylpyridine (5.00 g, 40.45 mmol) and 4-fluorophenylhydrazine hydrochloride (6.44 g, 38.43 mmol) are suspended in ethanol (70 mL) and heated to reflux. After 1 h, HCl (4M in dioxane, 150 mL, 600 mmol) is added and the mixture is heated to reflux for 16 h. The mixture is concentrated *in vacuo* and taken up in a little ethanol. The solid is filtered off and washed with ethanol to give a yellow solid. The filtrate is concentrated to dryness. The resulting solid is washed with small amounts of ice-cold ethanol and filtered off. The two fractions are combined and used in the next step without further purification.

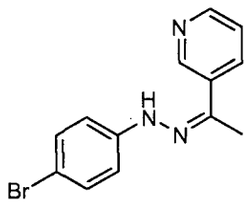
(b) 5-Fluoro-2-pyridin-3-yl-indole



A flaks is charged with polyphosphoric acid (1.2 g) and *N*-(4-fluoro-phenyl)-*N'*-[1-pyridin-3-yl-eth-(Z)-ylidene]-hydrazine (1.0 g) is added. The mixture is stirred with a thermometer and heated to 160 °C (internal temperature), whereupon the paste is allowed to cool to 100 °C. Water (90 mL) and ethyl acetate are added and the mixture is vigorously stirred until a discrete yellow precipitate is obtained. The precipitate is filtered off and the two phases are separated. The ethyl acetate phase is discarded. The solids and aqueous phase are combined and 1M aqueous NaOH is added, followed with chloroform, and the mixture is vigorously stirred until full dissolution. The aqueous phase is extracted with chloroform and the combined organic phase is dried over $MgSO_4$ and concentrated in vacuo. The residue is purified by silica gel flash chromatography (ethyl acetate-heptane, 7:3 to 9:1) to give as a brown solid. MS (ESI) *m/z* 213 $(M+H)^+$.

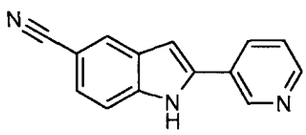
Example 8

(a) *N*-(4-Bromo-phenyl)-*N'*-[1-pyridin-3-yl-eth-(Z)-ylidene]-hydrazine hydrochloride



To a solution of 4-bromophenylhydrazine hydrochloride (11.5 g, 50 mmol) in anhydrous ethanol (200 mL) is added 3-acetylpyridine (6.1 g, 50 mmol). The mixture is heated to 90 °C and stirred for 3 h, cooled to room temperature and filtered through a sintered glass funnel. The solid is washed with ethanol and placed under high vacuum overnight to give *N*-(4-bromo-phenyl)-*N'*-[1-pyridin-3-yl-eth-(Z)-ylidene]-hydrazine hydrochloride as a yellow solid.

(b) 2-Pyridin-3-yl-1H-indole-5-carbonitrile



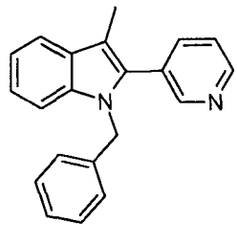
A flask fitted with a mechanical stirrer is charged with polyphosphoric acid (15 g) and *N*-(4-bromo-phenyl)-*N'*-[1-pyridin-3-yl-eth-(Z)-ylidene]-hydrazine hydrochloride (18 g) is heated to 210 °C (oil bath temperature) for 1 h. The paste is allowed to cool to ambient temperature and 1M aqueous NaOH is added, followed with chloroform, and the mixture is vigorously stirred until full dissolution. The aqueous phase is extracted with chloroform and the combined organic phase is dried over $MgSO_4$ and concentrated *in vacuo* to give 5-bromo-2-pyridin-3-yl-1H-indole as a brown solid which is used without further purification.

5-Bromo-2-pyridin-3-yl-1H-indole (7.0 g, 21.8 mmol) and copper (I) cyanide (2.3 g, 26.1 mmol) are placed in a round bottom flask which is flushed with N_2. *N*-Methylpyrrolidinone (40 mL) is added via syringe. The resulting mixture is heated to 160 °C under N_2 with vigorous stirring overnight. The mixture is cooled to room temperature and poured into 10% aqueous ammonia in saturated aqueous ammonium chloride (300 mL). The aqueous phase is extracted with dichloromethane (100 mL) five times. The combined organic phase is dried over sodium sulfate and concentrated. The residue is purified by silica gel flash chromatography (ethyl acetate-heptane, 0:1 to 1:0) to give 2-pyridin-3-yl-1H-indole-5-carbonitrile. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.20 (s, 1 H), 7.48 (dd, *J*=8.3, 1.5 Hz, 1 H), 7.51 - 7.55 (m, 1 H), 7.59 (d, *J*=8.6 Hz, 1 H), 8.12 (s, 1 H), 8.25 -

8.29 (m, 1 H), 8.56 (dd, *J*=4.8, 1.5 Hz, 1 H), 9.14 (d, *J*=1.8 Hz, 1 H), 12.27 (s, 1 H). HRMS (ESI) m/z 220.0869 [$(M+H)^+$ Calcd for $C_{14}H_9N_3$, 220.0875].

Example 9

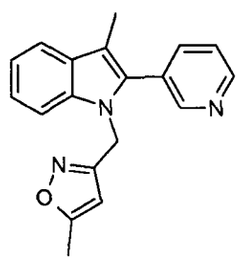
1-Benzyl-3-methyl-2-pyridin-3-yl-1H-indole



3-Methyl-2-pyridin-3-yl-1H-indole hydrochloride (Example 1, 0.110 g, 0.445 mmol) is suspended in THF (3 mL) and cooled to 0 °C. KHMDS (0.5M in toluene, 2 mL, 1 mmol) is added dropwise, the cooling bath is lowered and the mixture is stirred at room temperature for 15 min, whereupon it is lowered in the ice-water bath. Benzyl bromide (0.093 g, 0.534 mmol) is added dropwise. After 3 h, additional benzyl bromide (0.046 g, 0.267 mmol) is added, and upon reaction completion, the mixture is quenched with 1M aqueous HCl and diluted with ethyl acetate. The aqueous phase is extracted and the combined organic phase is dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification of the residue by silica gel flash chromatography (dichloromethane-methanol, 99:1) affords 1-benzyl-3-methyl-2-pyridin-3-yl-1H-indole as a pale yellow solid. ^{1}H NMR (400 MHz, MeOD) δ ppm 2.18 (s, 3 H), 5.19 (s, 2 H), 6.69 - 6.71 (m, 2 H), 7.01 - 7.11 (m, 5 H), 7.21 (d, *J*=8.1 Hz, 1 H), 7.37 - 7.41 (m, 1 H), 7.52 (d, *J*=7.8 Hz, 1 H), 7.67 - 7.70 (m, 1 H), 8.36 (s, 1 H), 8.43 - 8.45 (m, 1 H). MS (ESI) *m/z* 299 $(M+H)^+$.

Example 10

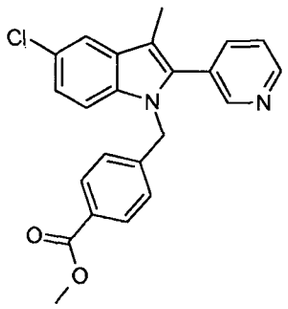
3-Methyl-1-(5-methyl-isoxazol-3-ylmethyl)-2-pyridin-3-yl-1H-indole hydrochloride



A flask is charged with 3-methyl-2-pyridin-3-yl-1H-indole hydrochloride (Example 1, 0.100 g, 0.408 mmol) in THF (2.5 mL) and cooled to 0 °C. KHMDS (0.5 M in toluene, 1.8 mL, 0.898 mmol) is added and the mixture is stirred at room temperature for 30 min, followed by addition of 3-bromomethyl-5-methyl-isoxazole (0.144 g, 0.817 mmol). The reaction mixture is stirred for 0.5 h, then quenched with saturated ammonium chloride solution and extracted with ethyl acetate. The organic layer is dried over sodium sulfate and concentrated *in vacuo*. The residue is purified by reverse phase HPLC with Xbridge Shield RP18 column and a 0.1% aqueous NH_4OH in acetonitrile gradientto afford 3-methyl-1-(5-methyl-isoxazol-3-ylmethyl)-2-pyridin-3-yl-1H-indole product as a colorless oil. The oil is dissolved in diethyl ether and few drops of concentrated HCl are added. The volatiles are removed in vacuo and the reside is lyophilized to afford the product as a yellow solid. ^{1}H NMR (400 MHz, MeOD) δ ppm (HCl salt) 2.30 (s, 3 H), 2.31 (s, 3 H), 5.30 (s, 2 H), 5.67 (s, 1 H), 7.18 (t, *J*=8.0 Hz, 1 H), 7.27 (ddd, *J*=7.6, 1.1 Hz, 1 H), 7.45 (d, *J*=8.1 Hz, 1 H), 7.56 - 7.69 (m, 2 H), 7.99 (dt, *J*=8.0, 1.9, 1.8 Hz, 1 H), 8.56 - 8.68 (m, 2 H). HRMS (ESI) m/z 304.1440 [$(M+H)^+$ Calcd for $C_{19}H_{18}N_3O$, 304.1450].

Example 11

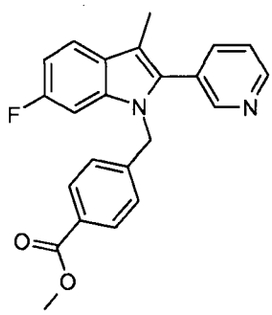
4-(5-Chloro-3-methyl-2-pyridin-3-yl-1H-indol-1-ylmethyl)-benzoic acid methyl ester



To a solution of 5-chloro-3-methyl-2-pyridin-3-yl-1H-indole hydrochloride (Example 2, 558 mg, 2.0 mmol) in THF (20 mL) is added 0.5 M KHMDS in toluene (8.8 mL, 4.4 mmol) and the mixture is stirred at room temperature for 30 min, whereupon 4-bromomethyl-benzoic acid methyl ester (916 mg, 4.0 mmol). The reaction mixture is stirred for 3 h. Methanol is added to quench the reaction and the solvents are removed *in vacuo*. The residue is purified by flash chromatography with 1-3% methanol in dichloromethane to give 4-(5-chloro-3-methyl-2-pyridin-3-yl-1H-indol-1-ylmethyl)-benzoic acid methyl ester. MS (ESI) *m/z* 391.3 and 393.3 $(M+H)^+$.

Example 12

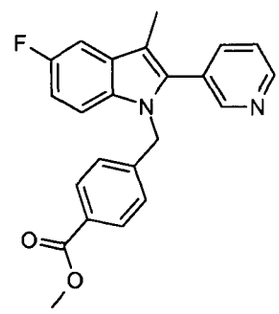
4-(6-Fluoro-3-methyl-2-pyridin-3-yl-1H-indol-1-ylmethyl)-benzoic acid methyl ester



The mixture of 4- and 6-fluoro-3-methyl-2-pyridin-3-yl-1H-indole hydrochloride (Example 4) and 4-bromomethyl-benzoic acid methyl ester are processed according to the method described in Example 11. Separation of the regioisomers is done on an X-Bridge RP18 eluting with a 30-70% gradient of acetonitrile in 0.1% NH_4OH to give 4-(6-fluoro-3-methyl-2-pyridin-3-yl-1H-indol-1-ylmethyl)-benzoic acid methyl ester. ^1H NMR (400 MHz, $CDCl_3$) δ ppm 2.30 (s, 3 H), 3.90 (s, 3 H), 5.22 (s, 2 H), 6.86 (dd, *J*=9.8, 2.1 Hz, 1 H), 6.93 - 7.00 (m, 3 H), 7.34 - 7.38 (m, 1 H), 7.55 - 7.61 (m, 2 H), 7.90 - 7.92 (m, 1 H), 7.92 - 7.94 (m, 1 H), 8.59 (dd, *J*=2.3, 0.9 Hz, 1 H), 8.63 (dd, *J*=4.9, 1.6 Hz, 1 H). HRMS (ESI) m/z 375.1498 $[(M+H)^+$ Calcd for $C_{23}H_{20}FN_2O_2$, 375.1509].

Example 13

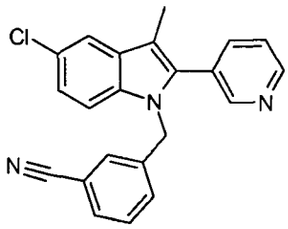
4-(4-Fluoro-3-methyl-2-pyridin-3-yl-1H-indol-1-ylmethyl)-benzoic acid methyl ester



The method described in Example 12 also yields 4-(4-fluoro-3-methyl-2-pyridin-3-yl-1H-indol-1-ylmethyl)-benzoic acid methyl ester. MS (ESI) *m/z* 375.2 $(M+H)^+$.

Example 14

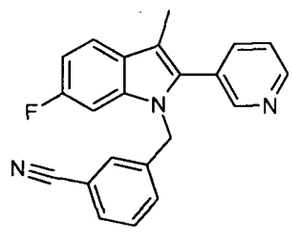
3-(5-Chloro-3-methyl-2-pyridin-3-yl-1H-indol-1-ylmethyl)-benzonitrile



5-Chloro-3-methyl-2-pyridin-3-yl-1H-indole hydrochloride (Example 2) and 3-bromomethyl-benzonitrile are processed according to the method described in Example 11 to give 3-(5-chloro-3-methyl-2-pyridin-3-yl-1H-indol-1-ylmethyl)-benzonitrile. ^{1}H NMR (400 MHz, MeOD) δ ppm 2.25 (s, 3 H), 5.36 (s, 2 H), 7.03 (d, *J*=7.8 Hz, 1 H), 7.14 (s, 1 H), 7.18 (dd, *J*=8.6, 2.0 Hz, 1 H), 7.33 (d, *J*=8.6 Hz, 1 H), 7.36 (t, *J*=7.7 Hz, 1 H), 7.49 - 7.56 (m, 2 H), 7.62 (d, *J*=2.0 Hz, 1 H), 7.81 (dt, *J*=7.8, 1.9 Hz, 1 H), 8.47 (d, *J*=2.3 Hz, 1 H), 8.58 (dd, *J*=5.1, 1.8 Hz, 1 H). HRMS (ESI) m/z 358.1102 [(M+H)$^+$ Calcd for $C_{22}H_{17}ClN_3$, 358.1111].

Example 15

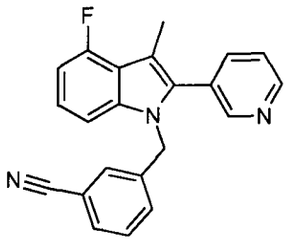
3-(6-Fluoro-3-methyl-2-pyridin-3-yl-1H-indol-1-ylmethyl)-benzonitrile hydrochloride



The mixture of 4- and 6-fluoro-3-methyl-2-pyridin-3-yl-1H-indole hydrochloride (Example 4) and 3-bromomethyl-benzonitrile are processed according to the method described in Example 11. Separation of the regioisomers is done on a Chiralcel® OD eluting with heptane-isopropanol 4:1 to give 3-(6-fluoro-3-methyl-2-pyridin-3-yl-1H-indol-1-ylmethyl)-benzonitrile. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm (HCl salt) 2.23 (s, 3 H), 5.41 (s, 2 H), 6.96 - 7.06 (m, 2 H), 7.27 (s, 1 H), 7.37 - 7.43 (m, 2 H), 7.62 - 7.69 (m, 2 H), 7.81 (t, *J*=6.3 Hz, 1 H), 8.17 (d, *J*=7.3 Hz, 1 H), 8.75 - 8.82 (m, 2 H). HRMS (ESI) m/z 342.1405 [(M+H)$^+$ Calcd for $C_{22}H_{17}FN_3$: 342.1407]

Example 16

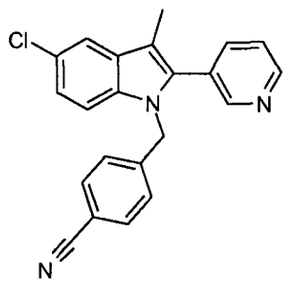
3-(4-Fluoro-3-methyl-2-pyridin-3-yl-1H-indol-1-ylmethyl)-benzonitrile hydrochloride



The mixture of 4- and 6-fluoro-3-methyl-2-pyridin-3-yl-1H-indole hydrochloride (Example 4) and 3-bromomethyl-benzonitrile are processed according to the method described in Example 11. Separation of the regioisomers is done on a Chiralcel® OD eluting with heptane-isopropanol 4:1 to give 3-(4-fluoro-3-methyl-2-pyridin-3-yl-1H-indol-1-ylmethyl)-benzonitrile. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm (HCl salt) 2.33 (s, 3 H), 5.41 (s, 2 H), 6.87 (dd, *J*=11.4, 7.8 Hz, 1 H), 7.06 (d, *J*=7.1 Hz, 1 H), 7.12 - 7.21 (m, 1 H), 7.26 - 7.34 (m, 2 H), 7.42 (t, *J*=7.7 Hz, 1 H), 7.66 (d, *J*=7.6 Hz, 1 H), 7.81 (dd, *J*=7.2, 5.2 Hz, 1 H), 8.18 (d, *J*=7.3 Hz, 1 H), 8.79 (br. s., 2 H). HRMS (ESI) m/z 342.1407 [(M+H)$^+$ Calcd for $C_{22}H_{17}FN_3$: 342.1407].

Example 17

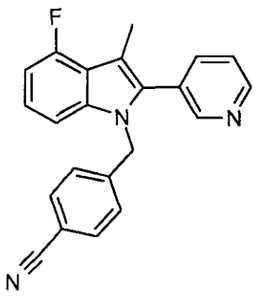
4-(5-Chloro-3-methyl-2-pyridin-3-yl-1H-indol-1-ylmethyl)-benzonitrile



5-Chloro-3-methyl-2-pyridin-3-yl-1H-indole hydrochloride (Example 2) and 4-bromomethyl-benzonitrile are processed according to the method described in Example 11 to give 4-(5-chloro-3-methyl-2-pyridin-3-yl-1H-indol-1-ylmethyl)-benzonitrile.
^{1}H NMR (400 MHz, MeOD) δ ppm 2.28 (s, 3 H), 5.42 (s, 2 H), 6.98 (d, *J*=8.3 Hz, 1 H), 7.20 (dd, *J*=8.6, 2.0 Hz, 1 H), 7.34 (d, *J*=8.8 Hz, 1 H), 7.55 (dd, *J*=7.8, 5.1 Hz, 1 H), 7.57 - 7.62 (m, 2 H), 7.66 (d, *J*=2.0 Hz, 1 H), 7.84 (dt, *J*=7.8, 1.9 Hz, 1 H), 8.50 (d, *J*=2.0 Hz, 1 H), 8.60 (dd, *J*=4.9, 1.6 Hz, 1 H). HRMS (ESI) m/z 358.1120 [(M+H)$^+$ Calcd for $C_{22}H_{17}ClN_3$: 358.1111].

Example 18

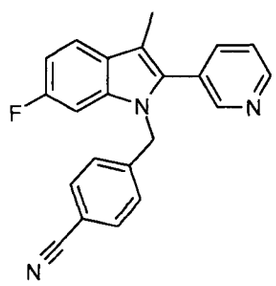
4-(4-Fluoro-3-methyl-2-pyridin-3-yl-1H-indol-1-ylmethyl)-benzonitrile hydrochloride



The mixture of 4- and 6-fluoro-3-methyl-2-pyridin-3-yl-1H-indole hydrochloride (Example 4) and 4-bromomethyl-benzonitrile are processed according to the method described in Example 11. Separation of the regioisomers is done on a Chiralcel® OD eluting with heptane-isopropanol 4:1 to give 4-(4-fluoro-3-methyl-2-pyridin-3-yl-1H-indol-1-ylmethyl)-benzonitrile. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm (HCl salt) 2.34 (s, 3 H), 5.46 (s, 2 H), 6.87 (dd, *J*=11.4, 7.8 Hz, 1 H), 6.96 (d, *J*=8.6 Hz, 2 H), 7.11 - 7.20 (m, 1 H), 7.29 (d, *J*=8.1 Hz, 1 H), 7.68 (d, *J*=8.3 Hz, 2 H), 7.72 - 7.80 (m, 1 H), 8.05 - 8.14 (m, 1 H), 8.71 - 8.79 (m, 2 H). HRMS (ESI) m/z 342.1407 [(M+H)$^+$ Calcd for $C_{22}H_{17}FN_3$: 342.1407].

Example 19

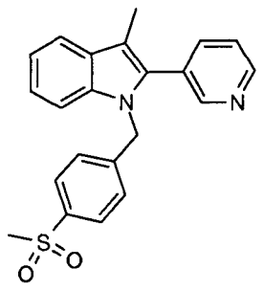
4-(6-Fluoro-3-methyl-2-pyridin-3-yl-1H-indol-1-ylmethyl)-benzonitrile



The mixture of 4- and 6-fluoro-3-methyl-2-pyridin-3-yl-1H-indole hydrochloride (Example 4) and 4-bromomethyl-benzonitrile are processed according to the method described in Example 11. Separation of the regioisomers is done on a Chiralcel® OD eluting with heptane-isopropanol 4:1 to give 4-(6-fluoro-3-methyl-2-pyridin-3-yl-1H-indol-1-ylmethyl)-benzonitrile. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 2.30 (s, 3 H), 5.22 (s, 2 H), 6.83 (dd, *J*=9.7, 2.1 Hz, 1 H), 6.93 - 7.01 (m, 3 H), 7.36 (dd, *J*=7.6, 5.1 Hz, 1 H), 7.49 - 7.63 (m, 4 H), 8.56 (d, *J*=1.3 Hz, 1 H), 8.64 (d, *J*=3.5 Hz, 1 H). HRMS (ESI) m/z 342.1390 [(M+H)$^+$ Calcd for $C_{22}H_{17}FN_3$: 342.1407].

Example 20

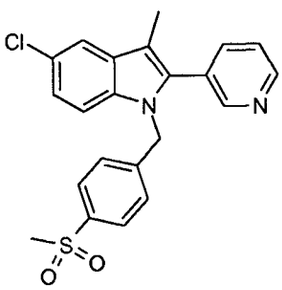
1-(4-Methanesulfonyl-benzyl)-3-methyl-2-pyridin-3-yl-1H-indole



3-Methyl-2-pyridin-3-yl-1H-indole hydrochloride (Example 1) and 1-bromomethyl-4-methanesulfonyl-benzene are processed according to the method described in Example 11 to give 1-(4-methanesulfonyl-benzyl)-3-methyl-2-pyridin-3-yl-1H-indole. ^{1}H NMR (400 MHz, MeOD) δ ppm 2.33 (s, 3 H), 3.08 (s, 3 H), 5.46 (s, 2 H), 7.08 (d, *J*=8.1 Hz, 2 H), 7.18 (t, *J*=7.3 Hz, 1 H), 7.24 (t, *J*=7.6 Hz, 1 H), 7.34 (d, *J*=8.1 Hz, 1 H), 7.55 (dd, *J*=7.8, 4.8 Hz, 1 H), 7.68 (d, *J*=7.8 Hz, 1 H), 7.81 (d, *J*=8.3 Hz, 2 H), 7.85 (dt, *J*=7.8, 1.9 Hz, 1 H), 8.52 (d, *J*=2.3 Hz, 1 H), 8.59 (dd, *J*=4.9, 1.6 Hz, 1 H). HRMS (ESI) m/z 377.1318 [$(M+H)^+$ Calcd for $C_{22}H_{21}N_2O_2S$: 377.1324].

Example 21

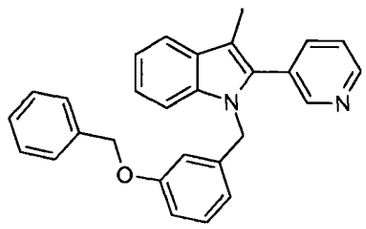
5-Chloro-1-(4-methanesulfonyl-benzyl)-3-methyl-2-pyridin-3-yl-1H-indole



5-Chloro-3-methyl-2-pyridin-3-yl-1H-indole hydrochloride (Example 2) and 1-bromomethyl-4-methanesulfonyl-benzene are processed according to the method described in Example 11 to give 5-chloro-1-(4-methanesulfonyl-benzyl)-3-methyl-2-pyridin-3-yl-1H-indole. ^{1}H NMR (400 MHz, MeOD) δ ppm 2.29 (s, 3 H), 3.09 (s, 3 H), 5.46 (s, 2 H), 7.20 (dd, *J*=8.6, 2.0 Hz, 1 H), 7.34 (d, *J*=8.8 Hz, 1 H), 7.53 – 7.57 (m, 1 H), 7.66 (d, *J*=1.8 Hz, 1 H), 7.79 - 7.84 (m, 1 H), 7.86 (dt, *J*=7.9, 2.0 Hz, 1 H), 8.52 (dd, *J*=2.3, 1.0 Hz, 1 H), 8.61 (dd, *J*=5.1, 1.8 Hz, 1 H). HRMS (ESI) m/z 411.0927 [$(M+H)^+$ Calcd for $C_{22}H_{20}N_2O_2SCl$: 411.0934].

Example 22

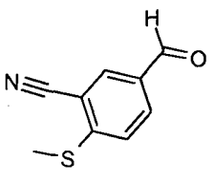
1-(3-Benzyloxy-benzyl)-3-methyl-2-pyridin-3-yl-1H-indole hydrochloride



3-Methyl-2-pyridin-3-yl-1H-indole hydrochloride (Example 1) and 1-benzyloxy-4-bromomethyl-benzene are processed according to the method described in Example 11 to give 1-(3-benzyloxy-benzyl)-3-methyl-2-pyridin-3-yl-1H-indole. ^{1}H NMR (400 MHz, MeOD) δ ppm (HCl salt) 2.31 (s, 3 H), 4.91 (s, 2 H), 5.28 (s, 2 H), 6.37 (s, 1 H), 6.45 (d, *J*=7.6 Hz, 1 H), 6.82 (dd, *J*=8.2, 2.1 Hz, 1 H), 7.12 (t, *J*=7.8 Hz, 1 H), 7.16 - 7.22 (m, 1 H), 7.22 - 7.38 (m, 7 H), 7.61 (dd, *J*=8.0, 5.2 Hz, 1 H), 7.68 (d, *J*=7.8 Hz, 1 H), 7.85 (dt, *J*=8.0, 1.8 Hz, 1 H), 8.46 (d, *J*=1.3 Hz, 1 H), 8.60 (dd, *J*=5.1, 1.5 Hz, 1 H). HRMS (ESI) m/z 405.1969 [(M+H)$^+$ Calcd for $C_{28}H_{25}N_2O$: 405.1967].

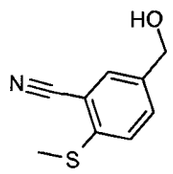
Example 23

(a) 5-Formyl-2-methylsulfanyl-benzonitrile



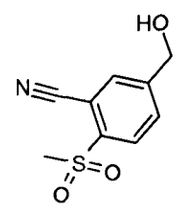
A flask is charged with 5-fluoro-2-formyl-benzonitrile (0.200 g, 1.34mmol), potassium carbonate (0.371 g, 0.268 mmol), sodium thiomethoxide (0.142 g, 2.01 mmol) and DMF (20 mL). The mixture is stirred at room temperature for 10 min, then diluted with ethyl acetate and washed with water. The organic layer is dried over sodium sulfate and concentrated *in vacuo* to afford 5-formyl-2-methylsulfanyl-benzonitrile as a yellow color solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 2.64 (s, 3 H), 7.41 (d, *J*=8.3 Hz, 1 H), 8.01 (dd, *J*=8.5, 1.9 Hz, 1 H), 8.07 (d, *J*=1.8 Hz, 1 H), 9.95 (s, 1 H).

(b) 5-Hydroxymethyl-2-methylsulfanyl-benzonitrile



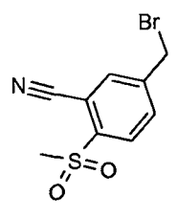
A flask is charged with 5-formyl-2-methylsulfanyl-benzonitrile (1.0 g, 5.68 mmol) in MeOH (20 mL) and cooled to 0 °C. Sodium borohydride (1.07 g, 28.40mmol) is added and the mixture is stirred at room temperature for 2 h, followed by removal of solvent *in vacuo*. The residue is re-dissolved in dichloromethane and washed with water twice. The organic layer is dried over sodium sulfate and concentrated *in vacuo* to afford 5-hydroxymethyl-2-methylsulfanyl-benzonitrile as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 2.57 (s, 3 H), 4.70 (d, *J*=5.1 Hz, 2 H), 7.33 (d, *J*=8.3 Hz, 1 H), 7.53 (dd, *J*=8.3, 1.0 Hz, 1 H), 7.62 (s, 1 H).

(c) 5-Hydroxymethyl-2-methanesulfonyl-benzonitrile



A flask is charged with 5-hydroxymethyl-2-methylsulfanyl-benzonitrile (0.866 g, 4.86 mmol) in a mixture of MeOH (10 mL) and water (10 mL). Oxone (7.47 g, 12.16 mmol) is added and the mixture is stirred at room temperature for 16 h. The residue is acidified to pH 1 using aqueous 1M HCl and then extracted with dichloromethane twice. The organic layer is dried over sodium sulfate and concentrated *in vacuo* to afford 5-hydroxymethyl-2-methanesulfonyl-benzonitrile as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 3.28 (s, 3 H), 4.89 (s, 2 H), 7.80 (d, *J*=8.1 Hz, 1 H), 7.95 (s, 1 H), 8.18 (d, *J*=8.1 Hz, 1 H).

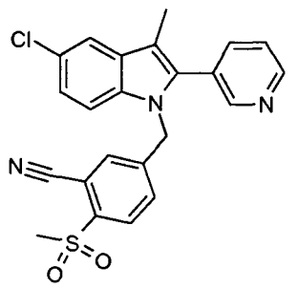
(d) 5-Bromomethyl-2-methanesulfonyl-benzonitrile



A flask is charged with 5-hydroxymethyl-2-methylsulfonyl-benzonitrile (0.788 g, 3.73 mmol) in toluene (5 mL) and heated at 40 °C. PBr_3 (0.175 mL, 1.86 mmol) is added and

the reaction is refluxed for 0.5 h. It is then cooled to room temperature, diluted with dichloromethane and washed with water. The aqueous layer is extracted with dichloromethane. The combined organic layer is dried over sodium sulfate and concentrated *in vacuo* to afford 5-bromomethyl-2-methanesulfonyl-benzonitrile as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 3.28 (s, 3 H), 4.89 (s, 2 H), 7.80 (d, *J*=8.3 Hz, 1 H), 7.94 (s, 1 H), 8.18 (d, *J*=8.1 Hz, 1 H).

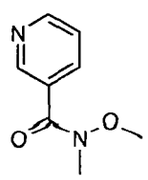
(e) 2-Methanesulfonyl-5-(3-methyl-2-pyridin-3-yl-indol-1-ylmethyl)-benzonitrile



The product in Example 1 is processed according to the method described in Example 11 to give 2-methanesulfonyl-5-(3-methyl-2-pyridin-3-yl-indol-1-ylmethyl)-benzonitrile. ^{1}H NMR (400 MHz, MeOD) δ ppm 2.35 (s, 3 H), 3.27 (s, 3 H), 5.53 (s, 2 H), 7.19 - 7.31 (m, 3 H), 7.37 (d, *J*=8.1 Hz, 1 H), 7.51 (d, *J*=1.3 Hz, 1 H), 7.65 (dd, *J*=7.8, 5.1 Hz, 1 H), 7.71 (d, *J*=7.6 Hz, 1 H), 7.98 (d, *J*=7.6 Hz, 1 H), 8.02 (d, *J*=8.1 Hz, 1 H), 8.60 (d, *J*=1.8 Hz, 1 H), 8.65 (dd, *J*=5.1, 1.5 Hz, 1 H). HRMS (ESI) m/z 402.1269 [$(M+H)^+$ Calcd for $C_{23}H_{20}N_3O_2S$: 402.1276].

Example 24

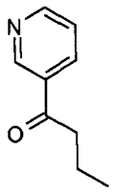
(a) *N*-methyl-*N*-methoxy-nicotinamide



A flask is charged with nicotinic acid (5.0 g, 40.6 mmol). Thionyl chloride (30.0 mL) is added and the reaction is refluxed for 1 h. It is then cooled to room temperature and concentrated *in vacuo*. The residue is dissolved in anhydrous dichloromethane (30 mL) and *O*,*N*-dimethyl-hydroxylamine (4.35 g, 44.0 mmol) is added, followed by addition of triethylamine (14.15 g, 100.0 mmol). The reaction mixture is stirred at room temperature

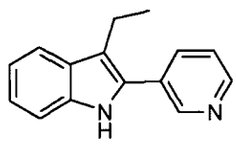
for 1.5 h. It is then washed with water and the aqueous phase is extracted with dichloromethane. The combined organic layer is dried over sodium sulfate and concentrated *in vacuo* to afford *N*-methyl-*N*-methoxy-nicotinamide as a brown oil. MS (ESI) *m/z* 167.0 $(M+H)^+$.

(b) 1-Pyridin-3-yl-butan-1-one



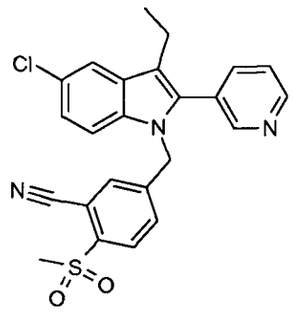
A flask is charged with *N*-methyl-*N*-methoxy-nicotinamide (1.0 g, 6.02 mmol) and THF (10 mL). Propyl magnesium chloride (2M in THF, 3.31 mL, 6.62 mmol) is added and the mixture is stirred at room temperature overnight. It is quenched with saturated sodium bicarbonate solution and extracted with dichloromethane. The combined organic layer is dried over sodium sulfate and concentrated *in vacuo* to afford 1-pyridin-3-yl-butan-1-one as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 1.03 (t, *J*=7.5 Hz, 3 H), 1.74 - 1.87 (m, 2 H), 2.97 (t, *J*=7.3 Hz, 2 H), 7.42 (dd, *J*=8.0, 4.9 Hz, 1 H), 8.24 (dt, *J*=8.0, 2.0, 1.9 Hz, 1 H), 8.78 (dd, *J*=4.9, 2.0 Hz, 1 H), 9.18 (d, *J*=2.0 Hz, 1 H).

(c) 3-Ethyl-2-pyridin-3-yl-1H-indole



A flask is charged with phenylhydrazine (0.873 g, 6.46 mmol) and EtOH (14 mL). 1-Pyridin-3-yl-butan-1-one (0.914 g, 6.13 mmol) is added and the reaction is refluxed for 1 h. After cooling to room temperature, HCl (4M in 1,4-dioxane, 6.45 mL, 25.83 mmol) is added. The reaction mixture is refluxed for 4 h. After cooling to room temperature, the precipitate formed is filtered to afford 3-ethyl-2-pyridin-3-yl-1H-indole as a yellow solid. MS (ESI) *m/z* 223.0 $(M+H)^+$.

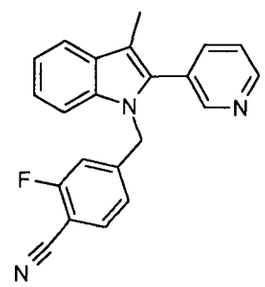
(d) 2-Methanesulfonyl-5-(3-ethyl-2-pyridin-3-yl-indol-1-ylmethyl)-benzonitrile



3-Ethyl-2-pyridin-3-yl-1H-indole and 2-methanesulfonyl-5-(3-ethyl-2-pyridin-3-yl-indol-1-ylmethyl)-benzonitrile (Example 23d) are processed according to the method described in Example 11 to give 2-methanesulfonyl-5-(3-ethyl-2-pyridin-3-yl-indol-1-ylmethyl)-benzonitrile. ^{1}H NMR (400 MHz, MeOD) δ ppm 1.27 (t, *J*=7.6 Hz, 3 H), 2.77 (q, *J*=7.6 Hz, 2 H), 3.27 (s, 3 H), 5.49 (s, 2 H), 7.14 - 7.31 (m, 3 H), 7.37 (d, *J*=8.1 Hz, 1 H), 7.49 (s, 1 H), 7.57 (dd, *J*=7.8, 5.1 Hz, 1 H), 7.74 (d, *J*=7.8 Hz, 1 H), 7.86 (dt, *J*=7.8, 1.8 Hz, 1 H), 8.03 (d, *J*=8.3 Hz, 1 H), 8.51 (d, *J*=2.0 Hz, 1 H), 8.62 (dd, *J*=4.9, 1.4 Hz, 1 H). HRMS (ESI) m/z 416.1424 [$(M+H)^+$ Calcd for $C_{24}H_{22}N_3O_2S$: 416.1433].

Example 25

3-Fluoro-4-(3-methyl-2-pyridin-3-yl-1H-indol-1-ylmethyl)-benzonitrile

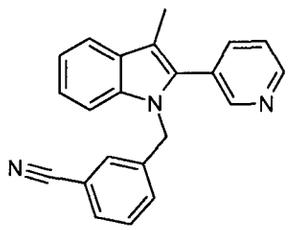


A flask is charged with 3-methyl-2-pyridin-3-yl-1H-indole hydrochloride (Example 1, 0.080 g, 0.326 mmol) and DMF (1.5 mL), and 60% NaH in mineral oil (0.028 g, 0.719 mmol) is added. The mixture is stirred at room temperature for 20 min, followed by addition of 4-bromomethyl-3-fluoro-benzonitrile (0.175 g, 0.817 mmol). The reaction mixture stirred at room temperature for 30 min. The residue is diluted with DMF (1.5 mL), filtered and purified by reverse phase HPLC with Xbridge Shield RP18 column and a 0.1% aqueous NH_4OH in acetonitrile gradient to afford 3-fluoro-4-(3-methyl-2-pyridin-3-yl-indol-1-ylmethyl)-benzonitrile as a yellow solid. ^{1}H NMR (400 MHz, MeOD) δ ppm 2.32 (s, 3 H), 5.47 (s, 2 H), 6.62 (t, *J*=7.6 Hz, 1 H), 7.20 (t, *J*=7.5 Hz, 1 H), 7.27 (t, *J*=7.6

Hz, 1 H), 7.38 (d, *J*=8.1 Hz, 2 H), 7.50 (d, *J*=9.9 Hz, 1 H), 7.56 (dd, *J*=7.8, 4.8 Hz, 1 H), 7.68 (d, *J*=7.8 Hz, 1 H), 7.86 (dd, *J*=7.8, 1.8 Hz, 1 H), 8.52 (s, 1 H), 8.60 (dd, *J*=4.9, 1.6 Hz, 1 H). HRMS (ESI) m/z 342.1394 [$(M+H)^+$ Calcd for $C_{22}H_{17}FN_3$: 342.1407].

Example 26

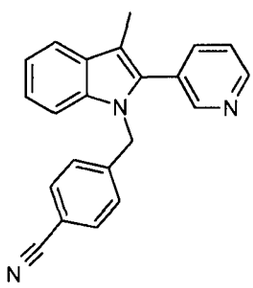
3-(3-methyl-2-pyridin-3-yl-1H-indol-1-ylmethyl)-benzonitrile



3-Methyl-2-pyridin-3-yl-1H-indole hydrochloride (Example 1) and 3-bromomethyl-benzonitrile are processed according to the method described in Example 25 to give 3-(3-methyl-2-pyridin-3-yl-1H-indol-1-ylmethyl)-benzonitrile. ^{1}H NMR (400 MHz, MeOD) δ ppm 2.33 (s, 3 H), 5.41 (s, 2 H), 7.08 (d, *J*=8.1 Hz, 1 H), 7.16 (s, 1 H), 7.20 (t, *J*=7.2 Hz, 1 H), 7.27 (ddd, *J*=7.6, 1.0 Hz, 1 H), 7.37 (d, *J*=5.8 Hz, 1 H), 7.38 - 7.42 (m, 1 H), 7.54 - 7.57 (m, 1 H), 7.57 (s, 1 H), 7.68 (d, *J*=7.8 Hz, 1 H), 7.85 (dt, *J*=7.8, 1.9 Hz, 1 H), 8.50 (d, *J*=2.0 Hz, 1 H), 8.60 (dd, *J*=4.8, 1.5 Hz, 1 H). HRMS (ESI) m/z 324.1491 [$(M+H)^+$ Calcd for $C_{22}H_{18}N_3$: 324.1501].

Example 27

4-(3-Methyl-2-pyridin-3-yl-1H-indol-1-ylmethyl)-benzonitrile

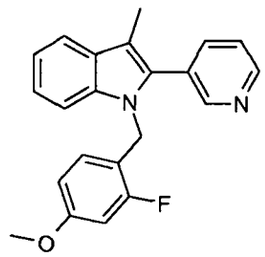


3-Methyl-2-pyridin-3-yl-1H-indole hydrochloride (Example 1) and 4-bromomethyl-benzonitrile are processed according to the method described in Example 25 to give 4-(3-methyl-2-pyridin-3-yl-1H-indol-1-ylmethyl)-benzonitrile. ^{1}H NMR (400 MHz, MeOD) δ ppm 2.32 (s, 3 H), 5.43 (s, 2 H), 6.99 (d, *J*=8.6 Hz, 2 H), 7.13 - 7.21 (m, 1 H), 7.25 (ddd, *J*=7.6, 1.3 Hz, 1 H), 7.34 (d, *J*=8.1 Hz, 1 H), 7.54 (dd, *J*=8.0, 4.9 Hz, 2 H), 7.58 (d, *J*=8.3

Hz, 1 H), 7.67 (d, *J*=7.6 Hz, 1 H), 7.84 (dt, *J*=7.9, 2.0 Hz, 1 H), 8.50 (d, *J*=1.5 Hz, 1 H), 8.59 (dd, *J*=4.9, 1.6 Hz, 1 H). HRMS (ESI) m/z 324.1501 [$(M+H)^+$ Calcd for $C_{22}H_{18}N_3$: 324.1501].

Example 28

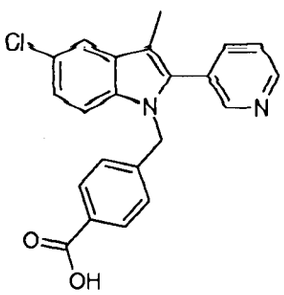
1-(2-Fluoro-4-methoxy-benzyl)-3-methyl-2-pyridin-3-yl-1H-indole hydrochloride



3-Methyl-2-pyridin-3-yl-1H-indole hydrochloride (Example 1) and 4-bromomethyl-2-fluoro-1-methoxy-benzene are processed according to the method described in Example 25 to give 1-(2-fluoro-4-methoxy-benzyl)-3-methyl-2-pyridin-3-yl-1H-indole hydrochloride. ^{1}H NMR (400 MHz, MeOD) δ ppm (HCl salt) 2.38 (s, 3 H), 3.82 (s, 3 H), 5.35 (s, 2 H), 6.54 - 6.62 (m, 2 H), 6.94 (t, *J*=8.6 Hz, 1 H), 7.22 (ddd, *J*=7.5, 0.9 Hz, 1 H), 7.33 (ddd, *J*=7.6, 1.1 Hz, 1 H), 7.45 (d, *J*=8.3 Hz, 1 H), 7.72 (d, *J*=7.8 Hz, 1 H), 8.12 (dd, *J*=8.2, 5.7 Hz, 1 H), 8.54 (dt, *J*=8.1, 1.6 Hz, 1 H), 8.80 - 8.89 (m, 2 H). HRMS (ESI) m/z 347.1568 [$(M+H)^+$ Calcd for $C_{22}H_{20}FN_2O$: 347.1560].

Example 29

4-(5-chloro-3-methyl-2-pyridin-3-yl-1H-indol-1-ylmethyl)-benzoic acid

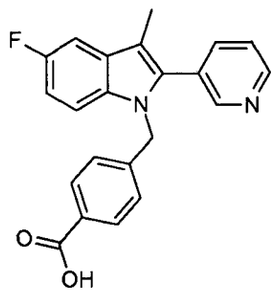


4-(5-Chloro-3-methyl-2-pyridin-3-yl-1H-indol-1-ylmethyl)-benzoic acid methyl ester (Example 11, 200 mg, 0.51 mmol) in methanol (5 mL) is added to 5M aqueous NaOH (1 mL, 5 mmol) and the mixture is stirred at room temperature for 5 h. Concentrated HCl (4.4 mL) is added to neutralize the reaction mixture and the solvents are removed *in*

vacuo. The residue is redissolved in methanol and purified by reverse phase HPLC with Xbridge Shield RP18 column and a 0.1% NH_4OH in acetonitrile gradient to afford 4-(5-chloro-3-methyl-2-pyridin-3-yl-1H-indol-1-ylmethyl)-benzoic acid. ^1H NMR (400 MHz, MeOD) δ ppm 2.25 (s, 3 H), 5.34 (s, 2 H), 6.82 (d, *J*=8.1 Hz, 2 H), 7.15 (dd, *J*=8.6, 2.0 Hz, 1 H), 7.31 (d, *J*=8.6 Hz, 1 H), 7.50 (dd, *J*=7.7, 4.9 Hz, 1 H), 7.61 (d, *J*=2.0 Hz, 1 H), 7.78 - 7.80 (m, 1 H), 7.81 (d, *J*=8.1 Hz, 2 H), 8.50 (s, 1 H), 8.56 (br. s, 1 H). HRMS (ESI) m/z 377.1072 [$(M+H)^+$ Calcd for $C_{22}H_{18}ClN_2O_2$: 377.1057].

Example 30

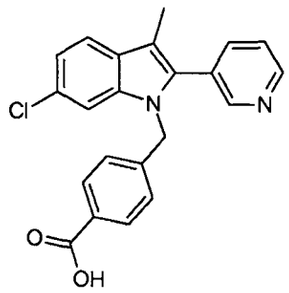
4-(5-Fluoro-3-methyl-2-pyridin-3-yl-1H-indol-1-ylmethyl)-benzoic acid



5-Fluoro-3-methyl-2-pyridin-3-yl-1H-indole (Example 3) is processed according to the method in Example 11 to give 4-(5-fluoro-3-methyl-2-pyridin-3-yl-1H-indol-1-ylmethyl)-benzoic acid methyl ester. 4-(5-Fluoro-3-methyl-2-pyridin-3-yl-1H-indol-1-ylmethyl)-benzoic acid methyl ester is processed according to the method described in Example 29 to give 4-(5-fluoro-3-methyl-2-pyridin-3-yl-1H-indol-1-ylmethyl)-benzoic acid.
^1H NMR (400 MHz, MeOD) δ ppm 2.25 (s, 3 H), 5.36 (s, 2 H), 6.88 (d, *J*=8.6 Hz, 2 H), 6.94 - 7.00 (m, 1 H), 7.28 - 7.29 (m, 1 H), 7.30 - 7.32 (m, 1 H), 7.49 - 7.53 (m, 1 H), 7.78 - 7.82 (m, 1 H), 7.82 - 7.86 (m, 2 H), 8.47 - 8.49 (m, 1 H), 8.56 (dd, *J*=4.9, 1.6 Hz, 1 H). HRMS (ESI) m/z 361.1360 [$(M+H)^+$ Calcd for $C_{22}H_{18}FN_2O_2$: 361.1352].

Example 31

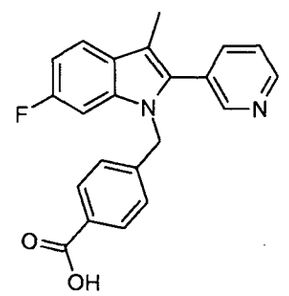
4-(6-Chloro-3-methyl-2-pyridin-3-yl-1H-indol-1-ylmethyl)-benzoic acid



A mixture of 4- and 6-chloro-3-methyl-2-pyridin-3-yl-1H-indole (Example 5) is processed according to the method in Example 11 to give 4-(6-chloro-3-methyl-2-pyridin-3-yl-1H-indol-1-ylmethyl)-benzoic acid methyl ester and 4-(4-chloro-3-methyl-2-pyridin-3-yl-1H-indol-1-ylmethyl)-benzoic acid methyl ester. This mixture is processed according to the method described in Example 29 to give 4-(6-chloro-3-methyl-2-pyridin-3-yl-1H-indol-1-ylmethyl)-benzoic acid after reverse-phase HPLC purification. ^{1}H NMR (400 MHz, MeOD) δ ppm (TFA salt) 2.30 (s, 3 H), 5.41 (s, 2 H), 6.89 (d, *J*=8.6 Hz, 2 H), 7.15 (dd, *J*=8.3, 1.8 Hz, 1 H), 7.44 (d, *J*=1.8 Hz, 1 H), 7.64 (d, *J*=8.6 Hz, 1 H), 7.81 - 7.88 (m, 3 H), 8.20 - 8.27 (m, 1 H), 8.68 (br. s., 1 H), 8.70 - 8.73 (m, 1 H). HRMS (ESI) m/z 377.1050 [$(M+H)^+$ Calcd for $C_{22}H_{18}ClN_2O_2$: 377.1057].

Example 32

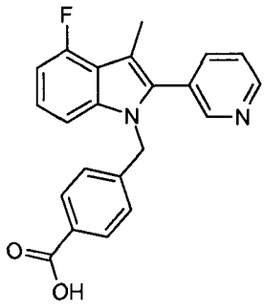
4-(6-Fluoro-3-methyl-2-pyridin-3-yl-1H-indol-1-ylmethyl)-benzoic acid



4-(6-Fluoro-3-methyl-2-pyridin-3-yl-1H-indol-1-ylmethyl)-benzoic acid methyl ester (Example 12) is processed according to the method described in Example 29 to give 4-(6-fluoro-3-methyl-2-pyridin-3-yl-1H-indol-1-ylmethyl)-benzoic acid. ^{1}H NMR (400 MHz, MeOD) δ ppm (TFA salt) 2.31 (s, 3 H), 5.40 (s, 2 H), 6.90 (d, *J*=8.6 Hz, 2 H), 6.93 - 7.00 (m, 1 H), 7.15 (dd, *J*=10.0, 2.1 Hz, 1 H), 7.65 (dd, *J*=8.8, 5.3 Hz, 1 H), 7.86 (d, *J*=8.6 Hz, 2 H), 7.88 - 7.92 (m, 1 H), 8.27 - 8.31 (m, 1 H), 8.70 (d, *J*=1.8 Hz, 1 H), 8.72 (dd, *J*=5.6, 1.5 Hz, 1 H). HRMS (ESI) m/z 361.1360 [$(M+H)^+$ Calcd for $C_{22}H_{18}FN_2O_2$: 361.1352].

Example 33

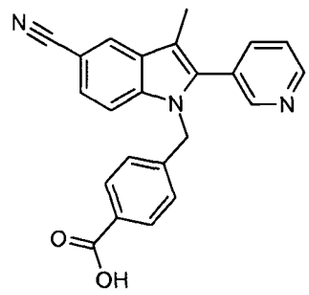
4-(4-Fluoro-3-methyl-2-pyridin-3-yl-1H-indol-1-ylmethyl)-benzoic acid



4-(4-Fluoro-3-methyl-2-pyridin-3-yl-1H-indol-1-ylmethyl)-benzoic acid methyl ester (Example 13) is processed according to the method described in Example 29 to give 4-(4-fluoro-3-methyl-2-pyridin-3-yl-1H-indol-1-ylmethyl)-benzoic acid. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.32 (s, 3 H), 5.37 (s, 2 H), 6.81 - 6.88 (m, 3 H), 7.08 - 7.15 (m, 1 H), 7.26 (d, *J*=8.1 Hz, 1 H), 7.50 (dd, *J*=7.8, 4.8 Hz, 1 H), 7.74 (d, *J*=8.3 Hz, 2 H), 7.77 - 7.81 (m, 1 H), 8.55 (d, *J*=1.5 Hz, 1 H), 8.62 (dd, *J*=4.9, 1.6 Hz, 1 H). MS (ESI) *m/z* 361.09 $(M+H)^+$.

Example 34

4-(5-Cyano-3-methyl-2-pyridin-3-yl-1H-indol-1-ylmethyl)-benzoic acid

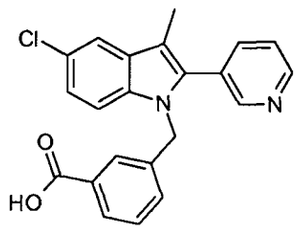


5-Cyano-3-methyl-2-pyridin-3-yl-indole (Example 6) is processed according to the method described in Example 11 to give 4-(5-cyano-3-methyl-2-pyridin-3-yl-indol-1-ylmethyl)-benzoic acid methyl ester. To a solution of 4-(5-cyano-3-methyl-2-pyridin-3-yl-indol-1-ylmethyl)-benzoic acid methyl ester (80 mg, 0.21 mmol) in methanol (5 mL) and THF (5 mL) is added 1M aqueous lithium hydroxide (2.5 mL, 2.5 mmol) and the mixture is stirred overnight at ambient temperature. The volatiles are removed *in vacuo* and the residue is redissolved in DMF and purified by Xbridge RP18 with a gradient of 0.1% aqueous ammonium hydroxide in acetonitrile to give 4-(5-cyano-3-methyl-2-pyridin-3-yl-

indol-1-ylmethyl)-benzoic acid. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.25 (s, 3 H), 5.40 (s, 2 H), 6.71 (d, *J*=8.1 Hz, 2 H), 7.47 - 7.55 (m, 2 H), 7.66 (t, *J*=8.6 Hz, 3 H), 7.79 - 7.83 (m, 1 H), 8.20 (d, *J*=1.3 Hz, 1 H), 8.58 (d, *J*=1.5 Hz, 1 H), 8.64 (dd, *J*=4.8, 1.5 Hz, 1 H). HRMS (ESI) m/z 368.1396 [(M+H)$^+$ Calcd for $C_{23}H_{18}N_3O_2$: 368.1399].

Example 35

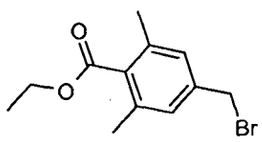
3-(5-Chloro-3-methyl-2-pyridin-3-yl-indol-1-ylmethyl)-benzoic acid



3-(5-Chloro-3-methyl-2-pyridin-3-yl-indol-1-ylmethyl)-benzonitrile (Example 14, 200 mg, 0.56 mmol) in acetic acid (3 mL) is added to a 20% HCl aqueous solution (3 mL). The reaction mixture is refluxed for 3 days. The volatiles are removed *in vacuo* and the residue is redissolved in methanol and purified by reverse phase HPLC with Xbridge Shield RP18 and a gradient of 0.1% NH_4OH in acetonitrileto give 3-(5-chloro-3-methyl-2-pyridin-3-yl-indol-1-ylmethyl)-benzoic acid. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.21 (s, 3 H), 5.36 (s, 2 H), 6.83 (d, *J*=7.1 Hz, 1 H), 7.13 - 7.23 (m, 2 H), 7.43 - 7.52 (m, 3 H), 7.64 - 7.70 (m, 2 H), 7.74 - 7.81 (m, 1 H), 8.55 (s, 1 H), 8.61 - 8.62 (m, 1 H). HRMS (ESI) m/z 377.1058 [(M+H)$^+$ Calcd for $C_{22}H_{18}ClN_2O_2$: 377.1057].

Example 36

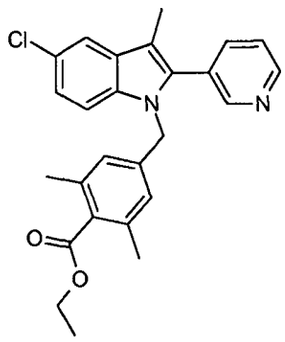
(a) 4-Bromomethyl-2,6-dimethyl-benzoic acid ethyl ester



Ethyl 2,4,6-trimethylbenzene (4.20 g, 21.41 mmol) and *N*-bromosuccinimide (4.23 g, 23.55 mmol) are taken up in carbon tetrachloride (200 mL), and benzoyl peroxide (0.53 g, 2.14 mmol) is added. The suspension is heated to reflux. After 4 h, the mixture is diluted with dichloromethane, washed with saturated aqueous sodium bicarbonate, water and brine, dried and concentrated *in vacuo*. The residue is purified by silica gel flash chromatography (heptane-ethyl acetate, 1 to 5%) to give partially purified 4-

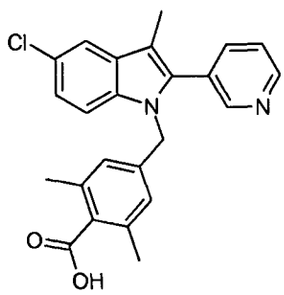
bromomethyl-2,6-dimethyl-benzoic acid ethyl ester, which is taken in the next step without further purification.

(b) 2,6-Dimethyl-4-(5-chloro-3-methyl-2-pyridin-3-yl-indol-1-ylmethyl)-benzoic acid ethyl ester



5-Chloro-3-methyl-2-pyridin-3-yl-1H-indole (Example 2, 1.350 g, 4.659 mmol) is suspended in THF (40 mL) and cooled to 0 °C. KHMDS (0.5M in toluene, 32.6 mL, 16.3 mmol) is added dropwise. After 1 h, 4-bromomethyl-2,6-dimethyl-benzoic acid ethyl ester (4.95 g, 18.2 mmol) in THF (10 mL) is added dropwise. The mixture is allowed to warm to room temperature overnight. The mixture is then quenched with saturated aqueous ammonium chloride and diluted with dichloromethane. The aqueous phase is extracted with ethyl acetate, dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification of the residue by silica gel chromatography (dichloromethane-methanol, 1:0 to 99:1 to 49:1 to 97:3) affords 2,6-dimethyl-4-(5-chloro-3-methyl-2-pyridin-3-yl-indol-1-ylmethyl)-benzoic acid ethyl ester as an orange solid. MS (ESI) *m/z* 399 $(M+H)^+$.

(c) 2,6-Dimethyl-4-(5-chloro-3-methyl-2-pyridin-3-yl-indol-1-ylmethyl)-benzoic acid

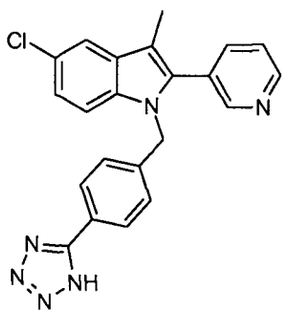


To a refluxing solution of lithium iodide (0.218 g, 1.626 mmol) in 2,6-lutidine (5 mL) is added 2,6-dimethyl-4-(5-chloro-3-methyl-2-pyridin-3-yl-indol-1-ylmethyl)-benzoic acid

ethyl ester (0.176 g, 0.407 mmol). The reaction is refluxed overnight. It is cooled to room temperature, acidified to pH 1 using 1M aqueous HCl solution and extracted with dichloromethane. The organic layer is dried over sodium sulfate and concentrated *in vacuo*. The residue is purified by reverse phase HPLC with Xbridge Shield RP18 column and a 0.1% aqueous NH_4OH in acetonitrile gradient to afford 2,6-dimethyl-4-(5-chloro-3-methyl-2-pyridin-3-yl-indol-1-ylmethyl)-benzoic acid as a solid. ^1H NMR (400 MHz, MeOD) δ ppm 2.22 (s, 6 H), 2.28 (s, 3 H), 5.22 (s, 2 H), 6.49 (s, 2 H), 7.15 (dd, *J*=8.6, 2.0 Hz, 1 H), 7.30 (d, *J*=8.8 Hz, 1 H), 7.51 - 7.57 (m, 1 H), 7.61 (d, *J*=1.8 Hz, 1 H), 7.81 (dt, *J*=8.1, 2.0, 1.8 Hz, 1 H), 8.58 (d, *J*=1.3 Hz, 1 H), 8.61 (dd, *J*=4.9, 1.6 Hz, 1 H). HRMS (ESI) m/z 405.1379 $[(M+H)^+$ Calcd for $C_{24}H_{21}ClN_2O_2$: 405.1370].

Example 37

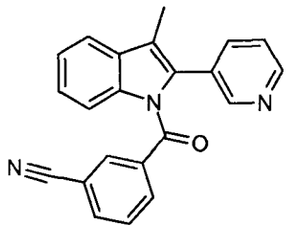
5-Chloro-3-methyl-2-pyridin-3-yl-1-[4-(2H-tetrazol-5-yl)-benzyl]-1H-indole



To a solution of 4-(5-chloro-3-methyl-2-pyridin-3-yl-indol-1-ylmethyl)-benzonitrile (Example 17, 179 mg, 0.5 mmol) in DMF (5 mL) is added sodium azide (97 mg, 1.5 mmol) and ammonium chloride (80 mg, 1.5 mmol) and the mixture is heated to 120 °C. The reaction mixture is cooled to room temperature and filtered. The filtrate is purified by reverse phase HPLC with Xbridge C18 and a gradient of 0.1% NH_4OH in acetonitrile to give 5-chloro-3-methyl-2-pyridin-3-yl-1-[4-(2H-tetrazol-5-yl)-benzyl]-1H-indole. ^1H NMR (400 MHz, DMSO-d_6) δ ppm 2.21 (s, 3 H), 5.34 (s, 2 H), 6.81 (d, *J*=8.1 Hz, 2 H), 7.11 (br. s., 1 H), 7.17 (dd, *J*=8.7, 2.1 Hz, 1 H), 7.48 - 7.53 (m, 2 H), 7.67 (d, *J*=2.0 Hz, 1 H), 7.77 (d, *J*=8.3 Hz, 2 H), 7.80 - 7.84 (m, 1 H), 8.60 (d, *J*=1.5 Hz, 1 H), 8.62 (dd, *J*=4.8, 1.5 Hz, 1 H). HRMS (ESI) m/z 401.1276 $[(M+H)^+$ Calcd for $C_{22}H_{18}N_6Cl$: 401.1281].

Example 38

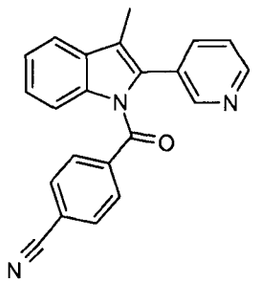
3-(3-Methyl-2-pyridin-3-yl-indole-1-carbonyl)-benzonitrile



A flask is charged with 3-methyl-2-pyridin-3-yl-1H-indole hydrochloride (Example 1, 0.100 g, 0.408 mmol) in THF (2.5 mL) and cooled to 0 °C. KHMDS (0.5 M in toluene, 1.8 mL, 0.898 mmol) is added and the mixture is stirred at room temperature for 30 min, followed by addition of 3-cyano-benzoyl chloride (0.135 g, 0.817 mmol). The reaction mixture is stirred for 0.5 h, then quenched with saturated ammonium chloride and extracted with ethyl acetate. The organic layer is dried over sodium sulfate and concentrated *in vacuo*. The residue is purified by reverse phase HPLC with Xbridge Shield RP18 column and a 0.1% aqueous NH_4OH in acetonitrile gradient to afford 3-(3-methyl-2-pyridin-3-yl-indole-1-carbonyl)-benzonitrile product as a yellow solid. ^1H NMR (400 MHz, MeOD) δ ppm 2.31 (s, 3 H), 7.32 (ddd, *J*=7.9, 4.9, 0.9 Hz, 1 H), 7.37 - 7.44 (m, 2 H), 7.66 - 7.70 (m, 4 H), 7.71 - 7.76 (m, 2 H), 7.85 - 7.91 (m, 1 H), 8.37 (dd, *J*=5.1, 1.5 Hz, 1 H), 8.46 (dd, *J*=2.3, 0.8 Hz, 1 H). HRMS (ESI) m/z 338.1293 [$(M+H)^+$ Calcd for $C_{22}H_{16}N_3O$: 338.1293].

Example 39

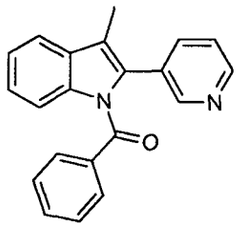
4-(3-Methyl-2-pyridin-3-yl-indole-1-carbonyl)-benzonitrile



4-Cyano-benzoyl chloride is processed according to the method described in Example 38 to give 4-(3-methyl-2-pyridin-3-yl-indole-1-carbonyl)-benzonitrile. ^1H NMR (400 MHz, MeOD) δ ppm 2.32 (s, 3 H), 7.32 (dd, *J*=7.8, 5.1 Hz, 1 H), 7.37 - 7.45 (m, 2 H), 7.49 (t, *J*=7.8 Hz, 1 H), 7.66 - 7.79 (m, 3 H), 7.79 - 7.83 (m, 1 H), 7.86 - 7.93 (m, 2 H), 8.34 (dd, *J*=4.8, 1.5 Hz, 1 H), 8.47 (d, *J*=1.5 Hz, 1 H). HRMS (ESI) m/z 338.1292 [$(M+H)^+$ Calcd for $C_{22}H_{16}N_3O$: 338.1293].

Example 40

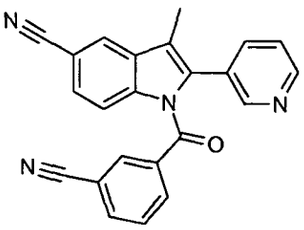
(3-Methyl-2-pyridin-3-yl-indol-1-yl)-phenyl-methanone



3-Methyl-2-pyridin-3-yl-1H-indole hydrochloride and benzoyl chloride are processed according to the method described in Example 38 to give (3-methyl-2-pyridin-3-yl-indol-1-yl)-phenyl-methanone. ^{1}H NMR (400 MHz, MeOD) δ ppm 2.33 (s, 3 H), 7.26 - 7.40 (m, 5 H), 7.45 - 7.52 (m, 1 H), 7.57 (d, *J*=1.3 Hz, 1 H), 7.59 (s, 1 H), 7.63 (dd, *J*=7.1, 1.3 Hz, 1 H), 7.68 - 7.73 (m, 1 H), 7.75 (dt, *J*=7.8, 1.9 Hz, 1 H), 8.33 (dd, *J*=5.1, 1.5 Hz, 1 H), 8.47 (d, *J*=1.3 Hz, 2 H). HRMS (ESI) m/z 313.1337 [(M+H)$^+$ Calcd for $C_{21}H_{17}N_2O$: 313.1341].

Example 41

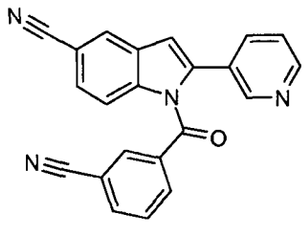
3-(5-Cyano-3-methyl-2-pyridin-3-yl-indole-1-carbonyl)-benzonitrile



KHMDS (0.5 M in toluene, 1.46 mL, 0.73 mmol) is added to a solution of 3-methyl-2-pyridin-3-yl-1H-indole-5-carbonitrile (Example 6, 122 mg, 0.480 mmol) in THF (10 mL) at room temperature. After 5 min, 3-cyanobenzoyl chloride (178 mg, 1.08 mmol) is added. The mixture is stirred under N_2 for 1 h, whereupon aqueous ammonium chloride (0.5 mL) is added. The solvents are removed *in vacuo* and the residue is purified by Xbridge RP18 with a 0.1% aqueous ammonium hydroxide in acetonitrile gradient to give 1-(3-cyano-benzoyl)-3-methyl-2-pyridin-3-yl-1H-indole-5-carbonitrile. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 2.35 (s, 3 H), 7.37 - 7.44 (m, 1 H), 7.47 - 7.52 (m, 1 H), 7.60 - 7.64 (m, 1 H), 7.68 - 7.83 (m, 5 H), 8.01 (d, *J*=1.5 Hz, 1 H), 8.51 (d, *J*=4.5 Hz, 1 H), 8.53 (s, 1 H). HRMS (ESI) m/z 363.1247 [(M+H)$^+$ Calcd for $C_{23}H_{15}N_4O$: 363.1246].

Example 42

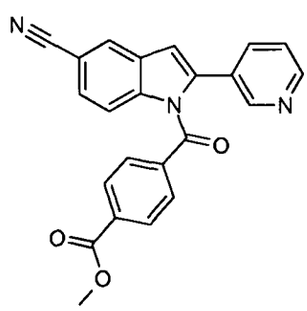
1-(3-Cyano-benzoyl)-2-pyridin-3-yl-1H-indole-5-carbonitrile



To a solution of 2-pyridin-3-yl-1H-indole-5-carbonitrile (Example 8, 210 mg, 0.96 mmol) in THF (20 mL) at room temperature is added 0.5 M KHMDS in toluene (4.10 mL, 2.05 mmol). After 30 min, 3-cyanobenzoyl chloride (510 mg, 3.08 mmol) is added. The mixture is stirred under N_2 overnight. The reaction is quenched with aqueous ammonium chloride and the volatiles are removed *in vacuo*. The residue is redissolved in dichloromethane and poured into saturated aqueous sodium bicarbonate (100 mL). Extraction with dichloromethane, drying over sodium sulfate followed by concentration affords a residue which is purified on an XBridge RP18 using a 0.1% ammonium hydroxide in acetonitrile gradient. Further purification by silica gel flash chromatography (heptane-ethyl acetate, 3:2 to 2:3) affords 1-(3-cyano-benzoyl)-2-pyridin-3-yl-1H-indole-5-carbonitrile. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.20 (d, J=0.5 Hz, 1 H), 7.22 - 7.26 (m, 1 H), 7.55 (t, J=7.8 Hz, 1 H), 7.73 - 7.79 (m, 2 H), 7.84 (d, 1 H), 7.92 - 7.98 (m, 2 H), 8.11 (t, J=1.5 Hz, 1 H), 8.29 - 8.33 (m, 1 H), 8.39 (dd, J=4.8, 1.5 Hz, 1 H), 8.60 (dd, J=2.3, 0.8 Hz, 1 H). HRMS (ESI) m/z 349.1106 [$(M+H)^+$ Calcd for $C_{22}H_{13}N_4O$: 349.1089].

Example 43

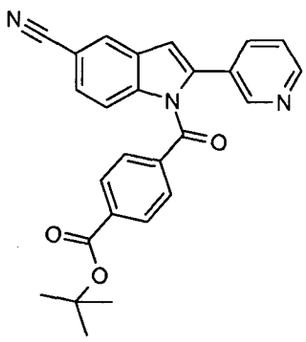
4-(5-Cyano-2-pyridin-3-yl-indole-1-carbonyl)-benzoic acid methyl ester



To a solution of 2-pyridin-3-yl-1H-indole-5-carbonitrile (Example 8, 240 mg, 1.09 mmol) in THF (10 mL) at room temperature is added 0.5 M KHMDS in toluene (4.0 mL, 2.0 mmol). After 30 min, 4-chlorocarbonyl-benzoic acid methyl ester (400 mg, 2.0 mmol) is added. The mixture is stirred under N_2 for 1 h. The reaction is quenched with aqueous sodium bicarbonate and the volatiles are removed *in vacuo*. Purification by silica gel flash chromatography using a heptane-ethyl acetate gradient affords 4-(5-cyano-2-pyridin-3-yl-indole-1-carbonyl)-benzoic acid methyl ester. ^{1}H NMR (400 MHz, MeOD) δ ppm 3.90 (s, 3 H), 7.12 (s, 1 H), 7.26 (dd, *J*=8.0, 4.9 Hz, 1 H), 7.63 - 7.72 (m, 3 H), 7.77 - 7.81 (m, 1 H), 7.91 - 7.96 (m, 3 H), 8.17 (d, *J*=1.5 Hz, 1 H), 8.32 (dd, *J*=4.8, 1.5 Hz, 1 H), 8.56 (d, *J*=2.3 Hz, 1 H). HRMS (ESI) m/z 382.1186 [$(M+H)^+$ Calcd for $C_{23}H_{16}N_3O_3$: 382.1192].

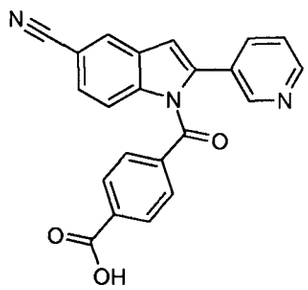
Example 44

(a) 4-(5-Cyano-2-pyridin-3-yl-indole-1-carbonyl)-benzoic acid tert-butyl ester



To 2-pyridin-3-yl-1H-indole-5-carbonitrile (575 mg, 2.62 mmol), 4-(butoxycarbonyl)benzoic acid (700 mg, 3.15 mmol) and DMAP (780 mg, 3.93 mmol) in DMF (30 mL) is added DCC (811 mg, 3.93 mmol). The reaction is stirred for 3 days and the mixture is poured into water (50 mL) and extracted with ethyl acetate, dried over Na_2SO_4 and concentrated. The residue is purified by silica gel flash chromatography (ethyl acetate-heptane gradient) to give 4-(5-cyano-2-pyridin-3-yl-indole-1-carbonyl)-benzoic acid tert-butyl ester as a white solid. MS (ESI) *m/z* 424 $(M+H)^+$.

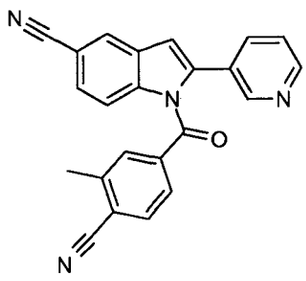
(b) 4-(5-cyano-2-pyridin-3-yl-indole-1-carbonyl)-benzoic acid



4-(5-Cyano-2-pyridin-3-yl-indole-1-carbonyl)-benzoic acid tert-butyl ester (100 mg) is dissolved in TFA (3 mL) and stirred at ambient temperature for 1 h. The solvent is removed *in vacuo* and the residue is triturated with diethyl ether twice. The residue is purified by reverse phase HPLC with Sunfire C18 and a gradient of acetonitrile in 0.1% aqueous TFA to afford 4-(5-cyano-2-pyridin-3-yl-indole-1-carbonyl)-benzoic acid as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm (TFA salt) 7.24 (s, 1 H), 7.28 (dd, *J*=7.9, 4.9 Hz, 1 H), 7.73 - 7.77 (m, 4 H), 7.81 (dt, *J*=8.1, 1.9, 1.8 Hz, 1 H), 7.87 - 7.91 (m, 2 H), 8.32 (t, *J*=1.1 Hz, 1 H), 8.41 (dd, *J*=4.9, 1.6 Hz, 1 H), 8.63 - 8.65 (m, 1 H), 13.40 (br. s., 1 H). HRMS (ESI) m/z 366.0868 [(M+H)$^+$ Calcd for $C_{22}H_{14}N_3O_3$: 366.0879].

Example 45

1-(4-cyano-3-methyl-benzoyl)-2-pyridin-3-yl-1H-indole-5-carbonitrile

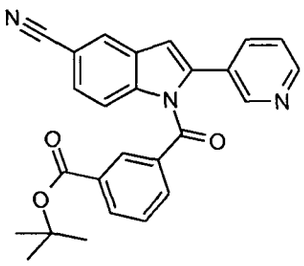


4-Cyano-3-methyl-benzoic acid is synthesized based on the method described in patent EP1512687A1. To a solution of 2-pyridin-3-yl-1H-indole-5-carbonitrile (20 mg, 0.09 mmol), 4-dimethylaminopyridine (22 mg, 0.01 mmol) and 4-cyano-3-methyl-benzoic acid (29 mg, 0.18 mmol) at 0 °C in dichloromethane (2 mL) is added DCC (38 mg, 0.18 mmol). After stirring for 10 min the reaction is warmed to room temperature. A precipitate forms and stirring is continued for 16 h. The mixture is filtered and the filtrate is diluted with dichloromethane (10 mL), washed with water and a saturated sodium chloride solution. The combined organic extracts are dried over sodium sulfate, filtered, and concentrated. The resulting residue is purified by silica gel flash chromatography (ethyl

acetate-heptane, 0:1 to 1:1) to furnish 1-(4-cyano-3-methyl-benzoyl)-2-pyridin-3-yl-1H-indole-5-carbonitrile. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 2.47 (s, 3 H), 6.91 (s, 1 H), 7.14 (dd, *J*=8.0, 4.9 Hz, 1 H), 7.43 - 7.48 (m, 2 H), 7.49 - 7.54 (m, 2 H), 7.61 (dd, *J*=8.7, 1.6 Hz, 1 H), 7.93 (d, *J*=8.6 Hz, 1 H), 8.03 (d, *J*=1.0\ Hz, 1 H), 8.44 (dd, *J*=4.8, 1.5 Hz, 1 H), 8.55 (d, *J*=1.8 Hz, 1 H). HRMS (ESI) m/z 363.1245 [$(M+H)^+$: Calcd for $C_{23}H_{15}N_4O$: 363.1246].

Example 46

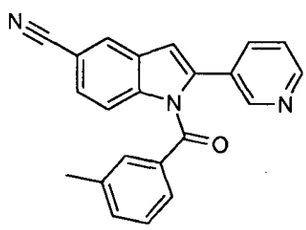
3-(5-Cyano-2-pyridin-3-yl-indole-1-carbonyl)-benzoic acid tert-butyl ester



Isophthalic acid mono-tert-butyl ester is processed according to the method described in Example 45 to give 3-(5-cyano-2-pyridin-3-yl-indole-1-carbonyl)-benzoic acid tert-butyl ester. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 1.58 (s, 9 H), 6.91 (s, 1 H), 7.10 (dd, *J*=7.6, 5.1 Hz, 1 H), 7.40 (t, *J*=7.8 Hz, 1 H), 7.52 - 7.59 (m, 2 H), 7.81 (dt, *J*=7.9, 1.5, 1.3 Hz, 1 H), 7.85 (d, *J*=8.7 Hz, 1 H), 8.02 - 8.06 (m, 2 H), 8.09 (t, *J*=1.6 Hz, 1 H), 8.40 (d, *J*=3.4 Hz, 1 H), 8.58 (d, *J*=1.8 Hz, 1 H). HRMS (ESI) m/z 424.1662 [$(M+H)^+$: Calcd for $C_{26}H_{22}N_3O_3$: 424.1661].

Example 47

1-(3-Methyl-benzoyl)-2-pyridin-3-yl-1H-indole-5-carbonitrile

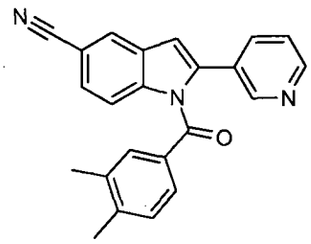


3-Methylbenzoic acid is processed according to the method described in Example 45 to give 1-(3-methyl-benzoyl)-2-pyridin-3-yl-1H-indole-5-carbonitrile. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 2.29 (s, 3 H), 6.89 (s, 1 H), 7.14 (dd, *J*=8.0, 4.9 Hz, 1 H), 7.19 - 7.24 (m, 1 H), 7.27 - 7.31 (m, 1 H), 7.39 - 7.44 (m, 2 H), 7.50 - 7.57 (m, 2 H), 7.71 (d, *J*=8.6 Hz, 1

H), 8.01 (d, *J*=1.0 Hz, 1 H), 8.42 (dd, *J*=4.8, 1.5 Hz, 1 H), 8.62 (d, *J*=1.8 Hz, 1 H). HRMS (ESI) m/z 338.1289 [$(M+H)^+$: Calcd for $C_{22}H_{16}N_3O$: 338.1293]

Example 48

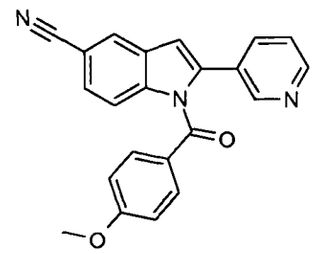
1-(3,4-Dimethyl-benzoyl)-2-pyridin-3-yl-1H-indole-5-carbonitrile



3,4-Dimethylbenzoic acid is processed according to the method described in Example 45 to give 1-(3,4-dimethyl-benzoyl)-2-pyridin-3-yl-1H-indole-5-carbonitrile. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 2.21 (s, 3 H), 2.26 (s, 3 H), 6.89 (s, 1 H), 7.10 (d, *J*=7.8 Hz, 1 H), 7.15 (dd, *J*=7.5, 5.2 Hz, 1 H), 7.37 - 7.43 (m, 2 H), 7.49 (dd, *J*=8.6, 1.5 Hz, 1 H), 7.57 (dt, *J*=8.3, 2.0, 1.6 Hz, 1 H), 7.61 (d, *J*=8.8 Hz, 1 H), 8.01 (d, *J*=2.0 Hz, 1 H), 8.44 (dd, *J*=4.8, 1.5 Hz, 1 H), 8.64 (d, *J*=2.3 Hz, 1 H). HRMS (ESI) m/z 352.1458 [$(M+H)^+$: Calcd for $C_{23}H_{18}N_3O$: 352.1450].

Example 49

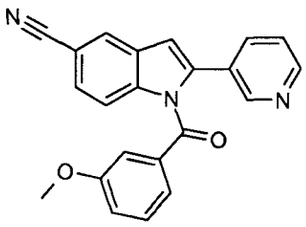
1-(4-Methoxy-benzoyl)-2-pyridin-3-yl-1H-indole-5-carbonitrile



4-Methoxybenzoic acid is processed according to the method described in Example 45 to give 1-(4-methoxy-benzoyl)-2-pyridin-3-yl-1H-indole-5-carbonitrile. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 3.83 (s, 3 H), 6.81 - 6.85 (m, 2 H), 6.90 (s, 1 H), 7.18 (dd, *J*=7.8, 3.0 Hz, 1 H), 7.49 (dd, *J*=8.6, 1.5 Hz, 1 H), 7.58 - 7.62 (m, 2 H), 7.62 - 7.66 (m, 2 H), 8.01 (d, *J*=1.5 Hz, 1 H), 8.46 (dd, *J*=4.8, 1.5 Hz, 1 H), 8.66 (d, *J*=3.0 Hz, 1 H). HRMS (ESI) m/z 354.1225 [$(M+H)^+$: Calcd for $C_{22}H_{16}N_3O_2$: 354.1243].

Example 50

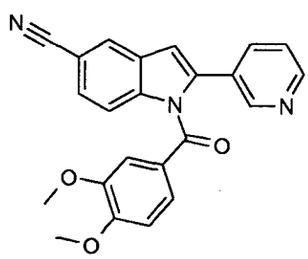
1-(3-Methoxy-benzoyl)-2-pyridin-3-yl-1H-indole-5-carbonitrile



3-Methoxybenzoic acid is processed according to the method described in Example 45 to give 1-(3-methoxy-benzoyl)-2-pyridin-3-yl-1H-indole-5-carbonitrile. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 3.78 (s, 3 H), 6.89 (s, 1 H), 7.02 (ddd, *J*=8.2, 2.6, 1.1 Hz, 1 H), 7.13 - 7.18 (m, 3 H), 7.23 (d, *J*=8.1 Hz, 1 H), 7.52 (dd, *J*=8.6, 1.5 Hz, 1 H), 7.57 (dt, *J*=8.0, 1.9 Hz, 1 H), 7.69 (d, *J*=8.8 Hz, 1 H), 8.01 (d, *J*=1.0 Hz, 1 H), 8.45 (dd, *J*=4.8, 1.5 Hz, 1 H), 8.64 (d, *J*=2.3 Hz, 1 H). HRMS (ESI) m/z 354.1231 [$(M+H)^+$: Calcd for $C_{22}H_{16}N_3O_2$: 354.1243].

Example 51

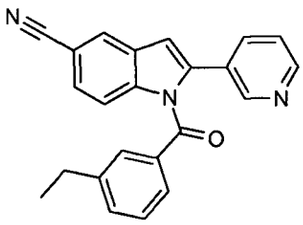
1-(3,4-Dimethoxy-benzoyl)-2-pyridin-3-yl-1H-indole-5-carbonitrile



3,4-Dimethoxybenzoic acid is processed according to the method described in Example 45 to give 1-(3,4-dimethoxy-benzoyl)-2-pyridin-3-yl-1H-indole-5-carbonitrile. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 3.87 (s, 3 H), 3.90 (s, 3 H), 6.75 (d, *J*=8.6 Hz, 1 H), 6.92 (s, 1 H), 7.19 (dd, *J*=7.8, 4.3 Hz, 1 H), 7.22 (dd, *J*=8.5, 2.2 Hz, 1 H), 7.29 (d, *J*=2.0 Hz, 1 H), 7.50 (dd, *J*=8.7, 1.6 Hz, 1 H), 7.58 - 7.63 (m, 2 H), 8.02 (d, *J*=1.0 Hz, 1 H), 8.47 (dd, *J*=4.8, 1.5 Hz, 1 H), 8.68 (dd, *J*=2.3, 0.8 Hz, 1 H). HRMS (ESI) m/z 384.1349 [$(M+H)^+$: Calcd for $C_{23}H_{18}N_3O_3$: 384.1348].

Example 52

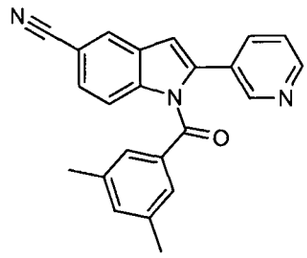
1-(3-Ethyl-benzoyl)-2-pyridin-3-yl-1H-indole-5-carbonitrile



3-Ethylbenzoic acid is processed according to the method described in Example 45 to give 1-(3-ethyl-benzoyl)-2-pyridin-3-yl-1H-indole-5-carbonitrile. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 1.16 (t, *J*=7.6 Hz, 3 H), 2.58 (q, *J*=7.6 Hz, 2 H), 6.89 (s, 1 H), 7.12 (dd, *J*=8.0, 4.9 Hz, 1 H), 7.22 - 7.25 (m, 1 H), 7.29 - 7.33 (m, 1 H), 7.40 (s, 1 H), 7.43 - 7.47 (m, 1 H), 7.51 - 7.57 (m, 2 H), 7.73 (d, *J*=8.8 Hz, 1 H), 8.02 (d, *J*=1.0 Hz, 1 H), 8.42 (dd, *J*=4.8, 1.5 Hz, 1 H), 8.63 (d, *J*=1.8 Hz, 1 H). HRMS (ESI) m/z 352.1443 [$(M+H)^+$: Calcd for $C_{23}H_{18}N_3O$: 352.1450].

Example 53

1-(3,5-Dimethyl-benzoyl)-2-pyridin-3-yl-1H-indole-5-carbonitrile

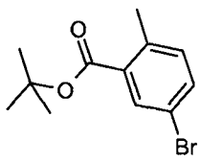


To a solution of 2-pyridin-3-yl-1H-indole-5-carbonitrile (Example 8, 200 mg, 0.913 mmol) at 0 °C in THF (6 mL) is added 60% sodium hydride (72 mg, 1.826 mmol) and the mixture is stirred for 10 min at 0 °C. The reaction mixture is then warmed to room temperature and stirred for 30 min. 3,5-Dimethyl-benzoyl chloride (460 mg, 2.740 mmol) in THF (2 mL) is added dropwise at 0 °C and the reaction is stirred at room temperature for 1 h. The reaction is quenched by adding saturated sodium bicarbonate. The THF is removed under vacuum, and the resulting residue is purified by silica gel flash chromatography (ethyl acetate-heptane, 0:1 to 1:1). The resulting product is further purified by HPLC using an X-bridge RP18 and an acetonitrile-0.1% ammonia hydroxide gradient to yield 1-(3,5-dimethyl-benzoyl)-2-pyridine-3-yl-1H-indole-5-carbonitrile. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 2.25 (s, 6 H), 6.88 (s, 1 H), 7.10 (s, 1 H), 7.14 (dd, *J*=7.6, 5.3 Hz, 1 H), 7.22 (s, 2 H), 7.50 - 7.56 (m, 2 H), 7.70 (d, *J*=8.8 Hz, 1 H), 8.01 (s, 1 H),

8.43 (dd, *J*=4.8, 1.5 Hz, 1 H), 8.62 (s, 1 H). HRMS (ESI) m/z 352.1452 [$(M+H)^+$: Calcd for $C_{23}H_{18}N_3O$: 352.1450].

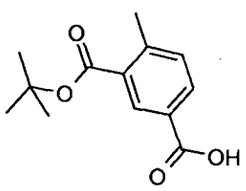
Example 54

(a) 5-Bromo-2-methyl-benzoic acid tert-butyl ester



To a suspension of anhydrous magnesium sulfate (4.5 g, 37.28 mmol) in dichloromethane (37 mL) is added concentrated H_2SO_4 (516 µl, 9.302 mmol) and the mixture is stirred vigorously for 15 min. 5-Bromo-2-methyl-benzoic acid (2 g, 9.302 mmol) is added, followed by t-butanol (4.39 mL, 46.51 mmol). The flask is capped tightly and stirred at room temperature for 24 h. After adding saturated sodium bicarbonate, the resulting solution is extracted with ethyl acetate. The organic layer is washed with a saturated sodium chloride solution, dried over sodium sulfate, filtered and concentrated. The resulting residue is purified by silica gel flash chromatography (ethyl acetate-heptane, 0:1 to 3:7) to furnish 5-bromo-2-methyl-benzoic acid *tert*-butyl ester. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.59 (s, 9 H), 2.51 (s, 3 H), 7.08 (d, *J*=8.1 Hz, 1 H), 7.46 (dd, *J*=8.3, 2.3 Hz, 1 H), 7.92 (d, *J*=2.3 Hz, 1 H)

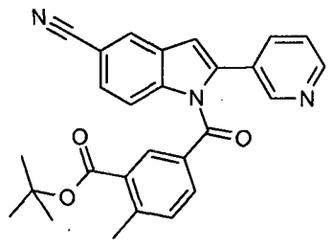
(b) 4-Methyl-isophthalic acid 3-*tert*-butyl ester



n-Butyllithium (1.6M in hexane,1.29 mL, 1.975 mmol) is slowly added to 5-bromo-2-methyl-benzoic acid *tert*-butyl ester (511 mg, 1.884 mmol) in THF (18 mL) at –78 °C under N_2. The reaction mixture is stirred at –78 °C for 30 min. Carbon dioxide gas is bubbled through the solution until the solution color changes to orange. After stirring at –78 °C for 10 min, the reaction mixture is warmed to room temperature. The reaction is quenched with saturated ammonium chloride, extracted with ethyl acetate, dried over sodium sulfate, filtered and concentrated. The resulting residue is purified by silica gel

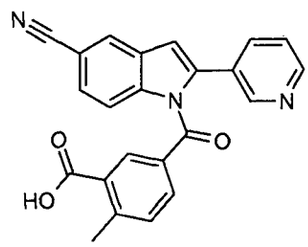
flash chromatography (ethyl acetate-heptane, 0:1 to 1:1) to furnish 4-methyl-isophthalic acid 3-*tert*-butyl ester. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 1.62 (s, 9 H), 2.65 (s, 3 H), 7.33 (d, *J*=7.83 Hz, 1 H), 8.07 (dd, *J*=7.96, 1.89 Hz, 1 H), 8.52 (d, *J*=2.02 Hz, 1 H).

(c) 5-(5-Cyano-2-pyridin-3-yl-indole-1-carbonyl)-2-methyl-benzoic acid tert-butyl ester



4-methyl-isophthalic acid 3-*tert*-butyl ester is processed according to the method described in Example 45 to give 5-(5-cyano-2-pyridin-3-yl-indole-1-carbonyl)-2-methyl-benzoic acid *tert*-butyl ester. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 1.57 (s, 9 H), 2.55 (s, 3 H), 6.91 (s, 1 H), 7.13 (dd, *J*=7.83, 4.29 Hz, 1 H), 7.20 (d, *J*=8.08 Hz, 1 H), 7.53 - 7.58 (m, 2 H), 7.66 (dd, *J*=7.96, 2.15 Hz, 1 H), 7.76 (d, *J*=8.59 Hz, 1 H), 7.98 (d, *J*=2.02 Hz, 1 H), 8.02 (d, *J*=1.01 Hz, 1 H), 8.43 (dd, *J*=4.80, 1.52 Hz, 1 H), 8.61 (d, *J*=2.27 Hz, 1 H).

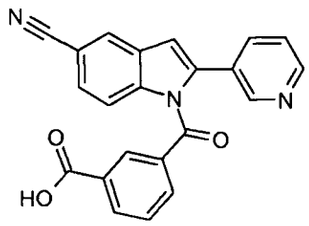
(d) 5-(5-Cyano-2-pyridin-3-yl-indole-1-carbonyl)-2-methyl-benzoic acid



5-(5-Cyano-2-pyridin-3-yl-indole-1-carbonyl)-2-methyl-benzoic acid *tert*-butyl ester is dissolved in trifluoroacetic acid (3 mL), and stirred at room temperature for 1 h. After removing the solvent, the residue is purified by HPLC with an X-bridge Phenyl using acetonitrile-0.1% trifluoroacetic acid as an eluent to yield 5-(5-cyano-2-pyridin-3-yl-indole-1-carbonyl)-2-methyl-benzoic acid. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm (TFA salt) 2.59 (s, 3 H), 7.32 (s, 1 H), 7.39 - 7.44 (m, 2 H), 7.71 - 7.75 (m, 1 H), 7.76 - 7.79 (m, 1 H), 7.81 (dd, *J*=7.8, 2.0 Hz, 1 H), 7.92 (dt, *J*=8.0, 1.8 Hz, 1 H), 8.11 (d, *J*=2.0 Hz, 1 H), 8.38 (d, *J*=1.5 Hz, 1 H), 8.52 (dd, *J*=5.0, 1.5 Hz, 1 H), 8.74 (d, *J*=2.0 Hz, 1 H). HRMS (ESI) m/z 382.1202 [$(M+H)^+$ Calcd for $C_{23}H_{16}N_3O_3$: 382.1192].

Example 55

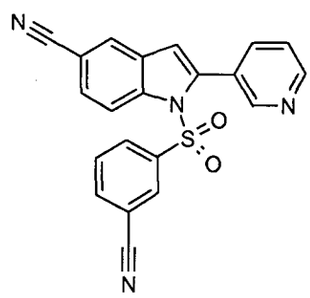
3-(5-Cyano-2-pyridin-3-yl-indole-1-carbonyl)-benzoic acid



3-(5-cyano-2-pyridin-3-yl-indole-1-carbonyl)-benzoic acid tert-butyl ester (Example 46) is processed according to the method described in Example 54d to give 5-(5-cyano-2-pyridin-3-yl-indole-1-carbonyl)-2-methyl-benzoic acid. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm (TFA salt) 7.16 - 7.21 (m, 2 H), 7.43 (t, *J*=7.8 Hz, 1 H), 7.67 (dd, *J*=8.7, 1.64 Hz, 1 H), 7.71 - 7.75 (m, 2 H), 7.82 (dt, *J*=8.0, 1.5, 1.3 Hz, 1 H), 7.97 (dt, *J*=7.8, 1.4 Hz, 1 H), 8.00 (t, *J*=1.5 Hz, 1 H), 8.25 (d, *J*=1.0 Hz, 1 H), 8.32 (dd, *J*=4.8, 1.5 Hz, 1 H), 8.55 (d, *J*=1.6 Hz, 1 H). HRMS (ESI) m/z 368.1040 [(M+H)$^+$ Calcd for $C_{22}H_{14}N_3O_3$: 368.1035]

Example 56

1-(3-Cyano-benzenesulfonyl)-2-pyridin-3-yl-1H-indole-5-carbonitrile

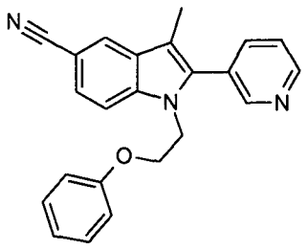


To a solution of 2-pyridin-3-yl-1H-indole-5-carbonitrile (Example 8, 300 mg, 1.37 mmol) at 0 °C in DMF (12 mL) is added 60% sodium hydride (82 mg, 2.06 mmol) and the mixture stirred for 10 min at 0 °C. The reaction mixture is then warmed to room temperature and stirred for 30 min. 3-Cyanobenzenesulfonyl chloride (552 mg, 2.74 mmol) in DMF (2 mL) is added dropwise at 0 °C and the reaction is stirred at room temperature for 1 h. The reaction is quenched by adding water (1 mL). The resulting mixture is purified by HPLC X-bridge RP18 using acetonitrile-0.1% ammonia hydroxide as an eluent to yield 1-(3-cyano-benzenesulfonyl)2-pyridin-3-yl-1H-indole-5-carbonitrile. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.11 (s, 1 H), 7.54 (dd, *J*=7.8, 4.8 Hz, 1 H), 7.66 (dd, *J*=8.1, 2.0 Hz, 1 H), 7.72 (t, *J*=7.7 Hz, 1 H), 7.86 (dd, *J*=8.7, 1.6 Hz, 1 H), 7.94 (t, *J*=1.5

Hz, 1 H), 7.98 (dt, *J*=8.2, 2.0, 1.8 Hz, 1 H), 8.16 (dd, *J*=7.6, 1.3 Hz, 1 H), 8.19 (d, *J*=1.0 Hz, 1 H), 8.34 (d, *J*=8.6 Hz, 1 H), 8.67 (d, *J*=2.8 Hz, 1 H), 8.71 (dd, *J*=4.9, 1.6 Hz, 1 H). HRMS (ESI) m/z 385.0763 [$(M+H)^+$ Calcd for $C_{21}H_{13}N_4O_2S$: 385.0759].

Example 57

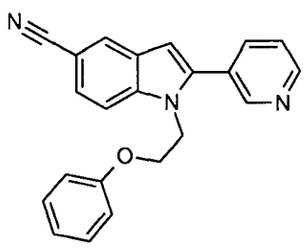
3-Methyl-1-(2-phenoxy-ethyl)-2-pyridin-3-yl-1H-indole-5-carbonitrile



To a solution of 3-methyl-2-pyridin-3-yl-1H-indole-5-carbonitrile (Example 6, 47 mg, 0.20 mmol) in THF (5 mL) at room temperature is added KHMDS (0.5 M in toluene, 0.60 mL, 0.30 mmol) followed with (2-bromo-ethoxy)-benzene (90 mg, 0.45 mmol). The mixture is stirred under N_2 for 2 days and aqueous ammonium chloride (1 mL) is added to quench the reaction. The volatiles are removed *in vacuo* and the residue is purified by silica gel flash chromatography (ethyl acetate-heptane, 1:4 to 1:0) to give 3-methyl-1-(2-phenoxy-ethyl)-2-pyridin-3-yl-1H-indole-5-carbonitrile. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 2.25 (s, 3 H), 4.10 (t, *J*=5.2 Hz, 2 H), 4.46 (t, *J*=5.3 Hz, 2 H), 6.66 (d, *J*=7.8 Hz, 2 H), 6.93 (t, *J*=7.3 Hz, 1 H), 7.17 - 7.25 (m, 2 H), 7.51 - 7.57 (m, 2 H), 7.59 - 7.65 (m, 1 H), 7.95 (d, *J*=8.6 Hz, 1 H), 7.98 (s, 1 H), 8.74 - 8.79 (m, 2 H). HRMS (ESI) m/z 354.1618 [$(M+H)^+$ Calcd for $C_{23}H_{20}N_3O$: 354.1606].

Example 58

1-(2-Phenoxy-ethyl)-2-pyridin-3-yl-1H-indole-5-carbonitrile

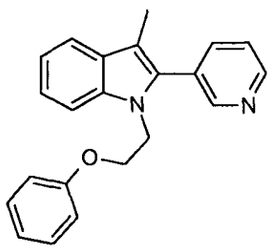


(2-Bromo-ethoxy)-benzene and 2-pyridin-3-yl-1H-indole-5-carbonitrile (Example 8) are processed according to the method described in Example 57 to give 1-(2-phenoxy-

ethyl)-2-pyridin-3-yl-1H-indole-5-carbonitrile. ^{1}H NMR (400 MHz, MeOD) δ ppm 4.19 (t, *J*=5.2 Hz, 2 H), 4.67 (t, *J*=5.1 Hz, 2 H), 6.63 (d, *J*=7.8 Hz, 2 H), 6.77 (s, 1 H), 6.84 (t, *J*=7.5 Hz, 1 H), 7.10 - 7.17 (m, 2 H), 7.53 (dd, *J*=8.6, 1.8 Hz, 1 H), 7.55 - 7.60 (m, 1 H), 7.77 (d, *J*=8.6 Hz, 1 H), 8.05 (s, 1 H), 8.08 - 8.13 (m, 1 H), 8.63 (dd, *J*=4.9, 1.6 Hz, 1 H), 8.79 (d, *J*=1.5 Hz, 1 H). HRMS (ESI) m/z 340.1453 [(M+H)$^+$ Calcd for $C_{22}H_{18}N_3O$: 340.1450].

Example 59

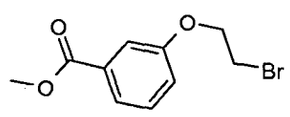
3-Methyl-1-(2-phenoxy-ethyl)-2-pyridin-3-yl-1H-indole



A flask is charged with 3-methyl-2-pyridin-3-yl-1H-indole hydrochloride (Example 1, 0.100 g, 0.408 mmol) and DMF (2 mL). The solution is cooled to 0 °C and 60% NaH in mineral oil (0.036g, 0.898 mmol) is added. The mixture is stirred at room temperature for 20 min followed by addition of (2-bromo-ethoxy)-benzene (0.205 mL, 1.021 mmol). The mixture is stirred at room temperature for 5 h, whereupon it is concentrated *in vacuo*. The residue is purified by reverse phase HPLC with Xbridge Shield RP18 column and a gradient of 0.1% aqueous TFA in acetonitrile to afford 3-methyl-1-(2-phenoxy-ethyl)-2-pyridin-3-yl-1H-indole as a yellow trifluoro acetate salt. ^{1}H NMR (400 MHz, MeOD) δ ppm (TFA salt) 2.29 (s, 3 H), 4.18 (t, *J*=5.2 Hz, 2 H), 4.55 (t, *J*=5.1 Hz, 2 H), 6.64 (d, *J*=7.8 Hz, 2 H), 6.87 (t, *J*=7.5 Hz, 1 H), 7.11 - 7.22 (m, 3 H), 7.33 (ddd, *J*=7.6, 1.1 Hz, 1 H), 7.58 (d, *J*=8.3 Hz, 1 H), 7.64 (d, *J*=7.8 Hz, 1 H), 7.96 (dd, *J*=8.0, 5.4 Hz, 1 H), 8.44 (dt, *J*=8.0, 1.9, 1.8 Hz, 1 H), 8.77 (dd, *J*=5.6, 1.3 Hz, 1 H), 8.89 (d, *J*=1.8 Hz, 1 H). HRMS (ESI) m/z 329.1646 [(M+H)$^+$ Calcd for $C_{22}H_{21}N_2O$: 329.1654].

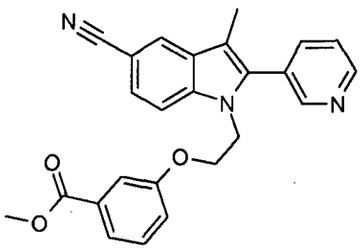
Example 60

(a) 3-(2-Bromo-ethoxy)-benzoic acid methyl ester



A flask is charged with 3-hydroxybenzoic acid methyl ester (2.54 g, 16.0 mmol) and acetone (50 mL).1,2-Dibromo-ethane (5.69 mL, 66.0 mmol) and potassium carbonate (2.76 g, 19.0 mmol) are added and the mixture is refluxed for 24 h. The reaction mixture is then cooled to room temperature. The solids are filtered off and the filtrate concentrated *in vacuo*. The residue is purified by silica gel flash chromatography (heptane-ethyl acetate, 3:1) to afford 3-(2-bromo-ethoxy)-benzoic acid methyl ester as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 3.66 (t, *J*=6.2 Hz, 2 H), 3.93 (s, 3 H), 4.35 (t, *J*=6.2 Hz, 2 H), 7.14 (m, 1 H) 7.37 (m, 1 H) 7.57 (m, 1 H) 7.68 (m, 1 H).

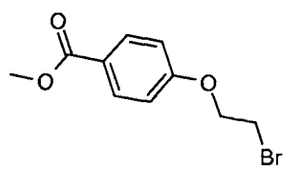
(b) 3-[2-(5-Cyano-3-methyl-2-pyridin-3-yl-indol-1-yl)-ethoxy]-benzoic acid methyl ester



3-(2-Bromo-ethoxy)-benzoic acid methyl ester and 5-cyano-3-methyl-2-pyridin-3-yl-indol-1-yl (Example 6) are processed according to the method described in Example 59 to give 3-[2-(5-cyano-3-methyl-2-pyridin-3-yl-indol-1-yl)-ethoxy]-benzoic acid methyl ester. ^{1}H NMR (400 MHz, MeOD) δ ppm 2.26 (s, 3 H), 3.90 (s, 3 H), 4.22 (t, *J*=4.9 Hz, 2 H), 4.60 (t, *J*=5.1 Hz, 2 H), 6.91 (dd, *J*=7.8, 2.3 Hz, 1 H), 7.21 - 7.24 (m, 1 H), 7.28 (t, *J*=8.0 Hz, 1 H), 7.52 - 7.59 (m, 2 H), 7.65 (dd, *J*=7.8, 5.1 Hz, 1 H), 7.76 (d, *J*=8.6 Hz, 1 H), 7.98 - 8.09 (m, 2 H), 8.56 - 8.77 (m, 2 H). HRMS (ESI) m/z 412.1664 [$(M+H)^+$ Calcd for $C_{25}H_{22}N_3O_3$: 412.1661].

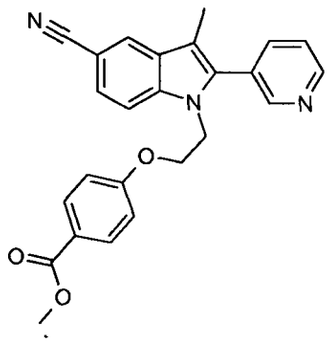
Example 61

(a) 4-(2-Bromo-ethoxy)-benzoic acid methyl ester



4-Hydroxybenzoic acid methyl ester is processed according to the method described in Example 60a to give 4-(2-Bromo-ethoxy)-benzoic acid methyl ester.

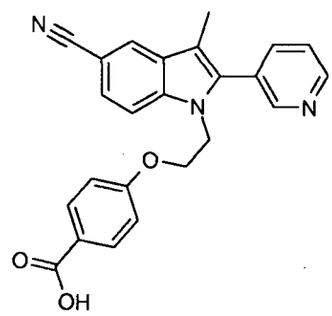
(b) 4-[2-(5-Cyano-3-methyl-2-pyridin-3-yl-indol-1-yl)-ethoxy]-benzoic acid methyl ester



4-(2-Bromo-ethoxy)-benzoic acid methyl ester and 5-cyano-3-methyl-2-pyridin-3-yl-indol-1-yl (Example 6) are processed according to the method described in Example 59 to give 4-[2-(5-cyano-3-methyl-2-pyridin-3-yl-indol-1-yl)-ethoxy]-benzoic acid methyl ester. ^{1}H NMR (400 MHz, MeOD) δ ppm 2.28 (s, 3 H), 3.87 (s, 3 H), 4.24 (t, *J*=5.1 Hz, 2 H), 4.61 (t, *J*=5.1 Hz, 2 H), 6.73 - 6.79 (m, 2 H), 7.58 (dd, *J*=8.5, 1.6 Hz, 1 H), 7.66 (ddd, *J*=7.9, 5.0, 0.8 Hz, 1 H), 7.77 (dd, *J*=8.6, 0.5 Hz, 1 H), 7.85 - 7.88 (m, 1 H), 7.88 - 7.90 (m, 1 H), 8.03 (dt, *J*=8.1, 1.9, 1.8 Hz, 1 H), 8.07 (dd, *J*=1.5, 0.6 Hz, 1 H), 8.52 - 8.84 (m, 2 H). HRMS (ESI) m/z 412.1660 [(M+H)$^+$ Calcd for $C_{25}H_{22}N_3O_3$: 412.1661].

Example 62

4-[2-(5-Cyano-3-methyl-2-pyridin-3-yl-indol-1-yl)-ethoxy]-benzoic acid

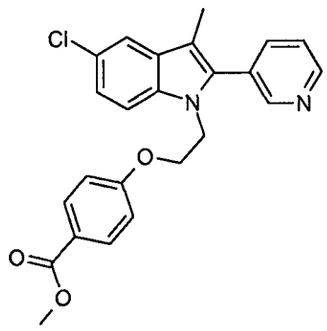


A flask is charged with 4-[2-(5-cyano-3-methyl-2-pyridin-3-yl-indol-1-yl)-ethoxy]-benzoic acid methyl ester (Example 61, 0.150 g, 0.36 mmol) in MeOH (5 mL). Aqueous lithium hydroxide (1 M, 0.912 mL, 0.912 mmol) is added and the mixture is refluxed overnight. The reaction mixture is then acidified to pH 1 using 1 M aqueous HCl solution and the methanol is removed *in vacuo*. The resulting solution is extracted with ethyl acetate. The organic layer is dried over sodium sulfate, filtered and concentrated. The resulting residue is purified by silica gel flash chromatography (dichloromethane-methanol, 9:1) to

afford 4-[2-(5-cyano-3-methyl-2-pyridin-3-yl-indol-1-yl)-ethoxy]-benzoic acid as a white solid. ^{1}H NMR (400 MHz, MeOD) δ ppm 2.27 (s, 3 H), 4.22 (t, *J*=5.1 Hz, 2 H), 4.60 (t, *J*=5.2 Hz, 2 H), 6.72 (d, *J*=8.8 Hz, 2 H), 7.57 (dd, *J*=8.6, 1.5 Hz, 1 H), 7.62 - 7.72 (m, 1 H), 7.76 (d, *J*=8.6 Hz, 1 H), 7.86 (d, *J*=8.6 Hz, 2 H), 8.02 (d, *J*=7.8 Hz, 1 H), 8.07 (s, 1 H), 8.72 (br. s., 2 H). HRMS (ESI) m/z 398.1487 [(M+H)$^+$ Calcd for $C_{24}H_{20}N_3O_3$: 398.1505].

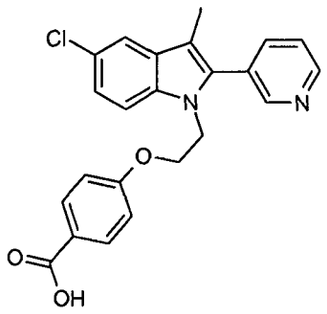
Example 63

(a) 4-[2-(5-Chloro-3-methyl-2-pyridin-3-yl-indol-1-yl)-ethoxy]-benzoic acid methyl ester.



4-(2-Bromo-ethoxy)-benzoic acid methyl ester (Example 61a) and 5-chloro-3-methyl-2-pyridin-3-yl-indol-1-yl (Example 2) are processed according to the method described in Example 59 to give 4-[2-(5-chloro-3-methyl-2-pyridin-3-yl-indol-1-yl)-ethoxy]-benzoic acid methyl ester. MS (ESI) m/z 421.01.

(b) 4-[2-(5-Chloro-3-methyl-2-pyridin-3-yl-indol-1-yl)-ethoxy]-benzoic acid

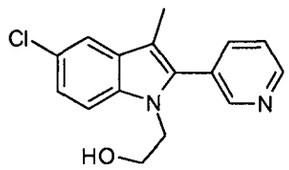


4-[2-(5-Chloro-3-methyl-2-pyridin-3-yl-indol-1-yl)-ethoxy]-benzoic acid methyl ester is processed according to the method described in Example 62 to give 4-[2-(5-chloro-3-methyl-2-pyridin-3-yl-indol-1-yl)-ethoxy]-benzoic acid. ^{1}H NMR (400 MHz, MeOD) δ ppm 2.22 (s, 3 H), 4.21 (t, *J*=5.1 Hz, 2 H), 4.54 (t, *J*=5.1 Hz, 2 H), 6.73 (d, *J*=8.8 Hz, 2 H),

7.25 (dd, *J*=8.7, 2.1 Hz, 1 H), 7.56 (d, *J*=8.6 Hz, 1 H), 7.59 (d, *J*=2.0 Hz, 1 H), 7.61 - 7.67 (m, 1 H), 7.87 (d, *J*=8.8 Hz, 2 H), 7.99 (d, *J*=7.8 Hz, 1 H), 8.68 (br. s., 2 H); HRMS (ESI) m/z 407.1157 [$(M+H)^+$ Calcd for $C_{23}H_{20}ClN_2O_3$: 407.1162].

Example 64

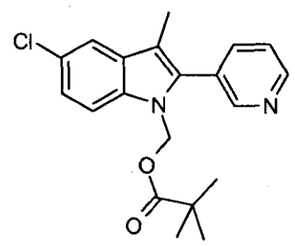
2-(5-Chloro-3-methyl-2-pyridin-3-yl-indol-1-yl)-ethanol



A flask is charged with 5-chloro-3-methyl-2-pyridin-3-yl-1H-indole hydrochloride (Example 2, 1.0 g, 3.58 mmol) and THF (20 mL) and cooled to 0 °C. KHMDS (0.5 M in toluene, 17.9 mL, 8.95 mmol) is added and the mixture is stirred at room temperature for 30 min, followed by addition of (2-chloro-ethoxy)-trimethylsilane (1.06 mL, 8.95 mmol). The reaction mixture is stirred for 48 h at 60 °C. After cooling to room temperature, aqueous 1M HCl (30 mL) is added and the mixture is stirred at room temperature for 30 min, then washed with water and extracted with ethyl acetate twice. The organic layer is dried over sodium sulfate and concentrated *in vacuo*. The residue is purified by silica gel flash chromatography (heptane-ethyl acetate, 1:4) to afford 2-(5-chloro-3-methyl-2-pyridin-3-yl-indol-1-yl)-ethanol as a solid. ^{1}H NMR (400 MHz, MeOD) δ ppm 2.22 (s, 3 H), 3.69 (t, *J*=5.9 Hz, 2 H), 4.18 (t, *J*=5.8 Hz, 2 H), 7.21 (dd, *J*=8.6, 2.0 Hz, 1 H), 7.47 (d, *J*=8.6 Hz, 1 H), 7.57 (d, *J*=1.8 Hz, 1 H), 7.61 - 7.67 (m, 1 H), 8.01 (dt, *J*=7.9, 2.0 Hz, 1 H), 8.61 - 8.71 (m, 2 H). HRMS (ESI) m/z 287.0953 [$(M+H)^+$ Calcd for $C_{16}H_{16}ClN_2O$: 287.0951].

Example 65

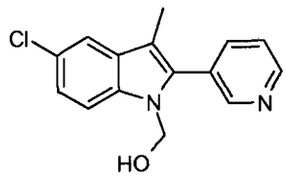
2,2-Dimethyl-propionic acid 5-chloro-3-methyl-2-pyridin-3-yl-indol-1-ylmethyl ester



A flask is charged with 5-chloro-3-methyl-2-pyridin-3-yl-1H-indole hydrochloride (Example 2, 1.0 g, 3.58 mmol) and THF (20 mL) and cooled to 0 °C. KHMDS (0.5 M in toluene, 17.9 mL, 8.95 mmol) is added and the mixture is stirred at room temperature for 30 min, followed by addition of 2,2-dimethyl-propionic acid chloromethyl ester (2.58 mL, 8.95 mmol). The reaction mixture is stirred at room temperature for 3.5 h, then washed with water and extracted with ethyl acetate twice. The organic layer is dried over sodium sulfate and concentrated *in vacuo*. The residue is purified by silica gel flash chromatography (heptane-ethyl acetate, 1:1) to afford an oil, which is taken up in diethyl ether. A few drops of concentrated HCl are added. Evaporation of the solvent and lyophilization give 2,2-dimethyl-propionic acid 5-chloro-3-methyl-2-pyridin-3-yl-indol-1-ylmethyl ester as a solid. ^{1}H NMR (400 MHz, MeOD) δ ppm (HCl salt) 1.12 (s, 9 H), 2.27 (s, 3 H), 6.06 (s, 2 H), 7.30 (dd, *J*=8.6, 2.0 Hz, 1 H), 7.60 (s, 1 H), 7.63 (d, *J*=2.3 Hz, 1 H), 7.74 (dd, *J*=7.8, 5.1 Hz, 1 H), 8.01 - 8.16 (m, 1 H), 8.64 - 8.79 (m, 2 H). HRMS (ESI) m/z 357.1121 [(M+H)$^+$ Calcd for $C_{20}H_{22}ClN_2O_2$: 357.1127].

Example 66

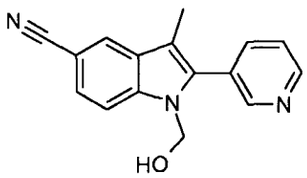
2-(5-Chloro-3-methyl-2-pyridin-3-yl-indol-1-yl)-methanol



A flask is charged with 2,2-dimethyl-propionic acid 5-chloro-3-methyl-2-pyridin-3-yl-indol-1-ylmethyl ester (Example 65, 0.607 g, 1.684 mmol) and dichloromethane (10 mL) and cooled to –78 °C. DIBAL-H (1M in hexane, 4.21 mL, 4.21 mmol) is added and the mixture is stirred at –78 °C for 1 h. The reaction is quenched with MeOH (1 mL) and then washed with saturated aqueous sodium potassium tartrate and extracted with ethyl acetate. The organic layer is dried over sodium sulfate and concentrated *in vacuo*, to give a residue which is purified by silica gel flash chromatography (heptane-ethyl acetate, 3:7) to afford (5-chloro-3-methyl-2-pyridin-3-yl-indol-1-yl)-methanol as a white color solid. ^{1}H NMR (400 MHz, MeOD) δ ppm 2.27 (s, 3 H), 5.46 (s, 2 H), 7.25 (dd, *J*=8.6, 2.0 Hz, 1 H), 7.55 (s, 1 H), 7.58 (s, 1 H), 7.59 (d, *J*=2.0 Hz, 1 H), 7.62 - 7.67 (m, 1 H), 8.08 (dt, *J*=8.1, 2.0, 1.8 Hz, 1 H), 8.66 (dd, *J*=4.9, 1.6 Hz, 1 H), 8.75 (d, *J*=1.3 Hz, 1 H). HRMS (ESI) m/z 273.0807 [(M+H)$^+$ Calcd for $C_{15}H_{14}ClN_2O$: 273.0795].

Example 67

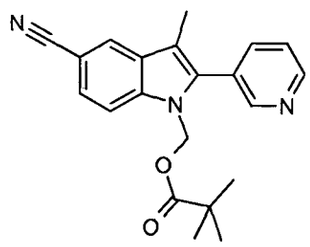
2-(5-Cyano-3-methyl-2-pyridin-3-yl-indol-1-yl)-methanol



A mixture of 5-cyano-3-methyl-2-pyridin-3-yl-indole (Example 6, 0.200 g, 0.587 mmol) in formaldehyde (4.0 mL) is refluxed for 5 h. The reaction is cooled to room temperature, diluted with ethyl acetate and washed with water. The organic layer is dried over sodium sulfate and concentrated *in vacuo*, to give a residue which is purified by silica gel flash chromatography (dichloromethane-acetonitrile, 7:3) and further purified by reverse phase HPLC with an Xbridge Shield RP18 column and a gradient of 0.1% aqueous TFA in acetonitrile to afford 2-(5-cyano-3-methyl-2-pyridin-3-yl-indol-1-yl)-methanol as the trifluoroacetate salt. ^{1}H NMR (400 MHz, MeOD) δ ppm (TFA salt) 2.37 (s, 3 H), 5.54 (s, 2 H), 7.61 (dd, *J*=8.6, 1.5 Hz, 1 H), 7.78 (d, *J*=8.6 Hz, 1 H), 8.01 (dd, *J*=7.3, 5.3 Hz, 1 H), 8.12 (d, *J*=1.0 Hz, 1 H), 8.54 (dt, *J*=7.9, 1.9 Hz, 1 H), 8.85 (dd, *J*=5.4, 1.4 Hz, 1 H), 9.01 (d, *J*=1.5 Hz, 1 H). HRMS (ESI) m/z 264.1134 [$(M+H)^+$ Calcd for $C_{16}H_{14}N_3O$: 264.1137].

Example 68

2,2-Dimethyl-propionic acid 5-cyano-3-methyl-2-pyridin-3-yl-indol-1-ylmethyl ester

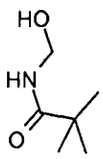


A flask is charged with 3-methyl-2-pyridin-3-yl-1H-indole-5-carbonitrile (Example 6, 0.200 g, 0.856 mmol) and DMF (10 mL). The mixture is cooled to 0 °C and 60% NaH in mineral oil (0.086g, 2.14 mmol) is added. The mixture is stirred at room temperature for 20 min followed by addition of 2,2-dimethyl-propionic acid chloromethyl ester (0.310 mL, 2.14 mmol). After stirring at room temperature for 1.5 h, the mixture is diluted with ethyl acetate and washed with water. The organic layer is dried over sodium sulfate and concentrated *in vacuo*. The residue is purified by reverse phase HPLC with Xbridge Shield RP18 column and a 0.1% aqueous NH_4OH in acetonitrile gradient to afford 2,2-

dimethyl-propionic acid 5-cyano-3-methyl-2-pyridin-3-yl-indol-1-ylmethyl ester product as a white solid. ^{1}H NMR (400 MHz, MeOD) δ ppm 1.12 (s, 9 H), 2.31 (s, 3 H), 6.10 (s, 2 H), 7.62 (dd, *J*=8.5, 1.6 Hz, 1 H), 7.68 (ddd, *J*=7.9, 5.0, 0.8 Hz, 1 H), 7.81 (d, *J*=8.6 Hz, 1 H), 8.04 (dt, *J*=8.1, 2.0, 1.8 Hz, 1 H), 8.09 (d, *J*=1.0 Hz, 1 H), 8.66 - 8.76 (m, 2 H). HRMS (ESI) m/z 348.1700 [$(M+H)^+$ Calcd for $C_{21}H_{22}N_3O_2$: 348.1712].

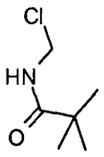
Example 69

(a) *N*-Hydroxymethyl-2,2-dimethyl-propionamide



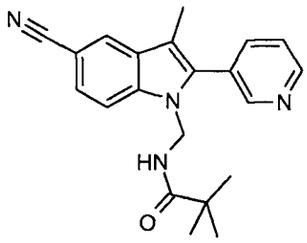
A flask is charged with 2,2-dimethyl-propionamide (1.00 g, 9.98 mmol), p-formaldehyde (0.736 g, 9.98 mmol), and potassium carbonate (0.054 g, 3.95 mmol). The reaction mixture is stirred at 75 °C for 16 h, whereupon it is cooled to room temperature and diluted with acetone. Filtration and concentration of the filtrate give a residue which is purified by silica gel flash chromatography (heptane-ethyl acetate, 4:1) to afford *N*-hydroxymethyl-2,2-dimethyl-propionamide as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 1.25 (s, 9 H), 4.73 (d, *J*=7.1 Hz, 2 H).

(b) *N*-Chloromethyl-2,2-dimethyl-propionamide



A flask is charged with *N*-hydroxymethyl-2,2-dimethyl-propionamide (0.500 g, 3.81 mmol) and dichloromethane (4 mL). Oxalyl chloride (0.8 mL, 9.52 mmol) is added and the reaction mixture is stirred at room temperature for 2 h. Concentration *in vacuo* gives *N*-chloromethyl-2,2-dimethyl-propionamide as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 1.23 (s, 9 H), 5.31 (s, 2 H).

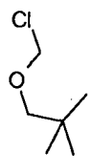
(c) *N*-(5-Cyano-3-methyl-2-pyridin-3-yl-indol-1-ylmethyl)-2,2-dimethyl-propionamide



N-Chloromethyl-2,2-dimethyl-propionamide and 3-methyl-2-pyridin-3-yl-1H-indole-5-carbonitrile (Example 6) are processed according to the method described in Example 68 to give *N*-(5-cyano-3-methyl-2-pyridin-3-yl-indol-1-ylmethyl)-2,2-dimethyl-propionamide. ^{1}H NMR (400 MHz, MeOD) δ ppm 1.06 (s, 9 H), 2.27 (s, 3 H), 5.54 (s, 2 H), 7.55 (dd, *J*=8.6, 1.8 Hz, 1 H), 7.66 (ddd, *J*=7.9, 5.0, 1.0 Hz, 1 H), 7.81 (d, *J*=8.6 Hz, 1 H), 8.01 - 8.09 (m, 2 H), 8.65 - 8.73 (m, 2 H). HRMS (ESI) m/z 347.1863 [(M+H)$^+$ Calcd for $C_{21}H_{23}N_4O$: 347.1872].

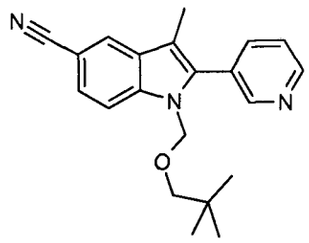
Example 70

(a) 1-Chloromethoxy-2,2-dimethyl-propane



A 2-neck flask is charged with formaldehyde (1.1 g, 36.8 mmol), 2,2-dimethyl-propan-1-ol (2.5 g, 28.3 mmol) and toluene (50 mL). The reaction mixture is cooled to –20 °C and HCl gas is bubbled through for 30 min. Sodium sulfate (5.9 g) is added to the reaction mixture, which is then stirred at –10 °C overnight, warmed to 0 °C and stirred for another 5 h. The solids are filtered off and the filtrate is concentrated *in vacuo* to afford 1-chloromethoxy-2,2-dimethyl-propane as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 0.95 (s, 9 H), 3.36 (s, 2 H), 5.54 (s, 2 H).

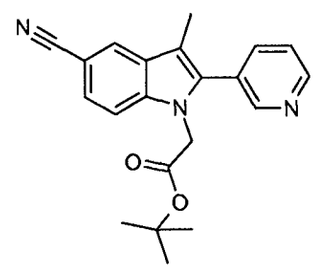
(b) 1-(2,2-Dimethyl-propoxymethyl)-3-methyl-2-pyridin-3-yl-1H-indole-5-carbonitrile



3-Methyl-2-pyridin-3-yl-1H-indole-5-carbonitrile (Example 6) and 1-chloromethoxy-2,2-dimethyl-propane are processed according to the method described in Example 68 to give 1-(2,2-dimethyl-propoxymethyl)-3-methyl-2-pyridin-3-yl-1H-indole-5-carbonitrile. ^{1}H NMR (400 MHz, MeOD) δ ppm 0.84 (s, 9 H), 2.33 (s, 3 H), 3.04 (s, 2 H), 5.48 (s, 2 H), 7.59 (dd, *J*=8.6, 1.5 Hz, 1 H), 7.66 (ddd, *J*=8.0, 4.9, 1.0 Hz, 1 H), 7.77 (dd, *J*=8.6, 0.5 Hz, 1 H), 8.07 (dt, *J*=7.8, 1.9 Hz, 1 H), 8.09 (dd, *J*=1.5, 0.8 Hz, 1 H), 8.70 (dd, *J*=4.9, 1.6 Hz, 1 H), 8.75 (dd, *J*=2.3, 0.8 Hz, 1 H). HRMS (ESI) m/z 334.1914 [$(M+H)^+$ Calcd for $C_{21}H_{24}N_3O$: 334.1919].

Example 71

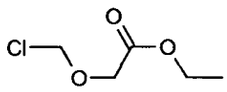
(5-Cyano-3-methyl-2-pyridin-3-yl-indol-1-yl)-acetic acid tert-butyl ester



3-Methyl-2-pyridin-3-yl-1H-indole-5-carbonitrile (Example 6) and tert-butyl bromoacetate are processed according to the method described in Example 68 to give (5-cyano-3-methyl-2-pyridin-3-yl-indol-1-yl)-acetic acid tert-butyl ester. ^{1}H NMR (400 MHz, MeOD) δ ppm 1.38 (s, 9 H), 2.31 (s, 3 H), 4.83 (s, 2 H), 7.56 (d, *J*=1.3 Hz, 2 H), 7.66 (ddd, *J*=7.8, 4.9, 0.9 Hz, 1 H), 7.95 (dt, *J*=7.8, 1.9 Hz, 1 H), 8.09 (s, 1 H), 8.63 (d, *J*=1.3 Hz, 1 H), 8.71 (dd, *J*=4.9, 1.6 Hz, 1 H). HRMS (ESI) m/z 348.1719 [$(M+H)^+$ Calcd for $C_{21}H_{22}N_3O_2$: 348.1712].

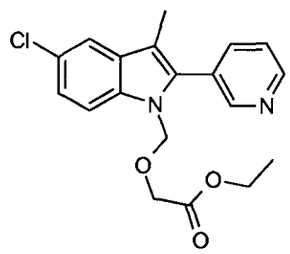
Example 72

(a) Chloromethoxy-acetic acid ethyl ester



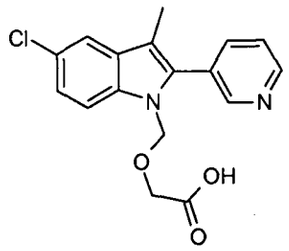
Chloromethoxy-acetic acid ethyl ester is prepared according to the method described in *Heterocycles* 2005, *65*, 1967. A 2-neck flask is charged with formaldehyde (0.747 g, 24.9 mol), hydroxy-acetic acid ethyl ester (2.0 g, 19.2 mmol) and toluene (50 mL). The reaction mixture is cooled to –20 °C, and HCl gas is bubbled through it for 30 min. Sodium sulfate (4 g) is added to the reaction mixture, which is then stirred at –10 °C overnight, warmed to 0 °C and stirred for another 5 h. The solids are filtered off and the filtrate is concentrated *in vacuo* to afford chloromethoxy-acetic acid ethyl ester as a colorless oil.

(b) (5-Chloro-3-methyl-2-pyridin-3-yl-indol-1-ylmethoxy)-acetic acid ethyl ester



A flask is charged with 5-chloro-3-methyl-2-pyridin-3-yl-1H-indole hydrochloride (Example 2) (0.930 g, 3.33 mmol) in THF (20 mL) and cooled to 0 °C. KHMDS (0.5 M in toluene, 16.65 mL, 8.32 mmol) is added and the mixture is stirred at room temperature for 30 min, followed by addition of chloromethoxy-acetic acid ethyl ester (1.27 g, 8.32 mmol). The reaction mixture is stirred for 3 h, then washed with water and extracted with ethyl acetate. The organic layer is dried over sodium sulfate and concentrated *in vacuo* to give a residue which is purified by silica gel flash chromatography (dichloromethane-methanol, 19:1) to afford (5-chloro-3-methyl-2-pyridinyl-indol-1-ylmethoxy)-acetic acid ethyl ester as a solid. MS (ESI) *m/z* 359.2 $(M+H)^+$.

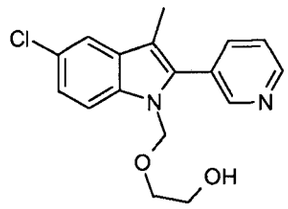
(c) (5-Chloro-3-methyl-2-pyridin-3-yl-indol-1-ylmethoxy)-acetic acid



A flask is charged with (5-chloro-3-methyl-2-pyridinyl-indol-1-ylmethoxy)-acetic acid ethyl ester (0.622 g, 1.737 mmol) in MeOH (10 mL). Aqueous lithium hydroxide (1M, 4.34 mL, 4.34 mmol) is added and the mixture is stirred at room temperature for 1.5 h. The reaction mixture is acidified to pH 1 using 1M aqueous HCl. The precipitate is filtered and re-crystallized in MeOH to afford (5-chloro-3-methyl-2-phenyl-indol-1-ylmethoxy)-acetic acid as a white solid. ^{1}H NMR (400 MHz, MeOD) δ ppm 2.27 (s, 3 H), 4.02 (s, 2 H), 5.54 (s, 2 H), 7.27 (dd, *J*=8.8, 2.0 Hz, 1 H), 7.59 - 7.68 (m, 3 H), 8.10 (ddd, *J*=8.0, 1.9, 1.8 Hz, 1 H), 8.67 (dd, *J*=4.9, 1.6 Hz, 1 H), 8.74 (d, *J*=1.5 Hz, 1 H). HRMS (ESI) m/z 331.0849 [(M+H)$^+$ Calcd for $C_{17}H_{16}ClN_2O_3$: 331.0849].

Example 73

2-(5-Chloro-3-methyl-2-pyridin-3-yl-indol-1-ylmethoxy)-ethanol

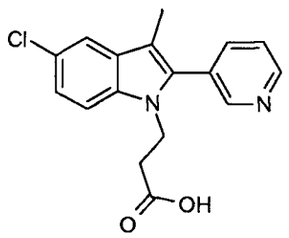


A flask is charged with (5-chloro-3-methyl-2-pyridin-3-yl-indol-1-ylmethoxy)-acetic acid ethyl ester (Example 72b, 1.00 g, 2.79 mmol) and THF (10 mL). The reaction mixture is cooled to 0 °C and lithium aluminum hydride (1M in THF, 6.98 mL, 6.98 mmol) is added. After stirring for 1 h at room temperature, the mixture is quenched with water (0.3 mL), followed with 16% aqueous NaOH (0.3 mL). Water (1 mL) is added and stirring is continued for 10 min. The solids are filtered off and the filtrate is concentrated *in vacuo*. The residue is purified by silica gel flash chromatography (dichloromethane-acetonitrile, 3:1), followed by a purification on Chiralcel® IA column (heptane-EtOH, 9:1) to afford 2-(5-chloro-3-methyl-2-pyridin-3-yl-indol-1-ylmethoxy)-ethanol as a white solid. ^{1}H NMR (400 MHz, MeOD) δ ppm 2.27 (s, 3 H), 3.42 - 3.49 (m, 2 H), 3.60 (t, *J*=4.8 Hz, 2 H), 5.47 (s, 2 H), 7.27 (dd, *J*=8.7, 1.9 Hz, 1 H), 7.57 - 7.62 (m, 2 H), 7.64 (dd, *J*=8.0, 4.9 Hz, 1 H),

8.10 (dt, *J*=7.8, 1.9 Hz, 1 H), 8.66 (dd, *J*=4.9, 1.6 Hz, 1 H), 8.74 (d, *J*=1.3 Hz, 1 H). HRMS (ESI) m/z 317.1056 [$(M+H)^+$ Calcd for $C_{17}H_{17}ClN_2O_2$: 317.1507].

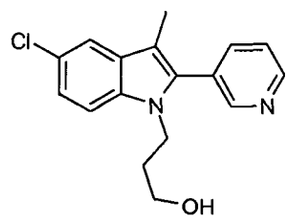
Example 74

(a) 3-(5-Chloro-3-methyl-2-pyridin-3-yl-indol-1-yl)-propionic acid



A flask is charged with 5-chloro-3-methyl-2-pyridin-3-yl-1H-indole hydrochloride (Example 2, 0.700 g, 2.50 mmol) in DMF (7 mL) and cooled to 0 °C. Potassium tert-butoxide (0.740 mg, 6.26 mmol) is added and the mixture is stirred at room temperature for 30 min, then lowered back into the ice bath. Acrylic acid methyl ester (0.680 mL, 7.52 mmol) is added, and the reaction mixture is stirred for 1.5 h. The reaction mixture is acidified to pH 1 using 1M aqueous HCl and extracted with ethyl acetate. The organic layer is dried over sodium sulfate and concentrated *in vacuo* to give a residue which is purified by silica gel flash chromatography (dichloromethane-methanol, 9:1) to afford 3-(5-chloro-3-methyl-2-pyridinyl-indol-1-yl)-propionic acid as a white solid. MS (ESI) *m/z* 315.18 $(M+H)^+$

(b) 3-(5-Chloro-3-methyl-2-pyridin-3-yl-indol-1-yl)-propan-1-ol

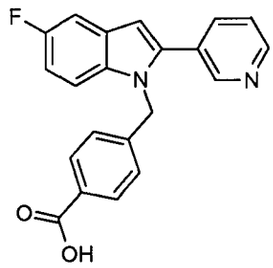


A flask is charged with 3-(5-chloro-3-methyl-2-pyridinyl-indol-1-yl)-propionic acid (0.344 g, 1.09 mmol) and THF (10 mL). The reaction mixture is cooled to 0 °C and LAH (1M in THF, 2.73 mL, 2.73 mmol) is added. After stirring at room temperature for 30 min, the mixture is cooled to 0 °C, quenched with aqueous $NaHCO_3$ and extracted with ethyl acetate. The organic layer is dried over sodium sulfate and concentrated *in vacuo* to give a residue which is purified by silica gel flash chromatography (dichloromethane-

methanol, 19:1) to afford 3-(5-chloro-3-methyl-2-pyridinyl-indol-1-yl)-propan-1-ol as a white solid. ^{1}H NMR (400 MHz, MeOD) δ ppm 1.71 - 1.82 (m, 2 H), 2.23 (s, 3 H), 3.38 (t, *J*=6.1 Hz, 2 H), 4.18 - 4.24 (m, 2 H), 7.21 (dd, *J*=8.8, 2.0 Hz, 1 H), 7.49 (d, *J*=8.6 Hz, 1 H), 7.57 (d, *J*=1.8 Hz, 1 H), 7.65 (ddd, *J*=7.9, 5.0, 1.0 Hz, 1 H), 7.98 (ddd, *J*=8.1, 2.0, 1.8 Hz, 1 H), 8.65 (dd, *J*=2.3, 0.8 Hz, 1 H), 8.67 (dd, *J*=5.1, 1.8 Hz, 1 H). HRMS (ESI) m/z 301.1108 [(M+H)$^+$ Calcd for $C_{17}H_{18}ClN_2O$: 301.1108].

Example 75

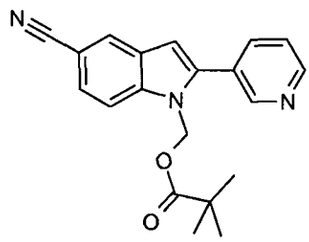
4-(5-Fluoro-2-pyridin-3-yl-indol-1-ylmethyl)-benzoic acid



A flask is charged with NaH (0.284 g, 7.093 mmol) and DMSO (1.5 mL). 5-Fluoro-2-pyridin-3-yl-indole (Example 7, 0.112 g, 0.507 mmol) in DMSO (0.5 mL) is added. The flask and syringes are rinsed with DMSO (2 times 0.5 mL). After 10 min, ethyl 4-(bromomethyl)benzoate (0.192 g, 0.760 mmol) is added neat. After 10 min, water is added. The resulting precipitate is filtered through a sintered funnel and washed with water and dichloromethane to give 4-(5-fluoro-2-pyridin-3-yl-indol-1-ylmethyl)-benzoic acid as an off-white solid. ^{1}H NMR (400 MHz, MeOD) δ ppm (sodium salt) 5.49 (s, 2 H), 6.77 (s, 1 H), 6.92 (d, *J*=8.1 Hz, 2 H), 6.95 - 7.00 (m, 1 H), 7.31 - 7.37 (m, 2 H), 7.49 (dd, *J*=7.7, 5.2 Hz, 1 H), 7.85 (d, *J*=8.1 Hz, 2 H), 7.87 - 7.92 (m, 1 H), 8.56 (dd, *J*=4.9, 1.5 Hz, 1 H), 8.68 (d, *J*=1.5 Hz, 1 H). HRMS (ESI) m/z 347.1212 [(M+H)$^+$ Calcd for $C_{21}H_{16}FN_2O_2$: 347.1196].

Example 76

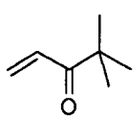
2,2-Dimethyl-propionic acid 5-cyano-2-pyridin-3-yl-indol-1-ylmethyl ester



To a solution of 2-pyridin-3-yl-1H-indole-5-carbonitrile (Example 8, 210 mg, 1.37 mmol) in THF (20 mL) at room temperature is added 0.5 M KHMDS in toluene (4.1 mL, 2.05 mmol). After 30 min, chloromethyl pivalate (510 mg, 3.08 mmol) is added. The mixture is stirred under N_2 for 1 h. Saturated aqueous sodium bicarbonate (0.5 mL) is added to quench the reaction. Silica gel is added to the mixture and the solvents are removed *in vacuo*. The residue is purified by silica gel flash chromatography (ethyl acetate-heptane, 0:1 to 1:0). Further purification by HPLC using an Xbridge RP18 with a gradient of 0.1% aqueous ammonium hydroxide in acetonitrile gives 2,2-dimethyl-propionic acid 5-cyano-2-pyridin-3-yl-indol-1-ylmethyl ester as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 1.20 (s, 9 H), 6.08 (s, 2 H), 6.77 (s, 1 H), 7.49 (ddd, *J*=7.8, 4.8, 0.8 Hz, 1 H), 7.56 (dd, *J*=8.6, 1.8 Hz, 1 H), 7.68 (d, *J*=8.6 Hz, 1 H), 7.94 (ddd, *J*=7.9, 2.0 Hz, 1 H), 8.01 (dd, *J*=1.5, 0.5 Hz, 1 H), 8.75 (dd, *J*=4.8, 1.8 Hz, 1 H), 8.87 (d, *J*=1.5 Hz, 1 H). HRMS (ESI) m/z 334.1566 [$(M+H)^+$ Calcd for $C_{20}H_{20}N_3O_2$: 334.1556].

Example 77

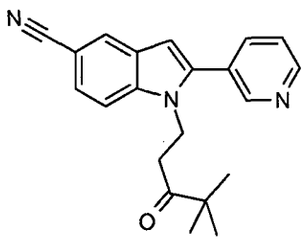
(a) 4,4-Dimethyl-pent-1-en-3-one



This procedure is adapted from *Tetrahedron Lett.* 1978, *32*, 2955. A flask is charged with 3,3-dimethyl-butan-2-one (1.00 g, 9.98 mmol), *p*-formaldehyde (1.34 g, 44.9 mmol), *N*-methylanilinium trifluoroacetate (3.31 g, 14.9 mmol) and THF (10 mL). The reaction mixture is refluxed for 16 h, followed by addition of additional quantities of *p*-formaldehyde (0.674 g, 22.45 mmol), and *N*-methylanilinium trifluoroacetate (1.64 g, 7.48 mmol). After another 5.5 h at reflux, the mixture is cooled to room temperature and pentane (20 mL) is added. A brown oil collects at the bottom of the flask. The supernatant is removed and pentane (25 mL) is added. After decantation, the supernatant is removed. The supernatants are combined and concentrated *in vacuo* to

afford 4,4-dimethyl-pent-1-en-3-one as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 1.18 (s, 9 H), 5.68 (dd, *J*=10.4, 2.0 Hz, 1 H), 6.36 (dd, *J*=16.9, 2.0 Hz, 1 H), 6.83 (dd, *J*=16.9, 10.4 Hz, 1 H).

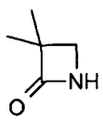
(b) 1-(4,4-Dimethyl-3-oxo-pentyl)-2-pyridin-3-yl-1H-indole-5-carbonitrile



To a solution of 2-pyridin-3-yl-1H-indole-5-carbonitrile (Example 8, 0.225 g, 1.026 mmol) in DMSO (5 mL) is added potassium tert-butoxide (0.182 g, 1.53 mmol) and the mixture is stirred at room temperature for 0.5 h. 4,4-Dimethyl-pent-1-en-3-one (0.345 g, 3.078 mmol) is added and the mixture is stirred at 50 °C overnight. Dilution with ethyl acetate gives a solution which is washed with water twice, dried over sodium sulfate and concentrated *in vacuo*. The residue is purified by Xbridge Shield RP18 with a gradient of acetonitrile in 0.1% NH_4OH to give an oil. Addition of diethyl ether and a few drops of concentrated HCl, followed by lyophilization affords 1-(4,4-dimethyl-3-oxo-pentyl)-2-pyridin-3-yl-1H-indole-5-carbonitrile as a light yellow color solid. ^{1}H NMR (400 MHz, MeOD) δ ppm (HCl salt) 0.90 (s, 9 H), 2.94 (t, *J*=6.4 Hz, 2 H), 4.61 (t, *J*=6.6 Hz, 2 H), 6.88 (s, 1 H), 7.59 (dd, *J*=8.7, 1.6 Hz, 1 H), 7.77 (d, *J*=8.6 Hz, 1 H), 7.93 (dd, *J*=8.0, 5.4 Hz, 1 H), 8.10 (d, *J*=1.0 Hz, 1 H), 8.44 (dt, *J*=7.9, 1.7 Hz, 1 H), 8.82 (dd, *J*=5.3, 1.3 Hz, 1 H), 8.96 (d, *J*=1.8 Hz, 1 H). HRMS (ESI) m/z 332.1762 [$(M+H)^+$ Calcd for $C_{21}H_{22}N_3O$: 332.1763].

Example 78

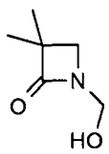
(a) 3,3-dimethyl-azetidin-2-one



A 250 mL Parr glass vessel is charged with Rh/Al_2O_3 (2.33 g, 1.13 mmol) and ethyl 2,2-dimethylcyanoacetate (2.0 g) dissolved in ethanol (90 mL). The flask is evacuated and filled with hydrogen (50 psi) and the mixture is shaken under 50 psi of hydrogen. After 48

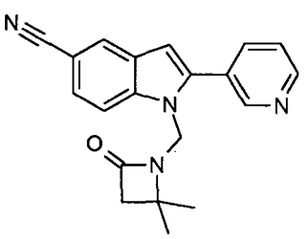
h, the mixture is filtered and concentrated *in vacuo* (50 Torr, 35 °C, 30 min) to give a crude mixture which is dissolved in anhydrous ether (60 mL) under nitrogen and cooled to 0 °C. LHMDS (1.0M in THF, 10 mL, 10 mmol) is added dropwise and the cooling bath is removed. After 2 h, the mixture is cooled to 0 °C and quenched with 1M aqueous sodium bisulfate and diluted with ether. The organic phase is washed with 1M aqueous sodium bisulfate and brine. The pH of the combined aqueous phase is adjusted to 14 with 4M aqueous sodium hydroxide and the aqueous phase is repeatedly extracted with dichloromethane. The dichloromethane phase is dried over magnesium sulfate, filtered and concentrated *in vacuo* to give a residue which is purified by silica gel flash chromatography (ethyl acetate) to give 3,3-dimethyl-azetidin-2-one as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 1.34 (s, 6 H), 3.13 (s, 2 H).

(b) 1-hydroxymethyl-3,3-dimethyl-azetidin-2-one



A flask is charged with 3,3-dimethyl-azetidin-2-one (0.159 g, 1.524 mmol), aqueous formaldehyde (37% wt., 0.124 g, 1.524 mmol) and crushed potassium carbonate (0.009 g, 0.061 mmol). The flask is lowered in a pre-heated oil bath (75 °C). After 15 min, the flask is removed from the oil bath and allowed to stand at room temperature. After 2 h, the mixture is taken up in acetone, dried over magnesium sulfate and filtered through a plug of silica gel. Concentration *in vacuo* (30 °C, 40 Torr) gives 1-hydroxymethyl-3,3-dimethyl-azetidin-2-one, which is used in the next step without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 1.32 (s, 6 H), 3.23 (s, 2 H), 4.69 (d, *J*=7.5 Hz, 2 H).

(c) 1-(3,3-dimethyl-2-oxo-azetidin-1-ylmethyl)-2-pyridin-3-yl-1H-indole-5-carbonitrile

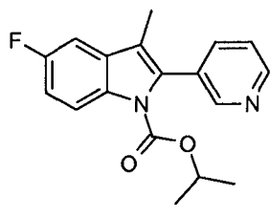


A flask is charged with 1-hydroxymethyl-3,3-dimethyl-azetidin-2-one (0.179 g, 1.317 mmol) and dichloromethane (5 mL), and thionyl chloride (0.63 g, 5.27 mmol) is added.

The mixture is stirred at room temperature overnight and concentrated *in vacuo* to yield an oil, which is redissolved in DMF (0.8 mL). 2-Pyridin-3-yl-1H-indole-5-carbonitrile (Example 8, 0.213 g, 0.922 mmol) is dissolved in DMF (5 mL), cooled to 0 °C, and NaH (0.053 g, 1.317 mmol) is added portionwise. After 30 min, the chloride solution is added. After 1 h, NaH (0.027 g, 0.67 mmol) is added and the mixture is stirred overnight. The mixture is quenched with a few drops of water and diluted with methanol and DMSO. The mixture is purified on Xbridge C18 eluting with a 9:1 to 1:9 water-acetonitrile gradient to give 1-(3,3-dimethyl-2-oxo-azetidin-1-ylmethyl)-2-pyridin-3-yl-1H-indole-5-carbonitrile. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 1.18 (s, 6 H), 2.82 (s, 2 H), 5.47 (s, 2 H), 6.71 (s, 1 H), 7.47 - 7.51 (m, 1 H), 7.56 (dd, *J*=8.6, 1.5 Hz, 1 H), 7.73 (d, *J*=8.6 Hz, 1 H), 7.80 - 7.83 (m, 1 H), 8.01 (d, *J*=1.5 Hz, 1 H), 8.75 - 8.76 (m, 2 H). HRMS (ESI) m/z 331.1558 [$(M+H)^+$ Calcd for $C_{20}H_{19}N_4O$: 331.1559].

Example 79

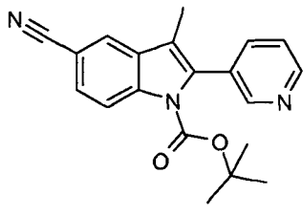
5-Fluoro-3-methyl-2-pyridin-3-yl-indole-1-carboxylic acid isopropyl ester



5-Fluoro-3-methyl-2-pyridin-3-yl-indole (Example 3, 0.246 g, 1.044 mmol) is dissolved in DMF (9 mL). NaH (60%, 0.054 g, 1.357 mmol) is added and the mixture is stirred for 1 h, whereupon isopropylchloroformate (1.0M in toluene 2.1 mL, 2.1 mmol) is added. The mixture is stirred overnight, quenched with saturated aqueous sodium bicarbonate and extracted with ethyl acetate. The organic phase is dried over $MgSO_4$ and concentrated *in vacuo* to give a residue, which is purified by silica gel flash chromatography (ethyl acetate-heptane, 1:4 to 2:3) to give 5-fluoro-3-methyl-2-pyridin-3-yl-indole-1-carboxylic acid isopropyl ester as a pale yellow solid. ^{1}H NMR (400 MHz, MeOD) δ ppm 1.07 (d, *J*=6.3 Hz, 6 H), 2.12 (s, 3 H), 4.93 - 5.04 (m, 1 H), 7.09 - 7.17 (m, 1 H), 7.30 (dd, *J*=8.8, 2.3 Hz, 1 H), 7.54 - 7.59 (m, 1 H), 7.84 - 7.89 (m, 1 H), 8.23 (dd, *J*=9.1, 4.5 Hz, 1 H), 8.53 - 8.56 (m, 1 H), 8.61 (dd, *J*=4.5, 1.6 Hz, 1 H). HRMS (ESI) m/z 313.1353 [$(M+H)^+$ Calcd for $C_{18}H_{18}FN_2O_2$: 313.1352].

Example 80

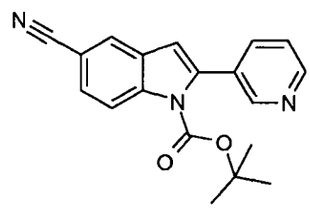
5-Cyano-3-methyl-2-pyridin-3-yl-indole-1-carboxylic acid tert-butyl ester



To a solution of 3-methyl-2-pyridin-3-yl-1H-indole-5-carbonitrile (Example 6, 96 mg, 0.40 mmol) in DMF (2 mL) at room temperature is added triethylamine (30 mg, 0.30 mmol), di-tert-butyl carbonate (65 mg, 0.30 mmol) and 4-(*N*,*N*-dimethylamino)pyridine (2 mg, 0.020 mmol). The mixture is stirred under N_2. The mixture is purified by Xbridge RP18 with a gradient of acetonitrile in 0.1% aqueous ammonium hydroxide to give 5-cyano-3-methyl-2-pyridin-3-yl-indole-1-carboxylic acid tert-butyl ester as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 1.30 (s, 9 H), 2.16 (s, 3 H), 7.47 - 7.55 (m, 1 H), 7.65 (dd, *J*=8.7, 1.6 Hz, 1 H), 7.76 (d, *J*=7.3 Hz, 1 H), 7.90 (d, *J*=1.0 Hz, 1 H), 8.35 (d, *J*=8.6 Hz, 1 H), 8.63 (d, *J*=1.8 Hz, 1 H), 8.69 (dd, *J*=5.1, 1.5 Hz, 1 H). HRMS (ESI) m/z 334.1566 [$(M+H)^+$ Calcd for $C_{20}H_{20}N_3O_2$: 334.1556].

Example 81

5-Cyano-2-pyridin-3-yl-indole-1-carboxylic acid tert-butyl ester

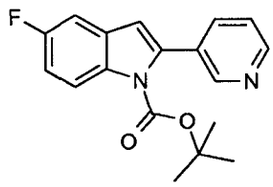


A mixture of 1-Boc-5-cyanoindole-2-boronic acid (339 mg, 1.19 mmol), 3-bromo-pyridine (150 mg, 93 uL, 0.95 mmol), aqueous sodium carbonate (2M, 0.95 mL, 1.9 mmol) and DME (4 mL) is degassed with nitrogen and PS-Pd(PPh_3) (285 mg, 0.11 mmol/g, 0.028 mmol) is added. The resulting mixture is then heated in the microwave at 120 °C for 20 min and at 130 °C for 25 min (three times). The reaction mixture is filtered through a sintered funnel and washed with dichloromethane (50 mL). The filtrate is dried over Na_2SO_4, filtered, and concentrated. The residue is purified by reverse phase HPLC (5 to 80% acetonitrile- 0.1% aqueous ammonia) to give 5-cyano-2-pyridin-3-yl-indole-1-carboxylic acid tert-butyl ester as a solid. ^{1}H NMR (400.3 MHz, $CDCl_3$) δ ppm 1.34 (s, 9H), 6.67 (s, 1H), 7.39 (dd, J = 4.9, 7.8 Hz, 1 H), 7.61 (dd, J= 1.6, 8.7 Hz, 1 H), 7.74 (m,

1 H), 7.92 (s, 1 H), 8.35 (d, J = 8.7 Hz, 1H), 8.65 (dd, J = 1.6 Hz, 4.9 Hz, 1 H), 8.69 (d, J = 2.2 Hz, 1 H). MS (ESI) *m/z* 320 $(M+H)^+$.

Example 82

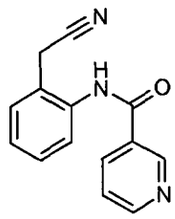
5-Fluoro-2-pyridin-3-yl-indole-1-carboxylic acid tert-butyl ester



To a solution of 5-fluoro-2-pyridin-3-yl-indole (Example 3, 0.100 g, 0.452 mmol) in DMF (1 mL) is added triethylamine (0.083 g, 0.814 mmol), DMAP (0.006 g, 0.045 mmol) and di-tert-butyl carbonate (0.120 g, 0.543 mmol). After 15 h, the mixture is diluted with ethyl acetate and washed with water. The organic phase is dried over $MgSO_4$, filtered and the filtrate is concentrated *in vacuo* to give a residue which is purified by silica gel chromatography (heptane-ethyl acetate, 9:1 to 4:1) to give 5-fluoro-2-pyridin-3-yl-indole-1-carboxylic acid tert-butyl ester as a yellow oil. Trituration with ether and heptane, followed by standing for several days affords a solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 1.35 (s, 9 H), 6.58 (s, 1 H), 7.07 - 7.12 (m, 1 H), 7.23 (dd, *J*=8.6, 2.5 Hz, 1 H), 7.36 (dd, *J*=7.8, 5.1 Hz, 1 H), 7.72 - 7.75 (m, 1 H), 8.21 (dd, *J*=9.1, 4.9 Hz, 1 H), 8.62 (dd, *J*=4.9, 1.5 Hz, 1 H), 8.69 (d, *J*=1.5 Hz, 1 H). MS (ESI) *m/z* 313 $(M+H)^+$.

Example 83

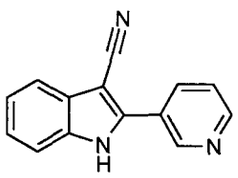
(a) N-(2-Cyanomethyl-phenyl)-nicotinamide



2-aminophenylacetonitrile (5.0 g, 37.1 mmol) and nicotinoyl chloride (7.5 g, 40.8 mmol) are taken up in dry dichloromethane (200 mL) and diisopropylethylamine (12.1 g, 92.7 mmol) is added while cooling the mixture with a cold water bath. The mixture is stirred overnight, whereupon it is washed twice with saturated aqueous sodium bicarbonate. The combined aqueous layer is back-extracted with ethyl acetate. The combined organic

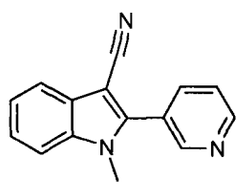
phase is dried over $MgSO_4$ and concentrated *in vacuo* to give a residue, which is purified by silica gel flash chromatography (dichloromethane-methanol, 1:0 to 19:1) to give N-(2-cyanomethyl-phenyl)-nicotinamide as an off-white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 4.02 (s, 2 H), 7.32 - 7.37 (m, 1 H), 7.39 - 7.44 (m, 2 H), 7.50 (d, *J*=7.1 Hz, 1 H), 7.59 (dd, *J*=8.1, 4.8 Hz, 1 H), 8.30 - 8.33 (m, 1 H), 8.78 (dd, *J*=4.8, 1.5 Hz, 1 H), 9.14 (d, *J*=1.8 Hz, 1 H), 10.36 (s, 1 H).

(b) 2-Pyridin-3-yl-1H-indole-3-carbonitrile



N-(2-cyanomethyl-phenyl)-nicotinamide (0.095 g, 0.384 mmol) is dissolved in DMF (3 mL). NaH (60%, 0.015 g, 0.384 mmol) is added and the mixture is heated to 130 °C. After 18 h, the mixture is cooled down, diluted with ethyl acetate, and washed with 1M aqueous sodium hydroxide. The combined washings are back-extracted with ethyl acetate. The combined organic phase is dried over magnesium sulfate, filtered and concentrated *in vacuo*. The residue is purified by silica gel flash chromatography (dichloromethane-methanol, 99:1 to 19:1) to give 2-pyridin-3-yl-1H-indole-3-carbonitrile as a brown solid. ^{1}H NMR (400 MHz, MeOD) δ ppm 7.29 - 7.32 (m, 1 H), 7.34 - 7.39 (m, 1 H), 7.57 (d, *J*=8.0 Hz, 1 H), 7.66 (dd, *J*=8.0, 4.9 Hz, 1 H), 7.70 (d, *J*=7.8 Hz, 1 H), 8.39 - 8.44 (m, 1 H), 8.68 (dd, *J*=4.8, 1.5 Hz, 1 H), 9.15 (d, *J*=1.5 Hz, 1 H).

(c) 1-Methyl-2-pyridin-3-yl-1H-indole-3-carbonitrile

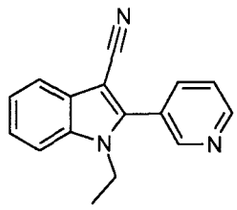


To 2-pyridin-3-yl-1H-indole-3-carbonitrile (1.0 g, 4.56 mmol) in DMF (17mL) is added 60% sodium hydride in mineral oil (547 mg, 13.68 mmol) and the suspension is stirred for 30 min. Iodomethane (971 mg, 6.84 mmol) is then added to the reaction mixture and stirred at ambient temperature for 1 h. Aqueous $NaHCO_3$ (3 mL) is added and the mixture is concentrated *in vacuo*. The residue is purified by purified by silica gel flash

chromatography (dichloromethane-methanol gradient) to give 1-methyl-2-pyridin-3-yl-1H-indole-3-carbonitrile as a white solid. ^{1}H NMR (400 MHz, MeOD) δ ppm 3.83 (s, 3 H), 7.35 (t, *J*=7.5 Hz, 1 H), 7.40 - 7.46 (m, 1 H), 7.64 (d, *J*=8.3 Hz, 1 H), 7.67 - 7.74 (m, 2 H), 8.16 (dt, *J*=8.0, 2.0, 1.9 Hz, 1 H), 8.76 (dd, *J*=5.1, 1.5 Hz, 1 H), 8.86 (d, *J*=1.5 Hz, 1 H). HRMS (ESI) m/z 234.1029 [(M+H)$^+$ Calcd for $C_{15}H_{12}N_3$: 234.1031].

Example 84

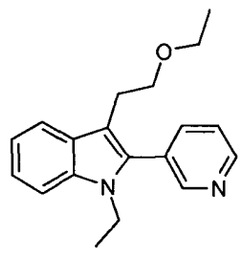
1-Ethyl-2-pyridin-3-yl-1H-indole-3-carbonitrile



To a solution of *N*-(2-cyanomethyl-phenyl)-nicotinamide (Example 83a, 400 mg, 1.69 mmol) in DMF (17 mL) is added Cs_2CO_3 (1.1 g, 3.37 mmol). The reaction is heated to 80 °C, at which time a solution of iodoethane (0.14 mL, 1.75 mmol) in DMF (5 mL) is added over 75 min. The temperature is then increased to 100 °C. After stirring for an additional 2 h, the reaction is cooled to room temperature and quenched with saturated aqueous NH_4Cl, and diluted with ethyl acetate and water. The layers are separated and the aqueous layer is extracted with ethyl acetate. The combined organic extracts are dried over sodium sulfate, filtered, and concentrated. The resulting residue is purified by silica gel flash chromatography (ethyl acetate-heptane, 3:10 to 1:0) to furnish 1-ethyl-2-pyridin-3-yl-1H-indole-3-carbonitrile. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 1.40 (t, *J*=7.2 Hz, 3 H), 4.22 (q, *J*=7.2 Hz, 2 H), 7.32 - 7.45 (m, 2 H), 7.47 - 7.51 (m, 1 H), 7.54 (dd, *J*=7.8, 5.6 Hz, 1 H), 7.82 (d, *J*=7.8 Hz, 1 H), 7.91 - 7.98 (m, 1 H), 8.78 - 8.85 (m, 2 H). HRMS (ESI) m/z 248.1190 [(M+H)$^+$ Calcd for $C_{16}H_{14}N_3$: 248.1188].

Example 85

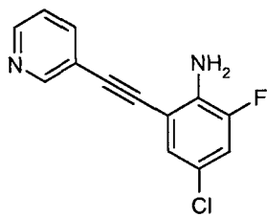
3-(2-Ethoxy-ethyl)-1-ethyl-2-pyridin-3-yl-1H-indole



To a solution of 1-ethyl-2-pyridin-3-yl-1H-indole-3-carbonitrile (Example 84, 590 mg, 2.4 mmol) in toluene (20 mL) at –60 °C is added a 1 M solution of DIBAL-H (3.6 mL, 3.6 mmol). The reaction is stirred for 1 h and kept below –40 °C. The reaction is then quenched with water (1 mL) and brought to room temperature. Anhydrous sodium sulfate (*ca.* 2 g) is then added to the reaction mixture. The reaction mixture is filtered through a plug of celite. Sulfuric acid (2M, ca. 5 mL) is added and upon complete conversion to the desired aldehyde, the reaction mixture is brought to pH 8 with the addition of Na_2CO_3, and extracted with ethyl acetate. The organic extract is washed with brine, dried over Na_2SO_4, filtered, and concentrated. The resulting 1-ethyl-2-pyridin-3-yl-1H-indole-3-carbaldehyde is used without further purification. To a solution of ethoxymethyltriphenylphosphonium chloride (0.32 g, 0.9 mmol) in THF (3 mL) is added potassium tert-butoxide (1 M in THF, 0.93 mL, 0.93 mmol). The resulting red solution is permitted to stir for 15 min, at which time a solution of 1-ethyl-2-pyridin-3-yl-1H-indole-3-carbaldehyde (75 mg, 0.3 mmol) in THF (3 mL) is added. The reaction is stirred for 1 h, quenched with saturated aqueous NH_4Cl, diluted with water and extracted with ethyl acetate. The organic extract is dried over Na_2SO_4, filtered, and concentrated. The resulting E/Z mixture of 3-(2-ethoxy-vinyl)-1-ethyl-2-pyridin-3-yl-1H-indole is then dissolved in methanol (5 mL) and 10% Pd/C (32 mg, 0.03 mmol) is added. The reaction mixture is stirred under an atmosphere of H_2 gas (balloon) for 2 h. The reaction is then filtered through a plug of celite and concentrated to dryness. The resulting residue is purified by silica gel flash chromatography (ethyl acetate-heptane, 0:1 to 2:5) to afford 3-(2-ethoxy-ethyl)-1-ethyl-2-pyridin-3-yl-1H-indole. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 1.17 (t, *J*=7.0 Hz, 3 H), 1.23 (t, *J*=7.2 Hz, 3 H), 2.94 (t, *J*=7.3 Hz, 2 H), 3.43 (q, *J*=7.1 Hz, 2 H), 3.61 (t, *J*=7.3 Hz, 2 H), 4.05 (q, *J*=7.3 Hz, 2 H), 7.19 (t, *J*=7.4 Hz, 1 H), 7.30 (t, *J*=7.1 Hz, 1 H), 7.40 (d, *J*=8.3 Hz, 1 H), 7.53 (dd, *J*=7.6, 5.1 Hz, 1 H), 7.69 (d, *J*=7.8 Hz, 1 H), 7.92 (d, *J*=7.8 Hz, 1 H), 8.72 (dd, *J*=4.9, 1.6 Hz, 1 H), 8.77 (d, *J*=1.5 Hz, 1 H). HRMS (ESI) m/z 295.1805 [$(M+H)^+$ Calcd for $C_{19}H_{23}N_2O$: 295.1810].

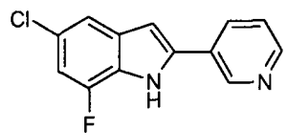
Example 86

(a) 4-Chloro-2-fluoro-6-pyridin-3-ylethynyl-phenylamine



To a mixture of 3-ethynylpyridine (1.13 g, 11 mmol) and 2-fluoro-4-chloro-6-iodoaniline (2.71 g, 10 mmol) in triethylamine (100 mL) is added $PdCl_2(PPh_3)_2$ (175 mg, 0.25 mmol) and CuI (95 mg, 0.50 mmol) and the mixture is refluxed for 1 h. The solvent is removed *in vacuo* and the residue is purified by silica gel flash chromatography (dichloromethane-methanol, 1:0 to 24:1) to give 4-chloro-2-fluoro-6-pyridin-3-ylethynyl-phenylamine. MS (ESI) *m/z* 247 $(M+H)^+$.

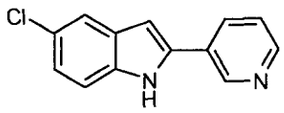
(b) 5-Chloro-7-fluoro-2-pyridin-3-yl-1H-indole



To a solution of 4-chloro-2-fluoro-6-pyridin-3-ylethynyl-phenylamine (3.1 g, 12.57 mmol) in NMP (40 mL) is added potassium tert-butoxide (2.1 g, 18.85 mmol) and the mixture is stirred overnight. Water (1 mL) is added to quench the reaction and the mixture is poured into water (100 mL). The mixture is extracted with diethyl ether five times. The combined organic phase is partially concentrated, resulting in precipitation of the product, which is filtered through a glass sintered funnel and washed with dichloromethane to afford 5-chloro-7-fluoro-2-pyridin-3-yl-1H-indole as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.10 - 7.15 (m, 2 H), 7.47 - 7.53 (m, 2 H), 8.31 (dt, *J*=8.2, 1.9, 1.8 Hz, 1 H), 8.55 (d, *J*=4.3 Hz, 1 H), 9.16 (s, 1 H), 12.23 (s, 1 H).

Example 87

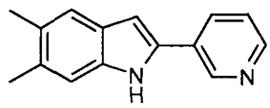
5-Chloro-2-pyridin-3-yl-1H-indole



3-Ethynylpyridine and 4-chloro-6-iodoaniline are processed according to the method described in Example 86 to give 5-chloro-2-pyridin-3-yl-1H-indole. ^{1}H NMR (400 MHz, MeOD) δ ppm 6.96 (s, 1 H), 7.14 (dd, *J*=8.6, 2.0 Hz, 1 H), 7.41 (d, *J*=8.8 Hz, 1 H), 7.54 (dd, *J*=8.0, 4.9 Hz, 1 H), 7.59 (d, *J*=2.0 Hz, 1 H), 8.25 (dt, *J*=8.0, 1.9 Hz, 1 H), 8.50 (d, *J*=4.5 Hz, 1 H), 9.02 (s, 1 H). HRMS (ESI) m/z 229.0522 [$(M+H)^+$ Calcd for $C_{13}H_{10}ClN_2$: 229.0533].

Example 88

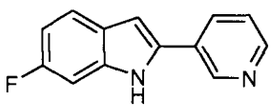
5,6-Dimethyl-2-pyridin-3-yl-1H-indole



3-Ethynylpyridine and 3,4-dimethyl-6-iodoaniline are processed according to the method described in Example 86 to give 5,6-dimethyl-2-pyridin-3-yl-1H-indole. MS (ESI) *m/z* 223.13 $(M+H)^+$.

Example 89

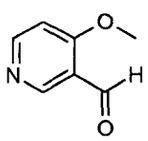
6-Fluoro-2-pyridin-3-yl-1H-indole



3-Ethynylpyridine and 3-fluoro-6-iodoaniline are processed according to the method described in Example 86 to give 6-fluoro-2-pyridin-3-yl-1H-indole. MS (ESI) m/z 213.0 $(M+H)^+$.

Example 90

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



A flask is charged with 1.7M tert-butyllithium in pentane (47.1 mL, 80.1 mmol) and THF (20 mL), and cooled to –78 °C. 2-Bromomesitylene (6.0 mL, 39 mmol) is added dropwise. The mixture is stirred for 1 h, and 4-methoxypyridine (3.0 mL, 30 mmol) is added dropwise. The mixture is warmed to –23 °C and stirred for 3 h. The mixture is

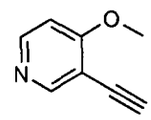
cooled again to –78 °C and dimethylformamide (3.5 mL, 45 mmol) is added. After 1 h, brine (50 mL) is added to the mixture at –78 °C and warmed to room temperature. The mixture is extracted with ether and the combined organic layer is dried over Na_2SO_4. Concentration followed by silica gel chromatography eluting with a 0 to 6% methanol-dichloromethane gradient gives 4-methoxy-pyridine-3-carbaldehyde. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 4.01 (s, 3 H), 6.94 (d, *J*=5.8 Hz, 1 H), 8.65 (d, *J*=5.8 Hz, 1 H), 8.90 (s, 1 H), 10.46 (s, 1 H).

(b) 3-(2,2-dibromo-vinyl)-4-methoxy-pyridine



A flask is charged with triphenylphosphine (21.4 g, 81.6 mmol), carbon tetrabromide (13.5 g, 40.8 mmol) and dichloromethane (300 mL). 4-Methoxy-pyridine-3-carbaldehyde (2.8 g, 20.4 mmol) in dichloromethane (300 mL) is added at 0 °C. The mixture is stirred at 0 °C for 1 h. The mixture is extracted with saturated aqueous ammonium chloride and the aqueous phase is neutralized with $NaHCO_3$ and extracted with dichloromethane. The organic phase is dried over Na_2SO_4, concentrated and purified by silica gel chromatography eluting with a 0 to 10% methanol-dichloromethane gradient to give 3-(2,2-dibromo-vinyl)-4-methoxy-pyridine. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 3.90 (s, 3 H), 6.81 (d, *J*=5.8 Hz, 1 H), 7.48 (s, 1 H), 8.48 (d, *J*=5.8 Hz, 1 H), 8.76 (s, 1 H).

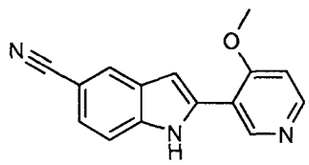
(c) 4-methoxy-3-ethynyl-pyridine



A flask is charged with 3-(2,2-dibromo-vinyl)-4-methoxy-pyridine (3.7 g, 12.63 mmol) and THF (100 mL), and 1.6 M nBuLi in pentane (17.4 mL, 27.79 mmol) is added dropwise at –78 °C. The mixture is stirred at –78 °C for 1 h before addition of saturated aqueous NH_4Cl (0.5 mL). The mixture is warmed to room temperature and poured into water (100 mL). The mixture is extracted with ethyl acetate and the combined organic phase is dried over Na_2SO_4. Concentration followed by silica gel flash chromatography eluting with a 0 to 5% methanol-dichloromethane gradient gives 4-methoxy-3-ethynyl-pyridine. ^{1}H NMR

(400 MHz, $CDCl_3$) δ ppm 3.39 (s, 1 H), 3.96 (s, 3 H), 6.82 (d, *J*=5.8 Hz, 1 H), 8.46 (d, *J*=5.8 Hz, 1 H), 8.58 (s, 1 H).

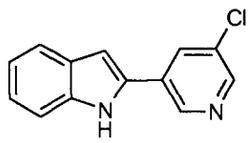
(d) 2-(4-Methoxy-pyridin-3-yl)-1H-indole-5-carbonitrile



4-Methoxy-3-ethynyl-pyridine and 4-cyano-6-iodoaniline are processed according to the method described in Example 86 to give 2-(4-methoxy-pyridin-3-yl)-1H-indole-5-carbonitrile. 2-(4-Methoxy-pyridin-3-yl)-1H-indole-5-carbonitrile is purified by HPLC using an Xbridge Shield RP18 with a gradient of acetonitrile in 0.1% NH_4OH. ^1H NMR (400 MHz, DMSO-d_6) δ ppm 4.04 (s, 3 H), 7.14 (d, *J*=1.3 Hz, 1 H), 7.25 (d, *J*=5.8 Hz, 1 H), 7.47 (dd, *J*=8.5, 1.6 Hz, 1 H), 7.61 (d, *J*=8.3 Hz, 1 H), 8.11 (s, 1 H), 8.47 (d, *J*=5.8 Hz, 1 H), 8.91 (s, 1 H), 11.91 (br. s., 1 H). HRMS (ESI) m/z 250.0968 [$(M+H)^+$ calcd for $C_{15}H_{12}N_3O$: 250.0980].

Example 91

2-(5-Chloro-pyridin-3-yl)-1H-indole

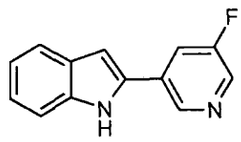


A flask is charged with N-Boc-indole-2-boronic acid (0.407 g, 1.55 mmol), 3-chloro-5-bromopyridine (0.200 g, 1.03 mmol), s-phos (0.021 g, 0.05 mmol), potassium phosphate (0.441 g, 2.07 mmol) and toluene (5 mL). The flask is evacuated and filled with N_2 thrice and $Pd_2(dba)_3$ (0.019 g, 0.02 mmol) is added. The flask is evacuated and filled with N_2 thrice. The mixture is refluxed for 1 h, then cooled to room temperature and filtered through celite. The filtrate is concentrated in vacuo to afford 2-(5-chloro-pyridin-3-yl)-indole-1-carboxylic acid tert-butyl ester as an oil. The residue is dissolved in DCM (5 mL) and trifluoroacetic acid (2 mL) is added. The reaction mixture is stirred at room temperature for 4 h, followed with quenching with a saturated sodium bicarbonate solution. Extraction with dichloromethane, drying of the organic layer over sodium sulfate and concentration *in vacuo* gives a residue which is purified by silica gel flash chromatography (heptane-ethyl acetate, 3:2) to afford 2-(5-chloro-pyridin-3-yl)-1H-indole.

^{1}H NMR (400 MHz, MeOD) δ ppm 7.06 (s, 1 H), 7.08 (d, *J*=7.8 Hz, 1 H), 7.20 (t, *J*=7.7 Hz, 1 H), 7.45 (d, *J*=8.3 Hz, 1 H), 7.61 (d, *J*=7.8 Hz, 1 H), 8.30 (t, *J*=2.1 Hz, 1 H), 8.47 (d, *J*=2.3 Hz, 1 H), 8.96 (d, *J*=1.8 Hz, 2 H). HRMS (ESI) m/z 229.0542 [(M+H)$^+$ calcd for $C_{13}H_{10}ClN_2$: 229.0533].

Example 92

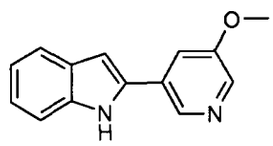
2-(5-Fluoro-pyridin-3-yl)-1H-indole



3-Fluoro-5-bromopyridine is processed according to the procedure described in Example 91 to give 2-(5-fluoro-pyridin-3-yl)-1H-indole. HRMS (ESI) m/z 213.0834 [(M+H)$^+$ Calcd for $C_{13}H_{10}N_2F$: 213.0828].

Example 93

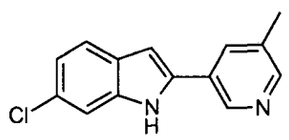
5-Methoxy-2-pyridin-3-yl-1H-indole



3-Bromopyridine and N-Boc-5-methoxy-indole-2-boronic acid are processed according to the procedure described in Example 91 to give 5-methoxy-2-pyridin-3-yl-1H-indole. HRMS (ESI) m/z 225.1026 [(M+H)$^+$ Calcd for $C_{14}H_{13}N_2O$: 225.1028]

Example 94

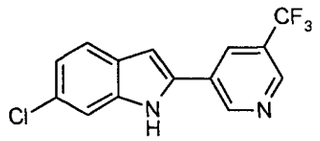
6-Chloro-2-(5-methyl-pyridin-3-yl)-1H-indole



3-Methyl-5-bromopyridine and N-Boc-6-chloro-indole-2-boronic acid are processed according to the procedure described in Example 91 to give 6-chloro-2-(5-methyl-pyridin-3-yl)-1H-indole. (ESI) *m/z* 243.0 (M+H)$^+$.

Example 95

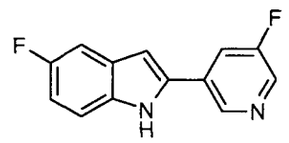
6-Chloro-2-(5-trifluoromethyl-pyridin-3-yl)-1H-indole



3-Trifluoromethyl-5-bromopyridine and N-Boc-6-chloro-indole-2-boronic acid are processed according to the procedure described in Example 91 to give 6-chloro-2-(5-trifluoromethyl-pyridin-3-yl)-1H-indole. (ESI) *m/z* 297.0 $(M+H)^+$.

Example 96

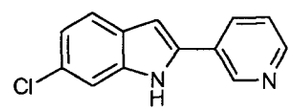
5-Fluoro-2-(5-fluoro-pyridin-3-yl)-1H-indole



3-Fluoro-5-bromopyridine and N-Boc-5-fluoro-indole-2-boronic acid are processed according to the procedure described in Example 91 to give 5-fluoro-2-(5-fluoro-pyridin-3-yl)-1H-indole. (ESI) *m/z* 231.04 $(M+H)^+$.

Example 97

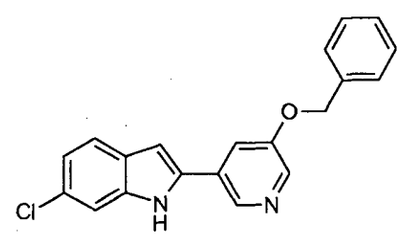
6-Chloro-2-pyridin-3-yl-1H-indole



3-Bromopyridine and N-Boc-6-chloro-indole-2-boronic acid are processed according to the procedure described in Example 91 to give 6-chloro-2-pyridin-3-yl-1H-indole. (ESI) *m/z* 229.0 $(M+H)^+$.

Example 98

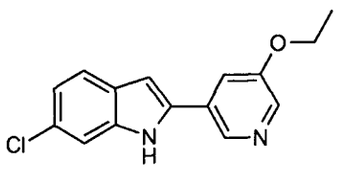
2-(5-Benzyloxy-pyridin-3-yl)-6-chloro-1H-indole



A flask is charged with 6-chloro-1-Boc-indole-2-boronic acid (0.839 g, 2.83 mmol), 1-benzyloxy-3-bromo-pyridine (0.500 g, 1.89 mmol), potassium phosphate (1.2 g, 5.67 mmol) and DMF (5 mL). The flask is evacuated and filled with nitrogen thrice and $Pd(PPh_3)_4$ (0.164 g, 0.141 mmol) is added. The flask is evacuated and filled with nitrogen thrice again, and heated to 80 °C for 3.5 h. The mixture is then diluted with ethyl acetate and washed with water thrice. The organic layer is dried over sodium sulfate and concentrated *in vacuo*. The residue is redissolved in DCM (1 mL) and trifluoroacetic acid (2 mL) is added. After 1 h, 4M aqueous NaOH is added and following extraction with DCM, the organic layer is dried over sodium sulfate and concentrated *in vacuo*. The residue is purified by silica gel flash chromatography (heptane- ethyl acetate, 1:1) to afford 2-(3-benzyloxy-phenyl)-6-chloro-1H-indole as a yellow solid. MS (ESI) *m/z* 335.07 $(M+H)^+$.

Example 99

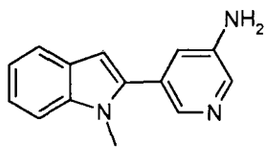
2-(5-Ethoxy-pyridin-3-yl)-6-chloro-1H-indole



1-Ethoxy-3-bromo-pyridine is processed according to the method described in Example 98 to give 2-(5-ethoxy-pyridin-3-yl)-6-chloro-1H-indole. MS (ESI) *m/z* 273.27 $(M+H)^+$

Example 100

2-(5-Amino-pyridin-3-yl)-1-methyl-1H-indole

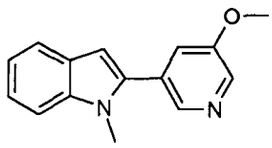


A flask is charged with 3-amino-5-bromopyridine (0.173 g, 0.950 mmol), *N*-methyl-indole boronic acid (0.262 g, 1.425 mmol), s-Phos (0.030 g, 0.071 mmol), finely crushed potassium phosphate (0.407 g, 1.900 mmol) and toluene (4 mL). After degassing for 30 min, Pd_2dba_3 (0.018 g, 0.019 mmol) is added, the flask is flushed with nitrogen and the mixture is heated to 85 °C. After 3 h, the mixture is allowed to cool to r.t., diluted with ethyl acetate and filtered through a plug of silica gel (elution with ethyl acetate). The

residue is purified by silica gel flash chromatography (heptane-ethyl acetate, 3:7 to 0:1) to give 2-(5-amino-pyridin-3-yl)-1-methyl-1H-indole as an off-white powder. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 3.74 (s, 3 H), 5.49 (s, 2 H), 6.56 (s, 1 H), 7.05 - 7.09 (m, 1 H), 7.09 - 7.10 (m, 1 H), 7.17 - 7.21 (m, 1 H), 7.49 (d, *J*=7.6 Hz, 1 H), 7.57 (d, *J*=7.6 Hz, 1 H), 7.94 (d, *J*=2.0 Hz, 1 H), 7.99 (d, *J*=2.5 Hz, 1 H). MS (ESI) *m/z* 224 $(M+H)^+$.

Example 101

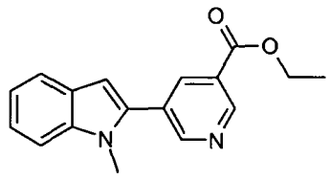
2-(5-Methoxy-pyridin-3-yl)-1-methyl-1H-indole



5-Methoxy-3-bromo-pyridine is processed according to the method described in Example 100 to give 2-(5-methoxy-pyridin-3-yl)-1-methyl-1H-indole. ^{1}H NMR (400 MHz, MeOD) δ ppm 3.82 (s, 3 H), 4.00 (s, 3 H), 6.69 (d, *J*=0.8 Hz, 1 H), 7.08 - 7.16 (m, 1 H), 7.23 - 7.30 (m, 1 H), 7.47 (dd, *J*=8.3, 0.8 Hz, 1 H), 7.58 - 7.66 (m, 2 H), 8.32 (d, *J*=2.8 Hz, 1 H), 8.37 (d, *J*=1.6 Hz, 1 H). HRMS (ESI) m/z 239.1175 [$(M+H)^+$ Calcd for $C_{15}H_{15}N_2O$: 239.1184].

Example 102

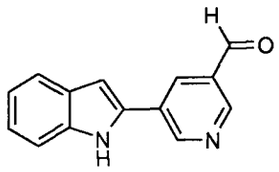
5-(1-Methyl-1H-indol-2-yl)-nicotinic acid ethyl ester



5-Bromo-nicotinic acid ethyl ester is processed according to the method described in Example 100 to give 5-(1-methyl-1H-indol-2-yl)-nicotinic acid ethyl ester. ^{1}H NMR (400 MHz, MeOD) δ ppm 1.47 (t, *J*=7.1 Hz, 3 H), 3.83 (s, 3 H), 4.50 (q, *J*=7.1 Hz, 2 H), 6.76 (s, 1 H), 7.14 (t, *J*=7.5 Hz, 1 H), 7.29 (t, *J*=7.6 Hz, 1 H), 7.50 (d, *J*=8.3 Hz, 1 H), 7.64 (d, *J*=8.1 Hz, 1 H), 8.56 (t, *J*=2.0 Hz, 1 H), 9.00 (d, *J*=2.0 Hz, 1 H), 9.17 (d, *J*=2.0 Hz, 1 H). HRMS (ESI) m/z 281.1297 [$(M+H)^+$ Calcd for $C_{17}H_{17}N_2O_2$: 281.1290].

Example 103

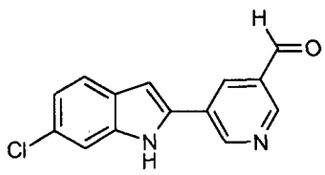
5-(1H-Indol-2-yl)-pyridine-3-carbaldehyde



A flask is charged with 3-bromopyridine-5-carboxaldehyde (4.12 g, 21.48 mmol), *N*-Boc-indoleboronic acid (8.59 g, 32.23 mmol), s-Phos (0.68 g, 1.61 mmol), finely crushed potassium phosphate (9.21 g, 42.97 mmol) and toluene (70 mL). After degassing for 1 h, Pd_2dba_3 (0.40 g, 0.43 mmol) is added, the flask is flushed with nitrogen and the mixture is heated to 85 °C. After 30 min, the mixture is allowed to cool to r.t., diluted with ethyl acetate and filtered through a plug of silica gel. Silica gel (50 g) is added to the filtrate and the mixture is concentrated *in vacuo*. The residue is heated to 60 °C with gentle stirring under oil pump vacuum overnight. The mixture is then loaded on a silica gel flash chromatography column and eluted (heptane-ethyl acetate, 4:1 to 2:3) to give 5-(1H-indol-2-yl)-pyridine-3-carbaldehyde. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.02 - 7.08 (m, 1 H), 7.14 - 7.19 (m, 1 H), 7.20 (d, *J*=1.5 Hz, 1 H), 7.45 (d, *J*=8.1 Hz, 1 H), 7.59 (d, *J*=8.1 Hz, 1 H), 8.66 (t, *J*=2.1 Hz, 1 H), 9.00 (d, *J*=1.8 Hz, 1 H), 9.39 (d, *J*=2.3 Hz, 1 H), 10.18 (s, 1 H), 11.86 (br. s., 1 H). MS (ESI) *m/z* 223.02 $(M+H)^+$.

Example 104

5-(6-Chloro-1H-indol-2-yl)-pyridine-3-carbaldehyde

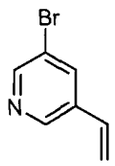


A flask is charged with *N*-(*tert*-butoxycarbonyl)-6-chloro-1H-indol-2-ylboronic acid (8.3 g, 28.1 mmol), 5-bromonicotinaldehyde (4.35 g, 23.4 mmol), K_3PO_4 (9.94 g, 46.8 mmol), s-Phos (0.480 g, 1.170 mmol) and $Pd_2(dba)_3$ (0.429 g, 0.468 mmol), and the flask is flushed with N_2. Toluene (250 mL) is added, and the mixture is heated to 85 °C for 1.5 h. The mixture is cooled to room temperature. Ethyl acetate (250 mL) is added and the mixture is filtered through a pad of silica gel, which is washed with EtOAc. Silica gel is added to the combined filtrate, which is concentrated *in vacuo*. The residue is placed under high vacuum at 63 °C overnight, and after elution with ethyl acetate, 5-(6-chloro-

1H-indol-2-yl)-pyridine-3-carbaldehyde is obtained. MS (ESI) *m/z* 257.0 and 258.9 $(M+H)^+$.

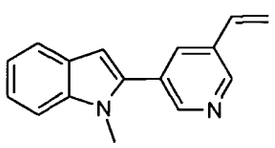
Example 105

(a) 3-Bromo-5-vinyl-pyridine



To a solution of methyltriphenylphosphine bromide (3.16 g, 8.87 mmol) in tetrahydrofuran (20 mL) is added sodium hexamethyldisilazane (1M solution in THF, 9.67 mL, 9.67 mmol) dropwise. The reaction mixture is stirred at room temperature for 30 min, whereupon 5-bromo-pyridine-3-carbaldehyde (1.5 g, 8.06 mmol) is added. The reaction mixture is allowed to stir at room temperature for 1 h. The mixture is concentrated and the residue is purified by silica gel flash chromatography (heptane-ethyl acetate, 7:3) to afford 3-bromo-5-vinyl-pyridine as a colorless oil. MS (ESI) *m/z* 185.91 $(M+H)^+$.

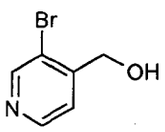
(b) 1-Methyl-2-(5-vinyl-pyridin-3-yl)-1H-indole



3-Bromo-5-vinyl-pyridine is processed according to the method described in Example 100 to give 1-methyl-2-(5-vinyl-pyridin-3-yl)-1H-indole. MS (ESI) *m/z* 235.40 $(M+H)^+$.

Example 106

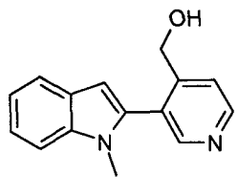
(a) (3-Bromo-pyridin-4-yl)-methanol



To a solution of 3-bromo-pyridine-4-carbaldehyde (0.500 g, 2.68 mmol) in MeOH (5 mL) at 0 °C is added sodium borohydride (0.122 g, 3.22 mmol). The mixture is stirred at room temperature for 1 h followed by removal of the solvent *in vacuo*. The residue is

redissolved in DCM and washed with water twice. The organic layer is dried over sodium sulfate and concentrated *in vacuo* to afford (3-bromo-pyridin-4-yl)-methanol as a yellow oil. MS (ESI) *m/z* 189.9 $(M+H)^+$

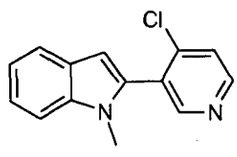
(b) [3-(1-Methyl-1H-indol-2-yl)-pyridin-4-yl]-methanol



A microwave reactor is charged with 1-methyl-indole-2-boronic acid (1.18 g, 6.78 mmol), (3-bromo-pyridin-4-yl)-methanol (0.850 g, 4.52 mmol), potassium phosphate (1.91 g, 9.04 mmol) and DMF (10 mL). The reactor is evacuated and filled with nitrogen thrice and $Pd(PPh_3)_4$ (0.261 g, 0.226 mmol) is added. The reactor is evacuated and filled with nitrogen thrice again. The mixture is heated to 120 °C for 1 h under microwave irradiation, then diluted with ethyl acetate and washed with water thrice. The organic layer is dried over sodium sulfate and concentrated *in vacuo* to give a residue which is purified by silica gel flash chromatography (dichloromethane-methanol, 19:1) to afford [3-(1-methyl-1H-indol-2-yl)-pyridin-4-yl]-methanol as a white solid. ^{1}H NMR (400 MHz, MeOD) δ ppm 3.58 (s, 3 H), 4.57 (s, 2 H), 6.54 (s, 1 H), 7.14 (t, *J*=7.5 Hz, 1 H), 7.27 (ddd, *J*=7.6, 1.1 Hz, 1 H), 7.46 (d, *J*=8.3 Hz, 1 H), 7.62 (d, *J*=7.8 Hz, 1 H), 7.81 (d, *J*=5.1 Hz, 1 H), 8.49 (s, 1 H), 8.67 (d, *J*=5.1 Hz, 1 H). HRMS (ESI) m/z 239.1177 $[(M+H)^+$ Calcd for $C_{15}H_{15}N_2O$: 239.1184].

Example 107

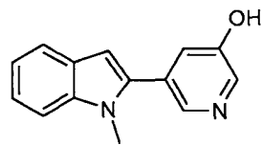
2-(4-Chloro-pyridin-3-yl)-1-methyl-1H-indole



3-Bromo-4-chloropyridine is processed according to the method described in Example 106b to give 2-(4-chloro-pyridin-3-yl)-1-methyl-1H-indole. ^{1}H NMR (400 MHz, MeOD) δ ppm 3.64 (s, 3 H), 6.61 (s, 1 H), 7.14 (t, *J*=7.5 Hz, 1 H), 7.28 (t, *J*=7.6 Hz, 1 H), 7.47 (d, *J*=8.3 Hz, 1 H), 7.64 (d, *J*=7.8 Hz, 1 H), 7.73 (d, *J*=5.3 Hz, 1 H), 8.62 (d, *J*=5.6 Hz, 1 H), 8.66 (s, 1 H). HRMS (ESI) m/z 243.0686 $[(M+H)^+$ Calcd for $C_{14}H_{12}ClN_2$: 243.0689].

Example 108

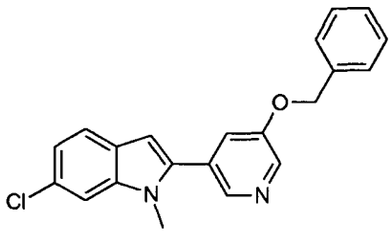
2-(5-Hydroxy-pyridin-3-yl)-1-methyl-1H-indole



3-Bromo-5-hydroxypyridine is processed according to the method described in Example 106b to give 2-(5-hydroxy-pyridin-3-yl)-1-methyl-1H-indole. HRMS (ESI) m/z 225.1028 [$(M+H)^+$ Calcd for $C_{14}H_{13}N_2O$: 225.1028].

Example 109

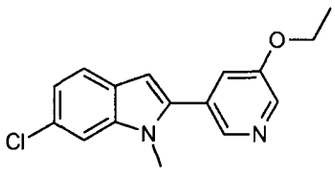
2-(5-Benzyloxy-pyridin-3-yl)-6-chloro-1-methyl-1H-indole



A flask is charged with 2-(5-benzyloxy-pyridin-3-yl)-6-chloro-1H-indole (Example 98, 0.435 g, 1.29 mmol), dimethyl carbonate (0.328 mL, 3.89 mmol), potassium carbonate (0.098 g, 0.714 mmol) and DMF (3 mL). The reaction mixture is stirred at 150 °C overnight. It is then cooled to room temperature, diluted with ethyl acetate and washed with water. The organic layer is dried over sodium sulfate and concentrated in vacuo, to give a residue which is purified by flash chromatography (heptane-ethyl acetate, 1:1) to afford 2-(5-benzyloxy-pyridin-3-yl)-6-chloro-1-methyl-1H-indole as a solid. ^{1}H NMR (400 MHz, MeOD) δ ppm 3.70 (s, 3 H), 5.31 (s, 2 H), 6.67 (d, *J*=0.8 Hz, 1 H), 7.10 (dd, *J*=8.3, 1.8 Hz, 1 H), 7.35 - 7.40 (m, 1 H), 7.41 - 7.47 (m, 2 H), 7.49 - 7.55 (m, 3 H), 7.57 (d, *J*=8.3 Hz, 1 H), 7.64 (dd, *J*=2.5, 1.8 Hz, 1 H), 8.35 (d, *J*=1.8 Hz, 1 H), 8.39 (d, *J*=2.8 Hz, 1 H); HRMS (ESI) m/z 349.1108 [$(M+H)^+$ Calcd for $C_{21}H_{18}ClN_2O$: 349.1108].

Example 110

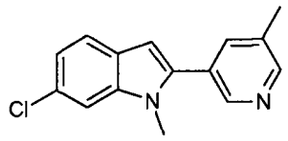
2-(5-Ethoxy-pyridin-3-yl)-6-chloro-1-methyl-1H-indole



2-(5-Ethoxy-pyridin-3-yl)-6-chloro-1H-indole (Example 99) is processed according to the method described in Example 109 to give 2-(5-ethoxy-pyridin-3-yl)-6-chloro-1-methyl-1H-indole. MS (ESI) *m/z* 287.07 $(M+H)^+$.

Example 111

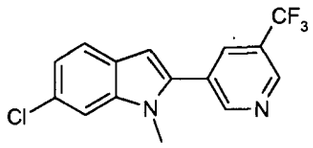
6-Chloro-2-(5-methyl-pyridin-3-yl)-1-methyl-1H-indole



6-Chloro-2-(5-methyl-pyridin-3-yl)-1H-indole (Example 94) is processed according to the method described in Example 109 to give 6-chloro-2-(5-methyl-pyridin-3-yl)-1-methyl-1H-indole. MS (ESI) *m/z* 257.1 $(M+H)^+$.

Example 112

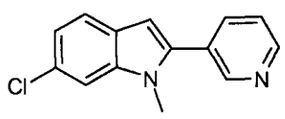
6-Chloro-2-(5-trifluoromethyl-pyridin-3-yl)-1-methyl-1H-indole



6-Chloro-2-(5-trifluoromethyl-pyridin-3-yl)-1H-indole (Example 95) is processed according to the method described in Example 109 to give 6-chloro-2-(5-trifluoromethyl-pyridin-3-yl)-1-methyl-1H-indole. MS (ESI) *m/z* 311.0 $(M+H)^+$.

Example 113

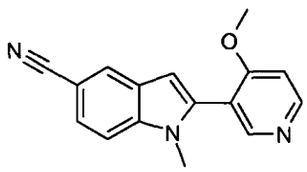
6-Chloro-2-pyridin-3-yl-1-methyl-1H-indole



6-Chloro-2-pyridin-3-yl-1H-indole (Example 97) is processed according to the method described in Example 109 to give 6-chloro-2-pyridin-3-yl-1-methyl-1H-indole. MS (ESI) *m/z* 243.02 $(M+H)^+$.

Example 114

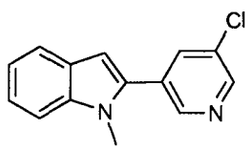
2-(4-Methoxy-pyridin-3-yl)-1-methyl-1H-indole-5-carbonitrile



To a solution of 2-(4-methoxy-pyridin-3-yl)-1H-indole-5-carbonitrile (Example 90, 178 mg, 0.649 mmol) in DMF (4 mL) is added 60% sodium hydride in mineral oil (78 mg, 1.95 mmol) and the suspension is stirred for 30 min. Iodomethane (138 mg, 0.97 mmol) is then added to the reaction mixture which is stirred at ambient temperature for 1 h. Aqueous $NaHCO_3$ (3 mL) is added to quench the reaction and the mixture is filtered and purified by HPLC using an Xbridge C18 with a gradient of acetonitrile in 0.1% NH_4OH to afford 2-(4-methoxy-pyridin-3-yl)-1-methyl-1H-indole-5-carbonitrile as a white solid. ^1H NMR (400 MHz, DMSO-d_6) δ ppm 3.59 (s, 3 H), 3.89 (s, 3 H), 6.67 (s, 1 H), 7.27 (d, *J*=5.8 Hz, 1 H), 7.54 (dd, *J*=8.6, 1.5 Hz, 1 H), 7.70 (d, *J*=8.6 Hz, 1 H), 8.11 (d, *J*=1.1 Hz, 1 H), 8.42 (s, 1 H), 8.60 (d, *J*=5.8 Hz, 1 H). HRMS (ESI) m/z 264.1138 $[(M+H)^+$ calcd for $C_{16}H_{14}N_3O$: 264.1137].

Example 115

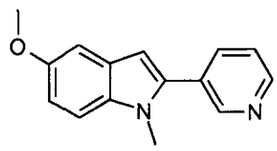
2-(5-Chloro-pyridin-3-yl)-1-methyl-1H-indole



2-(5-Chloro-pyridin-3-yl)-1H-indole (Example 91) is processed according to the method described in Example 114 to give 2-(5-chloro-pyridin-3-yl)-1-methyl-1H-indole. ^1H NMR (400 MHz, MeOD) δ ppm 3.83 (s, 3 H), 6.74 (s, 1 H), 7.14 (t, *J*=7.5 Hz, 1 H), 7.25 - 7.33 (m, 1 H), 7.49 (d, *J*=8.3 Hz, 1 H), 7.64 (dd, *J*=7.8, 0.6 Hz, 1 H), 8.14 (t, *J*=2.7 Hz, 1 H), 8.63 (dd, *J*=2.2, 0.9 Hz, 1 H), 8.74 (d, *J*=1.3 Hz, 1 H). HRMS (ESI) m/z 243.0686 $[(M+H)^+$ Calcd for $C_{14}H_{12}ClN_2$: 243.0689].

Example 116

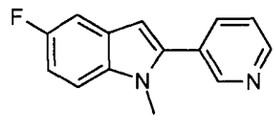
5-Methoxy-1-methyl-2-pyridin-3-yl-1H-indole



5-Methoxy-2-pyridin-3-yl-1H-indole (Example 93) is processed according to the procedure described in Example 114 to give 5-methoxy-1-methyl-2-pyridin-3-yl-1H-indole. ^{1}H NMR (400 MHz, MeOD) δ ppm 3.78 (s, 3 H), 3.87 (s, 3 H), 6.61 (d, *J*=0.8 Hz, 1 H), 6.93 (dd, *J*=8.9, 2.5 Hz, 1 H), 7.14 (d, *J*=2.4 Hz, 1 H), 7.37 (d, *J*=9.0 Hz, 1 H), 7.60 (ddd, *J*=8.0, 4.9, 0.9 Hz, 1 H), 8.06 (dt, *J*=7.9, 2.2, 1.6 Hz, 1 H). HRMS (ESI) m/z 239.1181 [(M+H)$^+$ Calcd for $C_{15}H_{15}N_2O$: 239.1184].

Example 117

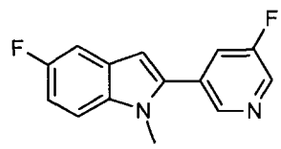
2-(5-Fluoro-pyridin-3-yl)-1-methyl-1H-indole



2-(5-Fluoro-pyridin-3-yl)-1H-indole (Example 92) is processed according to the procedure described in Example 114 to give 2-(5-fluoro-pyridin-3-yl)-1-methyl-1H-indole. ^{1}H NMR (400 MHz, MeOD) δ ppm 3.83 (s, 3 H), 6.74 (s, 1 H), 7.10 - 7.17 (m, 1 H), 7.26 - 7.32 (m, 1 H), 7.48 (d, *J*=8.3 Hz, 1 H), 7.63 (d, *J*=7.8 Hz, 1 H), 7.91 (ddd, *J*=9.6, 2.8, 1.8 Hz, 1 H), 8.54 (d, *J*=2.5 Hz, 1 H), 8.67 (t, *J*=1.5 Hz, 1 H). HRMS (ESI) m/z 227.0989 [(M+H)$^+$ Calcd for $C_{14}H_{12}FN_2$: 227.0985].

Example 118

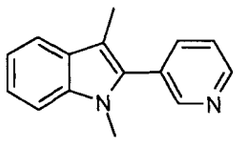
5-Fluoro-2-(5-fluoro-pyridin-3-yl)-1-methyl-1H-indole



5-Fluoro-2-(5-fluoro-pyridin-3-yl)-1H-indole (Example 96) is processed according to the procedure described in Example 114 to give 5-fluoro-2-(5-fluoro-pyridin-3-yl)-1-methyl-1H-indole. (ESI) *m/z* 245.34 $(M+H)^+$.

Example 119

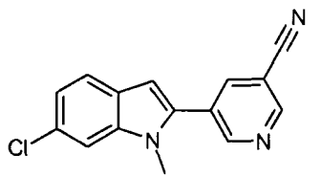
1,3-Dimethyl-2-(pyridin-3-yl)-1H-indole



3-Methyl-2-(pyridin-3-yl)-1H-indole hydrochloride (Exemple 1) is processed according to the procedure described in Example 114 to give 1,3-dimethyl-2-(pyridin-3-yl)-1H-indole. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.23 (s, 3 H), 3.62 (s, 3 H), 7.06 - 7.12 (m, 1 H), 7.22 (td, *J*=7.6, 1.1 Hz, 1 H), 7.48 (d, *J*=8.3 Hz, 1 H), 7.55 - 7.61 (m, 2 H), 7.93 (dt, *J*=7.9, 2.0 Hz, 1 H), 8.66 (dd, *J*=4.8, 1.5 Hz, 1 H), 8.69 (dd, *J*=2.3, 0.8 Hz, 1 H). HRMS: (ESI) m/z 223.1236 [(M+H)+ Calcd for $C_{15}H_{15}N_2$: 223.1230].

Example 120

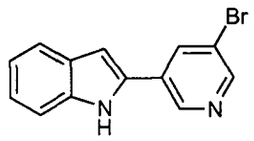
5-(6-Chloro-1-methyl-1H-indol-2-yl)-nicotinonitrile



3-Bromo-5-cyano-pyridine and *N*-Boc-6-chloro-indoleboronic acid are processed according to the procedure described in Example 103 to give 5-(6-chloro-1H-indol-2-yl)-nicotinonitrile, which is processed according to the procedure described in Example 114 to give 5-(6-Chloro-1-methyl-1H-indol-2-yl)-nicotinonitrile. ^{1}H NMR (400 MHz, MeOD) δ ppm 3.81 (s, 3 H), 6.81 (s, 1 H), 7.14 (dd, *J*=8.6, 1.8 Hz, 1 H), 7.56 (s, 1 H), 7.61 (d, *J*=8.3 Hz, 1 H), 8.46 (t, *J*=2.1 Hz, 1 H), 8.98 (d, *J*=2.0 Hz, 1 H), 9.06 (d, *J*=2.0 Hz, 1 H). HRMS (ESI) m/z 268.0636 $[(M+H)^+$ Calcd for $C_{15}H_{10}ClN_3$ 268.0636].

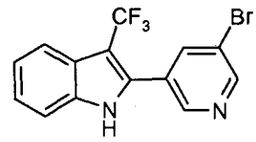
Example 121

(a) 2-(5-bromopyridin-3-yl)-1H-indole



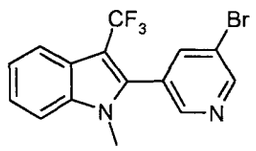
A flask containing 1-(tert-butoxycarbonyl)-1H-indol-2-ylboronic acid (2 g, 7.66 mmol), 3-bromo-5-iodopyridine (1.45 g, 5.11 mmol), 2M K_2CO_3 in water (5.11 mL,10.21 mmol), PS-Pd(PPh_3)$_4$ (2.84 g, 0.255 mmol) is flushed with N_2 and dioxane (50 mL) is added. The mixture is stirred at 60 °C for 3 h, whereupon another portion of 3-bromo-5-iodopyridine (300 mg, 1.06 mmol) is added. The mixture is stirred at 60 °C overnight. The mixture is cooled to room temperature and silica gel (20 g) is added. The suspension is concentrated *in vacuo* and the residue is placed under high vacuum at 60 °C over the weekend. The mixture is purified by silica chromatography eluting with a 1:9 to 7:3 EtOAc-heptane gradient to give 2-(5-bromopyridin-3-yl)-1H-indole. MS (ESI) *m/z* 273.0, 275.1 $(M+H)^+$.

(b) 2-(5-Bromopyridin-3-yl)-3-(trifluoromethyl)-1H-indole



A flask is charged with 2-(5-bromopyridin-3-yl)-1H-indole (1.2 g, 4.39 mmol), acetonitrile (100 mL), potassium carbonate (1.2 g, 8.79 mmol) and 5-(trifluoromethyl)-5H-dibenzo[b,d]thiophenium trifluoromethanesulfonate (2.65 g, 6.59 mmol). The flask is lowered into an oil bath preheated to 70 °C, and the mixture is stirred under N_2 overnight. The mixture is cooled to room temperature and silica gel (10 g) is added. The suspension is concentrated *in vacuo* and the residue is purified by silica chromatography eluting with a 0 to 30% EtOAc-heptane gradient to give 2-(5-bromopyridin-3-yl)-3-(trifluoromethyl)-1H-indole; ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.25 (t, *J*=7.6 Hz, 1 H), 7.33 (t, *J*=7.1 Hz, 1 H), 7.55 (d, *J*=8.1 Hz, 1 H), 7.69 (d, *J*=7.8 Hz, 1 H), 8.33 (t, *J*=2.0 Hz, 1 H), 8.79 (d, *J*=1.8 Hz, 1 H), 8.86 (d, *J*=2.0 Hz, 1 H).

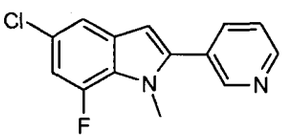
(c) 2-(5-Bromopyridin-3-yl)-1-methyl-3-(trifluoromethyl)-1H-indole



2-(5-Bromopyridin-3-yl)-3-(trifluoromethyl)-1H-indole is processed according to the method described in Example 114 to give 2-(5-bromopyridin-3-yl)-1-methyl-3-(trifluoromethyl)-1H-indole. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 3.62 (s, 3 H), 7.30 (t, J=8.0 Hz, 1 H), 7.37 - 7.44 (m, 1 H), 7.71 (d, J=8.8 Hz, 2 H), 8.36 (t, J=2.0 Hz, 1 H), 8.72 (d, J=1.8 Hz, 1 H), 8.92 (d, J=2.3 Hz, 1 H). HRMS: (ESI) m/z 355.0052 [(M+H)+ Calcd for $C_{15}H_{11}BrF_3N_2$: 355.0052].

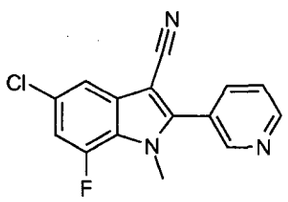
Example 122

(a) 5-Chloro-7-fluoro-1-methyl-2-pyridin-3-yl-1H-indole



To a solution of 5-chloro-7-fluoro-2-pyridin-3-yl-1H-indole (Example 86, 276 mg, 1.12 mmol) in DMF (4 mL) is added 60% sodium hydride in mineral oil (120 mg, 3.0 mmol) and the suspension is stirred for 30 min. Iodomethane (213 mg, 1.5 mmol) is then added to the reaction mixture and stirred at ambient temperature for 1 h. Water (2 mL) is added to quench the reaction. The mixture is filtered and purified by HPLC using Xbridge C18 with a gradient of acetonitrile in 0.1% NH_4OH to afford 5-chloro-7-fluoro-1-methyl-2-pyridin-3-yl-1H-indole. MS (ESI) *m/z* 261 $(M+H)^+$.

(b) 5-Chloro-7-fluoro-1-methyl-2-pyridin-3-yl-1H-indole-3-carbonitrile

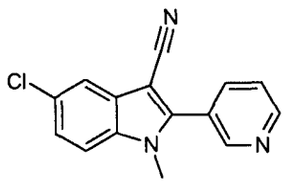


To a solution of 5-chloro-7-fluoro-1-methyl-2-pyridin-3-yl-1H-indole (130 mg, 0.50 mmol) in dichloromethane (10 mL) at ambient temperature is added chlorosulfonyl isocyanate (282 mg, 2.0 mmol) and the mixture is stirred for 11 h, whereupon anhydrous DMF (1 mL) is added. After 1 h, the mixture is concentrated and the residue is purified by HPLC

using an Xbridge C18 with a gradient of acetonitrile in 0.1% NH_4OH to afford 5-chloro-7-fluoro-1-methyl-2-pyridin-3-yl-1H-indole-3-carbonitrile as a white solid. ^1H NMR (400 MHz, DMSO-d_6) δ ppm 3.89 (d, J=1.8 Hz, 3 H), 7.46 (dd, J=12.4, 1.8 Hz, 1 H), 7.62 (d, J=1.8 Hz, 1 H), 7.71 (dd, J=7.5, 4.4 Hz, 1 H), 8.16 (dt, J=8.1, 2.0, 1.8 Hz, 1 H), 8.83 (dd, J=4.9, 1.6 Hz, 1 H), 8.89 (d, J=1.5 Hz, 1 H). HRMS (ESI) m/z 286.0558 [$(M+H)^+$ Calcd for $C_{15}H_{10}ClFN_3$: 286.0547].

Example 123

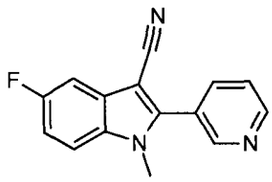
2-(5-Chloro-pyridin-3-yl)-1-methyl-1H-indole-3-carbonitrile



2-(5-Chloro-pyridin-3-yl)-1H-indole (Example 91) is processed according to the method described in Example 122 to give 2-(5-chloro-pyridin-3-yl)-1-methyl-1H-indole-3-carbonitrile. ^1H NMR (400 MHz, MeOD) δ ppm 3.87 (s, 3 H), 7.40 (t, J=7.6 Hz, 1 H), 7.48 (ddd, J=7.7, 1.3 Hz, 1 H), 7.68 (d, J=8.3 Hz, 1 H), 7.75 (d, J=8.1 Hz, 1 H), 8.28 (t, J=2.1 Hz, 1 H), 8.70 - 8.90 (m, 2 H). HRMS (ESI) m/z 268.0650 [$(M+H)^+$ Calcd for $C_{15}H_{11}ClN_3$: 268.0641].

Example 124

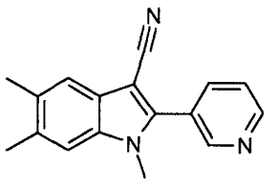
2-(5-Fluoro-pyridin-3-yl)-1-methyl-1H-indole-3-carbonitrile



2-(5-Fluoro-pyridin-3-yl)-1H-indole (Example 92) is processed according to the method described in Example 122 to give 2-(5-fluoro-pyridin-3-yl)-1-methyl-1H-indole-3-carbonitrile. ^1H NMR (400 MHz, MeOD) δ ppm 3.88 (s, 3 H), 7.40 (t, J=7.6 Hz, 1 H), 7.48 (ddd, J=7.8, 1.1 Hz, 1 H), 7.69 (d, J=8.3 Hz, 1 H), 7.76 (d, J=8.1 Hz, 1 H), 8.06 (dt, J=9.0, 2.2 Hz, 1 H), 8.74 (d, J=2.5 Hz, 1 H), 8.77 (s, 1 H). HRMS (ESI) m/z 252.0939 [$(M+H)^+$ Calcd for $C_{15}H_{11}FN_3$: 252.0937].

Example 125

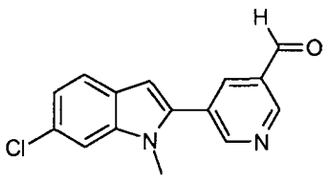
1,5,6-Tri-methyl-2-pyridin-3-yl-1H-indole-3-carbonitrile



5,6-dimethyl-2-pyridin-3-yl-1H-indole (Example 88) is processed according to the method described in Example 122 to give 1,5,6-tri-methyl-2-pyridin-3-yl-1H-indole-3-carbonitrile. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.38 (s, 3 H), 2.40 (s, 3 H), 3.75 (s, 3 H), 7.47 (s, 1 H), 7.54 (s, 1 H), 7.67 (dd, *J*=7.8, 4.8 Hz, 1 H), 8.14 (dt, *J*=8.1, 2.0, 1.8 Hz, 1 H), 8.78 (dd, *J*=4.8, 1.8 Hz, 1 H), 8.88 (d, *J*=1.5 Hz, 1 H). HRMS (ESI) m/z 262.1352 [$(M+H)^+$ Calcd for $C_{17}H_{16}N_3$: 262.1344].

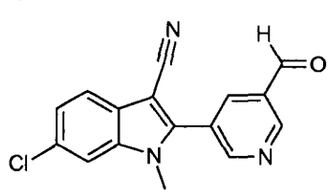
Example 126

a) 6-Chloro-2-(5-formyl-pyridin-3-yl)-1-methyl-1H-indole



A flask is charged with 5-(6-chloro-1H-indol-2-yl)-pyridine-3-carbaldehyde (Example 104, 7.8 g, 28.9 mmol), MeI (5.33 g, 37.5 mmol) and DMF (300 mL), and 60% NaH in mineral oil (1.386 g, 34.6 mmol) is added at 0 °C. The mixture is stirred for 2h. Water (100 mL) is added. The mixture is extracted with EtOAc twice and the combined organic phase is washed with water (2 × 200 mL) and brine (200 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue is purified by silica gel chromatography with a 0 to 2% methanol-DCM gradient to give 6-chloro-2-(5-formyl-pyridin-3-yl)-1-methyl-1H-indole. MS (ESI) *m/z* 271.0, 272.9 $(M+H)^+$.

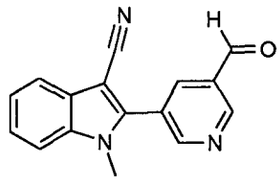
b) 6-Chloro-2-(5-formyl-pyridin-3-yl)-1-methyl-1H-indole-3-carbonitrile



A flask is charged with 6-chloro-2-(5-formyl-pyridin-3-yl)-1-methyl-1H-indole (10 g, 36.9 mmol) and acetonitrile (1 L), and chlorosulfonyl isocyanate (15.68 g, 111 mmol) is added at 0 °C. The mixture is stirred for 10 min. DMF (18.9 g, 259 mmol) is added at 0 °C. The mixture is stirred for 1.5 h. Saturated $NaHCO_3$ (20 mL) and triethylamine (51.5 mL, 369 mmol) are added to the reaction mixture, which is stirred for 10 min. The mixture is concentrated *in vacuo* to give a residue which is purified by silica gel flash chromatography eluting with a 0 to 5% methanol-DCM gradient to give 6-chloro-2-(5-formyl-pyridin-3-yl)-1-methyl-1H-indole-3-carbonitrile. MS (ESI) *m/z* 296.0, 297.8 $(M+H)^+$.

Example 127

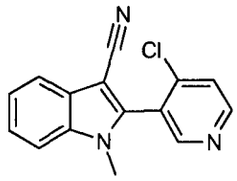
2-(5-formyl-pyridin-3-yl)-1-methyl-1H-indole-3-carbonitrile



5-(1H-indol-2-yl)-pyridine-3-carbaldehyde (Example 103) is processed according to the method described in Example 122 using acetonitrile instead of dichloromethane, to give 2-(5-formyl-pyridin-3-yl)-1-methyl-1H-indole-3-carbonitrile. MS (ESI) *m/z* 262.02 $(M+H)^+$.

Example 128

2-(4-Chloro-pyridin-3-yl)-1-methyl-1H-indole-3-carbonitrile

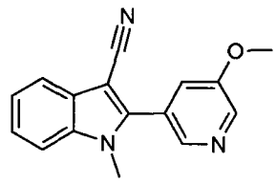


A flask is charged with 2-(4-chloro-pyridin-3-yl)-1-methyl-1H-indole (Example 107, 0.110 g, 0.418 mmol) and dichloromethane (5 mL). Chlorosulfonyl isocyanate (0.091 mL, 1.04 mmol) is added and the reaction is stirred for 2 min, whereupon DMF (1 mL) is added. After another 20 min, the reaction is concentrated *in vacuo* and the residue is purified by reverse phase HPLC with Xbridge Shield RP18 column and a 0.1% aqueous NH_4OH in acetonitrile gradient to afford 2-(4-chloro-pyridin-3-yl)-1H-indole-3-carbonitrile as a solid.

^{1}H NMR (400 MHz, MeOD) δ ppm 3.74 (s, 3 H), 7.41 (t, *J*=7.6 Hz, 1 H), 7.49 (t, *J*=7.7 Hz, 1 H), 7.69 (d, *J*=8.3 Hz, 1 H), 7.77 (d, *J*=8.1 Hz, 1 H), 7.84 (d, *J*=5.3 Hz, 1 H), 8.61 - 8.86 (m, 2 H). HRMS (ESI) m/z 268.0635 [(M+H)$^+$ Calcd for $C_{15}H_{11}ClN_3$: 268.0641].

Example 129

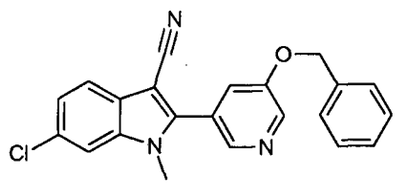
2-(5-Methoxy-pyridin-3-yl)-1-methyl-1H-indole-3-carbonitrile



2-(5-Methoxy-pyridin-3-yl)-1-methyl-1H-indole (Example 101) is processed according to the method described in Example 128 to give 2-(5-methoxy-pyridin-3-yl)-1-methyl-1H-indole-3-carbonitrile. ^{1}H NMR (400 MHz, MeOD) δ ppm 3.87 (s, 3 H), 4.02 (s, 3 H), 7.36 - 7.42 (m, 1 H), 7.47 (td, *J*=7.8, 1.1 Hz, 1 H), 7.67 (d, *J*=8.3 Hz, 1 H), 7.72 - 7.77 (m, 2 H), 8.45 (d, *J*=1.8 Hz, 1 H), 8.49 (d, *J*=2.8 Hz, 1 H). HRMS (ESI) m/z 264.1130 [(M+H)$^+$ Calcd for $C_{16}H_{14}N_3O$: 264.1137].

Example 130

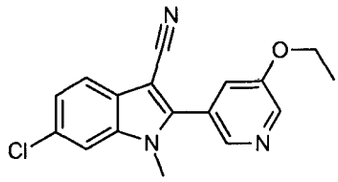
2-(5-Benzyloxy-pyridin-3-yl)-6-chloro-1-methyl-1H-indole-3-carbonitrile



2-(5-Benzyloxy-pyridin-3-yl)-6-chloro-1-methyl-1H-indole (Example 109) is processed according to the method described in Example 128 to give 2-(5-benzyloxy-pyridin-3-yl)-6-chloro-1-methyl-1H-indole-3-carbonitrile. ^{1}H NMR (400 MHz, MeOD) δ ppm 3.75 (s, 3 H), 5.33 (s, 2 H), 7.37 (dd, *J*=8.3, 1.8 Hz, 2 H), 7.44 (t, *J*=7.3 Hz, 2 H), 7.54 (d, *J*=7.1 Hz, 2 H), 7.71 (d, *J*=8.3 Hz, 1 H), 7.75 (d, *J*=1.5 Hz, 1 H), 7.78 (dd, *J*=2.8, 1.8 Hz, 1 H), 8.45 (d, *J*=1.8 Hz, 1 H), 8.56 (d, *J*=2.8 Hz, 1 H). HRMS (ESI) m/z 374.1070 [(M+H)$^+$ Calcd for $C_{22}H_{17}ClN_3O$: 374.1060].

Example 131

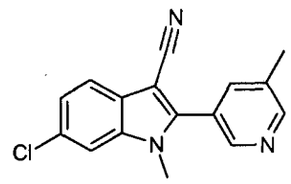
2-(5-Ethoxy-pyridin-3-yl)-6-chloro-1-methyl-1H-indole-3-carbonitrile



2-(5-Ethoxy-pyridin-3-yl)-6-chloro-1-methyl-1H-indole (Example 110) is processed according to the method described in Example 128 to give 2-(5-ethoxy-pyridin-3-yl)-6-chloro-1-methyl-1H-indole-3-carbonitrile. ^{1}H NMR (400 MHz, MeOD) δ ppm 1.51 (t, *J*=7.1 Hz, 3 H), 3.84 (s, 3 H), 4.27 (q, *J*=6.9 Hz, 2 H), 7.37 (dd, *J*=8.6, 1.8 Hz, 1 H), 7.66 - 7.74 (m, 2 H), 7.76 (d, *J*=1.5 Hz, 1 H), 8.43 (d, *J*=1.5 Hz, 1 H), 8.47 (d, *J*=2.8 Hz, 1 H). HRMS (ESI) m/z 312.0893 [(M+H)$^+$ Calcd for $C_{17}H_{15}ClN_3O$: 312.0904].

Example 132

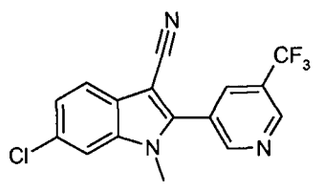
6-Chloro-2-(5-methyl-pyridin-3-yl)-1-methyl-1H-indole-3- carbonitrile



6-Chloro-2-(5-methyl-pyridin-3-yl)-1-methyl-1H-indole (Example 111) is processed according to the method described in Example 128 to give 6-chloro-2-(5-methyl-pyridin-3-yl)-1-methyl-1H-indole-3- carbonitrile. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.44 (s, 3 H), 3.78 (s, 3 H), 7.36 (dd, *J*=8.3, 1.8 Hz, 1 H), 7.71 (d, *J*=8.3 Hz, 1 H), 7.95 (d, *J*=1.5 Hz, 1 H), 7.97 (s, 1 H), 8.65 (d, *J*=1.5 Hz, 1 H), 8.68 (d, *J*=2.0 Hz, 1 H). HRMS (ESI) m/z 282.0803 [(M+H)$^+$ Calcd for $C_{16}H_{13}ClN_3$: 282.0798].

Example 133

6-Chloro-2-(5-trifluoromethyl-pyridin-3-yl)-1-methyl-1H-indole-3- carbonitrile

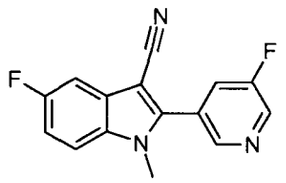


6-Chloro-2-(5-trifluoromethyl-pyridin-3-yl)-1-methyl-1H-indole (Example 112) is processed according to the method described in Example 128 to give 6-chloro-2-(5-trifluoromethyl-pyridin-3-yl)-1-methyl-1H-indole-3- carbonitrile. ^{1}H NMR (400 MHz,

DMSO-d_6) δ ppm 3.82 (s, 3 H), 7.39 (dd, *J*=8.5, 1.9 Hz, 1 H), 7.76 (d, *J*=8.3 Hz, 1 H), 8.00 (d, *J*=1.8 Hz, 1 H), 8.65 (s, 1 H), 9.22 (d, *J*=2.0 Hz, 1 H), 9.23 (d, *J*=1.3 Hz, 1 H). HRMS (ESI) m/z 377.0790 [$(M+H+CH_3CN)^+$ Calcd for $C_{18}H_{13}ClF_3N_4$: 377.0781].

Example 134

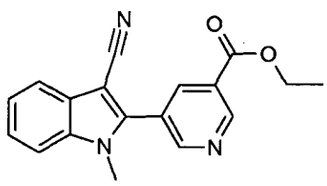
5-Fluoro-2-(5-fluoro-pyridin-3-yl)-1-methyl-1H-indole-3-carbonitrile



5-Fluoro-2-(5-fluoro-pyridin-3-yl)-1-methyl-1H-indole (Example 118) is processed according to the method described in Example 128 to give 5-fluoro-2-(5-fluoro-pyridin-3-yl)-1-methyl-1H-indole-3-carbonitrile. ^{1}H NMR (400 MHz, MeOD) δ ppm 3.87 (s, 3 H), 7.26 (td, *J*=9.2, 2.4 Hz, 1 H), 7.44 (dd, *J*=8.7, 2.4 Hz, 1 H), 7.70 (dd, *J*=9.1, 4.3 Hz, 1 H), 8.06 (dt, *J*=9.0, 2.4, 2.3 Hz, 1 H), 8.72 - 8.79 (m, 2 H). HRMS (ESI) m/z 270.0831 [$(M+H)^+$ Calcd for $C_{15}H_{10}F_2N_3$: 270.0843].

Example 135

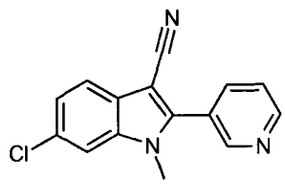
5-(3-Cyano-1-methyl-1H-indol-2-yl)-nicotinic acid ethyl ester



The product in Example 102 is processed according to the method described in Example 128 to give 5-(3-cyano-1-methyl-1H-indol-2-yl)-nicotinic acid ethyl ester. ^{1}H NMR (400 MHz, MeOD) δ ppm 1.47 (t, *J*=7.1 Hz, 3 H), 3.88 (s, 3 H), 4.51 (q, *J*=7.2 Hz, 2 H), 7.40 (t, *J*=7.6 Hz, 1 H), 7.49 (td, *J*=7.7, 1.3 Hz, 1 H), 7.69 (d, *J*=8.3 Hz, 1 H), 7.76 (d, *J*=7.8 Hz, 1 H), 8.69 (t, *J*=2.0 Hz, 1 H), 9.09 (d, *J*=2.0 Hz, 1 H), 9.34 (d, *J*=2.0 Hz, 1 H). HRMS (ESI) m/z 306.1246 [$(M+H)^+$ Calcd for $C_{18}H_{16}N_3O_2$: 306.1243].

Example 136

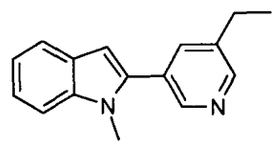
6-Chloro-2-pyridin-3-yl-1-methyl-1H-indole-3-carbonitrile



The product in Example 113 is processed according to the method described in Example 128 to give 6-chloro-2-pyridin-3-yl-1-methyl-1H-indole-3-carbonitrile. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 3.79 (s, 3 H), 7.37 (dd, *J*=8.5, 1.9 Hz, 1 H), 7.69 (dd, *J*=7.5, 4.4 Hz, 1 H), 7.73 (d, *J*=8.6 Hz, 1 H), 7.98 (d, *J*=1.5 Hz, 1 H), 8.17 (dt, *J*=8.1, 2.0, 1.8 Hz, 1 H), 8.82 (dd, *J*=4.9, 1.6 Hz, 1 H), 8.90 (d, *J*=1.5 Hz, 1 H). HRMS (ESI) m/z 268.0653 [(M+H)$^+$ Calcd for $C_{15}H_{11}ClN_3$: 268.0642].

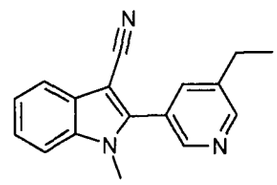
Example 137

(a) 1-Methyl-2-(5-ethyl-pyridin-3-yl)-1H-indole



To a solution of 1-methyl-2-(5-vinyl-pyridin-3-yl)-1H-indole (Example 105, 0.473 g, 2.02 mmol) in methanol (10 mL) is added palladium on carbon (0.215 g, 0.202 mmol). The reaction mixture is stirred at 55 °C under H_2 for 16 h. It is then cooled to room temperature and filtered through celite. The celite layer is washed with methanol thoroughly and the combined filtrate is concentrated *in vacuo*. The residue is purified by silica gel flash chromatography (heptane- ethyl acetate, 3:1) to afford 1-methyl-2-(5-ethyl-pyridin-3-yl)-1H-indole as a yellow oil. MS (ESI) *m/z* 237.24 (M+H)$^+$.

(b) 2-(5-Ethyl-pyridin-3-yl)-1-methyl-1H-indole-3-carbonitrile

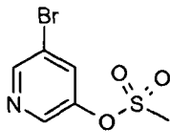


1-Methyl-2-(5-ethyl-pyridin-3-yl)-1H-indole is processed according to the method described in Example 128 to give 2-(5-ethyl-pyridin-3-yl)-1-methyl-1H-indole-3-carbonitrile. ^{1}H NMR (400 MHz, MeOD) δ ppm 1.40 (t, *J*=7.6 Hz, 3 H), 2.89 (q, *J*=7.7 Hz, 2 H), 3.87 (s, 3 H), 7.35 - 7.43 (m, 1 H), 7.43 - 7.50 (m, 1 H), 7.67 (d, *J*=8.3 Hz, 1 H),

7.75 (dd, *J*=7.9, 0.8 Hz, 1 H), 8.06 (t, *J*=2.1 Hz, 1 H), 8.66 (d, *J*=1.9 Hz, 1 H), 8.70 (d, *J*=2.0 Hz, 1 H). HRMS (ESI) m/z 262.1351 [$(M+H)^+$ Calcd for $C_{17}H_{16}N_3$: 262.1344].

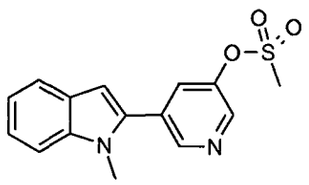
Example 138

(a) Methanesulfonic acid 5-bromo-pyridin-3-yl ester



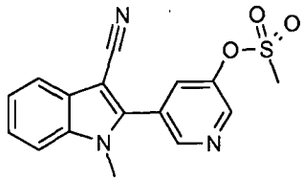
A flask is charged with 5-bromo-pyridin-3-ol (0.200 g, 1.126 mmol), potassium carbonate (0.212 g, 1.487 mmol) and acetone (3 mL). Methanesulfonyl chloride (0.143 g, 1.239 mmol) is then added dropwise. After 2 h, an other portion of methanesulfonyl chloride (0.071 g, 0.61 mmol) is added. After overnight stirring, the suspension is concentrated, diluted with ethyl acetate and filtered through a pad of silica gel. The filtrate is concentrated *in vacuo* to give a residue, which is purified by silica gel flash chromatography (heptane-ethyl acetate, 4:1 to 7:3) to give a mixture of product and starting material. The fractions are combined, washed three times with saturated aqueous sodium bicarbonate and dried over $MgSO_4$. Concentration *in vacuo* gives methanesulfonic acid 5-bromo-pyridin-3-yl ester as an oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 3.25 (s, 3 H), 7.86 (m, 1 H), 8.52 (d, *J*=2.3 Hz, 1 H), 8.67 (d, *J*=1.8 Hz, 1 H).

(b) Methanesulfonic acid 5-(1-methyl-1H-indol-2-yl)-pyridin-3-yl ester



Methanesulfonic acid 5-bromo-pyridin-3-yl ester is processed according to the method described in Example 100 to give methanesulfonic acid 5-(1-methyl-1H-indol-2-yl)-pyridin-3-yl ester. (ESI) *m/z* 303.1 $(M+H)^+$.

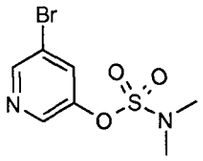
(c) Methanesulfonic acid 5-(3-cyano-1-methyl-1H-indol-2-yl)-pyridin-3-yl ester



Methanesulfonic acid 5-(1-methyl-1H-indol-2-yl)-pyridin-3-yl ester is processed according to the method described in Example 128 to give methanesulfonic acid 5-(3-cyano-1-methyl-1H-indol-2-yl)-pyridin-3-yl ester. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 3.57 (s, 3 H), 3.84 (s, 3 H), 7.35 - 7.40 (m, 1 H), 7.43 - 7.48 (m, 1 H), 7.74 (d, *J*=7.8 Hz, 1 H), 7.79 (d, *J*=8.3 Hz, 1 H), 8.30 (t, *J*=2.5 Hz, 1 H), 8.85 (d, *J*=2.5 Hz, 1 H), 8.94 (d, *J*=1.8 Hz, 1 H). HRMS (ESI) m/z 328.0771 [(M+H)$^+$ Calcd for $C_{16}H_{14}N_3O_3S$: 328.0756].

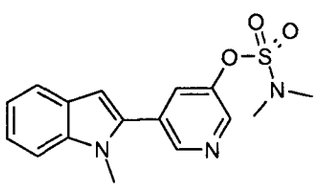
Example 139

(a) Dimethyl-sulfamic acid 5-bromo-pyridin-3-yl ester



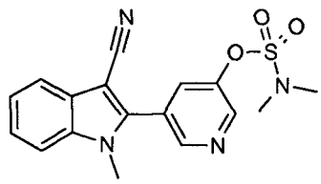
A flask is charged with 5-bromo-pyridin-3-ol (0.200 g, 1.126 mmol), potassium phosphate (0.631 g, 2.884 mmol) and acetone (5 mL) and cooled to 0 °C. Dimethylsulfamoyl chloride (0.261 g, 1.802 mmol) is then added dropwise and the cooling bath is removed. After 2 h, the mixture is diluted with acetone, filtered and the filtrate is concentrated *in vacuo*. The residue is dissolved in THF (30 mL) and polymer-supported trisamine (3.85 mmol/g, 0.7 g, 2.7 mmol) is added. After 1 h, the mixture is filtered. Concentration *in vacuo* gives a residue which is purified by silica gel flash chromatography (heptane-ethyl acetate, 9:1 to 4:1) to give dimethyl-sulfamic acid 5-bromo-pyridin-3-yl ester as a solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 3.05 (s, 3 H), 7.86 (m, 1 H), 8.50 (d, *J*=2.3 Hz, 1 H), 8.62 (d, *J*=1.9 Hz, 1 H).

(b) Dimethyl-sulfamic acid 5-(1-methyl-1H-indol-2-yl)-pyridin-3-yl ester



Dimethyl-sulfamic acid 5-bromo-pyridin-3-yl ester is processed according to the method described in Example 100 to give dimethyl-sulfamic acid 5-(1-methyl-1H-indol-2-yl)-pyridin-3-yl ester. MS (ESI) *m/z* 332.1 $(M+H)^+$.

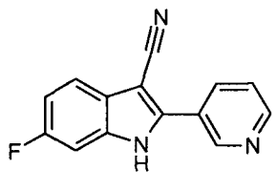
(c) Dimethyl-sulfamic acid 5-(3-cyano-1-methyl-1H-indol-2-yl)-pyridin-3-yl ester



Dimethyl-sulfamic acid 5-(1-methyl-1H-indol-2-yl)-pyridin-3-yl ester is processed according to the method described in Example 128 to give dimethyl-sulfamic acid 5-(3-cyano-1-methyl-1H-indol-2-yl)-pyridin-3-yl ester. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.99 (s, 6 H), 3.82 (s, 3 H), 7.35 - 7.40 (m, 1 H), 7.43 - 7.48 (m, 1 H), 7.74 (d, *J*=7.8 Hz, 1 H), 7.79 (d, *J*=8.3 Hz, 1 H), 8.24 (dd, *J*=2.5, 1.8 Hz, 1 H), 8.85 (d, *J*=2.5 Hz, 1 H), 8.91 (d, *J*=1.8 Hz, 1 H). HRMS (ESI) m/z 357.1018 [$(M+H)^+$ Calcd for $C_{17}H_{17}N_4O_3S$: 357.1021].

Example 140

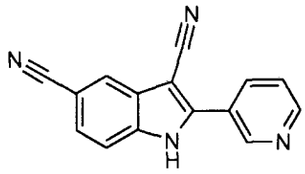
6-Fluoro-2-pyridin-3-yl-1H-indole-3-carbonitrile



To a solution of 6-fluoro-2-pyridin-3-yl-1H-indole (Example 89, 212 mg, 1.0 mmol) in dichloromethane (90 mL) at ambient temperature is added chlorosulfonyl isocyanate (0.71 g, 5 mmol) and the mixture is stirred overnight. Anhydrous DMF (1 mL) is added. After 1 h, the solvent is removed *in vacuo* and the residue purified by HPLC using an Xbridge C18 with a gradient of acetonitrile in 0.1% NH_4OH to give 6-fluoro-2-pyridin-3-yl-1H-indole-3-carbonitrile as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) d ppm 7.12 - 7.21 (m, 1 H), 7.39 (dd, *J*=9.5, 2.4 Hz, 1 H), 7.64 - 7.74 (m, 2 H), 8.27 - 8.35 (m, 1 H), 8.73 (dd, *J*=4.9, 1.6 Hz, 1 H), 9.14 (d, *J*=1.8 Hz, 1 H), 12.89 (s, 1 H). MS (ESI) m/z 238.0 $(M+H)^+$.

Example 141

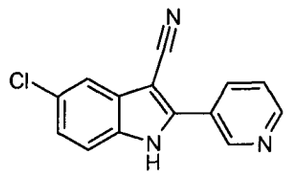
2-Pyridin-3-yl-1H-indole-3,5-dicarbonitrile



2-Pyridin-3-yl-1H-indole-5-carbonitrile (Example 8) is processed according to the method described in Example 140, using acetonitrile instead of dichloromethane, to give 2-pyridin-3-yl-1H-indole-3,5-dicarbonitrile. ^{1}H NMR (400 MHz, MeOD) δ ppm 7.68 (dd, *J*=8.6 Hz, 1 H), 7.72 (dd, *J*=8.1, 4.8 Hz, 1 H), 7.75 (d, *J*=8.3 Hz, 1 H), 8.17 (s, 1 H), 8.47 (dt, *J*=8.1, 1.9 Hz, 1 H), 8.76 (dd, *J*=4.8, 1.5 Hz, 1 H), 9.19 (d, *J*=1.5 Hz, 1 H). HRMS (ESI) m/z 245.0823 [$(M+H)^+$ calcd for $C_{15}H_9N_4$: 245.0827].

Example 142

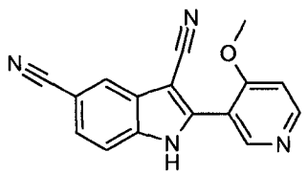
5-Chloro-2-pyridin-3-yl-1H-indole-3-carbonitrile



5-Chloro-2-pyridin-3-yl-1H-indole (Example 87) is processed according to the method described in Example 140, using acetontrile instead of dichloromethane, to give 5-chloro-2-pyridin-3-yl-1H-indole-3-carbonitrile. ^{1}H NMR (400 MHz, MeOD) δ ppm 7.36 (dd, *J*=8.6, 2.0 Hz, 1 H), 7.57 (d, *J*=8.6 Hz, 1 H), 7.65 - 7.77 (m, 2 H), 8.43 (dt, *J*=8.1, 2.0 Hz, 1 H), 8.72 (d, *J*=4.8 Hz, 1 H), 9.16 (s, 1 H). HRMS (ESI) m/z 254.0495 [$(M+H)^+$ calcd for $C_{14}H_9ClN_3$: 254.0485].

Example 143

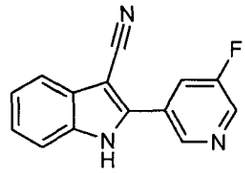
2-(4-Methoxy-pyridin-3-yl)-1H-indole-3,5-dicarbonitrile



2-(4-Methoxy-pyridin-3-yl)-1H-indole-5-carbonitrile (Example 128) is processed according to the method described in Example 140, using acetonitrile instead of dichloromethane, to give 2-(4-methoxy-pyridin-3-yl)-1H-indole-3,5-dicarbonitrile. MS (ESI) m/z 275.08 $(M+H)^+$.

Example 144

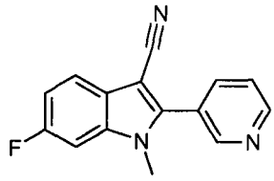
2-(5-Fluoro-pyridin-3-yl)-1H-indole-3-carbonitrile



2-(5-Fluoro-pyridin-3-yl)-1H-indole (Example 92) is processed according to the method described in Example 140, using a mixture of dichloromethane and acetonitrile instead of dichloromethane, to give 2-(5-fluoro-pyridin-3-yl)-1H-indole-3-carbonitrile. MS (ESI) m/z 238.0 $(M+H)^+$.

Example 145

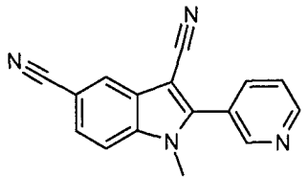
6-Fluoro-1-methyl-2-pyridin-3-yl-1H-indole-3-carbonitrile



A flask is charged with 6-fluoro-2-pyridin-3-yl-1H-indole-3-carbonitrile (Example 140, 50 mg, 0.21 mmol) and DMF (2 mL), and 60% sodium hydride (25 mg, 0.63 mmol) is added. The mixture is stirred at room temperature for 30 min before addition of iodomethane (45 mg, 0.315 mmol). After 1 h, saturated $NaHCO_3$ aqueous solution (3 mL) is added to quench the reaction and the mixture is filtered and purified on Xbridge C18 eluting with a 9:1 to 1:9 water-acetonitrile gradient to give 6-fluoro-1-methyl-2-pyridin-3-yl-1H-indole-3-carbonitrile. ^1H NMR (400 MHz, DMSO-d_6) δ ppm 3.77 (s, 3 H), 7.19 - 7.26 (m, 1 H), 7.66 - 7.76 (m, 3 H), 8.14 - 8.19 (m, 1 H), 8.80 (dd, J=4.9, 1.6 Hz, 1 H), 8.89 (dd, J=2.3, 0.8 Hz, 1 H). HRMS (ESI) m/z 293.1210 $[(M+H+CH_3CN)^+$ calcd for $C_{17}H_{14}FN_4$: 293.1203].

Example 146

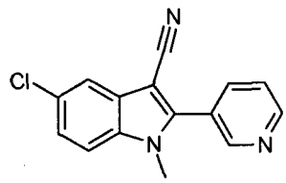
1-Methyl-2-pyridin-3-yl-1H-indole-3,5-dicarbonitrile



2-Pyridin-3-yl-1H-indole-3,5-dicarbonitrile (Example 141) is processed according to the method described in Example 145 to give 1-methyl-2-pyridin-3-yl-1H-indole-3,5-dicarbonitrile. ^{1}H NMR (400 MHz, MeOD) δ ppm 3.90 (s, 3 H), 7.65 - 7.79 (m, 2 H), 7.87 (d, *J*=8.6 Hz, 1 H), 8.20 (s, 1 H), 8.22 (dt, *J*=8.0, 1.9, 1.8 Hz, 1 H), 8.83 (dd, *J*=4.9, 1.6 Hz, 1 H), 8.92 (d, *J*=2.0 Hz, 1 H). HRMS (ESI) m/z 259.0979 [(M+H)$^+$ calcd for $C_{16}H_{11}N_4$: 259.0984].

Example 147

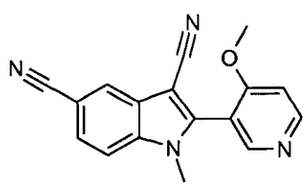
5-Chloro-1-methyl-2-pyridin-3-yl-1H-indole-3-carbonitrile



5-Chloro-2-pyridin-3-yl-1H-indole-3-carbonitrile (Example 142) is processed according to the method described in Example 145 to give 5-chloro-1-methyl-2-pyridin-3-yl-1H-indole-3-carbonitrile. ^{1}H NMR (400 MHz, MeOD) δ ppm 3.86 (s, 3 H), 7.44 (dd, *J*=8.8, 2.0 Hz, 1 H), 7.68 (d, *J*=8.8 Hz, 1 H), 7.71 - 7.81 (m, 2 H), 8.20 (dt, *J*=8.0, 1.9 Hz, 1 H), 8.81 (dd, *J*=4.9, 1.6 Hz, 1 H), 8.89 (d, *J*=1.5 Hz, 1 H). HRMS (ESI) m/z 268.0646 [(M+H)$^+$ calcd for $C_{15}H_{11}ClN_3$: 268.0641].

Example 148

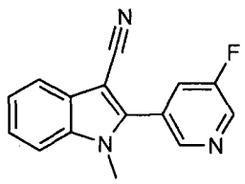
1-Methyl-2-(4-methoxy-pyridin-3-yl)-1H-indole-3,5-dicarbonitrile



2-(4-methoxy-pyridin-3-yl)-1H-indole-3,5-dicarbonitrile (Example 143) is processed according to the method described in Example 145 to give 1-methyl-2-(4-methoxy-pyridin-3-yl)-1H-indole-3,5-dicarbonitrile. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 3.69 (s, 3 H), 3.94 (s, 3 H), 7.38 (d, *J*=5.8 Hz, 1 H), 7.79 (dd, *J*=8.6, 1.5 Hz, 1 H), 7.95 (dd, *J*=8.7, 0.6 Hz, 1 H), 8.27 (dd, *J*=1.5, 0.6 Hz, 1 H), 8.57 (s, 1 H), 8.72 (d, *J*=5.8 Hz, 1 H). HRMS (ESI) m/z 289.1096 [(M+H)$^+$ calcd for $C_{17}H_{13}N_4O$: 289.1089].

Example 149

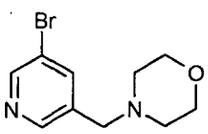
1-Methyl-2-(5-fluoro-pyridin-3-yl)-1H-indole-3-carbonitrile



2-(5-Fluoro-pyridin-3-yl)-1H-indole-3-carbonitrile (Example 144) is processed according to the method described in Example 145 to give 1-methyl-2-(5-fluoro-pyridin-3-yl)-1H-indole-3-carbonitrile. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 3.80 (s, 3 H), 7.30 (td, *J*=9.3, 2.5 Hz, 1 H), 7.52 (dd, *J*=9.0, 2.4 Hz, 1 H), 7.69 (dd, *J*=8.0, 4.9 Hz, 1 H), 7.82 (dd, *J*=9.1, 4.3 Hz, 1 H), 8.17 (dt, *J*=8.1, 2.0, 1.8 Hz, 1 H), 8.81 (dd, *J*=4.8, 1.5 Hz, 1 H), 8.90 (d, *J*=1.5 Hz, 1 H). HRMS (ESI) m/z 252.0948 [(M+H)$^+$ calcd for $C_{15}H_{11}FN_3$: 252.0937].

Example 150

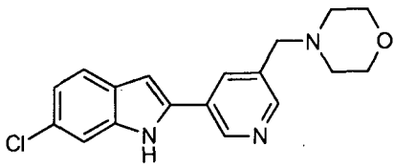
(a) 1-(5-Bromo-pyridin-3-ylmethyl)-morpholine



To a solution of 3-bromo-5-carboxaldehyde pyridine (0.400 g, 2.086 mmol) in dichloroethane (10 mL) at 0 °C is added morpholine (0.275 g, 3.129 mmol), followed with $Na(OAc)_3BH$ (0.931 g, 4.172 mmol). After 2 h, the cooling bath is removed. After stirring overnight, the mixture is diluted with dichloromethane (0.2 L) and washed twice with water and brine. The combined aqueous phase is extracted (twice) with dichloromethane. The combined organic phase is dried over $MgSO_4$, filtered and concentrated to give a residue which is purified by silica gel flash chromatography

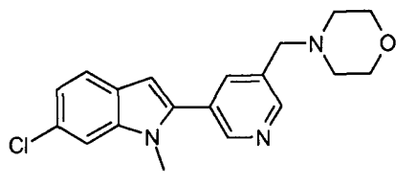
(dichloromethane-methanol, 99:1 to 49:1) gives 1-(5-bromo-pyridin-3-ylmethyl)-morpholine as a colorless oil. MS (ESI) *m/z* 257 and 259 $(M+H)^+$.

(b) 6-Chloro-2-(5-morpholin-4-ylmethyl-pyridin-3-yl)-1H-indole



1-(5-Bromo-pyridin-3-ylmethyl)-morpholine and 6-chloro-1-Boc-indole-2-boronic acid are processed according to the method described in Example 91 to give 6-chloro-2-(5-morpholin-4-ylmethyl-pyridin-3-yl)-1H-indole. MS (ESI) *m/z* 328.2 $(M+H)^+$.

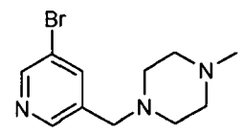
(c) 6-Chloro-1-methyl-2-(5-morpholin-4-ylmethyl-pyridin-3-yl)-1H-indole



6-chloro-2-(5-morpholin-4-ylmethyl-pyridin-3-yl)-1H-indole is processed according to the method described in Example 109 to afford 6-chloro-1-methyl-2-(5-morpholin-4-ylmethyl-pyridin-3-yl)-1H-indole. ^{1}H NMR (400 MHz, MeOD) δ ppm 2.52 - 2.60 (m, 4 H), 3.70 (s, 2 H), 3.72 - 3.77 (m, 4 H), 3.79 (s, 3 H), 6.70 (s, 1 H), 7.11 (dd, *J*=8.3, 1.8 Hz, 1 H), 7.53 (s, 1 H), 7.59 (d, *J*=8.6 Hz, 1 H), 8.06 (t, *J*=2.0 Hz, 1 H), 8.60 (d, *J*=1.8 Hz, 1 H), 8.69 (d, *J*=2.0 Hz, 1 H). HRMS (ESI) m/z 342.1369 [$(M+H)^+$ Calcd for $C_{19}H_{21}ClN_3O$: 342.1373].

Example 151

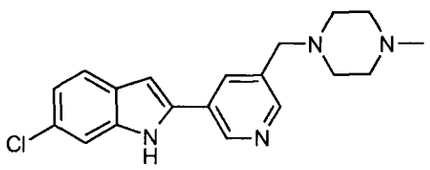
(a) 1-(5-Bromo-pyridin-3-ylmethyl)-4-methyl-piperazine



To a solution of 3-bromo-5-carboxaldehyde pyridine (0.400 g, 2.086 mmol) in dichloroethane (10 mL) at 0 °C is added 1-methylpiperazine (0.317 g, 3.129 mmol), followed with $Na(OAc)_3BH$ (0.931 g, 4.172 mmol). After 2 h, the cooling bath is removed. After stirring overnight, the mixture is diluted with dichloromethane (0.2 L) and washed

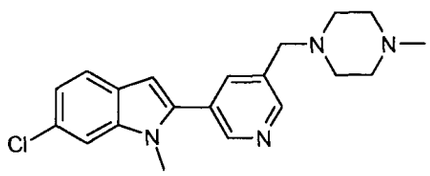
with saturated aqueous sodium bicarbonate. The organic phase is dried over $MgSO_4$, filtered and concentrated to give 1-(5-bromo-pyridin-3-ylmethyl)-4-methyl-piperazine as a yellow solid. (ESI) *m/z* 270 and 272 $(M+H)^+$.

(b) 6-Chloro-2-[5-(4-methyl-piperazin-1-ylmethyl)-pyridin-3-yl]-1H-indole



1-(5-Bromo-pyridin-3-ylmethyl)-4-methyl-piperazine and 6-chloro-1-Boc-indole-2-boronic acid are processed according to the method described in Example 91 to give 6-chloro-2-[5-(4-methyl-piperazin-1-ylmethyl)-pyridin-3-yl]-1H-indole. (ESI) *m/z* 341.1 $(M+H)^+$.

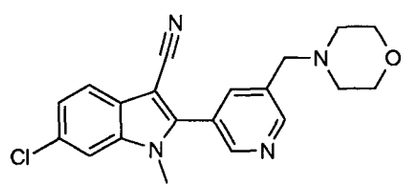
(c) 6-Chloro-1-methyl-2-[5-(4-methyl-piperazin-1-ylmethyl)-pyridin-3-yl]-1H-indole



6-Chloro-1-methyl-2-[5-(4-methyl-piperazin-1-ylmethyl)-pyridin-3-yl]-1H-indole is processed according to the method described in Example 109 to afford 6-chloro-1-methyl-2-[5-(4-methyl-piperazin-1-ylmethyl)-pyridin-3-yl]-1H-indole. ^1H NMR (400 MHz, MeOD) δ ppm 2.33 (s, 3 H), 2.60 (br. s., 8 H), 3.73 (s, 2 H), 3.79 (s, 3 H), 6.70 (s, 1 H), 7.11 (dd, *J*=8.5, 1.9 Hz, 1 H), 7.53 (d, *J*=1.8 Hz, 1 H), 7.59 (d, *J*=8.3 Hz, 1 H), 8.05 (t, *J*=2.0 Hz, 1 H), 8.59 (d, *J*=2.0 Hz, 1 H), 8.69 (d, *J*=2.0 Hz, 1 H). HRMS (ESI) m/z 355.1688 [$(M+H)^+$ Calcd for $C_{20}H_{24}ClN_4$: 355.1689].

Example 152

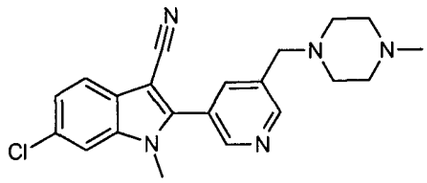
6-Chloro-1-methyl-2-(5-morpholin-4-ylmethyl-pyridin-3-yl)-1H-indole-3-carbonitrile



6-Chloro-1-methyl-2-(5-morpholin-4-ylmethyl-pyridin-3-yl)-1H-indole (Example 150) is processed according to the method described in Example 128 to give 6-chloro-1-methyl-2-(5-morpholin-4-ylmethyl-pyridin-3-yl)-1H-indole-3-carbonitrile. ^{1}H NMR (400 MHz, MeOD) δ ppm 2.51 - 2.66 (m, 4 H), 3.69 - 3.79 (m, 6 H), 3.85 (s, 3 H), 7.38 (dd, *J*=8.3, 1.8 Hz, 1 H), 7.72 (d, *J*=8.3 Hz, 1 H), 7.77 (d, *J*=1.5 Hz, 1 H), 8.20 (t, *J*=2.0 Hz, 1 H), 8.77 (dd, *J*=13.3, 2.1 Hz, 2 H). HRMS (ESI) m/z 367.1321 [(M+H)$^+$ Calcd for $C_{20}H_{20}ClN_4O$: 367.1326].

Example 153

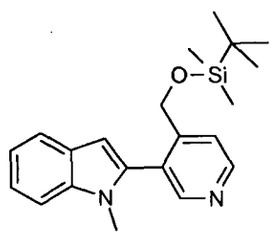
6-Chloro-1-methyl-2-[5-(4-methyl-piperazin-1-ylmethyl)-pyridin-3-yl]-1H-indole-3-carbonitrile



6-Chloro-1-methyl-2-[5-(4-methyl-piperazin-1-ylmethyl)-pyridin-3-yl]-1H-indole (Example 151) is processed according to the method described in Example 128 to give 6-chloro-1-methyl-2-[5-(4-methyl-piperazin-1-ylmethyl)-pyridin-3-yl]-1H-indole-3-carbonitrile. ^{1}H NMR (400 MHz, MeOD) δ ppm 2.34 (s, 3 H), 2.61 (br. s., 8 H), 3.77 (s, 2 H), 3.85 (s, 3 H), 7.38 (dd, *J*=8.6, 1.8 Hz, 1 H), 7.72 (d, *J*=8.6 Hz, 1 H), 7.77 (d, *J*=1.5 Hz, 1 H), 8.18 (t, *J*=2.0 Hz, 1 H), 8.75 (d, *J*=2.0 Hz, 1 H), 8.79 (d, *J*=2.3 Hz, 1 H). HRMS (ESI) m/z 380.1624 [(M+H)$^+$ Calcd for $C_{21}H_{23}ClN_5$: 380.1642].

Example 154

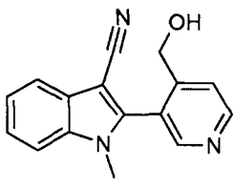
(a) 2-[4-(tert-Butyl-dimethyl-silanyloxymethyl)-pyridin-3-yl]-1-methyl-1H-indole



A flask is charged with [3-(1-methyl-1H-indol-2-yl)-pyridin-4-yl]-methanol (Example 106, 0.270 g, 1.13 mmol), tert-butyl di-methylsilyl chloride (0.187 g, 1.24 mmol), imidazole (0.231 g, 3.39 mmol), DMAP (0.025 g, 0.193 mmol) and DMF (3 mL). The reaction is

stirred at room temperature for 3 h. Water is added and the mixture is extracted with ethyl acetate. The combined organic layer is dried over sodium sulfate and concentrated *in vacuo* to afford 2-[4-(tert-butyl-dimethyl-silanyloxymethyl)-pyridin-3-yl]-1-methyl-1H-indole as an oil, which is used in the next step with no further purification. MS (ESI) *m/z* 353.31 $(M+H)^+$

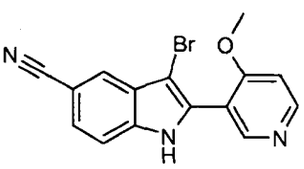
(b) 2-(4-Hydroxymethyl-pyridin-3-yl)-1-methyl-1H-indole-3-carbonitrile



To a solution of 2-[4-(tert-butyl-dimethyl-silanyloxymethyl)-pyridin-3-yl]-1-methyl-1H-indole (0.263 g, 0.747mmol) in DCM (5 mL) is added chlorosulfonyl isocyanate (0.162 mL, 1.867 mmol). After 5 min, DMF(1 mL) is added. After another 30 min, the reaction is concentrated under vacuo to afford 2-[4-(tert-butyl-dimethyl-silanyloxymethyl)-pyridin-3-yl]-1-methyl-1H-indole-3-carbonitrile as a light yellow solid, which is redissolved in DCM (3 mL). 4 M HCl in1,4-dioxane (1 mL) is added, and the mixture is stirred at room temperature for 30 min. Purification by reverse phase HPLC with Xbridge Shield RP18 column and a 0.1% aqueous NH_4OH in acetonitrile gradient affords 2-(4-hydroxymethyl-pyridin-3-yl)-1-methyl-1H-indole-3-carbonitrile as a solid. ^1H NMR (400 MHz, MeOD) δ ppm 3.67 (s, 3 H), 4.44 - 4.67 (m, 2 H), 7.39 (t, *J*=7.6 Hz, 1 H), 7.47 (t, *J*=8.3 Hz, 1 H), 7.66 (d, *J*=8.3 Hz, 1 H), 7.74 (d, *J*=7.8 Hz, 1 H), 7.87 (d, *J*=5.3 Hz, 1 H), 8.60 (s, 1 H), 8.80 (d, *J*=5.3 Hz, 1 H). HRMS (ESI) m/z 264.1142 $[(M+H)^+$ Calcd for $C_{16}H_{14}N_3O$: 264.11379].

Example 155

3-Bromo-2-(4-hydroxy-pyridin-3-yl)-1H-indole-5-carbonitrile

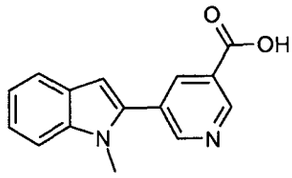


A flask is charged with 2-(4-methoxy-pyridin-3-yl)-1H-indole-5-carbonitrile (Example 90, 190 mg, 0.80 mmol) and DCE (8 mL), and 1.0 M BBr_3 in DCM (4.8 mL, 4.8 mmol) is added. The mixture is stirred at room temperature overnight. The reaction mixture is

poured into saturated aqueous $NaHCO_3$ and extracted with DCM. The aqueous phase is concentrated, acidified with 1M HCl in water and concentrated *in vacuo*. The residue is purified with an Xbridge C18 eluting with a 1:9 to 9:1 acetonitrile-water gradient to give 3-bromo-2-(4-hydroxy-pyridin-3-yl)-1H-indole-5-carbonitrile. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 6.40 (d, *J*=7.1 Hz, 1 H), 7.48 (dd, *J*=8.5, 1.6 Hz, 1 H), 7.71 (d, *J*=8.6 Hz, 1 H), 7.81 (dd, *J*=7.1, 1.3 Hz, 1 H), 7.86 (d, *J*=1.0 Hz, 1 H), 8.67 (d, *J*=1.3 Hz, 1 H). HRMS (ESI) m/z 313.9932 [$(M+H)^+$ calcd for $C_{14}H_9BrN_3O$: 313.9929].

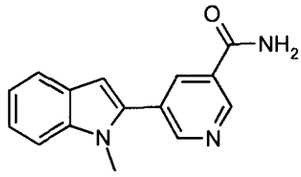
Example 156

(a) 5-(1-Methyl-1H-indol-2-yl)-nicotinic acid



To a solution of 5-(1-methyl-1H-indol-2-yl)-nicotinic acid ethyl ester (Example 102, 0.156g, 0.55 mmol) and MeOH (5 mL) is added aqueous 1M LiOH (1.4 mL, 1.39 mmol). The reaction is stirred at room temperature for 2.5 h. Purification by reverse phase HPLC with Xbridge Shield RP18 column and a 0.1% aqueous NH_4OH in acetonitrile gradient gives 5-(1-methyl-1H-indol-2-yl)-nicotinic acid. MS (ESI) *m/z* 253.34 $(M+H)^+$.

(b) 5-(1-Methyl-1H-indol-2-yl)-nicotinamide

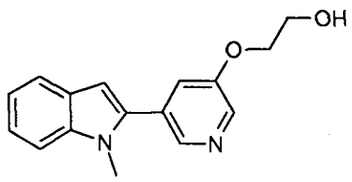


A flask is charged with 5-(1-methyl-1H-indol-2-yl)-nicotinic acid (0.037g, 0.146 mmol), HOBT (0.024 g, 0.175 mmol), EDCI (0.034 g, 0.175 mmol), DIPEA (0.076 mL, 0.439 mmol) and DMF (3 mL). Ammonium chloride (0.012 g, 0.219 mmol) is added and the reaction is stirred at room temperature overnight. Purification by reverse phase HPLC with Xbridge Shield RP18 column and a 0.1% aqueous NH_4OH in acetonitrile gradient gives 5-(1-methyl-1H-indol-2-yl)-nicotinamide. ^{1}H NMR (400 MHz, MeOD) δ ppm 3.85 (s, 3 H), 6.77 (d, *J*=0.6 Hz, 1 H), 7.08 - 7.19 (m, 1 H), 7.29 (ddd, *J*=8.2, 7.1, 1.1 Hz, 1 H), 7.50 (dd, *J*=8.3, 0.7 Hz, 1 H), 7.65 (d, *J*=8.0 Hz, 1 H), 8.49 (t, *J*=2.1 Hz, 1 H), 8.95 (d,

J=2.1 Hz, 1 H), 9.09 (d, *J*=2.1 Hz, 1 H). HRMS (ESI) m/z 252.1145 [(M+H)$^+$ Calcd for $C_{15}H_{14}N_3O$: 252.1137].

Example 157

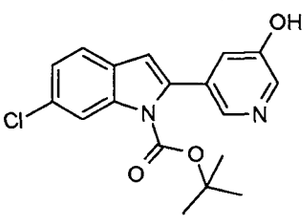
2-[5-(1-Methyl-1H-indol-2-yl)-pyridin-3-yloxy]-ethanol



To a solution of 5-(1-methyl-1H-indol-2-yl)-pyridin-3-ol (Example 108, 0.300g, 1.33 mmol), potassium carbonate (0.462 g, 3.34 mmol) and DMF (3 mL) is added (2-chloro-ethoxy)-trimethylsilane (0.324 mL, 2.00 mmol) and the reaction is stirred at 70 °C overnight and at 100 °C for another 24 h. It is then cooled to room temperature, diluted with ethyl acetate and washed with water. The organic layer is dried over sodium sulfate and concentrated *in vacuo* to afford a residue which is purified by reverse phase HPLC with Xbridge Shield RP18 column and a gradient of 0.1% aqueous NH_4OH in acetonitrile. The resulting oil is dissolved in diethyl ether and a few drops of concentrated HCl are added. Lyophilization gives 2-[5-(1-methyl-1H-indol-2-yl)-pyridin-3-yloxy]-ethanol as the HCl salt. ^{1}H NMR (400 MHz, MeOD) δ ppm (HCl salt) 3.78 (s, 3 H), 3.93 (t, *J*=4.8 Hz, 2 H), 4.22 (t, *J*=4.5 Hz, 2 H), 6.65 (s, 1 H), 7.09 (t, *J*=7.5 Hz, 1 H), 7.23 (ddd, *J*=7.6, 1.1 Hz, 1 H), 7.44 (d, *J*=8.1 Hz, 1 H), 7.58 (d, *J*=7.8 Hz, 1 H), 7.62 (dd, *J*=2.8, 1.8 Hz, 1 H), 8.31 (d, *J*=2.8 Hz, 1 H), 8.34 (d, *J*=1.5 Hz, 1 H). HRMS (ESI) m/z 269.1302 [(M+H)$^+$ Calcd for $C_{16}H_{17}N_2O_2$: 269.1290].

Example 158

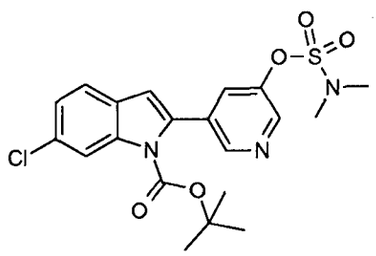
(a) 6-Chloro-2-(5-hydroxy-pyridin-3-yl)-indole-1-carboxylic acid tert-butyl ester



A microwave flask is charged with 6-chloro-1-Boc-indole-2-boronic acid (1.91 g, 6.46 mmol), 3-hydroxy-5-bromopyridine (0.750 g, 4.31 mmol), potassium phosphate (1.83 g, 8.62 mmol) and DMF (15 mL). The flask is evacuated and filled with nitrogen thrice and

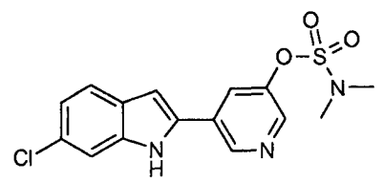
$Pd(PPh_3)_4$ (0.250 g, 0.215 mmol) is added. The flask is evacuated and filled with nitrogen thrice again, and heated to 110 °C under microwave irradiation for 45 min. $Pd(PPh_3)_4$ (0.100 g, 0.086 mmol) is added and the vial is heated again to 110 °C under microwave irradiation for 45 min. The mixture is then diluted with ethyl acetate and washed with water thrice. The organic layer is dried over sodium sulfate and concentrated *in vacuo*. The residue is purified by silica gel flash chromatography (dichloromethane-methanol, 19:1) to afford 6-chloro-2-(5-hydroxy-pyridin-3-yl)-indole-1-carboxylic acid tert-butyl ester as a solid. MS (ESI) *m/z* 345.06 $(M+H)^+$

(b) 6-Chloro-2-(5-diethylsulfamoyloxy-pyridin-3-yl)-indole-1-carboxylic acid tert-butyl ester



A flask is charged with 6-chloro-2-(5-hydroxy-pyridin-3-yl)-indole-1-carboxylic acid tert-butyl ester (0.200 g, 0.581 mmol) and acetone (5 mL). Diethylaminosulfamoyl chloride (0.150 g, 0.872 mmol) and potassium phosphate (0.308 g, 1.45 mmol) are added and the reaction is stirred at room temperature overnight. The mixture is then concentrated *in vacuo*. The residue is dissolved in DCM and washed with water. The organic layer is dried over sodium sulfate and concentrated to afford 6-chloro-2-(5-diethylsulfamoyloxy-pyridin-3-yl)-indole-1-carboxylic acid tert-butyl ester as an oil, which is used without further purification. MS (ESI) *m/z* 480.1 $(M+H)^+$.

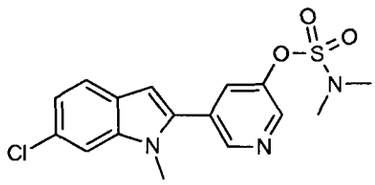
(c) Diethyl-sulfamic acid 5-(6-chloro-1H-indol-2-yl)-pyridin-3-yl ester



6-Chloro-2-(5-diethylsulfamoyloxy-pyridin-3-yl)-indole-1-carboxylic acid tert-butyl ester is redissolved in DCM (2 mL) and trifluoroacetic acid (2 mL) is added. After 1 h, saturated aqueous sodium bicarbonate is added and following extraction with dichloromethane,

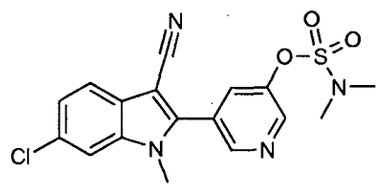
the organic layer is dried over sodium sulfate and concentrated to give diethyl-sulfamic acid 5-(6-chloro-1H-indol-2-yl)-pyridin-3-yl ester, which is used in the next step without further purification. MS (ESI) *m/z* 378.1 $(M+H)^+$

(d) Diethyl-sulfamic acid 5-(6-chloro-1-methyl-1H-indol-2-yl)-pyridin-3-yl ester



A flask is charged with diethyl-sulfamic acid 5-(6-chloro-1H-indol-2-yl)-pyridin-3-yl ester (0.175 g, 0.560 mmol) and DMF (5 mL). Dimethyl carbonate (0.116 mL, 1.38 mmol) and potassium carbonate (0.035 g, 0.253 mmol) are added and the reaction is stirred at 150 °C overnight. The reaction mixture is cooled to room temperature, diluted with ethyl acetate and washed with water. The organic layer is dried over sodium sulfate and concentrated *in vacuo*. The residue is purified by flash chromatography (heptane-ethyl acetate, 3:1) to afford diethyl-sulfamic acid 5-(6-chloro-1-methyl-1H-indol-2-yl)-pyridin-3-yl ester as a yellow solid. MS (ESI) *m/z* 394.04 $(M+H)^+$

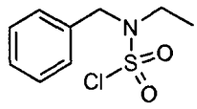
(e) Diethyl-sulfamic acid 5-(6-chloro-3-cyano-1-methyl-1H-indol-2-yl)-pyridin-3-yl ester



Diethyl-sulfamic acid 5-(6-chloro-1-methyl-1H-indol-2-yl)-pyridin-3-yl ester is processed according to the method described in Example 128 to give diethyl-sulfamic acid 5-(6-chloro-3-cyano-1-methyl-1H-indol-2-yl)-pyridin-3-yl ester. ^{1}H NMR (400 MHz, MeOD) δ ppm 1.28 (t, *J*=7.2 Hz, 6 H), 3.51 (q, *J*=7.1 Hz, 4 H), 3.85 (s, 3 H), 7.39 (dd, *J*=8.5, 1.9 Hz, 1 H), 7.74 (d, *J*=8.6 Hz, 1 H), 7.78 (d, *J*=1.8 Hz, 1 H), 8.15 (t, *J*=2.0 Hz, 1 H), 8.77 (d, *J*=2.5 Hz, 1 H), 8.84 (d, *J*=1.8 Hz, 1 H). HRMS (ESI) m/z 419.0966 [$(M+H)^+$ Calcd for $C_{19}H_{20}ClN_4O_3S$: 419.0945].

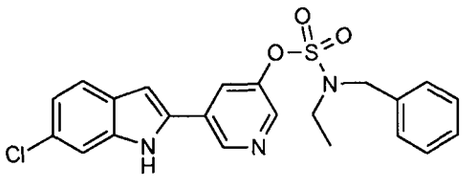
Example 159

(a) *N*-Ethyl-*N*-benzylaminosulfamoyl chloride



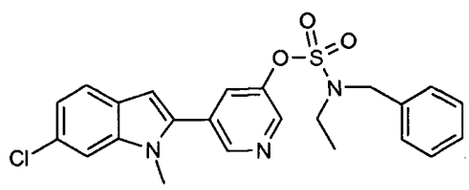
To a solution of sulfuryl chloride (1.19 mL, 14.8 mmol) in dichloromethane (10 mL) is added *N*-ethyl-*N*-benzylamine (2.0 g, 14.7 mmol) at −10 °C. The cooling bath is removed after 30 min and the mixture is stirred overnight. The mixture is washed with water and following back-extraction with DCM, the combined organic layer is dried over sodium sulfate and concentrated *in vacuo* to give *N*-ethyl-*N*-benzylaminosulfamoyl chloride. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 1.19 (t, *J*=7.2 Hz, 3 H), 3.40 (q, *J*=7.3 Hz, 2 H), 4.50 (br. s., 2 H), 7.32 - 7.48 (m, 5 H).

(b) Benzyl-ethyl-sulfamic acid 5-(6-chloro-1H-indol-2-yl)-pyridin-3-yl ester



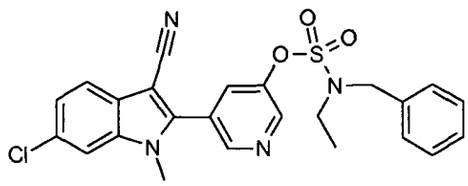
N-Ethyl-*N*-benzylaminosulfamoyl chloride and 6-chloro-2-(5-hydroxy-pyridin-3-yl)-indole-1-carboxylic acid tert-butyl ester (Example 158a) are processed according to the method described in Example 158b to give 2-[5-(benzyl-ethyl-sulfamoyloxy)-pyridin-3-yl]-6-chloro-indole-1-carboxylic acid tert-butyl ester. The crude product is loaded onto silica gel and heated to 50 °C overnight under vacuum. Elution with heptane-ethanol, 1:1 affords benzyl-ethyl-sulfamic acid 5-(6-chloro-1H-indol-2-yl)-pyridin-3-yl ester. MS (ESI) *m/z* 442.1 $(M+H)^+$.

(c) Benzyl-ethyl-sulfamic acid 5-(6-chloro-1-methyl-1H-indol-2-yl)-pyridin-3-yl ester



Benzyl-ethyl-sulfamic acid 5-(6-chloro-1H-indol-2-yl)-pyridin-3-yl ester is processed according to the method described in Example 114 to give benzyl-ethyl-sulfamic acid 5-(6-chloro-1-methyl-1H-indol-2-yl)-pyridin-3-yl ester. MS (ESI) *m/z* 456.0 $(M+H)^+$

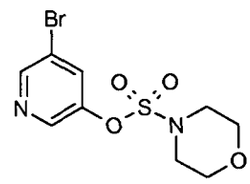
(d) Benzyl-ethyl-sulfamic acid 5-(6-chloro-3-cyano-1-methyl-1H-indol-2-yl)-pyridin-3-yl ester



Benzyl-ethyl-sulfamic acid 5-(6-chloro-1-methyl-1H-indol-2-yl)-pyridin-3-yl ester is processed according to the method described in Example 128 to give benzyl-ethyl-sulfamic acid 5-(6-chloro-3-cyano-1-methyl-1H-indol-2-yl)-pyridin-3-yl ester. ^{1}H NMR (400 MHz, MeOD) δ ppm 1.15 (t, *J*=7.2 Hz, 3 H), 3.43 (q, *J*=7.1 Hz, 2 H), 3.82 (s, 3 H), 4.61 (s, 2 H), 7.27 - 7.47 (m, 6 H), 7.73 (d, *J*=8.6 Hz, 1 H), 7.77 (d, *J*=1.5 Hz, 1 H), 8.06 (t, *J*=2.5 Hz, 1 H), 8.72 (d, *J*=2.5 Hz, 1 H), 8.83 (d, *J*=1.8 Hz, 1 H). HRMS (ESI) m/z 481.1085 [(M+H)$^+$ Calcd for $C_{24}H_{22}ClN_4O_3S$: 481.1101].

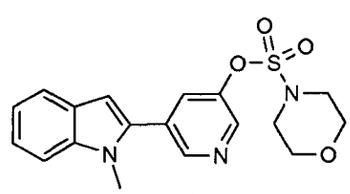
Example 160

(a) Morpholine-4-sulfonic acid 5-bromo-pyridin-3-yl ester



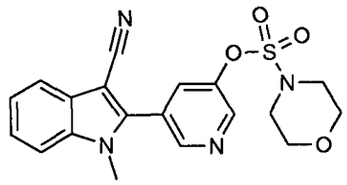
A flask is charged with 5-bromo-pyridin-3-ol (0.310 g, 1.78 mmol), potassium phosphate (0.982 g, 4.63 mmol) and acetone (10 mL), and morpholine-4-sulfonyl chloride (0.529 g, 2.85 mmol) is added dropwise at 0 °C. The mixture is stirred at room temperature overnight. Saturated $NaHCO_3$ in water (1 mL) is added and the mixture is concentrated *in vacuo*. The residue is purified on silica gel chromatography eluting with a 9:1 to 4:1 heptane-ethyl acetate gradient to give morpholine-4-sulfonic acid 5-bromo-pyridin-3-yl ester. MS (ESI) *m/z* 322.9 and 324.9 (M+H)$^+$.

(b) Morpholine-4-sulfonic acid 5-(1-methyl-1H-indol-2-yl)-pyridin-3-yl ester



Morpholine-4-sulfonic acid 5-bromo-pyridin-3-yl ester and *N*-methyl-indoleboronic acid are processed according to the method described in Example 100 to give morpholine-4-sulfonic acid 5-(1-methyl-1H-indol-2-yl)-pyridin-3-yl ester. MS (ESI) *m/z* 374.1 $(M+H)^+$

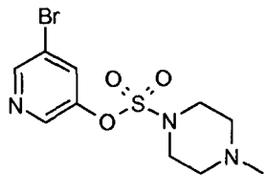
(c) Morpholine-4-sulfonic acid 5-(3-cyano-1-methyl-1H-indol-2-yl)-pyridin-3-yl ester



Morpholine-4-sulfonic acid 5-(1-methyl-1H-indol-2-yl)-pyridin-3-yl ester is processed according to the method described in Example 128 to give morpholine-4-sulfonic acid 5-(3-cyano-1-methyl-1H-indol-2-yl)-pyridin-3-yl ester. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 3.38 - 3.43 (m, 4 H), 3.66 - 3.70 (m, 4 H), 3.81 (s, 3 H), 7.34 - 7.39 (m, 1 H), 7.42 - 7.48 (m, 1 H), 7.73 (d, *J*=7.8 Hz, 1 H), 7.78 (d, *J*=8.3 Hz, 1 H), 8.26 (dd, *J*=2.5, 2.0 Hz, 1 H), 8.86 (d, *J*=2.5 Hz, 1 H), 8.90 (d, *J*=1.8 Hz, 1 H). HRMS (ESI) m/z 399.1124 [$(M+H)^+$ Calcd for $C_{19}H_{19}N_4O_4S$: 399.1127].

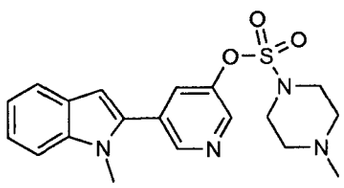
Example 161

(a) 4-Methyl-piperazine-1-sulfonic acid 5-bromo-pyridin-3-yl ester



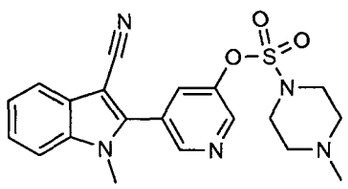
4-Methyl-piperazine-1-sulfonyl chloride is processed according to the method described in Example 160a to give 4-methyl-piperazine-1-sulfonic acid 5-bromo-pyridin-3-yl ester. MS (ESI) *m/z* 335.9 and 337.9 $(M+H)^+$.

(b) 4-Methyl-piperazine-1-sulfonic acid 5-(1-methyl-1H-indol-2-yl)-pyridin-3-yl ester



4-Methyl-piperazine-1-sulfonic acid 5-bromo-pyridin-3-yl ester and *N*-methyl-indoleboronic acid are processed according to the method described in Example 100 to give 4-Methyl-piperazine-1-sulfonic acid 5-(1-methyl-1H-indol-2-yl)-pyridin-3-yl ester. MS (ESI) *m/z* 387.1 $(M+H)^+$.

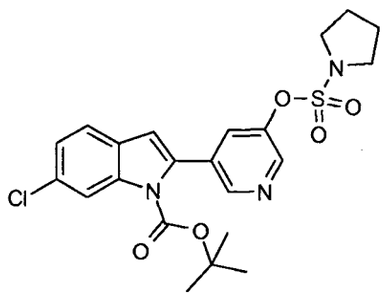
(c) 4-Methyl-piperazine-1-sulfonic acid 5-(3-cyano-1-methyl-1H-indol-2-yl)-pyridin-3-yl ester



4-Methyl-piperazine-1-sulfonic acid 5-(1-methyl-1H-indol-2-yl)-pyridin-3-yl ester is processed according to the method described in Example 128 to give 4-methyl-piperazine-1-sulfonic acid 5-(3-cyano-1-methyl-1H-indol-2-yl)-pyridin-3-yl ester. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.21 (s, 3 H), 2.38 - 2.43 (m, 4 H), 3.38 - 3.43 (m, 4 H), 3.81 (s, 3 H), 7.34 - 7.39 (m, 1 H), 7.42 - 7.48 (m, 1 H), 7.73 (d, *J*=7.8 Hz, 1 H), 7.78 (d, *J*=8.3 Hz, 1 H), 8.24 (dd, *J*=2.5, 1.8 Hz, 1 H), 8.84 (d, *J*=2.5 Hz, 1 H), 8.90 (d, *J*=1.8 Hz, 1 H). HRMS (ESI) m/z 412.1443 $[(M+H)^+$ Calcd for $C_{20}H_{22}N_5O_3S$: 412.1443].

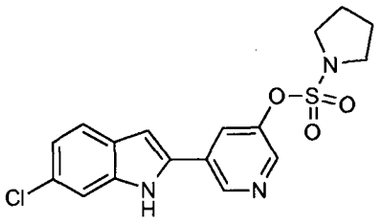
Example 162

(a) 6-Chloro-2-[5-(pyrrolidine-1-sulfonyloxy)-pyridin-3-yl]-indole-1-carboxylic acid tert-butyl ester



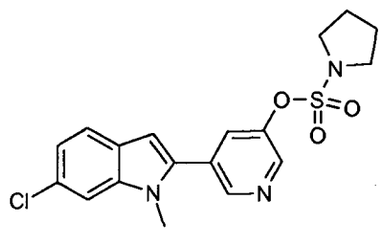
1-Pyrrolidine-sulfonyl chloride and 6-chloro-2-(5-hydroxy-pyridin-3-yl)-indole-1-carboxylic acid tert-butyl ester (Example 160a) are processed according to the method described in Example 160b to give 6-chloro-2-[5-(pyrrolidine-1-sulfonyloxy)-pyridin-3-yl]-indole-1-carboxylic acid tert-butyl ester, which is taken onto the next step without further purification. MS (ESI) *m/z* 478.1 $(M+H)^+$.

(b) Pyrrolidine-1-sulfonic acid 5-(6-chloro-1H-indol-2-yl)-pyridin-3-yl ester



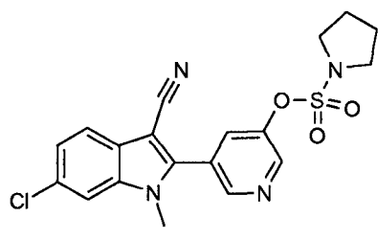
6-Chloro-2-[5-(pyrrolidine-1-sulfonyloxy)-pyridin-3-yl]-indole-1-carboxylic acid tert-butyl ester is dissolved in DCM (2 mL), and the mixture is cooled to 0 °C. TFA (2 mL) is added and the mixture is stirred at room temperature for 1 h. Saturated sodium bicarbonate is then added and the mixture is extracted with DCM. The organic layer is dried over sodium sulfate and concentrated *in vacuo* to afford pyrrolidine-1-sulfonic acid 5-(6-chloro-1H-indol-2-yl)-pyridin-3-yl ester as an oil which is taken onto the next step without further purification. MS (ESI) *m/z* 376.2 $(M+H)^+$.

(c) Pyrrolidine-1-sulfonic acid 5-(6-chloro-1-methyl-1H-indol-2-yl)-pyridin-3-yl ester



Pyrrolidine-1-sulfonic acid 5-(6-chloro-1H-indol-2-yl)-pyridin-3-yl ester is processed according to the method described in Example 109 to give pyrrolidine-1-sulfonic acid 5-(6-chloro-1-methyl-1H-indol-2-yl)-pyridin-3-yl ester. MS (ESI) *m/z* 392.0 $(M+H)^+$.

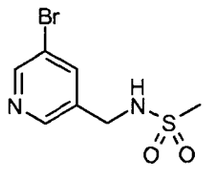
(d) Pyrrolidine-1-sulfonic acid 5-(6-chloro-3-cyano-1-methyl-1H-indol-2-yl)-pyridin-3-yl ester



Pyrrolidine-1-sulfonic acid 5-(6-chloro-1-methyl-1H-indol-2-yl)-pyridin-3-yl ester is processed according to the method described in Example 128 to give pyrrolidine-1-sulfonic acid 5-(6-chloro-3-cyano-1-methyl-1H-indol-2-yl)-pyridin-3-yl ester. ^{1}H NMR (400 MHz, MeOD) δ ppm 2.01 - 2.09 (m, 4 H), 3.53 - 3.60 (m, 4 H), 3.85 (s, 3 H), 7.39 (dd, *J*=8.3, 1.8 Hz, 1 H), 7.74 (d, *J*=8.6 Hz, 1 H), 7.79 (d, *J*=1.5 Hz, 1 H), 8.17 (dd, *J*=2.5, 1.8 Hz, 1 H), 8.81 (d, *J*=2.5 Hz, 1 H), 8.85 (d, *J*=1.8 Hz, 1 H). HRMS (ESI) *m/z* 417.0788 [(M+H)$^+$ Calcd for $C_{19}H_{19}N_4O_3SCl$: 417.0788].

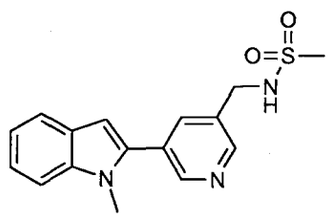
Example 163

(a) *N*-(5-Bromo-pyridin-3-ylmethyl)-methanesulfonamide



To a solution of 5-bromo-3-pyridine-carboxaldehyde (1.5 g, 7.9 mmol), methanesulfonamide (0.5 g, 5.3 mmol), acetic acid (0.637 g, 10.6 mmol), triethylamine (1.07 g, 10.6 mmol) in DCE (50 mL) at ambient temperature is added $NaBH(OAc)_3$ (3.14 g, 14.84 mmol). The reaction mixture is stirred overnight. Aqueous $NaHCO_3$ (20 mL) is added and the organic phase is separated. The aqueous phase is extracted with dichloromethane and the combined organic phase is dried over Na_2SO_4. Concentration affords a residue which is purified by silica gel flash chromatography with a methanol in dichloromethane gradient to afford *N*-(5-bromo-pyridin-3-ylmethyl)-methanesulfonamide as a solid. MS (ESI) *m/z* 266.9 (M+H)$^+$.

(b) *N*-[5-(1-Methyl-1H-indol-2-yl)-pyridin-3-ylmethyl]-methanesulfonamide

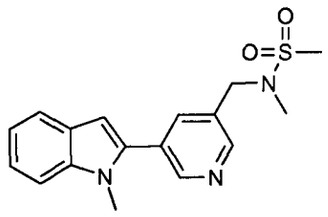


N-(5-Bromo-pyridin-3-ylmethyl)-methanesulfonamide and *N*-methyl-indoleboronic acid are processed according to the method described in Example 100 to give *N*-[5-(1-methyl-1H-indol-2-yl)-pyridin-3-ylmethyl]-methanesulfonamide. ^{1}H NMR (400 MHz, MeOD) δ ppm 3.03 (s, 3 H), 3.82 (s, 3 H), 4.45 (s, 2 H), 6.70 (s, 1 H), 7.13 (t, *J*=7.5 Hz, 1

H), 7.23 - 7.31 (m, 1 H), 7.48 (d, *J*=8.1 Hz, 1 H), 7.63 (d, *J*=7.8 Hz, 1 H), 8.10 (t, *J*=2.0 Hz, 1 H), 8.62 (d, *J*=2.0 Hz, 1 H), 8.72 (d, *J*=2.0 Hz, 1 H). HRMS (ESI) *m/z* 316.1108 $[(M+H)^+$ Calcd for $C_{16}H_{18}N_3O_2S$: 316.1120].

Example 164

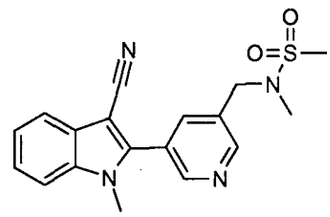
N-Methyl-*N*-[5-(1-methyl-1H-indol-2-yl)-pyridin-3-ylmethyl]-methanesulfonamide



N-[5-(1-Methyl-1H-indol-2-yl)-pyridin-3-ylmethyl]-methanesulfonamide (Example 163) is processed according to the method described in Example 114 to give *N*-methyl-*N*-[5-(1-methyl-1H-indol-2-yl)-pyridin-3-ylmethyl]-methanesulfonamide. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.77 (s, 3 H), 3.02 (s, 3 H), 3.78 (s, 3 H), 4.41 (s, 2 H), 6.72 (s, 1 H), 7.07 - 7.13 (m, 1 H), 7.20 - 7.25 (m, 1 H), 7.54 (d, *J*=8.3 Hz, 1 H), 7.61 (d, *J*=7.8 Hz, 1 H), 7.95 (t, *J*=2.0 Hz, 1 H), 8.60 (d, *J*=2.0 Hz, 1 H), 8.78 (d, *J*=2.0 Hz, 1 H). MS (ESI) *m/z* 330.1 $(M+H)^+$.

Example 165

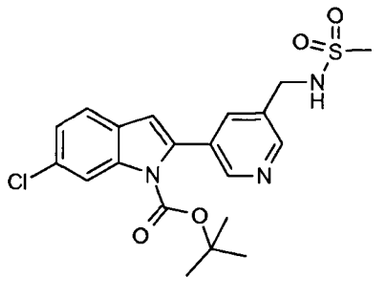
N-Methyl-*N*-[5-(1-methyl-3-cyano-1H-indol-2-yl)-pyridin-3-ylmethyl]-methanesulfonamide



N-Methyl-*N*-[5-(1-methyl-1H-indol-2-yl)-pyridin-3-ylmethyl]-methanesulfonamide (Example 164) is processed according to the method described in Example 128 to give *N*-methyl-*N*-[5-(1-methyl-3-cyano-1H-indol-2-yl)-pyridin-3-ylmethyl]-methanesulfonamide. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.80 (s, 3 H), 3.03 (s, 3 H), 3.82 (s, 3 H), 4.46 (s, 2 H), 7.34 - 7.39 (m, 1 H), 7.42 - 7.47 (m, 1 H), 7.72 (d, *J*=7.8 Hz, 1 H), 7.77 (d, *J*=8.3 Hz, 1 H), 8.09 (t, *J*=2.1 Hz, 1 H), 8.77 (d, *J*=2.0 Hz, 1 H), 8.87 (d, *J*=2.3 Hz, 1 H). HRMS (ESI) m/z 355.1229 $[(M+H)^+$ Calcd for $C_{18}H_{19}N_4O_2S$: 355.1229].

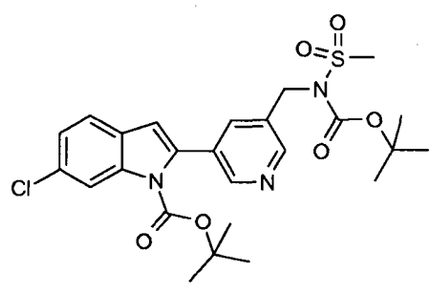
Example 166

(a) 6-Chloro-2-[5-(methanesulfonyl-amino-methyl)-pyridin-3-yl]-indole-1-carboxylic acid tert-butyl ester



A flask is charged with *N*-(5-bromo-pyridin-3-ylmethyl)-methanesulfonamide (Example 163a, 530 mg, 2 mmol), *N*-Boc-6-chloro-indole-2-boronic acid (525 mg, 3.0 mmol), s-Phos (41 mg, 0.10 mmol), finely crushed potassium phosphate (849 mg, 4.0 mmol) and toluene (20 mL), and the mixture is degassed for 15 min. Pd_2dba_3 (37 mg, 0.04 mmol) is added and the mixture is stirred at 85 °C for 1 h. The mixture is cooled to room temperature, diluted with DCM and silica gel (10 g) is added. The mixture is concentrated *in vacuo* and the residue is purified by silica gel flash chromatography eluting with a 0 to 90% ethyl acetate-heptane gradient to give 6-chloro-2-[5-(methanesulfonylamino-methyl)-pyridin-3-yl]-indole-1-carboxylic acid tert-butyl ester. MS (ESI) *m/z* 436.1 and 437.9 $(M+H)^+$.

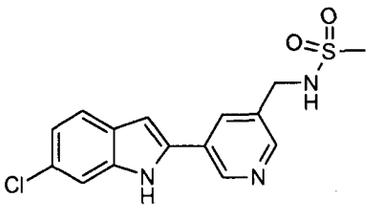
(b) 6-Chloro-2-[5-(methanesulfonyl-(tert-butoxycarbonyl)-amino-methyl)-pyridin-3-yl]-indole-1-carboxylic acid tert-butyl ester



To a solution of 6-chloro-2-[5-(methanesulfonylamino-methyl)-pyridin-3-yl]-indole-1-carboxylic acid tert-butyl ester (530 mg, 1.22 mmol) in acetonitrile (10 mL) are added Boc_2O (398 mg, 1.82 mmol) and DMAP (15 mg, 0.12 mmol). The mixture is stirred for 1 h. Silica gel (1 g) is added and the mixture is concentrated *in vacuo*. The residue is

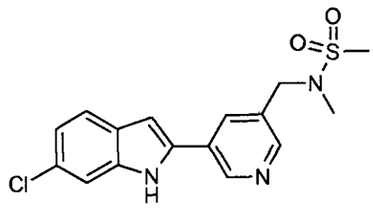
purified by silica gel chromatography to give 6-chloro-2-[5-(methanesulfonyl-(tert-butoxycarbonyl)-amino-methyl)-pyridin-3-yl]-indole-1-carboxylic acid tert-butyl ester. MS (ESI) *m/z* 536.2 and 538.1 $(M+H)^+$.

(c) *N*-[5-(6-Chloro-1H-indol-2-yl)-pyridin-3-ylmethyl]-methanesulfonamide



A flask is charged with 6-chloro-2-[5-(methanesulfonyl-(tert-butoxycarbonyl)-amino-methyl)-pyridin-3-yl]-indole-1-carboxylic acid tert-butyl ester (0.52 g, 0.97 mmol) and TFA (5 mL) and the mixture is stirred at room temperature for 1 h. The mixture is concentrated in vacuo to give *N*-[5-(6-chloro-1H-indol-2-yl)-pyridin-3-ylmethyl]-methanesulfonamide which is used in the next step without further purification. MS (ESI) *m/z* 336.0 and 337.9 $(M+H)^+$.

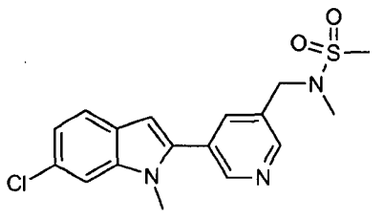
(d) *N*-[5-(6-Chloro-1H-indol-2-yl)-pyridin-3-ylmethyl]-*N*-methyl-methanesulfonamide



A flask is charged with *N*-[5-(6-chloro-1H-indol-2-yl)-pyridin-3-ylmethyl]-methanesulfonamide (670 mg, 1.49 mmol), DMF (10 mL), dimethyl carbonate (403 mg, 4.47 mmol) and potassium carbonate (319 mg, 2.31 mmol), and the mixture is stirred at 150 °C for 5 h. The mixture is cooled to room temperature and purified using Xbridge C18 eluting with a 1:9 to 9:1 acetonitrile-water gradient to give *N*-[5-(6-chloro-1H-indol-2-yl)-pyridin-3-ylmethyl]-*N*-methyl-methanesulfonamide. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.74 (s, 3 H), 3.02 (s, 3 H), 4.35 (s, 2 H), 7.04 (dd, *J*=8.5, 1.9 Hz, 1 H), 7.09 (d, *J*=1.5 Hz, 1 H), 7.43 (d, *J*=1.8 Hz, 1 H), 7.59 (d, *J*=8.6 Hz, 1 H), 8.14 (t, *J*=2.1 Hz, 1 H), 8.47 (d, *J*=2.0 Hz, 1 H), 9.05 (d, *J*=2.3 Hz, 1 H), 11.92 (s, 1 H). HRMS (ESI) m/z 350.0738 [$(M+H)^+$ Calcd for $C_{16}H_{17}ClN_3O_2S$: 350.0730].

Example 167

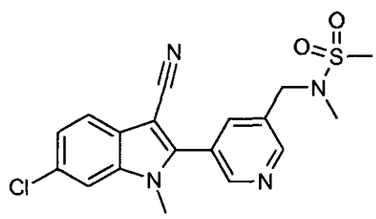
N-[5-(6-Chloro-1-methyl-1H-indol-2-yl)-pyridin-3-ylmethyl]-*N*-methyl-methanesulfonamide



The method described in Example 166d also generates *N*-[5-(6-chloro-1-methyl-1H-indol-2-yl)-pyridin-3-ylmethyl]-N-methyl-methanesulfonamide. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.78 (s, 3 H), 3.02 (s, 3 H), 3.77 (s, 3 H), 4.41 (s, 2 H), 6.76 (d, *J*=0.8 Hz, 1 H), 7.11 (dd, *J*=8.5, 1.9 Hz, 1 H), 7.62 (d, *J*=8.5 Hz, 1 H), 7.70 (d, *J*=1.8 Hz, 1 H), 7.96 (t, *J*=2.2 Hz, 1 H), 8.62 (d, *J*=2.2 Hz, 1 H), 8.78 (d, *J*=2.2 Hz, 1 H). MS (ESI) *m/z* 364.1 $(M+H)^+$.

Example 168

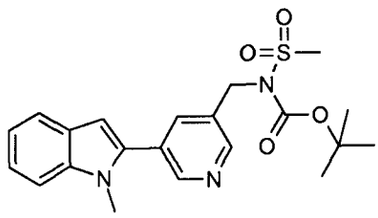
N-[5-(6-Chloro-3-cyano-1-methyl-1H-indol-2-yl)-pyridin-3-ylmethyl]-*N*-methyl-methanesulfonamide



N-[5-(6-Chloro-1-methyl-1H-indol-2-yl)-pyridin-3-ylmethyl]-*N*-methyl-methanesulfonamide (Example 167) is processed according to the method described in Example 128 to give *N*-[5-(6-chloro-3-cyano-1-methyl-1H-indol-2-yl)-pyridin-3-ylmethyl]-*N*-methyl-methanesulfonamide. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.78 (s, 3 H), 3.02 (s, 3 H), 3.79 (s, 3 H), 4.45 (s, 2 H), 7.37 (dd, *J*=8.5, 1.9 Hz, 1 H), 7.73 (d, *J*=8.6 Hz, 1 H), 7.97 (d, *J*=1.5 Hz, 1 H), 8.08 (t, *J*=2.0 Hz, 1 H), 8.76 (d, *J*=2.0 Hz, 1 H), 8.85 (d, *J*=2.0 Hz, 1 H). HRMS (ESI) m/z 389.0835 $[(M+H)^+$ Calcd for $C_{18}H_{18}ClN_4O_2S$: 389.0839].

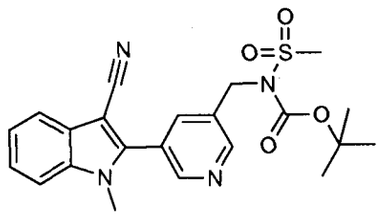
Example 169

(a) 2-[5-(Methanesulfonyl-(tert-butoxycarbonyl)-amino-methyl)-pyridin-3-yl]-1-methyl-indole



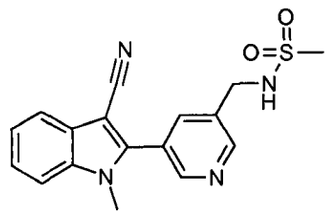
To a solution of *N*-[5-(1-Methyl-1H-indol-2-yl)-pyridin-3-ylmethyl]-methanesulfonamide (Example 163b) (337 mg, 0.200 mmol) in acetonitrile (5 mL) are added Boc_2O (293 mg, 1.34 mmol) and DMAP (14 mg, 0.11 mmol). The reaction mixture is stirred for 1 h and after removal of the solvent, the residue is purified by silica gel flash chromatography to afford 2-[5-(methanesulfonyl-(tert-butoxycarbonyl)-amino-methyl)-pyridin-3-yl]-1-methyl-indole. MS (ESI) *m/z* 416.2 $(M+H)^+$.

(b) 2-[5-(Methanesulfonyl-(tert-butoxycarbonyl)-amino-methyl)-pyridin-3-yl]-1-methyl-3-cyano-indole



To a solution of 2-[5-(methanesulfonyl-(tert-butoxycarbonyl)-amino-methyl)-pyridin-3-yl]-1-methyl-indole (350 mg, 0.842 mmol) in dichloromethane (10 mL) is added chlorosulfonyl isocyanate (0.358 g, 2.53 mmol). The mixture is stirred at ambient temperature for 20 min, whereupon anhydrous DMF (2 mL) is added. After 1 h, the mixture is concentrated to a volume of 3 mL, and filtered. Purification by RP HPLC affords 2-[5-(methanesulfonyl-(tert-butoxycarbonyl)-amino-methyl)-pyridin-3-yl]-1-methyl-3-cyano-indole. MS (ESI) *m/z* 441.1 $(M+H)^+$.

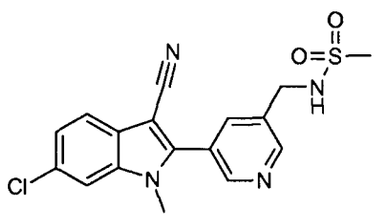
(c) *N*-[5-(3-Cyano-1-methyl-1H-indol-2-yl)-pyridin-3-ylmethyl]-methanesulfonamide



2-[5-(Methanesulfonyl-(tert-butoxycarbonyl)-amino-methyl)-pyridin-3-yl]-1-methyl-3-cyano-indole (260 mg, 0.59 mmol) in TFA (3 mL) at ambient temperature is stirred for 30 min. The solvent is then removed *in vacuo* and the residue is purified by RP HPLC. The fractions containing the product are pooled and concentrated and the residue is further purified by flash silica gel flash chromatography (methanol-dichloromethane gradient) to give *N*-[5-(3-cyano-1-methyl-1H-indol-2-yl)-pyridin-3-ylmethyl]-methanesulfonamide. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.97 (s, 3 H), 3.79 (s, 3 H), 4.36 (br. s., 2 H), 7.33 - 7.39 (m, 1 H), 7.40 - 7.46 (m, 1 H), 7.69 - 7.79 (m, 3 H), 8.10 (t, *J*=2.1 Hz, 1 H), 8.77 (d, *J*=2.3 Hz, 1 H), 8.81 (d, *J*=2.3 Hz, 1 H). HRMS (ESI) *m/z* 341.1068 [(M+H)$^+$ Calcd for $C_{17}H_{17}N_4O_2S$: 341.1072].

Example 170

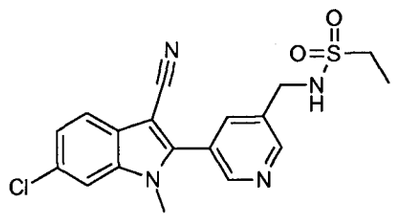
N-[5-(6-chloro-3-cyano-1-methyl-1H-indol-2-yl)-pyridin-3-ylmethyl]-methanesulfonamide



6-Chloro-2-(5-formyl-pyridin-3-yl)-1-methyl-1H-indole-3-carbonitrile (Example 126, 50 mg, 0.169 mmol) and methanesulfonamide (24 mg, 0.254 mmol), acetic acid (20 mg, 0.338 mmol), triethylamine (34 mg, 0.338 mmol) in DCE (10 mL) are stirred for 30 min at ambient temperature before adding $NaBH(OAc)_3$ (100 mg, 0.473 mmol). The reaction mixture is stirred overnight. $NaHCO_3$ (1 mL) is added and the solvents are removed *in vacuo*. The residue is purified using a Sunfire C18 with a gradient of acetonitrile in 0.1% aqueous TFA and further purified with an Xbridge C18 using a gradient of acetonitrile in 0.1% NH_4OH to give *N*-[5-(6-chloro-3-cyano-1-methyl-1H-indol-2-yl)-pyridin-3-ylmethyl]-methanesulfonamide as a solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.97 (s, 3 H), 3.78 (s, 3 H), 4.36 (s, 2 H), 7.37 (dd, *J*=8.6, 1.8 Hz, 1 H), 7.73 (d, *J*=8.6 Hz, 1 H), 7.75 (br. s., 1 H), 7.97 (d, *J*=1.8 Hz, 1 H), 8.10 (t, *J*=2.1 Hz, 1 H), 8.78 (d, *J*=2.0 Hz, 1 H), 8.81 (d, *J*=2.3 Hz, 1 H). HRMS (ESI) *m/z* 375.0681 [(M+H)$^+$ Calcd for $C_{17}H_{16}ClN_4O_2S$: 375.0682].

Example 171

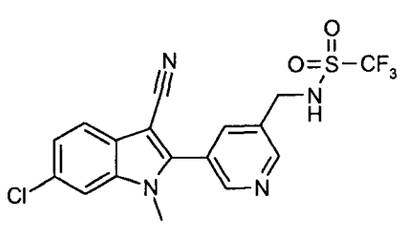
N-[5-(6-chloro-3-cyano-1-methyl-1H-indol-2-yl)-pyridin-3-ylmethyl]-ethanesulfonamide



6-Chloro-2-(5-formyl-pyridin-3-yl)-1-methyl-1H-indole-3-carbonitrile (Example 126b, 2.0 g, 6.09 mmol), ethanesulfonamide (1.33 g, 12.17 mmol) and toluene (250 mL), and titanium(IV) isopropoxide (2.59 g, 9.13 mmol) is added dropwise. The mixture is stirred at 120 °C overnight. The mixture is then concentrated *in vacuo*. The residue is taken up in DCM (150 mL) and MeOH (150 mL), and $NaBH_4$ (0.461 g, 12.17 mmol) is added at 0 °C. The mixture is stirred at 0 °C for 30 min. Water (50 mL) is added and the mixture is stirred for 5 min. The suspension is filtered through a pad of celite. The celite layer is washed with DCM (3 × 50 mL). The combined organic phase is dried over Na_2SO_4 and concentrated to give a residue is purified by silica gel flash chromatography (ethyl acetate). The resulting fractions containing the product are concentrated and repurified by silica gel flash chromatography (dichloromethane-methanol, 1:0 to 97:3). The concentrated product is redissolved in MeOH (500 mL) at 60 °C and concentrated *in vacuo* to give *N*-[5-(6-chloro-3-cyano-1-methyl-1H-indol-2-yl)-pyridin-3-ylmethyl]-ethanesulfonamide. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.20 (t, *J*=7.3 Hz, 3 H), 3.06 (q, *J*=7.3 Hz, 2 H), 3.78 (s, 3 H), 4.34 (d, J=6.3 Hz, 2 H), 7.37 (dd, *J*=8.6, 1.8 Hz, 1 H), 7.73 (d, *J*=8.3 Hz, 1 H), 7.77 (t, *J*=6.2 Hz, 1 H), 7.97 (d, *J*=1.8 Hz, 1 H), 8.09 (t, *J*=2.1 Hz, 1 H), 8.78 (d, *J*=1.8 Hz, 1 H), 8.80 (d, *J*=1.8 Hz, 1 H). HRMS (ESI) *m/z* 389.0853 [(M+H)$^+$ Calcd for $C_{18}H_{17}ClN_4O_2S$: 389.0839].

Example 172

N-[5-(6-chloro-3-cyano-1-methyl-1H-indol-2-yl)-pyridin-3-ylmethyl]- *C,C,C*-trifluoromethanesulfonamide

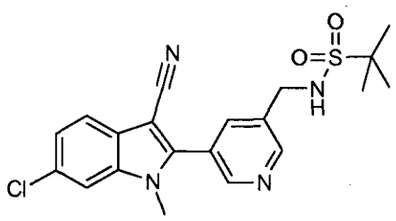


6-Chloro-2-(5-formyl-pyridin-3-yl)-1-methyl-1H-indole-3-carbonitrile (Example 126) and trifluoromethanesulfonamide are processed according to the method described in

Example 170 to give *N*-[5-(6-chloro-3-cyano-1-methyl-1H-indol-2-yl)-pyridin-3-ylmethyl]-*C*,*C*,*C*-trifluoromethanesulfonamide. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 3.78 (s, 3 H), 4.56 (s, 2 H), 7.37 (dd, *J*=8.5, 1.9 Hz, 1 H), 7.73 (d, *J*=8.6 Hz, 1 H), 7.97 (d, *J*=1.5 Hz, 1 H), 8.09 (t, *J*=2.1 Hz, 1 H), 8.78 (d, *J*=2.3 Hz, 1 H), 8.83 (d, *J*=2.0 Hz, 1 H), 10.16 (br. s., 1 H). HRMS (ESI) *m/z* 429.0412 [(M+H)$^+$ Calcd for $C_{17}H_{13}ClF_3N_4O_2S$: 429.0400].

Example 173

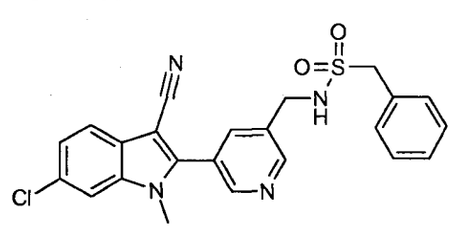
2-Methyl-propane-2-sulfonic acid [5-(6-chloro-3-cyano-1-methyl-1H-indol-2-yl)-pyridin-3-ylmethyl]-amide



6-Chloro-2-(5-formyl-pyridin-3-yl)-1-methyl-1H-indole-3-carbonitrile (Example 126) and 2-methyl-propane-2-sulfonic acid amide are processed according to the method described in Example 170 to give 2-methyl-propane-2-sulfonic acid [5-(6-chloro-3-cyano-1-methyl-1H-indol-2-yl)-pyridin-3-ylmethyl]-amide. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.32 (s, 9 H), 3.78 (s, 3 H), 4.43 (d, *J*=6.1 Hz, 2 H), 7.37 (dd, *J*=8.6, 1.8 Hz, 1 H), 7.65 (t, *J*=6.2 Hz, 1 H), 7.73 (d, *J*=8.3 Hz, 1 H), 7.97 (d, *J*=1.5 Hz, 1 H), 8.06 (t, *J*=2.1 Hz, 1 H), 8.77 (d, *J*=1.8 Hz, 1 H), 8.80 (d, *J*=2.0 Hz, 1 H). HRMS (ESI) *m/z* 417.1150 [(M+H)$^+$ Calcd for $C_{20}H_{21}ClN_4O_2S$: 417.1152].

Example 174

N-[5-(6-Chloro-3-cyano-1-methyl-1H-indol-2-yl)-pyridin-3-ylmethyl]-*C*-phenyl-methanesulfonamide

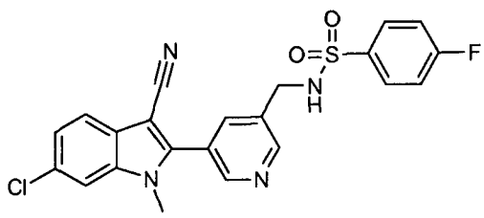


6-Chloro-2-(5-formyl-pyridin-3-yl)-1-methyl-1H-indole-3-carbonitrile (Example 126) and phenyl-methanesulfonamide are processed according to the method described in

Example 170 to give *N*-[5-(6-chloro-3-cyano-1-methyl-1H-indol-2-yl)-pyridin-3-ylmethyl]-*C*-phenyl-methanesulfonamide. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 3.77 (s, 3 H), 4.31 (s, 2 H), 4.44 (s, 2 H), 7.30 - 7.41 (m, 6 H), 7.73 (d, *J*=8.3 Hz, 1 H), 7.83 (br. s., 1 H), 7.97 (d, *J*=1.5 Hz, 1 H), 8.03 (t, *J*=2.1 Hz, 1 H), 8.73 (d, *J*=2.0 Hz, 1 H), 8.79 (d, *J*=2.0 Hz, 1 H). HRMS (ESI) *m/z* 451.1006 [(M+H)$^+$ Calcd for $C_{23}H_{20}ClN_4O_2S$: 451.0996].

Example 175

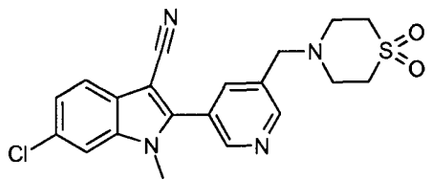
N-[5-(6-Chloro-3-cyano-1-methyl-1H-indol-2-yl)-pyridin-3-ylmethyl]-4-fluoro-benzenesulfonamide



6-Chloro-2-(5-formyl-pyridin-3-yl)-1-methyl-1H-indole-3-carbonitrile (Example 126) and 4-fluoro-benzenesulfonamide are processed according to the method described in Example 170 to give *N*-[5-(6-chloro-3-cyano-1-methyl-1H-indol-2-yl)-pyridin-3-ylmethyl]-4-fluoro-benzenesulfonamide. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 3.74 (s, 3 H), 4.23 (s, 2 H), 7.33 - 7.41 (m, 3 H), 7.72 (d, *J*=8.6 Hz, 1 H), 7.82 - 7.88 (m, 2 H), 7.95 (d, *J*=1.5 Hz, 2 H), 8.44 (s, 1 H), 8.62 (d, *J*=2.0 Hz, 1 H), 8.73 (d, *J*=2.0 Hz, 1 H). HRMS (ESI) *m/z* 455.0746 [(M+H)$^+$ Calcd for $C_{22}H_{17}ClFN_4O_2S$: 455.0745].

Example 176

6-Chloro-2-[5-(1,1-dioxo-1lambda*6*-thiomorpholin-4-ylmethyl)-pyridin-3-yl]-1-methyl-1H-indole-3-carbonitrile

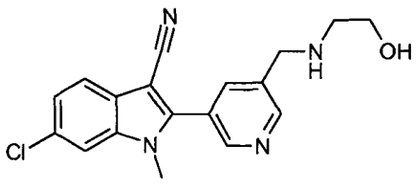


6-Chloro-2-(5-formyl-pyridin-3-yl)-1-methyl-1H-indole-3-carbonitrile (Example 126) and thiomorpholine-1,1-dioxide are processed according to the method described in Example 170 to give 6-chloro-2-[5-(1,1-dioxo-1lambda*6*-thiomorpholin-4-ylmethyl)-pyridin-3-yl]-1-methyl-1H-indole-3-carbonitrile. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.93 - 2.98 (m, 4 H), 3.12 - 3.18 (m, 4 H), 3.81 (s, 3 H), 3.87 (s, 2 H), 7.37 (dd, *J*=8.5, 1.9 Hz, 1 H), 7.73

(d, *J*=8.3 Hz, 1 H), 7.97 (d, *J*=1.5 Hz, 1 H), 8.13 (t, *J*=2.0 Hz, 1 H), 8.75 (d, *J*=2.0 Hz, 1 H), 8.81 (d, *J*=2.3 Hz, 1 H). HRMS (ESI) *m/z* 415.1015 $[(M+H)^+$ Calcd for $C_{20}H_{20}ClN_4O_2S$: 415.0996].

Example 177

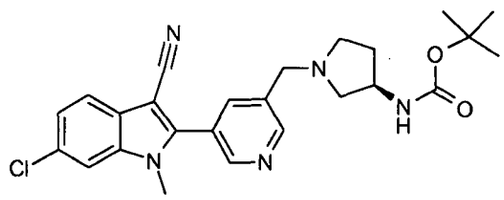
6-Chloro-2-{5-[(2-hydroxy-ethylamino)-methyl]-pyridin-3-yl}-1-methyl-1H-indole-3-carbonitrile



6-Chloro-2-(5-formyl-pyridin-3-yl)-1-methyl-1H-indole-3-carbonitrile (Example 126) and 2-amino-ethanol are processed according to the method described in Example 170 to give 6-chloro-2-{5-[(2-hydroxy-ethylamino)-methyl]-pyridin-3-yl}-1-methyl-1H-indole-3-carbonitrile. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.65 - 2.72 (m, 2 H), 3.49 - 3.55 (m, 2 H), 3.79 (s, 3 H), 3.92 - 3.98 (m, 2 H), 4.61 (br. s., 1 H), 7.37 (dd, *J*=8.3, 1.8 Hz, 1 H), 7.73 (d, *J*=8.3 Hz, 1 H), 7.97 (d, *J*=1.8 Hz, 1 H), 8.10 - 8.13 (m, 1 H), 8.75 - 8.79 (m, 2 H). HRMS (ESI) *m/z* 341.1175 $[(M+H)^+$ Calcd for $C_{19}H_{18}ClN_4O$: 341.1169].

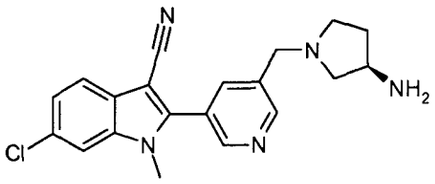
Example 178

(a) {(*R*)-1-[5-(6-Chloro-3-cyano-1-methyl-1H-indol-2-yl)-pyridin-3-ylmethyl]-pyrrolidin-3-yl}-carbamic acid tert-butyl ester



6-Chloro-2-(5-formyl-pyridin-3-yl)-1-methyl-1H-indole-3-carbonitrile (Example 126) and (R)-pyrrolidin-3-yl-carbamic acid tert-butyl ester are processed according to the method described in Example 170 to give {(*R*)-1-[5-(6-chloro-3-cyano-1-methyl-1H-indol-2-yl)-pyridin-3-ylmethyl]-pyrrolidin-3-yl}-carbamic acid tert-butyl ester. MS (ESI) *m/z* 466.17 $(M+H)^+$.

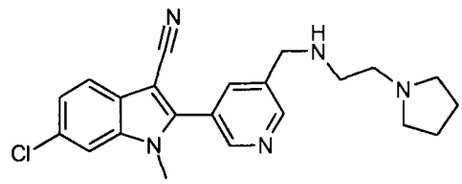
(b) 2-[5-((*R*)-3-Amino-pyrrolidin-1-ylmethyl)-pyridin-3-yl]-6-chloro-1-methyl-1H-indole-3-carbonitrile



To a solution of {(*R*)-1-[5-(6-chloro-3-cyano-1-methyl-1H-indol-2-yl)-pyridin-3-ylmethyl]-pyrrolidin-3-yl}-carbamic acid tert-butyl ester (140 mg, 0.3 mmol) in dichloromethane (5 mL) is added TFA (2 mL) and the mixture is stirred at room temperature for 2 h. The solvents are then removed *in vacuo* and the residue is purified by Xbridge C18 with a gradient of acetonitrile in 0.1% NH_4OH to give 2-[5-((*R*)-3-amino-pyrrolidin-1-ylmethyl)-pyridin-3-yl]-6-chloro-1-methyl-1H-indole-3-carbonitrile. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.33 - 1.43 (m, 1 H), 1.64 (br. s., 2 H), 1.97 - 2.08 (m, 1 H), 2.21 (dd, *J*=9.0, 4.9 Hz, 1 H), 2.59 - 2.68 (m, 1 H), 2.71 (dd, *J*=9.1, 6.6 Hz, 1 H), 3.32 - 3.39 (m, 1 H), 3.72 (q, *J*=13.6 Hz, 2 H), 3.79 (s, 3 H), 7.36 (dd, *J*=8.3, 1.8 Hz, 1 H), 7.72 (d, *J*=8.6 Hz, 1 H), 7.96 (d, *J*=1.5 Hz, 1 H), 8.05 (t, *J*=2.0 Hz, 1 H), 8.72 (d, *J*=2.0 Hz, 1 H), 8.77 (d, *J*=2.3 Hz, 1 H). HRMS (ESI) *m/z* 366.1483 [(M+H)$^+$ Calcd for $C_{20}H_{21}ClN_5$: 366.1485].

Example 179

6-Chloro-1-methyl-2-{5-[(2-pyrrolidin-1-yl-ethylamino)-methyl]-pyridin-3-yl}-1H-indole-3-carbonitrile

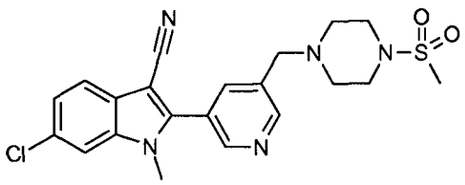


6-Chloro-2-(5-formyl-pyridin-3-yl)-1-methyl-1H-indole-3-carbonitrile (Example 126) and 2-pyrrolidin-1-yl-ethylamine are processed according to the method described in Example 170 to give 6-chloro-1-methyl-2-{5-[(2-pyrrolidin-1-yl-ethylamino)-methyl]-pyridin-3-yl}-1H-indole-3-carbonitrile. The free base is taken up in 4M HCl in dioxane, concentrated *in vacuo*, dissolved in water and lyophilized to give the HCl salt. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm (HCl salt) 1.83 - 1.93 (m, 2 H), 2.04 (br. s., 2 H), 3.06 (br. s., 2 H), 3.50 (br. s., 2 H), 3.54 - 3.60 (m, 2 H), 3.66 (br. s., 2 H), 3.84 (s, 3 H), 4.43 (br. s., 2 H), 7.39 (dd, *J*=8.6, 1.8 Hz, 1 H), 7.75 (d, *J*=8.3 Hz, 1 H), 8.01 (d, *J*=1.5 Hz, 1 H),

8.43 (t, *J*=2.0 Hz, 1 H), 8.94 (d, *J*=2.0 Hz, 1 H), 8.99 (d, *J*=2.0 Hz, 1 H), 9.97 (br. s., 2 H), 10.89 (br. s., 1 H). HRMS (ESI) *m/z* 394.1803 [$(M+H)^+$ Calcd for $C_{22}H_{25}ClN_5$: 394.1798].

Example 180

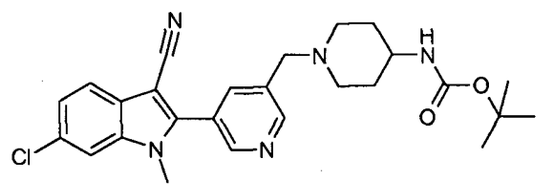
6-Chloro-2-[5-(4-methanesulfonyl-piperazin-1-ylmethyl)-pyridin-3-yl]-1-methyl-1H-indole-3-carbonitrile



6-Chloro-2-(5-formyl-pyridin-3-yl)-1-methyl-1H-indole-3-carbonitrile (Example 126) and 1-methanesulfonyl-piperazine are processed according to the method described in Example 170 to give 6-chloro-2-[5-(4-methanesulfonyl-piperazin-1-ylmethyl)-pyridin-3-yl]-1-methyl-1H-indole-3-carbonitrile. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.55 (t, *J*=4.5 Hz, 4 H), 3.14 (t, *J*=4.5 Hz, 4 H), 3.30 (s, 3 H), 3.72 (s, 2 H), 3.80 (s, 3 H), 7.36 (dd, *J*=8.5, 1.9 Hz, 1 H), 7.72 (d, *J*=8.3 Hz, 1 H), 7.96 (d, *J*=1.5 Hz, 1 H), 8.06 (t, *J*=2.0 Hz, 1 H), 8.73 (d, *J*=2.0 Hz, 1 H), 8.80 (d, *J*=2.0 Hz, 1 H). HRMS (ESI) *m/z* 444.1265 [$(M+H)^+$ Calcd for $C_{22}H_{25}ClN_5$: 444.1261].

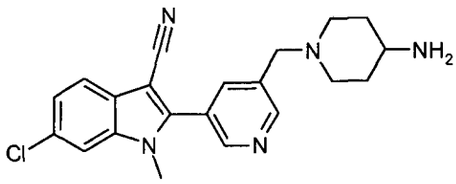
Example 181

(a) {1-[5-(6-Chloro-3-cyano-1-methyl-1H-indol-2-yl)-pyridin-3-ylmethyl]-piperidin-4-yl}-carbamic acid tert-butyl ester



6-Chloro-2-(5-formyl-pyridin-3-yl)-1-methyl-1H-indole-3-carbonitrile (Example 126) and piperidin-4-yl-carbamic acid tert-butyl ester are processed according to the method described in Example 170 to give {1-[5-(6-chloro-3-cyano-1-methyl-1H-indol-2-yl)-pyridin-3-ylmethyl]-piperidin-4-yl}-carbamic acid tert-butyl ester. MS (ESI) *m/z* 480.1 $(M+H)^+$.

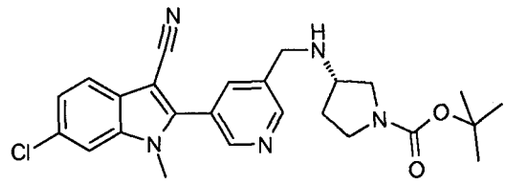
(b) 2-[5-(4-Amino-piperidin-1-ylmethyl)-pyridin-3-yl]-6-chloro-1-methyl-1H-indole-3-carbonitrile



{1-[5-(6-Chloro-3-cyano-1-methyl-1H-indol-2-yl)-pyridin-3-ylmethyl]-piperidin-4-yl}-carbamic acid tert-butyl ester is processed according to the method described in Example 178b to give 2-[5-(4-amino-piperidin-1-ylmethyl)-pyridin-3-yl]-6-chloro-1-methyl-1H-indole-3-carbonitrile. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm (trifluoroacetate salt) 1.75 (br. s., 2 H), 2.07 (s, 3 H), 3.08 (br. s., 2 H), 3.54 (br. s., 2 H), 3.84 (s, 3 H), 4.47 (br. s., 2 H), 7.39 (dd, *J*=8.3, 1.8 Hz, 1 H), 7.75 (d, *J*=8.3 Hz, 1 H), 8.01 (d, *J*=1.5 Hz, 1 H), 8.09 (br. s., 3 H), 8.27 (s, 1 H), 8.89 (s, 1 H), 9.01 (s, 1 H), 10.11 (br. s., 1 H). HRMS (ESI) *m/z* 380.1630 [(M+H)$^+$ Calcd for $C_{21}H_{23}ClN_5$: 380.1642].

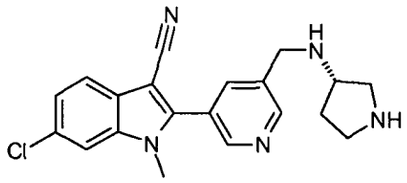
Example 182

(a) (*S*)-3-{[5-(6-Chloro-3-cyano-1-methyl-1H-indol-2-yl)-pyridin-3-ylmethyl]-amino}-pyrrolidine-1-carboxylic acid tert-butyl ester



6-Chloro-2-(5-formyl-pyridin-3-yl)-1-methyl-1H-indole-3-carbonitrile (Example 126) and (*S*)-3-amino-pyrrolidine-1-carboxylic acid tert-butyl ester are processed according to the method described in Example 170 to give (S)-3-{[5-(6-chloro-3-cyano-1-methyl-1H-indol-2-yl)-pyridin-3-ylmethyl]-amino}-pyrrolidine-1-carboxylic acid tert-butyl ester. MS (ESI) *m/z* 466.1 (M+H)$^+$.

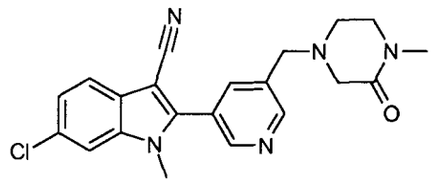
(b) 6-Chloro-1-methyl-2-[5-((*S*)-pyrrolidin-3-ylaminomethyl)-pyridin-3-yl]-1H-indole-3-carbonitrile



(*S*)-3-{[5-(6-chloro-3-cyano-1-methyl-1H-indol-2-yl)-pyridin-3-ylmethyl]-amino}-pyrrolidine-1-carboxylic acid tert-butyl ester is processed according to the method described in Example 178b to give 6-chloro-1-methyl-2-[5-((*S*)-pyrrolidin-3-ylaminomethyl)-pyridin-3-yl]-1H-indole-3-carbonitrile. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.50 - 1.59 (m, 1 H), 1.77 - 1.88 (m, 1 H), 2.64 - 2.69 (m, 1 H), 2.72 - 2.79 (m, 1 H), 2.84 (dd, *J*=11.2, 5.9 Hz, 1 H), 2.88 - 2.96 (m, 1 H), 3.13 - 3.20 (m, 1 H), 3.31 (br. s., 2 H), 3.79 (s, 3 H), 3.82 (s, 2 H), 7.37 (dd, *J*=8.6, 1.8 Hz, 1 H), 7.72 (d, *J*=8.6 Hz, 1 H), 7.97 (d, *J*=1.5 Hz, 1 H), 8.09 (t, *J*=2.1 Hz, 1 H), 8.73 - 8.77 (m, 2 H). HRMS (ESI) *m/z* 366.1495 [(M+H)$^+$ Calcd for $C_{20}H_{21}ClN_5$: 366.1485].

Example 183

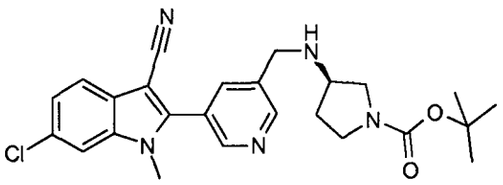
6-Chloro-1-methyl-2-[5-(4-methyl-3-oxo-piperazin-1-ylmethyl)-pyridin-3-yl]-1H-indole-3-carbonitrile



6-Chloro-2-(5-formyl-pyridin-3-yl)-1-methyl-1H-indole-3-carbonitrile (Example 126) and 1-methyl-piperazin-2-one are processed according to the method described in Example 170 to give 6-chloro-1-methyl-2-[5-(4-methyl-3-oxo-piperazin-1-ylmethyl)-pyridin-3-yl]-1H-indole-3-carbonitrile. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.70 (br. s., 2 H), 2.82 (s, 3 H), 3.09 (s, 2 H), 3.29 (dd, *J*=11.0, 5.4 Hz, 2 H), 3.73 (s, 2 H), 3.80 (s, 3 H), 7.36 (dd, *J*=8.6, 1.8 Hz, 1 H), 7.72 (d, *J*=8.3 Hz, 1 H), 7.96 (d, *J*=1.5 Hz, 1 H), 8.09 (s, 1 H), 8.74 (d, *J*=2.0 Hz, 1 H), 8.81 (d, *J*=2.0 Hz, 1 H). HRMS (ESI) *m/z* 394.1437 [(M+H)$^+$ Calcd for $C_{21}H_{21}ClN_5O$: 394.1435].

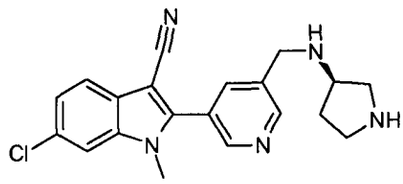
Example 184

(a) (*R*)-3-{[5-(6-Chloro-3-cyano-1-methyl-1H-indol-2-yl)-pyridin-3-ylmethyl]-amino}-pyrrolidine-1-carboxylic acid tert-butyl ester



6-Chloro-2-(5-formyl-pyridin-3-yl)-1-methyl-1H-indole-3-carbonitrile (Example 126) and (*R*)-3-amino-pyrrolidine-1-carboxylic acid tert-butyl ester are processed according to the method described in Example 170 to give (*R*)-3-{[5-(6-chloro-3-cyano-1-methyl-1H-indol-2-yl)-pyridin-3-ylmethyl]-amino}-pyrrolidine-1-carboxylic acid tert-butyl ester. MS (ESI) *m/z* 466.11 $(M+H)^+$.

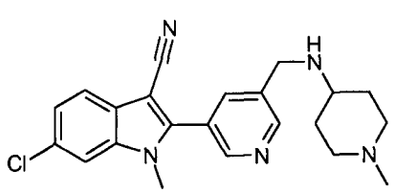
(b) 6-Chloro-1-methyl-2-[5-((*R*)-pyrrolidin-3-ylaminomethyl)-pyridin-3-yl]-1H-indole-3-carbonitrile



(*R*)-3-{[5-(6-Chloro-3-cyano-1-methyl-1H-indol-2-yl)-pyridin-3-ylmethyl]-amino}-pyrrolidine-1-carboxylic acid tert-butyl ester is processed according to the method described in Example 178b to give 6-chloro-1-methyl-2-[5-((*R*)-pyrrolidin-3-ylaminomethyl)-pyridin-3-yl]-1H-indole-3-carbonitrile. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.52 - 1.61 (m, 1 H), 1.79 - 1.88 (m, 1 H), 2.70 (dd, *J*=11.2, 3.9 Hz, 1 H), 2.75 - 2.82 (m, 1 H), 2.86 (dd, *J*=11.1, 5.8 Hz, 1 H), 2.90 - 2.98 (m, 1 H), 3.14 - 3.21 (m, 1 H), 3.39 (br. s., 2 H), 3.79 (s, 3 H), 3.83 (s, 2 H), 7.37 (dd, *J*=8.3, 1.8 Hz, 1 H), 7.72 (d, *J*=8.6 Hz, 1 H), 7.96 (d, *J*=1.5 Hz, 1 H), 8.10 (t, *J*=2.1 Hz, 1 H), 8.74 - 8.77 (m, 2 H). HRMS (ESI) *m/z* 366.1486 [$(M+H)^+$ Calcd for $C_{20}H_{21}ClN_5$ 366.1485].

Example 185

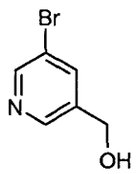
6-Chloro-1-methyl-2-{5-[(1-methyl-piperidin-4-ylamino)-methyl]-pyridin-3-yl}-1H-indole-3-carbonitrile



To a solution of 6-chloro-2-(5-formyl-pyridin-3-yl)-1-methyl-1H-indole-3-carbonitrile (Example 126, 0.150 g, 0.482 mmol) in THF (3 mL) and DMF(1 mL) is added 4-amino-1-methylpiperidine (0.067 g, 0.578 mmol), followed with MP-$NaBH_3CN$ (2.42 mmol/g, 0.498 g, 1.205 mmol). After 16 h, MP-$NaBH_3CN$ (2.42 mmol/g, 0.200 g, 0.484 mmol) is added. After another 46 h and PL-benzaldehyde (1.8 mmol/g, 0.268 g, 0.482 mmol) is added and after another 8 h, the mixture is filtered and the solids are washed with THF. After evaporation of the solvents, the residue is purified by reverse phase HPLC on a Sunfire C18, eluting with a gradient of 0.1% aqueous TFA-acetonitrile to give 6-chloro-1-methyl-2-{5-[(1-methyl-piperidin-4-ylamino)-methyl]-pyridin-3-yl}-1H-indole-3-carbonitrile as a gum which is triturated with 1M HCl in ether to give the HCl salt. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm (HCl salt) 1.46-1.66 (m, 2 H), 1.93 - 2.04 (m, 2 H), 2.50-2.57 (m, 4 H), 2.66-2.76 (m, 2 H), 3.10-3.20 (m, 2 H), 3.80 (s, 3 H), 3.95 (br. s., 2 H), 7.37 (dd, *J*=8.6, 1.8 Hz, 1 H), 7.73 (d, *J*=8.6 Hz, 1 H), 7.98 (d, *J*=1.8 Hz, 1 H), 8.16 (s, 1 H), 8.79 (d, *J*=2.0 Hz, 1 H), 8.80 (d, *J*=2.0 Hz, 1 H). HRMS (ESI) *m/z* 394.1804 [$(M+H)^+$ Calcd for $C_{22}H_{25}ClN_5$: 394.1798].

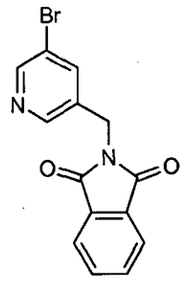
Example 186

(a) 2-(5-Bromo-pyridin-3-yl)-methanol



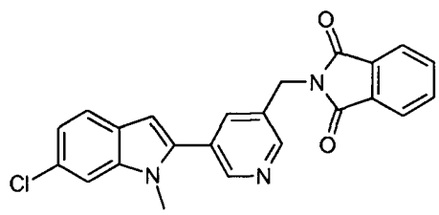
A flask is charged with 5-bromo-pyridine-3-carbaldehyde (5.0 g, 26.1 mmol) and methanol (200 mL) and cooled to 0 °C. Sodium borohydride (2.99 g, 78.23 mmol) is added and the reaction is stirred at room temperature for 2 h. The solvent is removed *in vacuo*. The residue is redissolved in dichloromethane and washed with water twice. The combined aqueous layer is saturated with sodium chloride and extracted with ethyl acetate. The combined organic layer is dried over sodium sulfate and concentrated *in vacuo* to afford 2-(5-bromo-pyridin-3-yl)-methanol as a solid. MS (ESI) *m/z* 189.9 $(M+H)^+$

(b) 2-(5-bromo-pyridin-3-ylmethyl)-isoindole-1,3-dione



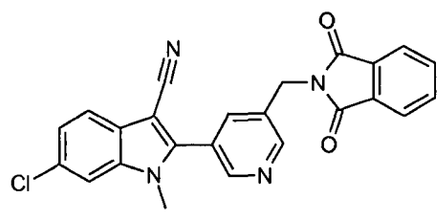
A flask is charged with 2-(5-bromo-pyridin-3-yl)-methanol (4.70 g, 23.75 mmol), phthalimide (3.92 g, 26.12 mmol), tributylphosphine (11.04 mL, 44.527 mmol) and THF (50 mL). 1,1'-(Azodicarbonyl)dipiperidine (11.80 g, 46.31 mmol) is added and the reaction is stirred at room temperature for 6 h, diluted with ethyl acetate and washed with water thrice. The organic layer is dried over sodium sulfate and concentrated *in vacuo* to give a residue which is purified by silica gel flash chromatography (heptane-ethyl acetate, 1:1) to afford 2-(5-bromo-pyridin-3-ylmethyl)-isoindole-1,3-dione as a solid. MS (ESI) *m/z* 319.1 $(M+H)^+$.

(c) 2-[5-(6-chloro-1-methyl-1H-indol-2-yl)-pyridin-3-ylmethyl]-isoindole-1,3-dione



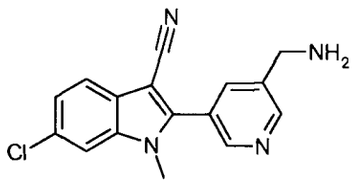
6-Chloro-1-methyl-indole-2-boronic acid and 2-(5-bromo-pyridin-3-ylmethyl)-isoindole-1,3-dione are processed according to the method described in Example 100 to give 2-[5-(6-chloro-1-methyl-1H-indol-2-yl)-pyridin-3-ylmethyl]-isoindole-1,3-dione. MS (ESI) *m/z* 402.1 $(M+H)^+$.

(d) 6-chloro-2-[5-(1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-pyridin-3-yl]-1-methyl-1H-indole-3-carbonitrile



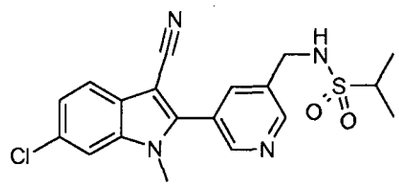
2-[5-(6-Chloro-1-methyl-1H-indol-2-yl)-pyridin-3-ylmethyl]-isoindole-1,3-dione is processed according to the method described in Example 128 to give 6-chloro-2-[5-(1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-pyridin-3-yl]-1-methyl-1H-indole-3-carbonitrile as a solid. MS (ESI) *m/z* 427.0 $(M+H)^+$.

(e) 2-(5-Aminomethyl-pyridin-3-yl)-6-chloro-1-methyl-1H-indole-3-carbonitrile



To a solution of 6-chloro-2-[5-(1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-pyridin-3-yl]-1-methyl-1H-indole-3-carbonitrile (8.96 g, 18.89 mmol) in ethanol (200 mL) is added hydrazine (12.10 mL, 378 mmol) and the reaction mixture is stirred ovemight. The mixture is then filtered and the solids are washed with ethyl acetate. The filtrate is partially concentrated to remove ethyl acetate. 1M aqueous HCl is added, and the aqueous mixture is washed with EtOAc. The aqueous layer is then basified with 4M aqueous NaOH and extracted with dichloromethane thrice. The dichloromethane extracts are dried over Na_2SO_4 and concentrated *in vacuo* to afford 2-(5-aminomethyl-pyridin-3-yl)-6-chloro-1-methyl-1H-indole-3-carbonitrile as a solid. MS (ESI) *m/z* 297.0 $(M+H)^+$

(f) Propane-2-sulfonic acid [5-(6-chloro-3-cyano-1-methyl-1H-indol-2-yl)-pyridin-3-ylmethyl]-amide

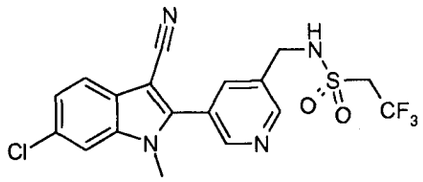


A flask is charged with 2-(5-aminomethyl-pyridin-3-yl)-6-chloro-1-methyl-1H-indole-3-carbonitrile (0.075 g, 0.253 mmol) and dichloromethane (2 mL). Isopropylsulfonyl chloride (0.031 mL, 0.278 mmol) and triethylamine (0.071 mL, 0.506 mmol) are added and the reaction is stirred at room temperature overnight. The reaction mixture is concentrated *in vacuo*. The residue is purified by reverse phase HPLC with Xbridge Shield RP18 column and a 0.1% aqueous NH_4OH in acetonitrile gradient to afford

propane-2-sulfonic acid [5-(6-chloro-3-cyano-1-methyl-1H-indol-2-yl)-pyridin-3-ylmethyl]-amide as a solid. ^{1}H NMR (400 MHz, MeOD) δ ppm 1.40 (d, *J*=6.8 Hz, 6 H), 3.25 - 3.32 (m, 1 H), 3.84 (s, 3 H), 4.50 (s, 2 H), 7.38 (dd, *J*=8.6, 1.8 Hz, 1 H), 7.72 (d, *J*=8.6 Hz, 1 H), 7.77 (d, *J*=1.5 Hz, 1 H), 8.18 (t, *J*=2.0 Hz, 1 H), 8.81 (t, *J*=1.9 Hz, 2 H). HRMS (ESI) *m/z* 403.0997 [(M+H)$^+$ Calcd for $C_{19}H_{20}ClN_4O_2S$: 403.0996].

Example 187

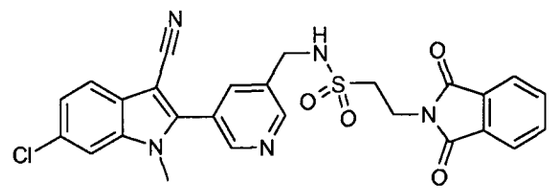
2,2,2-Trifluoro-ethanesulfonic acid [5-(6-chloro-3-cyano-1-methyl-1H-indol-2-yl)-pyridin-3-ylmethyl]-amide



2-(5-Aminomethyl-pyridin-3-yl)-6-chloro-1-methyl-1H-indole-3-carbonitrile (Example 186e) and 2,2,2-trifluoro-ethanesulfonyl chloride are processed according to the method described in Example 186f to give 2,2,2-trifluoro-ethanesulfonic acid [5-(6-chloro-3-cyano-1-methyl-1H-indol-2-yl)-pyridin-3-ylmethyl]-amide. ^{1}H NMR (400 MHz, MeOD) δ ppm 3.84 (s, 3 H), 4.29 (q, *J*=9.6 Hz, 2 H), 4.54 (s, 2 H), 7.39 (dd, *J*=8.6, 1.8 Hz, 1 H), 7.73 (d, *J*=8.3 Hz, 1 H), 7.78 (d, *J*=1.8 Hz, 1 H), 8.18 (t, *J*=2.0 Hz, 1 H), 8.81 (d, *J*=2.0 Hz, 1 H), 8.83 (d, *J*=2.0 Hz, 1 H). HRMS (ESI) *m/z* 443.0557 [(M+H)$^+$ Calcd for $C_{18}H_{15}N_4O_2F_3SCl$: 443.0556].

Example 188

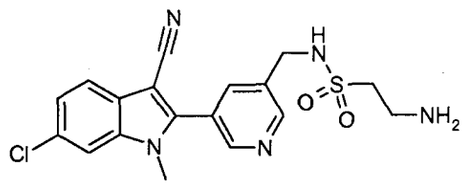
(a) 2-(1,3-Dioxo-1,3-dihydro-isoindol-2-yl)-ethanesulfonic acid [5-(6-chloro-3-cyano-1-methyl-1H-indol-2-yl)-pyridin-3-ylmethyl]-amide



A flask is charged with 2-(5-aminomethyl-pyridin-3-yl)-6-chloro-1-methyl-1H-indole-3-carbonitrile (Example 186e, 0.050 g, 0.160 mmol) and dichloromethane (2 mL). 2-(1,3-Dioxo-1,3-dihydro-isoindol-2-yl)-ethanesulfonyl chloride (0.068 g, 0.239 mmol) and triethylamine (0.045 mL, 0.319 mmol) are added and the reaction is stirred at room

temperature for 5 min. The reaction mixture is washed with water and extracted with dichloromethane twice. The combined organic phase is separated, dried over sodium sulfate and concentrated *in vacuo* to give a residue which is purified by silica gel flash chromatography (dichloromethane-methanol, 19:1) to afford 2-(1,3-dioxo-1,3-dihydro-isoindol-2-yl)-ethane sulfonic acid [5-(6-chloro-3-cyano-1-methyl-1H-indol-2-yl)-pyridin-3-ylmethyl]-amide as a white solid. MS (ESI) *m/z* 537.3 $(M+H)^+$.

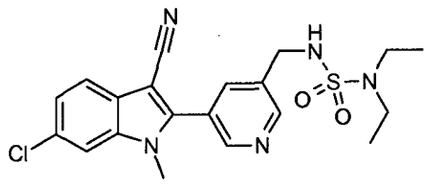
(b) 2-Amino-ethanesulfonic acid [5-(6-chloro-3-cyano-1-methyl-1H-indol-2-yl)-pyridin-3-ylmethyl]-amide



A flask is charged with 2-(1,3-dioxo-1,3-dihydro-isoindol-2-yl)-ethanesulfonic acid [5-(6-chloro-3-cyano-1-methyl-1H-indol-2-yl)-pyridin-3-ylmethyl]-amide (0.065 g, 0.109 mmol) and MeOH (4 mL). Hydrazine (0.069 mL, 2.183 mmol) is added and the reaction is stirred at room temperature overnight. 2M aqueous HCl is added, followed by concentration *in vacuo*. Dichloromethane is added and the mixture is filtered through celite. The organic layer is washed with water once and the aqueous layer is basified to using 4M aqueous NaOH and extracted with dichloromethane thrice. The combined dichloromethane fraction is dried over sodium sulfate and concentrated *in vacuo* to afford a residue which is purified by reverse-phase HPLC to afford 2-amino-ethanesulfonic acid [5-(6-chloro-3-cyano-1-methyl-1H-indol-2-yl)-pyridin-3-ylmethyl]-amide as a solid. ^{1}H NMR (400 MHz, MeOD) δ ppm 3.12 (t, *J*=6.6 Hz, 2 H), 3.29 (t, *J*=6.6 Hz, 2 H), 3.84 (s, 3 H), 4.49 (s, 2 H), 7.38 (dd, *J*=8.6, 1.8 Hz, 1 H), 7.73 (d, *J*=8.6 Hz, 1 H), 7.78 (d, *J*=1.5 Hz, 1 H), 8.19 (t, *J*=2.1 Hz, 1 H), 8.81 (d, *J*=2.3 Hz, 1 H), 8.82 (d, *J*=2.3 Hz, 1 H). HRMS (ESI) *m/z* 404.0944 [$(M+H)^+$ Calcd for $C_{18}H_{19}ClN_5O_2S$: 404.0948].

Example 189

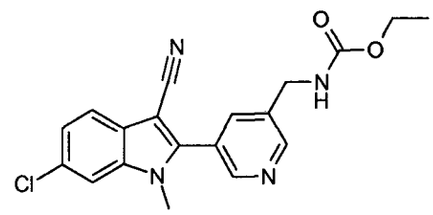
N,N-diethyl-*N'*-[5-(6-chloro-3-cyano-1-methyl-1H-indol-2-yl)-pyridin-3-ylmethyl]-sulfamide



A flask is charged with 2-(5-aminomethyl-pyridin-3-yl)-6-chloro-1-methyl-1H-indole-3-carbonitrile (Example 186e, 0.103 g, 0.349 mmol) and dichloromethane (2 mL). Diethylaminosulfamoyl chloride (0.072 g, 0.419 mmol) and triethylamine (0.100 mL, 0.699 mmol) are added and the reaction is stirred at room temperature overnight. The reaction mixture is concentrated *in vacuo* and the residue is purified by reverse phase HPLC with Xbridge Shield RP18 column and a 0.1% aqueous NH_4OH in acetonitrile gradient to afford *N,N*-diethyl-*N'*-[5-(6-chloro-3-cyano-1-methyl-1H-indol-2-yl)-pyridin-3-ylmethyl]-sulfamide as a solid. ^1H NMR (400 MHz, MeOD) δ ppm 1.20 (t, *J*=7.1 Hz, 6 H), 3.30 (q, *J*=7.1 Hz, 4 H), 3.83 (s, 3 H), 4.35 (s, 2 H), 7.38 (dd, *J*=8.6, 1.8 Hz, 1 H), 7.71 (d, *J*=8.6 Hz, 1 H), 7.77 (d, *J*=1.5 Hz, 1 H), 8.17 (t, *J*=2.1 Hz, 1 H), 8.79 (dd, *J*=3.7, 2.1 Hz, 2 H). HRMS (ESI) *m/z* 432.1278 [$(M+H)^+$ Calcd for $C_{20}H_{23}ClN_5O_2S$: 432.1261].

Example 190

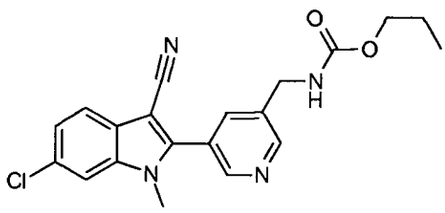
5-(6-chloro-3-cyano-1H-indol-2-yl)-pyridin-3-ylmethyl]-carbamic acid ethyl ester



A flask is charged with 2-(5-aminomethyl-pyridin-3-yl)-6-chloro-1-methyl-1H-indole-3-carbonitrile (Example 186e, 0.100 g, 0.349 mmol) and dichloromethane (4 mL). Ethyl chloroformate (0.055 g, 0.506 mmol) and triethylamine (0.100 mL, 0.675 mmol) are added and the reaction is stirred at room temperature for 10 min. The reaction mixture is concentrated *in vacuo* and the residue is purified by reverse phase HPLC with Xbridge Shield RP18 column and a 0.1% aqueous NH_4OH in acetonitrile gradient to afford 5-(6-chloro-3-cyano-1H-indol-2-yl)-pyridin-3-ylmethyl]-carbamic acid ethyl ester as a solid. ^1H NMR (400 MHz, MeOD) δ ppm 1.28 (t, *J*=7.1 Hz, 3 H), 3.83 (s, 3 H), 4.15 (q, *J*=7.1 Hz, 2 H), 4.48 (s, 2 H), 7.37 (dd, *J*=8.6, 1.8 Hz, 1 H), 7.71 (d, *J*=8.6 Hz, 1 H), 7.76 (d, *J*=1.5 Hz, 1 H), 8.09 (t, *J*=1.9 Hz, 1 H), 8.73 (d, *J*=2.0 Hz, 1 H), 8.78 (d, *J*=2.0 Hz, 1 H). HRMS (ESI) *m/z* 369.1125 [$(M+H)^+$ Calcd for $C_{19}H_{18}ClN_4O_2$: 369.1118].

Example 191

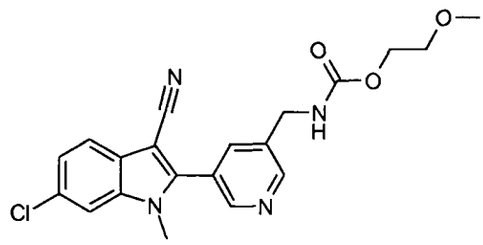
[5-(6-chloro-3-cyano-1H-indol-2-yl)-pyridin-3-ylmethyl]-carbamic acid propyl ester



2-(5-aminomethyl-pyridin-3-yl)-6-chloro-1-methyl-1H-indole-3-carbonitrile (Example 186e) and *N*-propyl chloroformate are processed according to the method described in Example 190 to give [5-(6-chloro-3-cyano-1H-indol-2-yl)-pyridin-3-ylmethyl]-carbamic acid propyl ester as a solid. ^{1}H NMR (400 MHz, MeOD) δ ppm 0.98 (t, *J*=7.3 Hz, 3 H), 1.58 - 1.74 (m, 2 H), 3.83 (s, 3 H), 4.06 (t, *J*=6.6 Hz, 2 H), 4.49 (s, 2 H), 7.38 (dd, *J*=8.6, 1.77 Hz, 1 H), 7.72 (d, *J*=8.6 Hz, 1 H), 7.77 (d, *J*=1.5 Hz, 1 H), 8.09 (t, *J*=2.0 Hz, 1 H), 8.74 (d, *J*=2.0 Hz, 1 H), 8.78 (d, *J*=2.0 Hz, 1 H). HRMS (ESI) *m/z* 383.1260 [(M+H)$^+$ Calcd for $C_{20}H_{20}ClN_4O_2$: 383.1275].

Example 192

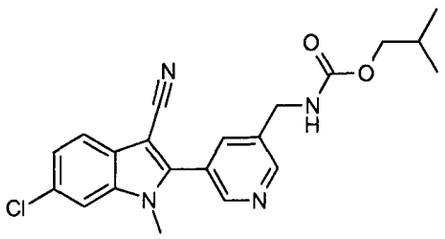
5-(6-Chloro-3-cyano-1-methyl-1H-indol-2-yl)-pyridin-3-ylmethyl]-carbamic acid 2-methoxy-ethyl ester



2-(5-aminomethyl-pyridin-3-yl)-6-chloro-1-methyl-1H-indole-3-carbonitrile (Example 186e) and 3-methoxy-ethyl chloroformate are processed according to the method described in Example 190 to give 5-(6-chloro-3-cyano-1-methyl-1H-indol-2-yl)-pyridin-3-ylmethyl]-carbamic acid 2-methoxy-ethyl ester as a solid. ^{1}H NMR (400 MHz, MeOD) δ ppm 3.37 (s, 3 H), 3.58 - 3.65 (m, 2 H), 3.83 (s, 3 H), 4.14 - 4.27 (m, 2 H), 4.50 (s, 2 H), 7.38 (dd, *J*=8.6, 1.8 Hz, 1 H), 7.72 (d, *J*=8.6 Hz, 1 H), 7.77 (d, *J*=1.5 Hz, 1 H), 8.10 (s, 1 H), 8.74 (d, *J*=2.0 Hz, 1 H), 8.78 (d, *J*=2.0 Hz, 1 H). HRMS (ESI) *m/z* 399.1221 [(M+H)$^+$ Calcd for $C_{20}H_{20}ClN_4O_3$: 399.1224].

Example 193

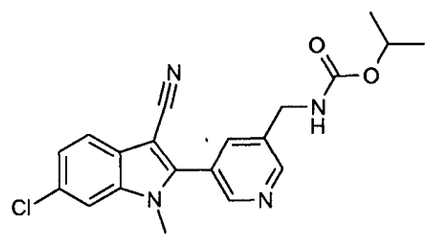
5-(6-Chloro-3-cyano-1-methyl-1H-indol-2-yl)-pyridin-3-ylmethyl]-carbamic acid isobutyl ester



2-(5-Aminomethyl-pyridin-3-yl)-6-chloro-1-methyl-1H-indole-3-carbonitrile (Example 186e) and isobutyl chloroformate are processed according to the method described in Example 190 to give 5-(6-chloro-3-cyano-1-methyl-1H-indol-2-yl)-pyridin-3-ylmethyl]-carbamic acid isobutyl ester. ^{1}H NMR (400 MHz, MeOD) δ ppm 0.97 (d, *J*=6.6 Hz, 6 H), 1.85 - 2.01 (m, 1 H), 3.83 (s, 3 H), 3.89 (d, *J*=6.6 Hz, 2 H), 4.49 (s, 2 H), 7.38 (dd, *J*=8.6, 1.8 Hz, 1 H), 7.72 (d, *J*=8.3 Hz, 1 H), 7.77 (d, *J*=1.8 Hz, 1 H), 8.09 (t, *J*=2.1 Hz, 1 H), 8.74 (d, *J*=1.8 Hz, 1 H), 8.78 (d, *J*=2.0 Hz, 1 H). HRMS (ESI) m/z 397.1424 [(M+H)$^+$ Calcd for $C_{21}H_{22}ClN_4O_2$: 397.1431].

Example 194

5-(6-Chloro-3-cyano-1-methyl-1H-indol-2-yl)-pyridin-3-ylmethyl]-carbamic acid isopropyl ester

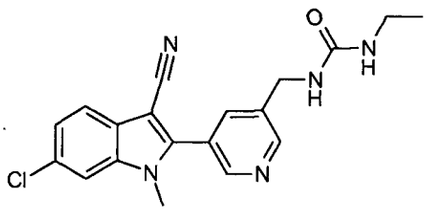


2-(5-Aminomethyl-pyridin-3-yl)-6-chloro-1-methyl-1H-indole-3-carbonitrile (Example 186e) and isopropyl chloroformate are processed according to the method described in Example 190 to give 5-(6-chloro-3-cyano-1-methyl-1H-indol-2-yl)-pyridin-3-ylmethyl]-carbamic acid isopropyl ester. ^{1}H NMR (400 MHz, MeOD) δ ppm 1.27 (d, *J*=6.3 Hz, 6 H), 3.83 (s, 3 H), 4.48 (s, 2 H), 4.88 - 4.94 (m, 1 H), 7.38 (dd, *J*=8.6, 1.8 Hz, 1 H), 7.72 (d, *J*=8.6 Hz, 1 H), 7.77 (d, *J*=1.5 Hz, 1 H), 8.09 (t, *J*=1.9 Hz, 1 H), 8.73 (d, *J*=1.8 Hz, 1

H), 8.78 (d, *J*=2.0 Hz, 1 H). HRMS (ESI) *m/z* 383.1266 [(M+H)$^+$ Calcd for $C_{20}H_{20}ClN_4O_2$: 383.1275].

Example 195

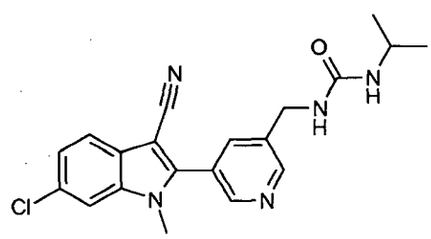
1-[5-(6-Chloro-3-cyano-1-methyl-1H-indol-2-yl)-pyridin-3-ylmethyl]-3-ethyl-urea



To a solution of 2-(5-aminomethyl-pyridin-3-yl)-6-chloro-1-methyl-1H-indole-3-carbonitrile (Example 186e, 0.100 g, 0.337 mmol) in dichloromethane (3 mL) is added ethyl isocyanate (0.030 g, 0.422 mmol) and the reaction is stirred at room temperature for 45 min. The mixture is then washed with water and extracted with dichloromethane twice. The organic phase is concentrated *in vacuo* to give a residue which is purified by reverse phase HPLC with Xbridge Shield RP18 column and a 0.1% aqueous NH_4OH in acetonitrile gradient to afford 1-[5-(6-chloro-3-cyano-1-methyl-1H-indol-2-yl)-pyridin-3-ylmethyl]-3-ethyl-urea as a solid. ^{1}H NMR (400 MHz, MeOD) δ ppm 1.14 (t, *J*=7.2 Hz, 3 H), 3.20 (q, *J*=7.3 Hz, 2 H), 3.82 (s, 3 H), 4.52 (s, 2 H), 7.38 (dd, *J*=8.3, 1.8 Hz, 1 H), 7.71 (d, *J*=8.6 Hz, 1 H), 7.76 (d, *J*=1.5 Hz, 1 H), 8.08 (t, *J*=2.1 Hz, 1 H), 8.73 (d, *J*=2.0 Hz, 1 H), 8.76 (d, *J*=2.3 Hz, 1 H). HRMS (ESI) *m/z* 368.1275 [(M+H)$^+$ Calcd for $C_{19}H_{19}ClN_5O$: 368.1278].

Example 196

1-[5-(6-Chloro-3-cyano-1-methyl-1H-indol-2-yl)-pyridin-3-ylmethyl]-3-isopropyl-urea

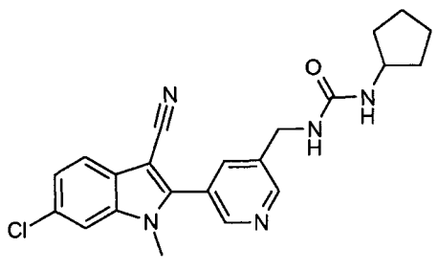


To a solution of 2-(5-aminomethyl-pyridin-3-yl)-6-chloro-1-methyl-1H-indole-3-carbonitrile (Example 186e, 0.060 g, 0.192 mmol) in dichloromethane (3 mL) is added isopropyl isocyanate (0.027 g, 0.240 mmol) and the reaction is stirred at room temperature for 45

min. The mixture is then washed with water and extracted with dichloromethane twice. The organic phase is concentrated *in vacuo* to give a residue which is redissolved in methanol. A precipitate crashes out upon standing. The solid is filtered to afford 1-[5-(6-chloro-3-cyano-1-methyl-1H-indol-2-yl)-pyridin-3-ylmethyl]-3-isopropyl-urea as a solid. ^{1}H NMR (400 MHz, MeOD) δ ppm 1.17 (d, *J*=6.6 Hz, 6 H), 3.76 - 3.91 (m, 4 H), 4.52 (s, 2 H), 7.38 (dd, *J*=8.5, 1. 9 Hz, 1 H), 7.72 (d, *J*=8.3 Hz, 1 H), 7.77 (d, *J*=1.5 Hz, 1 H), 8.08 (t, *J*=2.1 Hz, 1 H), 8.73 (d, *J*=2.0 Hz, 1 H), 8.76 (d, *J*=2.0 Hz, 1 H). HRMS (ESI) *m/z* 382.1431 [(M+H)$^+$ Calcd for $C_{20}H_{21}N_5OCl$: 382.1435].

Example 197

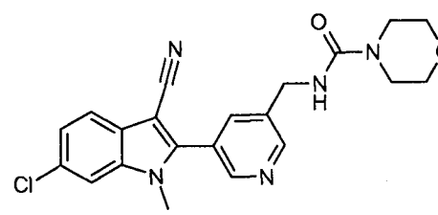
1-[5-(6-Chloro-3-cyano-1-methyl-1H-indol-2-yl)-pyridin-3-ylmethyl]-3-cyclopentyl-urea



2-(5-Aminomethyl-pyridin-3-yl)-6-chloro-1-methyl-1H-indole-3-carbonitrile (Example 186e) and cyclopentyl isocyanate are processed according to the method described in Example 196 to give 1-[5-(6-chloro-3-cyano-1-methyl-1H-indol-2-yl)-pyridin-3-ylmethyl]-3-cyclopentyl-urea as a solid. ^{1}H NMR (400 MHz, MeOD) δ ppm 1.31 - 1.54 (m, 2 H), 1.56 - 1.68 (m, 2 H), 1.68 - 1.78 (m, 2 H), 1.86 - 2.13 (m, 2 H), 3.83 (s, 3 H), 3.94 - 4.09 (m, 1 H), 4.52 (s, 2 H), 7.38 (dd, *J*=8.3, 1.8 Hz, 1 H), 7.72 (d, *J*=8.6 Hz, 1 H), 7.77 (d, *J*=1.5 Hz, 1 H), 8.08 (t, *J*=2.0 Hz, 1 H), 8.72 (d, *J*=2.0 Hz, 1 H), 8.76 (d, *J*=2.0 Hz, 1 H). HRMS (ESI) *m/z* 408.1591 [(M+H)$^+$ Calcd for $C_{22}H_{23}N_5OCl$: 408.1591].

Example 198

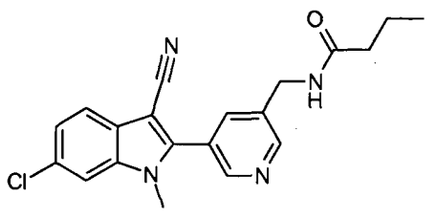
Morpholine-4-carboxylic acid [5-(6-chloro-3-cyano-1-methyl-1H-indol-2-yl)-pyridin-3-ylmethyl]-amide



To a solution of 2-(5-aminomethyl-pyridin-3-yl)-6-chloro-1-methyl-1H-indole-3-carbonitrile (Example 186e, 0.060 g, 0.202 mmol) in dichloromethane (2 mL) are added morpholine-4-carbonyl chloride (0.026 g, 0.222 mmol) and triethylamine (0.056 mL, 0.405 mmol) and the reaction is stirred at room temperature overnight. The mixture is then washed with water and extracted with dichloromethane twice. The organic phase is dried over sodium sulfate and concentrated *in vacuo*. The residue is purified by silica gel flash chromatography (dichloromethane-methanol, 19:1) to afford morpholine-4-carboxylic acid [5-(6-chloro-3-cyano-1-methyl-1H-indol-2-yl)-pyridin-3-ylmethyl]-amide as a solid. ^{1}H NMR (400 MHz, MeOD) δ ppm 3.41 - 3.47 (m, 4 H), 3.66 - 3.72 (m, 4 H), 3.84 (s, 3 H), 4.55 (s, 2 H), 7.38 (dd, *J*=8.5, 1.9 Hz, 1 H), 7.72 (d, *J*=8.6 Hz, 1 H), 7.77 (d, *J*=1.8 Hz, 1 H), 8.11 (t, *J*=2.1 Hz, 1 H), 8.73 (d, *J*=2.0 Hz, 1 H), 8.76 (d, *J*=2.0 Hz, 1 H). MS (ESI) *m/z* 410.00 $(M+H)^+$.

Example 199

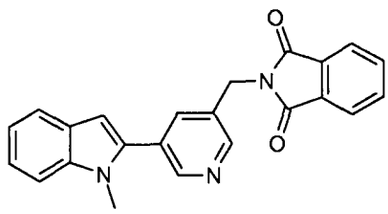
N-[5-(6-Chloro-3-cyano-1-methyl-1H-indol-2-yl)-pyridin-3-ylmethyl]-butyramide



To a solution of 2-(5-aminomethyl-pyridin-3-yl)-6-chloro-1-methyl-1H-indole-3-carbonitrile (Example 186e, 0.060 g, 0.202 mmol) in dichloromethane (2 mL) is added butyryl chloride (0.024 g, 0.222 mmol) and triethylamine (0.056 mL, 0.405 mmol), and the reaction is stirred at room temperature for 30 min. The reaction mixture is diluted with dichloromethane and washed with water. The organic layer is dried over sodium sulfate and concentrated *in vacuo*. The residue is purified by silica gel flash chromatography (dichloromethane-methanol, 19:1) to afford *N*-[5-(6-chloro-3-cyano-1-methyl-1H-indol-2-yl)-pyridin-3-ylmethyl]-butyramide as a white solid. ^{1}H NMR (400 MHz, MeOD) δ ppm 0.98 (t, *J*=7.5 Hz, 3 H), 1.65 - 1.77 (m, 2 H), 2.29 (t, *J*=7.5 Hz, 2 H), 3.82 (s, 3 H), 4.57 (s, 2 H), 7.38 (dd, *J*=8.6, 1.8 Hz, 1 H), 7.72 (d, *J*=8.6 Hz, 1 H), 7.77 (d, *J*=1.5 Hz, 1 H), 8.09 (t, *J*=2.1 Hz, 1 H), 8.73 (d, *J*=2.0 Hz, 1 H), 8.78 (d, *J*=2.0 Hz, 1 H). HRMS (ESI) *m/z* 367.1327 [$(M+H)^+$ Calcd for $C_{20}H_{20}N_4OCl$: 367.1326].

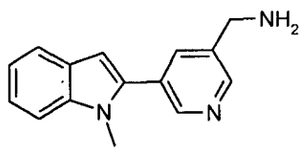
Example 200

(a) 2-[5-(1-Methyl-1H-indol-2-yl)-pyridin-3-ylmethyl]-isoindole-1,3-dione



2-(5-Bromo-pyridin-3-ylmethyl)-isoindole-1,3-dione (Example 186b) and 1-methyl-indole-2-boronic acid are processed according to the method described in Example 100 to give 2-[5-(1-methyl-1H-indol-2-yl)-pyridin-3-ylmethyl]-isoindole-1,3-dione as a solid. MS (ESI) *m/z* 368.09 $(M+H)^+$.

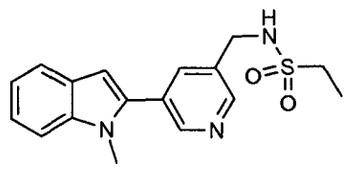
(b) *C*-[5-(1-Methyl-1H-indol-2-yl)-pyridin-3-yl]-methylamine



2-[5-(1-Methyl-1H-indol-2-yl)-pyridin-3-ylmethyl]-isoindole-1,3-dione is processed according to the method described in Example 186e to give C-[5-(1-methyl-1H-indol-2-yl)-pyridin-3-yl]-methylamine as a solid. MS (ESI) *m/z* 238.06 $(M+H)^+$.

Example 201

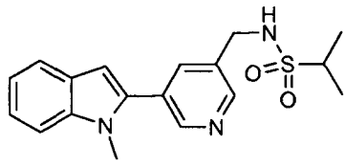
N-[5-(1-Methyl-1H-indol-2-yl)-pyridin-3-ylmethyl]-ethanesulfonamide



C-[5-(1-Methyl-1H-indol-2-yl)-pyridin-3-yl]-methylamine (Example 200b) and ethanesulfonyl chloride are processed according to the method described in Example 186f to give *N*-[5-(1-methyl-1H-indol-2-yl)-pyridin-3-ylmethyl]-ethanesulfonamide. ^1H NMR (400 MHz, MeOD) δ ppm 1.37 (t, *J*=7.3 Hz, 3 H), 3.13 (q, *J*=7.4 Hz, 2 H), 3.82 (s, 3 H), 4.43 (s, 2 H), 6.70 (s, 1 H), 7.01 - 7.18 (m, 1 H), 7.20 - 7.36 (m, 1 H), 7.48 (d, *J*=8.3 Hz, 1 H), 7.62 (d, *J*=7.8 Hz, 1 H), 8.10 (t, *J*=2.1 Hz, 1 H), 8.61 (d, *J*=2.0 Hz, 1 H), 8.71 (d, *J*=2.0 Hz, 1 H). HRMS (ESI) *m/z* 330.1288 [$(M+H)^+$ Calcd for $C_{17}H_{20}N_3O_2S$: 330.1276].

Example 202

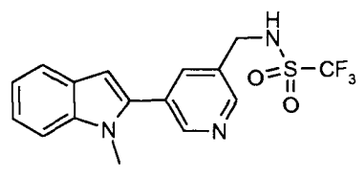
N-[5-(1-Methyl-1H-indol-2-yl)-pyridin-3-ylmethyl]-isopropylsulfonamide



C-[5-(1-Methyl-1H-indol-2-yl)-pyridin-3-yl]-methylamine (Example 200b) and isopropylsulfonyl chloride are processed according to the method described in Example 186f to give *N*-[5-(1-methyl-1H-indol-2-yl)-pyridin-3-ylmethyl]-isopropylsulfonamide. ^{1}H NMR (400 MHz, MeOD) δ ppm 1.40 (d, *J*=6.82 Hz, 6 H), 3.23 - 3.32 (m, 1 H), 3.83 (s, 3 H), 4.45 (s, 2 H), 6.70 (s, 1 H), 7.09 - 7.17 (m, 1 H), 7.27 (ddd, *J*=7.6, 1.14 Hz, 1 H), 7.48 (d, *J*=8.3 Hz, 1 H), 7.63 (d, *J*=8.1 Hz, 1 H), 8.11 (t, *J*=2.1 Hz, 1 H), 8.61 (d, *J*=2.0 Hz, 1 H), 8.71 (d, *J*=2.0 Hz, 1 H). HRMS (ESI) *m/z* 344.1431 [(M+H)$^+$ Calcd for $C_{18}H_{22}N_3O_2S$: 344.1433].

Example 203

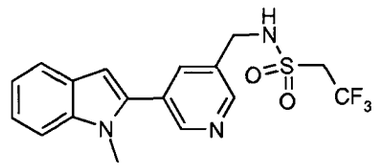
C,C,C-Trifluoro-N-[5-(1-methyl-1H-indol-2-yl)-pyridin-3-ylmethyl]-methanesulfonamide



C-[5-(1-Methyl-1H-indol-2-yl)-pyridin-3-yl]-methylamine (Example 200b) and trifluoromethanesulfonyl chloride are processed according to the method described in Example 186f to give *C,C,C*-trifluoro-*N*-[5-(1-methyl-1H-indol-2-yl)-pyridin-3-ylmethyl]-methanesulfonamide. ^{1}H NMR (400 MHz, MeOD) δ ppm 3.78 (s, 3 H), 4.23 (q, *J*=9.6 Hz, 2 H), 6.66 (d, *J*=0.5 Hz, 1 H), 7.04 - 7.13 (m, 1 H), 7.23 (ddd, *J*=7.7, 1.1 Hz, 1 H), 7.44 (d, *J*=8.2 Hz, 1 H), 7.58 (d, *J*=7.8 Hz, 1 H), 8.04 (t, *J*=2.0 Hz, 1 H), 8.56 (d, *J*=2.0 Hz, 1 H), 8.68 (d, *J*=1.9 Hz, 1 H). HRMS (ESI) *m/z* 370.0835 [(M+H)$^+$ Calcd for $C_{16}H_{15}F_3N_3O_2S$: 370.0837].

Example 204

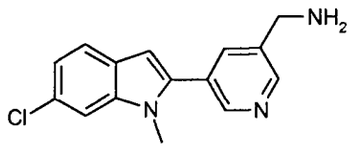
2,2,2-Trifluoro-ethanesulfonic acid [5-(1-methyl-1H-indol-2-yl)-pyridin-3-ylmethyl]-amide



C-[5-(1-Methyl-1H-indol-2-yl)-pyridin-3-yl]-methylamine (Example 200b) and 2,2,2-trifluoro-ethanesulfonyl chloride are processed according to the method described in Example 186f to give 2,2,2-trifluoro-ethanesulfonic acid [5-(1-methyl-1H-indol-2-yl)-pyridin-3-ylmethyl]-amide. ^{1}H NMR (400 MHz, MeOD) δ ppm 3.78 (s, 3 H), 4.23 (q, *J*=9.6 Hz, 2 H), 4.44 (s, 2 H), 6.66 (d, *J*=0.5 Hz, 1 H), 7.06 - 7.12 (m, 1 H), 7.23 (ddd, *J*=7.7, 1.1 Hz, 1 H), 7.44 (d, *J*=8.2 Hz, 1 H), 7.58 (d, *J*=7.8 Hz, 1 H), 8.04 (t, *J*=2.0Hz, 1 H), 8.56 (d, *J*=2.0 Hz, 1 H), 8.68 (d, *J*=1.9 Hz, 1 H). HRMS (ESI) *m/z* 384.0999 [(M+H)$^+$ Calcd for $C_{17}H_{17}F_3N_3O_2S$: 384.0994].

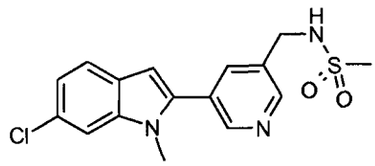
Example 205

(a) *C*-[5-(6-Chloro-1-methyl-1H-indol-2-yl)-pyridin-3-yl]-methylamine



2-[5-(6-Chloro-1-methyl-1H-indol-2-yl)-pyridin-3-ylmethyl]-isoindole-1,3-dione (Example 186c) is processed according to the method described in Example 186e to give C-[5-(6-chloro-1-methyl-1H-indol-2-yl)-pyridin-3-yl]-methylamine. MS (ESI) *m/z* 272.01 (M+H)$^+$.

(b) *N*-[5-(6-Chloro-1-methyl-1H-indol-2-yl)-pyridin-3-ylmethyl]-methanesulfonamide

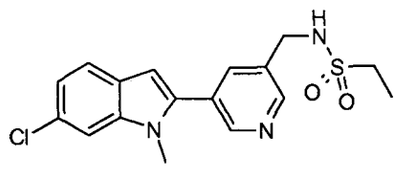


C-[5-(6-Chloro-1-methyl-1H-indol-2-yl)-pyridin-3-yl]-methylamine and methanesulfonyl chloride are processed according to the method described in Example 186f to give *N*-[5-(6-chloro-1-methyl-1H-indol-2-yl)-pyridin-3-ylmethyl]-methanesulfonamide. ^{1}H NMR (400 MHz, MeOD) δ ppm 3.03 (s, 3 H), 3.80 (s, 3 H), 4.45 (s, 2 H), 6.71 (s, 1 H), 7.12 (dd, *J*=8.3, 1.8 Hz, 1 H), 7.54 (s, 1 H), 7.59 (d, *J*=8.6 Hz, 1 H), 8.09 (t, *J*=2.2 Hz, 1 H), 8.63

(d, *J*=2. Hz, 1 H), 8.71 (d, *J*=2. Hz, 1 H). HRMS (ESI) *m/z* 350.0728 [(M+H)$^+$ Calcd for $C_{16}H_{17}ClN_3O_2S$: 350.0730].

Example 206

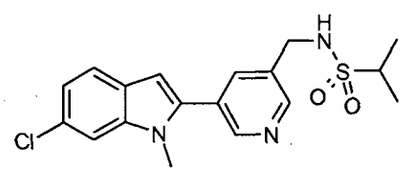
N-[5-(6-Chloro-1-methyl-1H-indol-2-yl)-pyridin-3-ylmethyl]-ethanesulfonamide



A flask is charged with 6-chloro-2-(5-formyl-pyridin-3-yl)-1-methyl-1H-indole (Example 126a, 1.2 g, 4.43 mmol), ethanesulfonamide (0.726 g, 6.65 mmol), titanium(IV) isopropoxide (2.60 mL, 8.87 mmol) and toluene (50 mL). The reaction mixture is refluxed overnight and then concentrated to dryness. The crude material (1.60 g) is dissolved in MeOH (24 mL) and DCM (24 mL), and sodium borohydride (0.335 g, 8.87 mmol) is added. The reaction mixture is stirred at room temperature for 2 h, then concentrated *in vacuo*. The residue is taken up in DCM and washed with water twice. The organic layer is dried over sodium sulfate, filtered and concentrated *in vacuo*. Purification is achieved by silica gel flash chromatograpy to give *N*-[5-(6-Chloro-1-methyl-1H-indol-2-yl)-pyridin-3-ylmethyl]-ethanesulfonamide. ^{1}H NMR (400 MHz, MeOD) δ ppm 1.38 (t, *J*=7.3 Hz, 3 H), 3.14 (q, *J*=7.3 Hz, 2 H), 3.80 (s, 3 H), 4.43 (s, 2 H), 6.72 (s, 1 H), 7.12 (dd, *J*=8.5, 1.9 Hz, 1 H), 7.54 (d, *J*=1.8 Hz, 1 H), 7.59 (d, *J*=8.6 Hz, 1 H), 8.10 (t, *J*=2.1 Hz, 1 H), 8.63 (d, *J*=2.0 Hz, 1 H), 8.71 (d, *J*=2.0 Hz, 1 H). HRMS (ESI) *m/z* 364.0869 [(M+H)$^+$ Calcd for $C_{17}H_{19}ClN_3O_2S$: 364.0887].

Example 207

N-[5-(6-Chloro-1-methyl-1H-indol-2-yl)-pyridin-3-ylmethyl]-isopropylsulfonamide

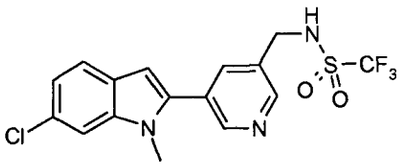


C-[5-(6-Chloro-1-methyl-1H-indol-2-yl)-pyridin-3-yl]-methylamine (Example 205a) and isopropylsulfonyl chloride are processed according to the method described in Example 186f to give *N*-[5-(6-chloro-1-methyl-1H-indol-2-yl)-pyridin-3-ylmethyl]-isopropylsulfonamide. ^{1}H NMR (400 MHz, MeOD) δ ppm 1.35 (d, *J*=6.8 Hz, 6 H), 3.19 -

3.27 (m, 1 H), 3.76 (s, 3 H), 4.40 (s, 2 H), 6.67 (d, *J*=0.6 Hz, 1 H), 7.07 (dd, *J*=8.4, 1.8 Hz, 1 H), 7.49 (d, *J*=1.6 Hz, 1 H), 7.55 (d, *J*=8.5 Hz, 1 H), 8.06 (t, *J*=2.0 Hz, 1 H), 8.58 (d, *J*=1.9 Hz, 1 H), 8.66 (d, *J*=2.0 Hz, 1 H). HRMS (ESI) *m/z* 378.1036 [(M+H)$^+$ Calcd for $C_{18}H_{21}ClN_3O_2S$: 378.1043].

Example 208

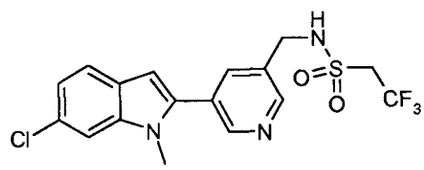
C,C,C-Trifluoro-*N*-[5-(6-chloro-1-methyl-1H-indol-2-yl)-pyridin-3-ylmethyl]-methanesulfonamide



C-[5-(6-Chloro-1-methyl-1H-indol-2-yl)-pyridin-3-yl]-methylamine (Example 205a) and trifluoromethanesulfonyl chloride are processed according to the method described in Example 186f to give *C,C,C*-trifluoro-N-[5-(6-chloro-1-methyl-1H-indol-2-yl)-pyridin-3-ylmethyl]-methanesulfonamide. ^{1}H NMR (400 MHz, MeOD) δ ppm 3.80 (s, 3 H), 4.59 (s, 2 H), 6.72 (s, 1 H), 7.12 (dd, *J*=8.5, 1.9 Hz, 1 H), 7.54 (s, 1 H), 7.60 (d, *J*=8.6 Hz, 1 H), 8.05 (t, *J*=2.1 Hz, 1 H), 8.63 (d, *J*=2.0 Hz, 1 H), 8.76 (d, *J*=2.0 Hz, 1 H). HRMS (ESI) *m/z* 404.0443 [(M+H)$^+$ Calcd for $C_{16}H_{14}ClF_3N_3O_2S$: 404.0447].

Example 209

2,2,2-Trifluoro-ethanesulfonic acid [5-(6-chloro-1-methyl-1H-indol-2-yl)-pyridin-3-ylmethyl]-amide

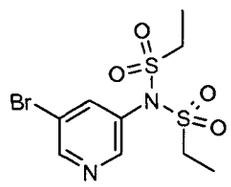


C-[5-(6-Chloro-1-methyl-1H-indol-2-yl)-pyridin-3-yl]-methylamine (Example 205a) and 2,2,2-trifluoro-ethanesulfonyl chloride are processed according to the method described in Example 186f to give 2,2,2-trifluoro-ethanesulfonic acid [5-(6-chloro-1-methyl-1H-indol-2-yl)-pyridin-3-ylmethyl]-amide. ^{1}H NMR (400 MHz, MeOD) δ ppm 3.75 (d, *J*=0.6 Hz, 3 H), 4.16 - 4.28 (m, 2 H), 4.44 (s, 2 H), 6.67 (s, 1 H), 7.07 (ddd, *J*=8.4, 1.8, 0.8 Hz, 1 H), 7.50 (s, 1 H), 7.55 (d, *J*=8.3 Hz, 1 H), 8.04 (d, *J*=0.6 Hz, 1 H), 8.58 (d, *J*=1.4 Hz, 1

H), 8.68 (d, *J*=1.6 Hz, 1 H). HRMS (ESI) *m/z* 418.06107[(M+H)$^+$ Calcd for $C_{17}H_{16}N_3O_2F_3SCl$: 418.06039].

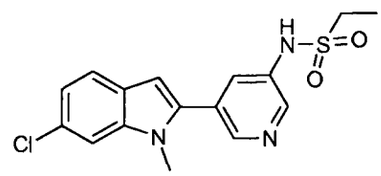
Example 210

(a) Bis-ethanesulfonic acid (5-bromo-pyridin-3-yl)-amide



To a solution of 3-amino-5-bromo-pyridine (4.300 g, 23.611 mmol) in dichloromethane (100 mL) is added ethanesulfonyl chloride (6.849 g, 70.834 mmol), followed with di-isopropylethylamine (16.61 mL, 94.445 mmol). The mixture is stirred at room temperature for 5 h, whereupon it is diluted with ethyl acetate and washed with water twice. The organic layer is dried over sodium sulfate and concentrated *in vacuo*. The residue is purified by silica gel flash chromatography (heptane-ethyl acetate, 3:2) to afford bis-ethanesulfonic acid (5-bromo-pyridin-3-yl)-amide as a solid. MS (ESI) *m/z* 359.0 (M+H)$^+$.

(b) Ethanesulfonic acid 3-(6-chloro-1-methyl-1H-indol-2-yl)-benzylamide

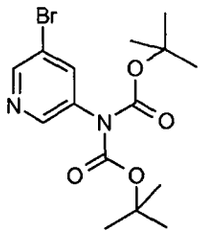


A flask is charged with 6-chloro-1-methyl-indole-2-boronic acid (0.165 g, 0.756 mmol), bis-ethanesulfonic acid (5-bromo-pyridin-3-yl)-amide (0.200 g, 0.504 mmol), potassium phosphate (0.221 g, 1.008 mmol) and DMF (5 mL). The flask is evacuated and back-filled with N_2 thrice and $Pd(PPh_3)_4$ (0.029 g, 0.025 mmol) is added. The mixture evacuated and back-filled with N_2 thrice again, and stirred at 90 °C overnight. It is then cooled to room temperature, diluted with ethyl acetate and washed with water thrice. The organic layer is dried over sodium sulfate and concentrated *in vacuo*. The residue is purified by silica gel flash chromatography (dichloromethane-methanol, 19:1) and further purified by reverse phase HPLC with Xbridge Shield RP18 column and a 0.1% aqueous NH_4OH in acetonitrile gradient to afford ethanesulfonic acid 3-(6-chloro-1-methyl-1H-

indol-2-yl)-benzylamide as a solid. ^{1}H NMR (400 MHz, MeOD) δ ppm 1.40 (t, *J*=7.3 Hz, 3 H), 3.24 (q, *J*=7.3 Hz, 2 H), 3.80 (s, 3 H), 6.71 (s, 1 H), 7.12 (dd, *J*=8.3, 1.8 Hz, 1 H), 7.54 (s, 1 H), 7.59 (d, *J*=8.3 Hz, 1 H), 7.92 (t, *J*=2.1 Hz, 1 H), 8.47 (d, *J*=2.5 Hz, 1 H), 8.49 (d, *J*=1.8 Hz, 1 H). HRMS (ESI) *m/z* 350.0731 $[(M+H)^+$ Calcd for $C_{16}H_{17}ClN_3O_2S$: 350.0730].

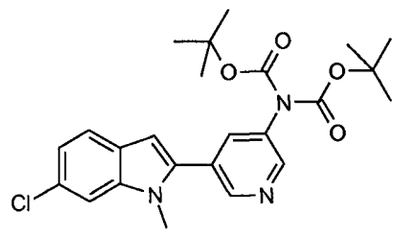
Example 211

(a) 3-[Bis[[(1,1-dimethylethyl)oxy]carbonyl]amino]-5-bromo-pyridine



To 5-amino-3-bromo-pyridine (1.73 g, 10 mmol) and Boc_2O (4.8 g, 22 mmol) in acetonitrile (100 mL) at ambient temperature is added DMAP (212 mg, 1 mmol) and the reaction mixture is heated to 50 °C and stirred overnight. Boc_2O (2.2 g, 10 mmol) is added to the reaction mixture, which is stirred at 50 °C for another 4 h. The reaction mixture is then cooled to room temperature. The solvent is removed *in vacuo* and the residue is purified by silica gel flash chromatography to afford 3-[bis[[(1,1-dimethylethyl)oxy]carbonyl]amino]-5-bromo-pyridine as a white solid. MS (ESI) *m/z* 374.9 $(M+H)^+$.

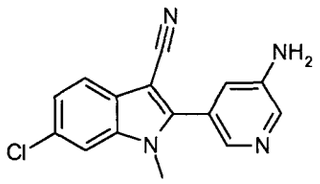
(b) 3-[Bis[[(1,1-dimethylethyl)oxy]carbonyl]amino]-5-(6-chloro-1-methyl-1H-indol-2-yl)-pyridine



A flask is charged with 3-[bis[[(1,1-dimethylethyl)oxy]carbonyl]amino]-5-bromo-pyridine (1.12 g, 3.0 mmol), *N*-methyl-6-chloroindole-2-boronic acid (754 mg, 3.6 mmol), finely crushed potassium phosphate (1.27 g, 6.0 mmol) and DMF (20 mL). After degassing for 15 min, $Pd(PPh_3)_4$ (173 mg, 0.15 mmol) is added. The flask is flushed with nitrogen and

the mixture is heated to 90 °C and stirred for 5 h. The mixture is then cooled to room temperature and poured into water (100 mL). The mixture is extracted with EtOAc three times and the combined organic phase is washed with water (10 mL) twice. The organic phase is then dried over Na_2SO_4 and concentrated. The residue is purified by silica gel flash chromatography (ethyl acetate-heptane, 0:1 to 1:9) to give 3-[bis[[(1,1-dimethylethyl)oxy]carbonyl]amino]-5-(6-chloro-1-methyl-1H-indol-2-yl)-pyridine. MS (ESI) *m/z* 458.1 $(M+H)^+$.

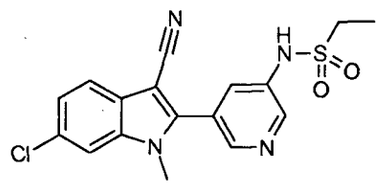
(c) 2-(5-Amino-pyridin-3-yl)-6-chloro-1-methyl-1H-indole-3-carbonitrile



Chlorosulfonyl isocyanate (1.63 g, 11.5 mmol) is added to a solution of 3-[bis[[(1,1-dimethylethyl)oxy]carbonyl]amino]-5-(6-chloro-1-methyl-1H-indol-2-yl)-pyridine (0.91 g, 1.99 mmol) in acetontrile (200 mL) and the reaction mixture is stirred for 10 min. DMF (3 mL) is added and the reaction mixture is stirred for 3 h. 20 g silica gel is added to the mixture and the solvent is removed *in vacuo*. The resulting solid is heated to 65 °C under high vacuum for 2 h. The mixture is cooled to room temperature and then purified by silica gel flash chromatography (dichloromethane-methanol-triethylamine, 83:8:9) to afford 2-(5-amino-pyridin-3-yl)-6-chloro-1-methyl-1H-indole-3-carbonitrile. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 3.76 (s, 3 H), 5.72 (s, 2 H), 7.15 (t, *J*=2.3 Hz, 1 H), 7.35 (dd, *J*=8.5, 1.9 Hz, 1 H), 7.69 (d, *J*=8.3 Hz, 1 H), 7.92 (d, *J*=1.8 Hz, 1 H), 7.97 (d, *J*=1.8 Hz, 1 H), 8.12 (d, *J*=2.5 Hz, 1 H). MS (ESI) *m/z* 283.0 $(M+H)^+$.

Example 212

Ethanesulfonic acid [5-(6-chloro-3-cyano-1-methyl-1H-indol-2-yl)-pyridin-3-yl]-amide

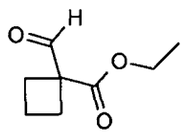


To a solution of 2-(5-amino-pyridin-3-yl)-6-chloro-1-methyl-1H-indole-3-carbonitrile (Example 211, 85 mg, 0.3 mmol) in DCM (15 mL) is added triethylamine (122 mg, 1.2

mmol) and ethanesulfonyl chloride (77 mg, 0.6 mmol) and the reaction mixture is stirred overnight. The solvent is removed and the residue is redissolved in methanol (15 mL). Aqueous 1M NaOH (1 mL) is added and the reaction mixture is stirred overnight. The solvent is removed *in vacuo* and the residue is purified by silica gel flash chromatography (methanol in dichloromethane gradient) to give ethanesulfonic acid [5-(6-chloro-3-cyano-1-methyl-1H-indol-2-yl)-pyridin-3-yl]-amide as a solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.25 (t, *J*=7.3 Hz, 3 H), 3.23 - 3.33 (m, 2 H), 3.79 (s, 3 H), 7.36 (dd, *J*=8.6, 1.8 Hz, 1 H), 7.72 (d, *J*=8.6 Hz, 1 H), 7.90 (t, *J*=2.3 Hz, 1 H), 7.95 (d, *J*=1.5 Hz, 1 H), 8.61 (d, *J*=2.3 Hz, 2 H), 10.43 (s, 1 H). HRMS (ESI) *m/z* 375.0692 [(M+H)$^+$ Calcd for $C_{17}H_{16}ClN_4O_2S$: 375.0682].

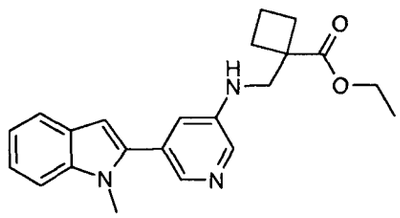
Example 213

(a) 1-Formyl-cyclobutanecarboxylic acid ethyl ester



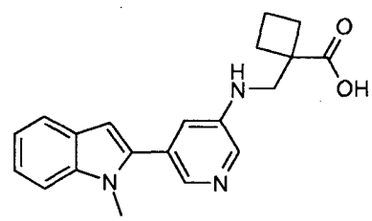
To a solution of diethyl 1,1'-cyclobutanedicarboxylate (9.9 g, 48.4 mmol) in dichloromethane (100 mL) cooled with a dry-ice/acetone bath is added DIBAL-H (20% wt in toluene, 101 mL, 121.1 mmol) by canula over 10 min. The mixture is stirred for another 30 min, whereupon the acetone bath is replaced with an ice water bath and 2M aqueous HCl (250 mL) is added cautiously, with vigorous stirring. Vigorous stirring is continued for 20 min, whereupon two clear phases are obtained. The two phases are separated, the aqueous phase is washed with dichloromethane and the combined organic phase is dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue is purified by silica gel flash chromatography (heptane-ethyl acetate, 1:0 to 9:1) to give 1-formyl-cyclobutanecarboxylic acid ethyl ester as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 1.29 (t, *J*=7.1 Hz, 3 H), 1.88-2.05 (m, 2 H), 2.45-2.49 (m, 4 H), 4.24 (t, *J*=7.1 Hz, 2 H), 9.78 (s, 2 H).

(b) 1-{[5-(1-methyl-1H-indol-2-yl)-pyridin-3-ylamino]-methyl}-cyclobutanecarboxylic acid ethyl ester



To a solution of 2-(5-amino-pyridin-3-yl)-1-methyl-1H-indole (Example 100, 0.400 g, 1.756 mmol) and 1-formyl-cyclobutanecarboxylic acid ethyl ester (0.457 g, 2.633 mmol) in dichloromethane (13 mL) is added acetic acid (0.102 g, 1.756 mmol) and the mixture is refluxed. After 2 h, the mixture is cooled with an ice-water bath and sodium tri-acetoxyborohydride (1.175 g, 5.267 mmol) is added. After 13 h, the mixture is heated to reflux for 1.5 h, cooled to room temperature, diluted with dichloromethane, washed with 1M aqueous NaOH, water and brine. The combined aqueous phase is extracted once with dichloromethane and the combined organic phase is dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue is purified by silica gel flash chromatography (heptane-ethyl acetate, 1:1) to give 1-{[5-(1-methyl-1H-indol-2-yl)-pyridin-3-ylamino]-methyl}-cyclobutanecarboxylic acid ethyl ester as an oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 1.28 (t, *J*=7.1 Hz, 3 H), 1.99 - 2.12 (m, 4 H), 2.49 - 2.59 (m, 2 H), 3.53 (d, *J*=5.8 Hz, 2 H), 3.78 (s, 3 H), 4.12 - 4.18 (m, 1 H), 4.20 (q, *J*=7.1 Hz, 2 H), 6.61 (d, *J*=0.8 Hz, 1 H), 7.04 (dd, *J*=2.8, 1.9 Hz, 1 H), 7.15 - 7.19 (m, 1 H), 7.26 - 7.30 (m, 1 H), 7.39 (dd, *J*=8.2, 0.8 Hz, 1 H), 7.65 (d, *J*=7.7 Hz, 1 H), 8.09 (d, *J*=2.8 Hz, 1 H), 8.12 (d, *J*=1.9 Hz, 1 H).

(c) 1-{[5-(1-Methyl-1H-indol-2-yl)-pyridin-3-ylamino]-methyl}-cyclobutanecarboxylic acid

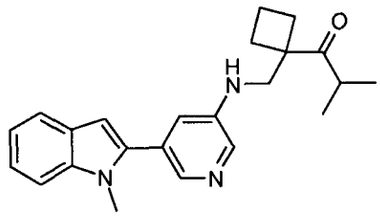


To a solution of 1-{[5-(1-methyl-1H-indol-2-yl)-pyridin-3-ylamino]-methyl}-cyclobutanecarboxylic acid ethyl ester (0.107 g, 0.288 mmol) in THF (2 mL) and methanol (1 mL) is added aqueous lithium hydroxide (1M, 0.58 mL, 0.58 mmol) and the solution is stirred overnight. The product is isolated by RP HPLC on an Xbridge C18 eluting with an acetonitrile in 0.1% aqueous NH_4OH gradient to give 1-{[5-(1-methyl-1H-indol-2-yl)-pyridin-3-ylamino]-methyl}-cyclobutanecarboxylic acid as a white powder.

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.74 - 1.86 (m, 1 H), 1.87 - 1.97 (m, 3 H), 2.26 - 2.35 (m, 2 H), 3.33 (br. s., 1 H), 3.39 (s, 2 H), 3.75 (s, 3 H), 6.60 (s, 1 H), 7.05 - 7.09 (m, 1 H), 7.15 (m, 1 H), 7.17 - 7.21 (m, 1 H), 7.50 (d, *J*=8.3 Hz, 1 H), 7.57 (d, *J*=7.7 Hz, 1 H), 7.94 (d, *J*=1.8 Hz, 1 H), 8.06 (d, *J*=2.7 Hz, 1 H). MS (ESI) *m/z* 336 $(M+H)^+$.

Example 214

2-Methyl-1-(1-{[5-(1-methyl-1H-indol-2-yl)-pyridin-3-ylamino]-methyl}-cyclobutyl)-propan-1-one

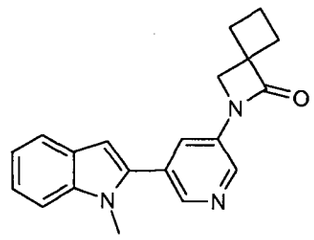


To a solution of 1-{[5-(1-methyl-1H-indol-2-yl)-pyridin-3-ylamino]-methyl}-cyclobutanecarboxylic acid ethyl ester (Example 213b, 0.45 g, 1.21 mmol) in THF (150 mL) cooled with an ice-water bath is added iPrMgCl (2.0M in THF, 2.43 mL, 4.85 mmol) dropwise. After 45 min, the mixture is quenched with 1M aqueous $NaHSO_4$ (5 mL), washed with saturated aqueous sodium bicarbonate and brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue is purified by silica gel flash chromatography (heptane-ethyl acetate, 3:2 to 1:1), followed by purification by RP HPLC on an Xbridge RP18 eluting with a gradient of acetonitrile in 0.1% aqueous NH_4OH to give 2-methyl-1-(1-{[5-(1-methyl-1H-indol-2-yl)-pyridin-3-ylamino]-methyl}-cyclobutyl)-propan-1-one.

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 0.95 (d, *J*=6.8 Hz, 6 H), 1.68 - 1.78 (m, 1 H), 1.95 - 2.03 (m, 3 H), 2.31 - 2.41 (m, 2 H), 2.97 - 3.09 (m, 1 H), 3.60 (d, *J*=5.7 Hz, 2 H), 3.76 (s, 3 H), 5.77 (t, *J*=5.7 Hz, 1 H), 6.61 (s, 1 H), 7.06 - 7.10 (m, 1 H), 7.16 - 7.25 (m, 2 H), 7.51 (d, *J*=8.2 Hz, 1 H), 7.58 (d, *J*=7.8 Hz, 1 H), 7.99 (s, 1 H), 8.12 (d, *J*=2.1 Hz, 1 H). MS (ESI) *m/z* 362 $(M+H)^+$.

Example 215

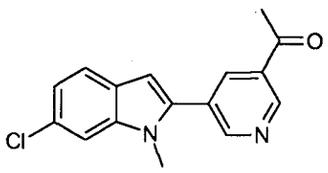
2-[5-(1-Methyl-1H-indol-2-yl)-pyridin-3-yl]-2-aza-spiro[3.3]heptan-1-one



The method described in Example 214 also affords 2-[5-(1-methyl-1H-indol-2-yl)-pyridin-3-yl]-2-aza-spiro[3.3]heptan-1-one. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.88 - 2.03 (m, 2 H), 2.32 - 2.45 (m, 4 H), 3.77 (s, 3 H), 3.83 (s, 2 H), 6.71 (d, *J*=0.8 Hz, 1 H), 7.06 - 7.14 (m, 1 H), 7.19 - 7.27 (m, 1 H), 7.54 (m, 1 H), 7.61 (m, 1 H), 7.85 (dd, *J*=2.4, 1.9 Hz, 1 H), 8.54 (d, *J*=1.9 Hz, 1 H), 8.68 (d, *J*=2.4 Hz, 1 H). MS (ESI) *m/z* 318.1 $(M+H)^+$.

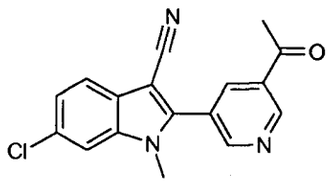
Example 216

(a) 1-[5-(6-Chloro-1-methyl-1H-indol-2-yl)-pyridin-3-yl]-ethanone



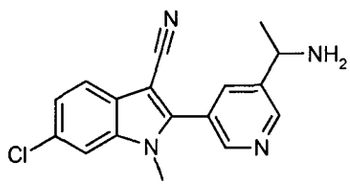
6-Chloro-1-methyl-indole-2-boronic acid and 5-acetyl-3-bromo-pyridine are processed according to the method described in Example 100 to give 1-[5-(6-chloro-1-methyl-1H-indol-2-yl)-pyridin-3-yl]-ethanone. MS (ESI) *m/z* 284.98 $(M+H)^+$.

(b) 2-(5-Acetyl-pyridin-3-yl)-6-chloro-1-methyl-1H-indole-3-carbonitrile



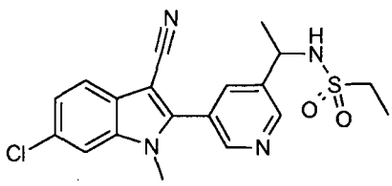
1-[5-(6-Chloro-1-methyl-1H-indol-2-yl)-pyridin-3-yl]-ethanone is processed according to the method described in Example 128 to give 2-(5-acetyl-pyridin-3-yl)-6-chloro-1-methyl-1H-indole-3-carbonitrile. MS (ESI) *m/z* 310.07 $(M+H)^+$.

(c) 2-[5-(1-Amino-ethyl)-pyridin-3-yl]-6-chloro-1-methyl-1H-indole-3-carbonitrile



Ammonium acetate (0.567 g, 7.207 mmol) is added to a solution of 2-(5-acetyl-pyridin-3-yl)-6-chloro-1-methyl-1H-indole-3-carbonitrile (0.470 g, 1.441 mmol) in MeOH (10 mL), and the reaction is stirred at 50 °C for 48 h. Sodium triacetoxyborohydride (2.251 g, 10.09 mmol) is added and the reaction is stirred for 24 h at 50 °C. Additional sodium triacetoxyborohydride (2.251 g, 10.09 mmol) is added and the reaction is stirred for another 24 h at 50 °C. It is then diluted with ethyl acetate and washed with water thrice. The organic layer is dried over sodium sulfate and concentrated *in vacuo* to give 6-chloro-2-[5-(1-hydroxy-ethyl)-pyridin-3-yl]-1-methyl-1H-indole-3-carbonitrile and minor amounts of 2-[5-(1-amino-ethyl)-pyridin-3-yl]-6-chloro-1-methyl-1H-indole-3-carbonitrile. The mixture is redissolved in THF (5 mL) and phthalimide (0.181 g, 1.206 mmol) and triphenylphosphine (0.172 g, 0.804 mmol) are added, followed with di-isopropylazodicarboxylate (0.157 mL, 0.804 mmol). The reaction is stirred at room temperature for 4 h. It is then diluted with ethyl acetate and washed with water thrice. The organic layer is dried over sodium sulfate and concentrated *in vacuo*, to give a residue which is purified by silica gel flash chromatography (heptane-ethyl acetate, 1:1) to afford a mixture of 6-chloro-2-{5-[1-(1,3-dioxo-1,3-dihydro-isoindol-2-yl)-ethyl]-pyridin-3-yl}-1-methyl-1H-indole-3-carbonitrile and triphehyl phosphine. The mixture is redissolved in ethanol (5 mL). Hydrazine hydrate (65%) (0.411 mL, 8.506 mmol) is added and the reaction is stirred at room temperature overnight. It is then acidified with 2M aqueous HCl and concentrated *in vacuo*. The residue is redissolved in dichloromethane and filtered through celite to remove the precipitate formed. The organic layer is washed with water. The aqueous layer is separated and basified to with 4M aqueous NaOH, and then extracted with dichloromethane thrice. The organic layer is dried over sodium sulfate and concentrated *in vacuo* to afford 2-[5-(1-amino-ethyl)-pyridin-3-yl]-6-chloro-1-methyl-1H-indole-3-carbonitrile as a solid. MS (ESI) *m/z* 311.1 $(M+H)^+$

(d) Ethanesulfonic acid {1-[5-(6-chloro-3-cyano-1-methyl-1H-indol-2-yl)-pyridin-3-yl]-ethyl}-amide



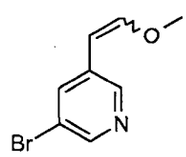
A flask is charged with 2-[5-(1-amino-ethyl)-pyridin-3-yl]-6-chloro-1-methyl-1H-indole-3-carbonitrile (0.072 g, 0.209 mmol) and dichloromethane (3 mL). Ethanesulfonyl chloride (0.060 g, 0.525 mmol) and triethylamine (0.059 mL, 0.417 mmol) are added and the reaction is stirred at room temperature overnight. The reaction mixture is concentrated *in vacuo* to give a residue which is purified by silica gel flash chromatography (heptane-ethyl acetate, 1:1) to afford ethanesulfonic acid {1-[5-(6-chloro-3-cyano-1-methyl-1H-indol-2-yl)-pyridin-3-yl]-ethyl}-amide as a white solid. ^{1}H NMR (400 MHz, MeOD) δ ppm 1.32 (t, *J*=7.5 Hz, 3 H), 1.65 (d, *J*=7.1 Hz, 3 H), 2.96 - 3.15 (m, 2 H), 3.84 (s, 3 H), 4.75 - 4.86 (m, 1 H), 7.39 (dd, *J*=8.6, 1.8 Hz, 1 H), 7.73 (d, *J*=8.6 Hz, 1 H), 7.78 (d, *J*=1.5 Hz, 1 H), 8.20 (t, *J*=2.0 Hz, 1 H), 8.80 (d, *J*=2.0 Hz, 1 H), 8.83 (d, *J*=2.3 Hz, 1 H). HRMS (ESI) *m/z* 403.1005 [(M+H)$^+$ Calcd for $C_{19}H_{20}N_4O_2SCl$: 403.0996].

(e) (*R*) and (*S*)-ethanesulfonic acid {1-[5-(6-chloro-3-cyano-1-methyl-1H-indol-2-yl)-pyridin-3-yl]-ethyl}-amide

Racemic ethanesulfonic acid {1-[5-(6-chloro-3-cyano-1-methyl-1H-indol-2-yl)-pyridin-3-yl]-ethyl}-amide is resolved by chiral chromatography using a Chiralpak® AS column, eluting with a 3:2 heptane-ethanol mixture to give (*R*) and (*S*)-ethanesulfonic acid {1-[5-(6-chloro-3-cyano-1-methyl-1H-indol-2-yl)-pyridin-3-yl]-ethyl}-amide. The retention times are 6.9 and 9.2 min at 0.8 mL/min on an analytical Chiralpak® AS column.

Example 217

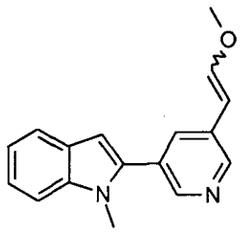
(a) 3-Bromo-5-(2-methoxy-vinyl)-pyridine



A flask is charged with methoxymethyltriphenylphosphine chloride (3.04 g, 8.87 mmol) and tetrahydrofuran (20 mL). The mixture is cooled to –78 °C and sodium hexamethyldisilazane (1M solution in THF, 9.60 mL, 9.67 mmol) is added dropwise. The reaction mixture is stirred at –78 °C for 30 min, whereupon 5-bromo-pyridine-3-

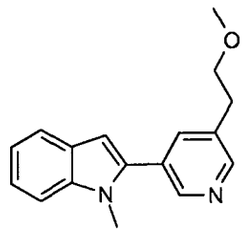
carbaldehyde (1.5 g, 8.06 mmol) is added. The mixture is allowed to warm to room temperature and stirred overnight. Purification by silica gel flash chromatography (heptane-ethyl acetate, 4:1) affords an *E/Z* mixture of 3-bromo-5-(2-methoxy-vinyl)-pyridine as a colorless oil. MS (ESI) *m/z* 215.95 $(M+H)^+$.

(b) 2-[5-(2-Methoxy-vinyl)-pyridin-3-yl]-1-methyl-1H-indole



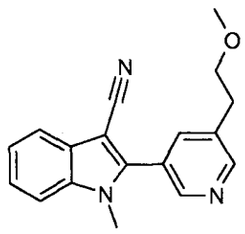
3-Bromo-5-(2-methoxy-vinyl)-pyridine is processed according to the method described in Example 106b to give an *E/Z* mixture of 2-[5-(2-methoxy-vinyl)-pyridin-3-yl]-1-methyl-1H-indole as an oil. MS (ESI) *m/z* 265.20 $(M+H)^+$.

(c) 2-[5-(2-Methoxy-ethyl)-pyridin-3-yl]-1-methyl-1H-indole



A flask is charged with 2-[5-(2-methoxy-vinyl)-pyridin-3-yl]-1-methyl-1H-indole (0.550 g, 2.08 mmol) and methanol (5 mL). Palladium on carbon (0.221 g, 0.208 mmol) is added and the reaction mixture is stirred at 50 °C under H_2 for 16 h. It is then cooled to room temperature and filtered through celite. The celite layer is thoroughly washed with methanol. The filtrate is concentrated *in vacuo*, to give a residue which is purified by silica gel flash chromatography (heptane-ethyl acetate, 7:3) to afford 2-[5-(2-methoxy-ethyl)-pyridin-3-yl]-1-methyl-1H-indole as an oil. MS (ESI) *m/z* 267.36 $(M+H)^+$.

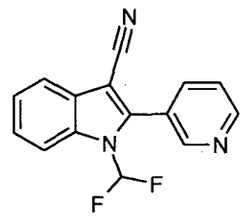
(d) 2-[5-(2-Methoxy-ethyl)-pyridin-3-yl]-1-methyl-1H-indole-3-carbonitrile



2-[5-(2-Methoxy-ethyl)-pyridin-3-yl]-1-methyl-1H-indole is processed according to the method described in Example 128 to give 2-[5-(2-methoxy-ethyl)-pyridin-3-yl]-1-methyl-1H-indole-3-carbonitrile as a solid. ^{1}H NMR (400 MHz, MeOD) δ ppm 3.09 (t, *J*=6.2 Hz, 2 H), 3.41 (s, 3 H), 3.76 (t, *J*=6.3 Hz, 2 H), 3.87 (s, 3 H), 7.36 - 7.42 (m, 1 H), 7.44 - 7.51 (m, 1 H), 7.68 (d, *J*=8.3 Hz, 1 H), 7.75 (dd, *J*=7.8, 1.1 Hz, 1 H), 8.10 (t, *J*=2.1 Hz, 1 H), 8.68 (d, *J*=2.0 Hz, 1 H), 8.74 (d, *J*=2.1 Hz, 1 H). HRMS (ESI) *m/z* 292.1458 [(M+H)$^+$ Calcd for $C_{18}H_{18}N_3O$: 292.1450].

Example 218

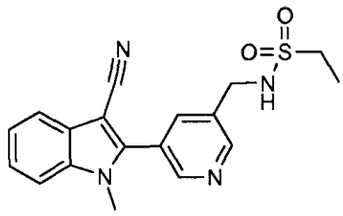
1-Difluoromethyl-2-pyridin-3-yl-1H-indole-3-carbonitrile



A flask is charged with 2-pyridin-3-yl-1H-indole-3-carbonitrile (Example 83b, 340 mg, 1.55 mmol) and DMF (10 mL), and 60% NaH in mineral oil (68 mg, 1.71 mmol) is added. The mixture is stirred at room temperature for 20 min. $CClF_2H$ is bubbled into the reaction mixture while the reaction temperature is raised to 100°C. The reaction temperature is raised to 150°C for 30 min. The mixture is cooled to room temperature and water (1 mL) is added. The mixture is then filtered and the filtrate is purified on Xbridge C18 eluting with a 1:9 to 9:1 acetonitrile-water gradient to give 1-difluoromethyl-2-pyridin-3-yl-1H-indole-3-carbonitrile. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.48 - 7.53 (m, 1 H), 7.56 (td, *J*=7.7, 1.3 Hz, 1 H), 7.68 - 7.73 (m, 1 H), 7.86 (t, *J*=56.6 Hz, 1 H), 7.86 (dd, *J*=37.6, 8.1 Hz, 1 H), 7.91 (d, *J*=8.3 Hz, 1 H), 8.13 (dt, *J*=8.0, 2.0, 1.9 Hz, 1 H), 8.85 (dd, *J*=4.9, 1.6 Hz, 1 H), 8.87 (d, *J*=1.8 Hz, 1 H). HRMS (ESI) *m/z* 270.0841 [(M+H)$^+$ Calcd for $C_{15}H_{10}F_2N_3$: 270.0843].

Example 219

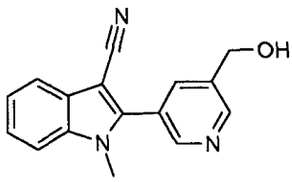
Ethanesulfonic acid [5-(3-cyano-1-methyl-1H-indol-2-yl)-pyridin-3-ylmethyl]-amide



2-(5-Formyl-pyridin-3-yl)-1-methyl-1H-indole-3-carbonitrile (Example 127) and ethanesulfonamide are processed according to the method described in Example 170 to give ethanesulfonic acid [5-(3-cyano-1-methyl-1H-indol-2-yl)-pyridin-3-ylmethyl]-amide. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.20 (t, *J*=7.3 Hz, 3 H), 3.07 (q, *J*=7.4 Hz, 2 H), 3.79 (s, 3 H), 4.34 (d, *J*=6.1 Hz, 2 H), 7.34 - 7.38 (m, 1 H), 7.41 - 7.46 (m, 1 H), 7.72 (d, *J*=7.6 Hz, 1 H), 7.75 - 7.82 (m, 2 H), 8.09 (t, *J*=2.1 Hz, 1 H), 8.77 (d, *J*=2.0 Hz, 1 H), 8.81 (d, *J*=2.1 Hz, 1 H). HRMS (ESI) *m/z* 355.1247 [(M+H)$^+$ Calcd for $C_{18}H_{19}N_4O_2S$: 355.1229].

Example 220

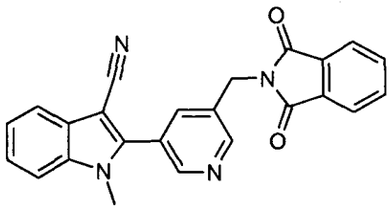
2-(5-Hydroxymethyl-pyridin-3-yl)-1-methyl-1H-indole-3-carbonitrile



The method described in Example 219 using 2-(5-formyl-pyridin-3-yl)-1-methyl-1H-indole-3-carbonitrile (Example 127) also affords 2-(5-hydroxymethyl-pyridin-3-yl)-1-methyl-1H-indole-3-carbonitrile as a product of the reaction. MS (ESI) *m/z* 264.07 (M+H)$^+$.

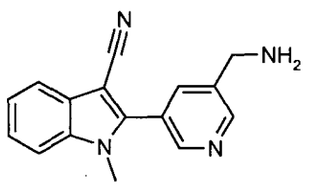
Example 221

(a) 2-[5-(1,3-Dioxo-1,3-dihydro-isoindol-2-ylmethyl)-pyridin-3-yl]-1-methyl-1H-indole-3-carbonitrile



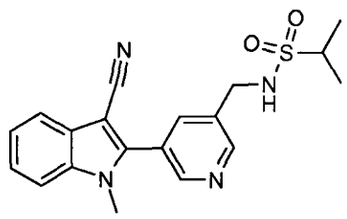
To a solution of 2-(5-hydroxymethyl-pyridin-3-yl)-1-methyl-1H-indole-3-carbonitrile (Example 220, 190 mg, 0.72 mmol) in THF (5 mL) are added sequentially phthalimide (116 mg, 0.79 mmol), 1,1'-(azodicarbonyl)dipiperidine (346 mg, 1.37 mmol) and tributylphosphine (277 mg, 1.37 mmol). The mixture is stirred at room temperature overnight. The mixture is then concentrated *in vacuo* and the residue is purified by silica gel flash chromatography (heptane-ethyl acetate, 1:0 to 0:1) to give 2-[5-(1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-pyridin-3-yl]-1-methyl-1H-indole-3-carbonitrile. MS (ESI) *m/z* 393.02 $(M+H)^+$.

(b) 2-(5-Aminomethyl-pyridin-3-yl)-1-methyl-1H-indole-3-carbonitrile



To a solution of 2-[5-(1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-pyridin-3-yl]-1-methyl-1H-indole-3-carbonitrile (200 mg, 0.51 mmol) in ethanol (15 mL) is added hydrazine hydrate (327 mg, 10.2 mmol). The mixture is stirred at room temperature overnight. The reaction mixture is poured into dichloromethane (100 mL) and extracted with 1M HCl in water. The combined aqueous phase is basified with 5M NaOH in water and extracted with dichloromethane. The combined organic phase is dried over Na_2SO_4 and concentrated *in vacuo* to give 2-(5-aminomethyl-pyridin-3-yl)-1-methyl-1H-indole-3-carbonitrile, which is used in the next step without further purification. MS (ESI) *m/z* 263.27 $(M+H)^+$.

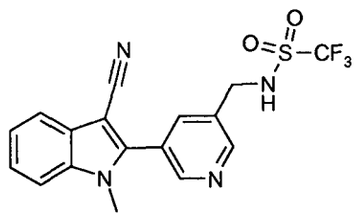
(c) Propane-2-sulfonic acid [5-(3-cyano-1-methyl-1H-indol-2-yl)-pyridin-3-ylmethyl]-amide



A flask is charged with 2-(5-aminomethyl-pyridin-3-yl)-1-methyl-1H-indole-3-carbonitrile (130 mg, 0.5 mmol), DBU (304 mg, 2.0 mmol) and DCE (15 mL), and isopropylsulfonyl chloride (142 mg, 1.0 mmol) is added. The mixture is stirred at room temperature for 1 h and concentrated *in vacuo*. The residue is purified by silica gel flash chromatography (dichloromethane-methanol, 1:0 to 97:3) to give propane-2-sulfonic acid [5-(3-cyano-1-methyl-1H-indol-2-yl)-pyridin-3-ylmethyl]-amide. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.24 (d, *J*=6.8 Hz, 6 H), 3.18 - 3.26 (m, 1 H), 3.79 (s, 3 H), 4.37 (d, *J*=6.1 Hz, 2 H), 7.34 - 7.38 (m, 1 H), 7.41 - 7.46 (m, 1 H), 7.70 - 7.79 (m, 3 H), 8.08 (t, *J*=2.0 Hz, 1 H), 8.77 (d, *J*=2.3 Hz, 1 H), 8.81 (d, *J*=2.3 Hz, 1 H). HRMS (ESI) *m/z* 369.1389 [(M+H)$^+$ Calcd for $C_{19}H_{21}N_4O_2S$: 369.1385].

Example 222

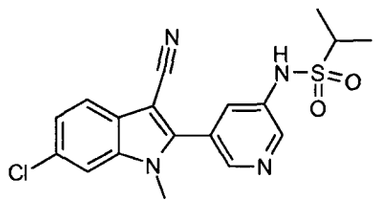
Trifluoromethanesulfonic acid [5-(3-cyano-1-methyl-1H-indol-2-yl)-pyridin-3-ylmethyl]-amide



2-(5-Formyl-pyridin-3-yl)-1-methyl-1H-indole-3-carbonitrile (Example 127) and trifluoromethanesulfonamide are processed according to the method described in Example 170 to give trifluoromethanesulfonic acid [5-(3-cyano-1-methyl-1H-indol-2-yl)-pyridin-3-ylmethyl]-amide. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 3.79 (s, 3 H), 4.58 (s, 2 H), 7.34 - 7.39 (m, 1 H), 7.42 - 7.47 (m, 1 H), 7.72 (d, *J*=7.7 Hz, 1 H), 7.77 (d, *J*=8.3 Hz, 1 H), 8.10 (t, *J*=2.1 Hz, 1 H), 8.78 (d, *J*=2.1 Hz, 1 H), 8.85 (d, *J*=2.1 Hz, 1 H), 10.19 (br. s., 1 H). HRMS (ESI) *m/z* 395.0779 [(M+H)$^+$ Calcd for $C_{17}H_{14}F_3N_4O_2S$: 395.0790].

Example 223

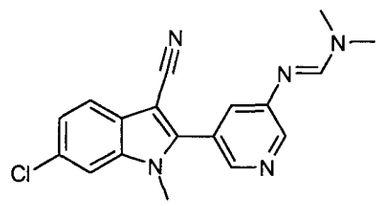
Propane-2-sulfonic acid [5-(6-chloro-3-cyano-1-methyl-1H-indol-2-yl)-pyridin-3-yl]-amide



2-(5-Amino-pyridin-3-yl)-6-chloro-1-methyl-1H-indole-3-carbonitrile (Example 211) is processed according to the method described in Example 221c to give to give propane-2-sulfonic acid [5-(6-chloro-3-cyano-1-methyl-1H-indol-2-yl)-pyridin-3-yl]-amide. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.30 (d, *J*=6.8 Hz, 6 H), 3.46 (dq, *J*=6.8 Hz, 1 H), 3.79 (s, 3 H), 7.37 (dd, *J*=8.5, 1.9 Hz, 1 H), 7.73 (d, *J*=8.6 Hz, 1 H), 7.93 (t, *J*=2.1 Hz, 1 H), 7.96 (d, *J*=1.8 Hz, 1 H), 8.60 (d, *J*=1.8 Hz, 1 H), 8.63 (d, *J*=2.5 Hz, 1 H), 10.41 (s, 1 H). HRMS (ESI) *m/z* 389.0836 [(M+H)$^+$ Calcd for $C_{18}H_{18}ClN_4O_2S$: 389.0839].

Example 224

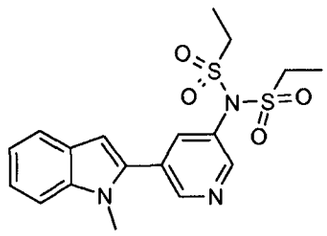
N'-[5-(6-Chloro-3-cyano-1-methyl-1H-indol-2-yl)-pyridin-3-yl]-*N*,N-dimethyl-formamidine



To a solution of 2-(5-amino-pyridin-3-yl)-6-chloro-1-methyl-1H-indole-3-carbonitrile (Example 211, 85 mg, 0.3 mmol) in DMF (5 mL) is added 60% NaH in mineral oil (48 mg, 1.2 mmol), followed with propane-2-sulfonyl chloride (86 mg, 60.6 mmol). The mixture is stirred at room temperature for 5 h. The mixture is filtered and the filtrate is purified on Xbridge C18 eluting with a 1:9 to 9:1 acetonitrile-water gradient to give *N'*-[5-(6-chloro-3-cyano-1-methyl-1H-indol-2-yl)-pyridin-3-yl]-*N*,*N*-dimethyl-formamidine. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.98 (s, 3 H), 3.06 (s, 3 H), 3.79 (s, 3 H), 7.35 (dd, *J*=8.3, 1.8 Hz, 1 H), 7.62 (t, *J*=2.1 Hz, 1 H), 7.70 (d, *J*=8.3 Hz, 1 H), 7.95 (d, *J*=1.8 Hz, 1 H), 7.96 (s, 1 H), 8.37 - 8.39 (m, 2 H). HRMS (ESI) *m/z* 338.1182 [(M+H)$^+$ Calcd for $C_{18}H_{17}ClN_5$: 338.1173].

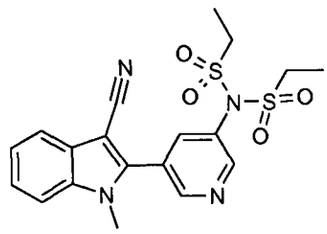
Example 225

(a) Ethanesulfonic acid [5-(1-methyl-1H-indol-2-yl)-pyridin-3-yl]-*N*-ethanesulfonyl-amide



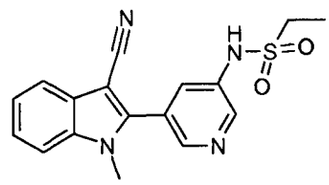
To a solution of 2-(5-amino-pyridin-3-yl)-1-methyl-1H-indole (Example 100) (223 mg, 1.0 mmol) in dichloromethane (20 mL) is added ethanesulfonyl chloride (386 mg, 3.0 mmol) and di-isopropylethylamine (517 mg, 4.0 mmol). The mixture is stirred at room temperature for 1 h. Saturated $NaHCO_3$ in water (0.5 mL) and silica gel (10 g) are added and the mixture is concentrated *in vacuo*. The residue is purified by silica gel chromatography (heptane-ethyl acetate, 1:0 to 1:9) to give ethanesulfonic acid [5-(1-methyl-1H-indol-2-yl)-pyridin-3-yl]-*N*-ethanesulfonyl-amide. MS (ESI) *m/z* 408.1 $(M+H)^+$.

(b) Ethanesulfonic acid [5-(3-cyano-1-methyl-1H-indol-2-yl)-pyridin-3-yl]-*N*-ethanesulfonyl-amide



Ethanesulfonic acid [5-(1-methyl-1H-indol-2-yl)-pyridin-3-yl]-*N*-ethanesulfonyl-amide is processed according to the method described in Example 128 to give ethanesulfonic acid [5-(3-cyano-1-methyl-1H-indol-2-yl)-pyridin-3-yl]-*N*-ethanesulfonyl-amide. MS (ESI) *m/z* 432.96 $(M+H)^+$.

(c) Ethanesulfonic acid [5-(3-cyano-1-methyl-1H-indol-2-yl)-pyridin-3-yl]-amide

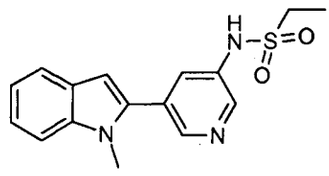


A solution of ethanesulfonic acid [5-(3-cyano-1-methyl-1H-indol-2-yl)-pyridin-3-yl]-*N*-ethanesulfonyl-amide in DMF (2 mL), methanol (10 mL) and 5 M NaOH in water (1 mL)

is stirred at room temperature for 1 h. The mixture is purified on Xbridge C18 eluting with a 1:9 to 9:1 acetonitrile-water gradient to give ethanesulfonic acid [5-(3-cyano-1-methyl-1H-indol-2-yl)-pyridin-3-yl]-amide. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.25 (t, *J*=7.3 Hz, 3 H), 3.24 - 3.32 (m, 2 H), 3.80 (s, 3 H), 7.32 - 7.38 (m, 1 H), 7.43 (td, *J*=7.8, 1.1 Hz, 1 H), 7.70 (d, *J*=7.8 Hz, 1 H), 7.75 (d, *J*=8.3 Hz, 1 H), 7.90 (t, *J*=2.3 Hz, 1 H), 8.58 - 8.62 (m, 2 H), 10.42 (s, 1 H). HRMS (ESI) *m/z* 341.1078 [(M+H)$^+$ Calcd for $C_{17}H_{17}N_4O_2S$: 341.1072].

Example 226

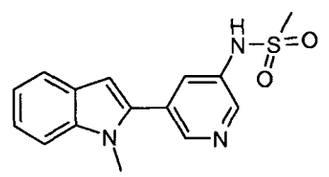
Ethanesulfonic acid [5-(1-methyl-1H-indol-2-yl)-pyridin-3-yl]-amide



Ethanesulfonic acid [5-(1-methyl-1H-indol-2-yl)-pyridin-3-yl]-N-ethanesulfonyl-amide (Example 225a) is processed according to the method described in Example 225c to give ethanesulfonic acid [5-(1-methyl-1H-indol-2-yl)-pyridin-3-yl]-amide. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.26 (t, *J*=7.3 Hz, 3 H), 3.26 (q, *J*=7.3 Hz, 2 H), 3.77 (s, 3 H), 6.71 (s, 1 H), 7.08 - 7.13 (m, 1 H), 7.20 - 7.27 (m, 1 H), 7.54 (d, *J*=8.1 Hz, 1 H), 7.61 (d, *J*=7.8 Hz, 1 H), 7.79 (t, *J*=2.3 Hz, 1 H), 8.48 (d, *J*=2.5 Hz, 1 H), 8.56 (d, *J*=1.8 Hz, 1 H), 10.23 (s, 1 H). HRMS (ESI) *m/z* 316.1125 [(M+H)$^+$ Calcd for $C_{16}H_{18}N_3O_2S$: 316.1120].

Example 227

Methanesulfonic acid [5-(1-methyl-1H-indol-2-yl)-pyridin-3-yl]-amide

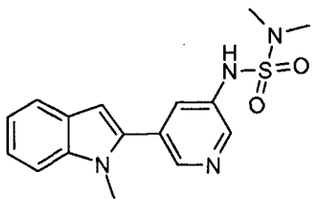


2-(5-amino-pyridin-3-yl)-1-methyl-1H-indole (Example 100) and methanesulfonyl chloride are processed according to the methods described in Example 225a and 225c to give methanesulfonic acid [5-(1-methyl-1H-indol-2-yl)-pyridin-3-yl]-amide. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 3.15 (s, 3 H), 3.77 (s, 3 H), 6.71 (s, 1 H), 7.06 - 7.13 (m, 1 H), 7.23 (ddd, *J*=8.2, 7.1, 1.1 Hz, 1 H), 7.53 (d, *J*=7.6 Hz, 1 H), 7.61 (d, *J*=7.6 Hz, 1 H), 7.79 (t,

J=2.2 Hz, 1 H), 8.48 (d, *J*=2.3 Hz, 1 H), 8.58 (d, *J*=2.0 Hz, 1 H), 10.18 (s, 1 H). HRMS: (ESI) m/z 302.0966 $[(M+H)^+$ Calcd for $C_{15}H_{16}N_3O_2S$ 302.0958].

Example 228

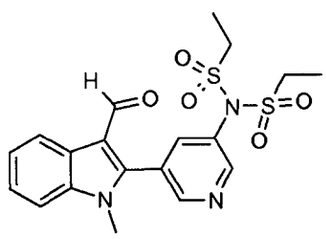
Diethyl-sulfamic acid 5-(1-methyl-1H-indol-2-yl)-pyridin-3-yl-amide



To a solution of 2-(5-amino-pyridin-3-yl)-1-methyl-1H-indole (Example 100, 60 mg, 0.269 mmol) and dimethylsulfamoyl chloride (58 mg, 0.403 mmol) in dichloromethane (1 mL) is added triethylamine (54 mg, 0.537 mmol). After overnight stirring, the mixture is concentrated and purified by silica gel flash chromatography (heptane-ethyl acetate, 3:7) to give diethyl-sulfamic acid 5-(1-methyl-1H-indol-2-yl)-pyridin-3-yl-amide. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.77 (s, 6 H), 3.76 (s, 3 H), 6.89 (s, 1 H), 7.07 - 7.12 (m, 1 H), 7.20 - 7.25 (m, 1 H), 7.53 (d, *J*=8.3 Hz, 1 H), 7.61 (d, *J*=7.8 Hz, 1 H), 7.75 (t, *J*=2.1 Hz, 1 H), 8.46 (d, *J*=2.5 Hz, 1 H), 8.52 (d, *J*=2.0 Hz, 1 H). HRMS: (ESI) *m/z* 331.1226 $[(M+H)^+$ Calcd for $C_{16}H_{18}N_4O_2S$ 331.1223].

Example 229

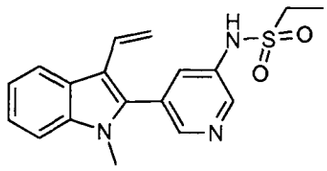
(a) Ethanesulfonic acid [5-(1-methyl-3-carboxaldehyde-1H-indol-2-yl)-pyridin-3-yl]-N-ethanesulfonyl-amide



A flask is charged with DMF (10 mL) and cooled to 0 °C. Phosphorus oxychloride (0.297 ml, 3.19 mmol) is added and the reaction mixture is stirred at 0 °C for 20 min followed by the addition of a solution of ethanesulfonic acid [5-(1-methyl-1H-indol-2-yl)-pyridin-3-yl]-N-ethanesulfonyl-amide (Example 225a, 1.00 g, 2.454 mmol) in DMF (10 mL). The reaction mixture is stirred at room temperature for 16 h. The reaction is stopped, washed

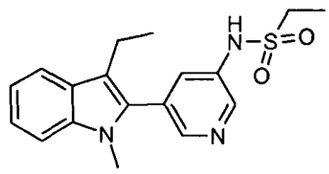
with saturated $NaHCO_3$ solution and extracted with ethyl acetate. The organic layer is separated and washed with water thrice, then dried over Na_2SO_4 and concentrated *in vacuo* to afford ethanesulfonic acid [5-(1-methyl-3-carboxaldehyde-1H-indol-2-yl)-pyridin-3-yl]-N-ethanesulfonyl-amide. MS (ESI) *m/z* 436.2 $(M+H)^+$

(b) Ethanesulfonic acid [5-(1-methyl-3-vinyl-1H-indol-2-yl)-pyridin-3-yl]-amide



A flask is charged with methyl triphenyl phosphine bromide (0.492 g, 1.378 mmol) and THF (20 mL). The reaction mixture is cooled to –78 °C and 1M NaHMDS in THF (1.515 ml, 1.515 mmol) is added. The reaction is stirred at –78 °C for 1 h followed by the addition of ethanesulfonic acid [5-(1-methyl-3-carboxaldehyde-1H-indol-2-yl)-pyridin-3-yl]-N-ethanesulfonyl-amide (0.300 g, 0.689 mmol) at –78 °C. The reaction mixture is allowed to warm to room temperature and stirred overnight. The mixture is washed with water and extracted with ethyl acetate. The organic layer is dried over sodium sulfate and concentrated *in vacuo*. The crude is purified by silica gel flash chromatography (heptane-ethyl acetate, 1:0 to 0-1) to afford ethanesulfonic acid [5-(1-methyl-3-vinyl-1H-indol-2-yl)-pyridin-3-yl]-amide product. MS (ESI) *m/z* 342.2 $(M+H)^+$

(c) Ethanesulfonic acid [5-(1-methyl-3-ethyl-1H-indol-2-yl)-pyridin-3-yl]-amide

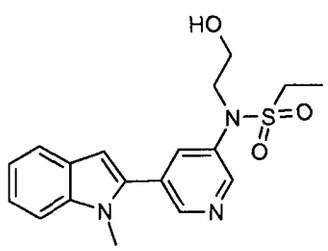


A flask is charged with ethanesulfonic acid [5-(1-methyl-3-vinyl-1H-indol-2-yl)-pyridin-3-yl]-amide (35 mg, 0.082 mmol) and MeOH (5 mL). The flask is evacuated and flushed with N_2 thrice. Pd/C (4.36 mg) is added and the reaction stirred under H_2 overnight at 50 °C. The reaction is filtered over celite and the celite layer is washed thoroughly with MeOH. The filtrate is concentrated *in vacuo*. The crude is purified by silica gel flash chromatography (dichloromethane-methanol, 19:1) followed by HPLC purification using Xbridge C18 eluting with a 10 to 100% acetonitile-water gradient to afford the pure

product ethanesulfonic acid [5-(3-ethyl-1-methyl-1H-indol-2-yl)-pyridin-3-yl]-amide. ^{1}H NMR (400 MHz, MeOD) δ ppm 1.27 (t, *J*=7.6 Hz, 3 H), 1.40 (t, *J*=7.3 Hz, 3 H), 2.76 (q, *J*=7.6 Hz, 2 H), 3.25 (q, *J*=7.3 Hz, 2 H), 3.66 (s, 3 H), 7.09 - 7.17 (m, 1 H), 7.23 - 7.31 (m, 1 H), 7.43 (d, *J*=8.3 Hz, 1 H), 7.65 (d, *J*=7.8 Hz, 1 H), 7.83 (t, *J*=2.3 Hz, 1 H), 8.36 (d, *J*=1.8 Hz, 1 H), 8.49 (d, *J*=2.5 Hz, 1 H). HRMS: (ESI) m/z 344.1435 [(M+H)$^+$ Calcd for $C_{18}H_{21}N_3O_2S$ 344.1427].

Example 230

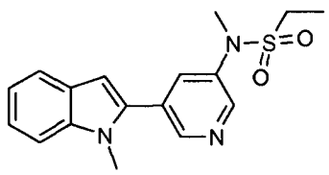
Ethanesulfonic acid (2-hydroxy-ethyl)-[5-(1-methyl-1H-indol-2-yl)-pyridin-3-yl]-amide



A flask is charged with ethanesulfonic acid [5-(1-methyl-1H-indol-2-yl)-pyridin-3-yl]-amide (example 226, 200 mg, 0.634 mmol) and DMF (3 mL). The reaction is cooled to 0 °C and sodium hydride (38.0 mg, 0.951 mmol) is added. The reaction is stirred at room temperature for 10 min, then 2-chloro-ethoxytrimethylsilane (0.154 mL, 0.951 mmol) is added. The reaction is stirred at 100 °C for 16 h then cooled to room temperature. Aqueous 1M HCl (1 mL) is added and stirring is continued for 30 min. The mixture is purified using an Xbridge C18 eluting with a 10 to 100% acetonitrile-water gradient to afford ethanesulfonic acid (2-hydroxy-ethyl)-[5-(1-methyl-1H-indol-2-yl)-pyridin-3-yl]-amide. MS (ESI) *m/z* 360.1 (M+H)$^+$. ^{1}H NMR (400 MHz, MeOD) δ ppm 1.42 (t, *J*=7.3 Hz, 3 H), 3.29 (t, 2 H), 3.70 (t, *J*=5.6 Hz, 2 H), 3.84 (s, 3 H), 3.96 (t, *J*=5.6 Hz, 2 H), 6.75 (s, 1 H), 7.14 (td, *J*=7.5, 0.9 Hz, 1 H), 7.28 (td, *J*=7.7, 1.0 Hz, 1 H), 7.49 (d, *J*=8.3 Hz, 1 H), 7.64 (d, *J*=7.6 Hz, 1 H), 8.18 (t, *J*=2.1 Hz, 1 H), 8.71 (d, *J*=2.3 Hz, 1 H), 8.75 (d, *J*=1.8 Hz, 1 H). HRMS (ESI) m/z 360.1383 [(M+H)$^+$ Calcd for $C_{18}H_{12}N_3O_3S$ 360.1376].

Example 231

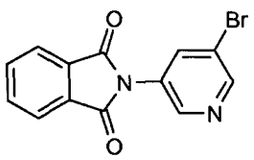
Ethanesulfonic acid methyl-[5-(1-methyl-1H-indol-2-yl)-pyridin-3-yl]-amide



A flask is charged with ethanesulfonic acid [5-(1-methyl-1H-indol-2-yl)-pyridin-3-yl]-amide (example 226, 100 mg, 0.317 mmol) and DMF (4 mL). The reaction is cooled to 0 °C and sodium hydride (15.85 mg, 0.396 mmol) is added. The reaction is stirred at 0 °C for 10 min, then methyl iodide (56.3 mg, 0.396 mmol) is added. The reaction is stirred for 1 hour at room temperature. The reaction is quenched with water (0.5 mL) and filtered. The filtrate is purified using Xbridge C18 eluting with a 10 to 100% acetontrile-water gradient to afford ethanesulfonic acid methyl-[5-(1-methyl-1H-indol-2-yl)-pyridin-3-yl]-amide. ^{1}H NMR (400 MHz, MeOD) δ ppm 1.39 (t, *J*=7.5 Hz, 3 H), 3.28 (q, *J*=7.5 Hz, 2 H), 3.49 (s, 3 H), 3.84 (s, 3 H), 6.74 (s, 1 H), 7.14 (t, *J*=7.6 Hz, 1 H), 7.28 (ddd, *J*=7.6, 1.1 Hz, 1 H), 7.49 (d, *J*=8.3 Hz, 1 H), 7.63 (d, *J*=7.8 Hz, 1 H), 8.13 (t, *J*=2.1 Hz, 1 H), 8.70 (d, *J*=2.0 Hz, 1 H), 8.70 (d, *J*=2.5 Hz, 1 H). HRMS (ESI) m/z 330.1281 [(M+H)$^+$ Calcd for $C_{17}H_{19}N_3O_2S$ 330.1270].

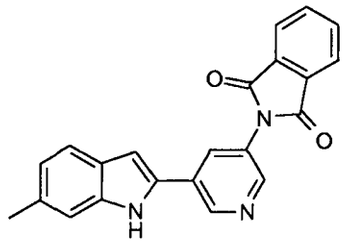
Example 232

(a) 2-(5-Bromo-pyridin-3-yl)-isoindole-1,3-dione



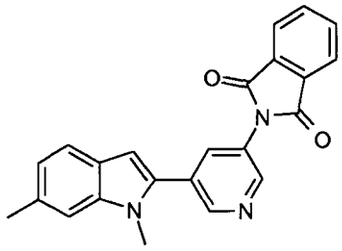
A flask is charged with 3-amino-5-bromo pyridine (1.00 g, 5.78 mmol), phthalic anhydride (0.856 g, 5.78 mmol) and acetic acid (20 mL). The reaction is refluxed overnight. The reaction is then cooled to room temperature and concentrated *in vacuo*. The crude is dissolved in ethyl acetate and washed with water once. The organic layer is dried over sodium sulfate and concentrated *in vacuo* to afford 2-(5-bromo-pyridin-3-yl)-isoindole-1,3-dione. MS (ESI) *m/z* 305.1 (M+H)$^+$

(b) 2-[5-(6-Methyl-1H-indol-2-yl)-pyridin-3-yl]-isoindole-1,3-dione



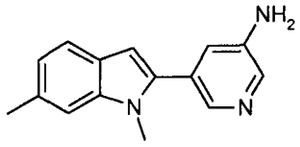
2-(5-Bromo-pyridin-3-yl)-isoindole-1,3-dione and *N*-Boc-6-methyl-indoleboronic acid are processed according to the procedure described in Example 103 to give 2-[5-(6-methyl-1H-indol-2-yl)-pyridin-3-yl]-isoindole-1,3-dione. MS (ESI) *m/z* 354.1 $(M+H)^+$

(c) 2-[5-(1,6-DiMethyl-1H-indol-2-yl)-pyridin-3-yl]-isoindole-1,3-dione



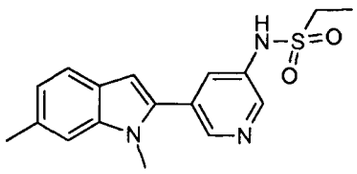
2-[5-(6-methyl-1H-indol-2-yl)-pyridin-3-yl]-isoindole-1,3-dione is processed according to the procedure described in Example 114 to give 2-[5-(1,6-dimethyl-1H-indol-2-yl)-pyridin-3-yl]-isoindole-1,3-dione. MS (ESI) *m/z* 368.3 $(M+H)^+$

(d) 5-(1,6-Dimethyl-1H-indol-2-yl)-pyridin-3-ylamine



A flask is charged with 2-[5-(1,6-dimethyl-1H-indol-2-yl)-pyridin-3-yl]-isoindole-1,3-dione (1.10 g, 2.096 mmol) and EtOH (30 mL). Hydrazine (1.316 mL, 41.9 mmol) is added and the reaction mixture is refluxed for 1 hour. The reaction mixture is cooled to room temperature, filtered and the precipitate is washed thoroughly with ethyl acetate. The filtrate is concentrated *in vacuo*. The crude is taken up 1M HCl solution and then extracted with EtOAc. The aqueous layer is separated, basified to pH 14 using 4M aqueous NaOH and extracted with DCM thrice. The organic layer is dried over Na_2SO_4 and concentrated *in vacuo* to afford 5-(1,6-dimethyl-1H-indol-2-yl)-pyridin-3-ylamine. MS (ESI) *m/z* 238.4 $(M+H)^+$

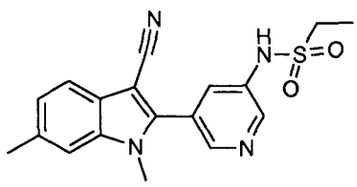
(e) Ethanesulfonic acid [5-(1,6-dimethyl-1H-indol-2-yl)-pyridin-3-yl]-amide



5-(1,6-Dimethyl-1H-indol-2-yl)-pyridin-3-ylamine is processed according to the procedures described in Example 225a and 225c to give ethanesulfonic acid [5-(1,6-dimethyl-1H-indol-2-yl)-pyridin-3-yl]-amide. ^{1}H NMR (400 MHz, MeOD) δ ppm 1.40 (t, *J*=7.3 Hz, 3 H), 2.53 (s, 3 H), 3.26 (q, *J*=7.3 Hz, 2 H), 3.79 (s, 3 H), 6.65 (s, 1 H), 6.98 (d, *J*=8.1 Hz, 1 H), 7.28 (s, 1 H), 7.50 (d, *J*=8.1 Hz, 1 H), 7.93 (t, *J*=2.3 Hz, 1 H), 8.46 (d, *J*=2.3 Hz, 1 H), 8.53 (d, *J*=1.8 Hz, 1 H). HRMS (ESI) m/z 330.1285 [(M+H)$^+$ Calcd for $C_{17}H_{19}N_3O_2S$ 330.1270].

Example 233

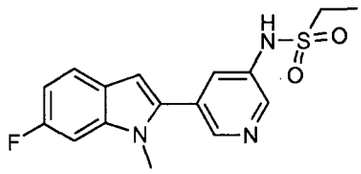
Ethanesulfonic acid [5-(1,6-dimethyl-3-cyano-1H-indol-2-yl)-pyridin-3-yl]-amide



5-(1,6-Dimethyl-1H-indol-2-yl)-pyridin-3-ylamine (Example 232d) is processed according to the procedures described in Example 225a, 128 and 225c to give ethanesulfonic acid [5-(1,6-dimethyl-3-cyano-1H-indol-2-yl)-pyridin-3-yl]-amide. ^{1}H NMR (400 MHz, MeOD) δ ppm 1.39 (t, *J*=7.3 Hz, 3 H), 2.57 (s, 3 H), 3.22 (q, *J*=7.3 Hz, 2 H), 3.84 (s, 3 H), 7.22 (d, *J*=8.1 Hz, 1 H), 7.46 (s, 1 H), 7.60 (d, *J*=8.1 Hz, 1 H), 7.92 - 7.94 (m, 1 H), 8.39 (d, *J*=1.8 Hz, 1 H), 8.50 (d, *J*=2.5 Hz, 1 H). HRMS: (ESI) m/z 355.1230 [(M+H)$^+$ Calcd for $C_{18}H_{18}N_4O_2S$ 355.1223].

Example 234

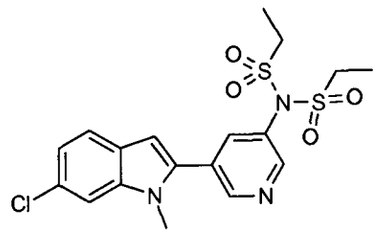
Ethanesulfonic acid [5-(1-methyl-6-fluoro-1H-indol-2-yl)-pyridin-3-yl]-amide



6-Fluoro-1-methyl-indole boronic acid and 3-bromo-5-aminopyridine are processed according to procedures described in examples 100, 225a and 225c to give ethanesulfonic acid [5-(1-methyl-6-fluoro-1H-indol-2-yl)-pyridin-3-yl]-amide. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.24 (t, *J*=7.3 Hz, 3 H), 3.17 - 3.28 (m, 5 H), 6.53 (d, *J*=3.0 Hz, 1 H), 7.01 (dd, *J*=10.2, 8.7 Hz, 1 H), 7.29 (d, *J*=3.3 Hz, 1 H), 7.60 - 7.68 (m, 2 H), 8.41 (d, *J*=1.8 Hz, 1 H), 8.53 (d, *J*=2.5 Hz, 1 H), 10.23 (s, 1 H). HRMS (ESI) m/z 334.1029 [(M+H)$^+$ Calcd for $C_{16}H_{16}FN_3O_2S$ 334.1020].

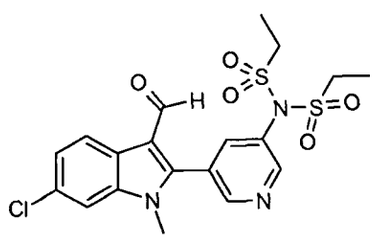
Example 235

(a) Bis-ethanesulfonic acid [5-(1-methyl-6-chloro-1H-indol-2-yl)-pyridin-3-yl)-amide



Bis-ethanesulfonic acid (5-bromo-pyridin-3-yl)-amide (Example 210a) and 6-chloro-1-methyl-indole-2-boronic acid are processed according to the procedure described in Example 100 to give bis-ethanesulfonic acid [5-(1-methyl-6-chloro-1H-indol-2-yl)-pyridin-3-yl)-amide. MS (ESI) *m/z* 442.1 (M+H)$^+$

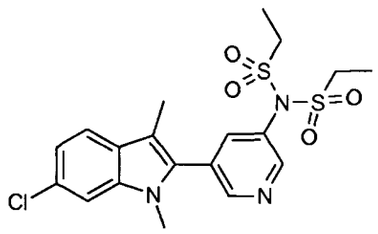
(b) Bis-ethanesulfonic acid [5-(1-methyl-3-carboxaldehyde-6-chloro-1H-indol-2-yl)-pyridin-3-yl)-amide



A flask is charged with DMF (10 mL) and cooled to 0 °C. Phosphorus oxychloride (0.205 ml, 2.178 mmol) is added and the reaction mixture is stirred for 20 min. Bis-

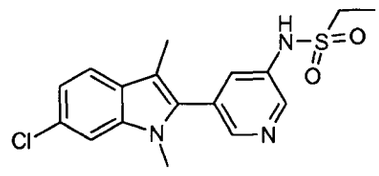
ethanesulfonic acid [5-(1-methyl-6-chloro-1H-indol-2-yl)-pyridin-3-yl)-amide (0.875 g, 1.980 mmol) is added and reaction mixture is left to stir at room temperature overnight. The reaction is washed with saturated aqueous $NaHCO_3$ and extracted with ethyl acetate. The organic layer is separated and washed with water thrice, then dried over Na_2SO_4 and concentrated *in vacuo* to afford bis-ethanesulfonic acid [5-(1-methyl-3-carboxaldehyde-6-chloro-1H-indol-2-yl)-pyridin-3-yl)-amide. MS (ESI) *m/z* 469.9 $(M+H)^+$.

(c) Bis-ethanesulfonic acid [5-(1,3-dimethyl-6-chloro-1H-indol-2-yl)-pyridin-3-yl)-amide



A flask is charged with bis-ethanesulfonic acid [5-(1-methyl-3-carboxaldehyde-6-chloro-1H-indol-2-yl)-pyridin-3-yl)-amide (0.225 g, 0.479 mmol), zinc iodide (0.2320 g, 0.718 mmol), $NaCN(BH)_3$ (0.228 g, 3.591 mmol) and dichloroethane (5 mL). The reaction is refluxed for 1.5 hours. The reaction mixture is cooled to room temperature and filtered over celite. The celite layer is washed with DCM. The filtrate is washed with a buffer solution containing 1:1 saturated ammonium hydroxide and saturated ammonium chloride solution. The organic layer is dried over sodium sulfate and concentrated *in vacuo* to give bis-ethanesulfonic acid [5-(1,3-dimethyl-6-chloro-1H-indol-2-yl)-pyridin-3-yl)-amide. MS (ESI) *m/z* 455.9 $(M+H)^+$

(d) Ethanesulfonic acid [5-(1,3-dimethyl-6-chloro-1H-indol-2-yl)-pyridin-3-yl)-amide

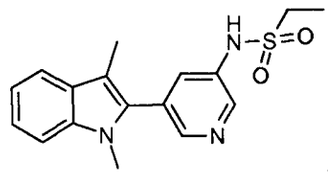


Bis-ethanesulfonic acid [5-(1,3-dimethyl-6-chloro-1H-indol-2-yl)-pyridin-3-yl)-amide is processed according to the procedure described in Example 225c to give ethanesulfonic acid [5-(1,3-dimethyl-6-chloro-1H-indol-2-yl)-pyridin-3-yl)-amide. ^1H NMR (400 MHz, MeOD) δ ppm 1.41 (t, *J*=7.33 Hz, 3 H), 2.31 (s, 3 H), 3.26 (q, *J*=7.33 Hz, 2 H), 3.67 (s, 3 H), 7.12 (dd, *J*=8.46, 1.89 Hz, 1 H), 7.49 (d, *J*=1.77 Hz, 1 H), 7.57 (d, *J*=8.34 Hz, 1 H),

7.81 - 7.86 (m, 1 H), 8.41 (d, *J*=1.77 Hz, 1 H), 8.51 (d, *J*=2.27 Hz, 1 H). HRMS (ESI) m/z 364.0894 [(M+H)$^+$ Calcd for $C_{17}H_{18}N_3O_2SCl$ 364.0881].

Example 236

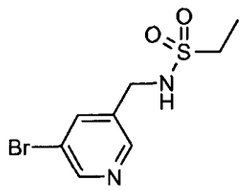
Ethanesulfonic acid [5-(1,3-dimethyl-1H-indol-2-yl)-pyridin-3-yl)-amide



Ethanesulfonic acid [5-(1-methyl-1H-indol-2-yl)-pyridin-3-yl]-*N*-ethanesulfonyl-amide (Example 225a) is processed according to the procedures described in Example 235b, 235c and 225c to give ethanesulfonic acid [5-(1,3-dimethyl-1H-indol-2-yl)-pyridin-3-yl)-amide. ^{1}H NMR (400 MHz, MeOD) δ ppm 1.41 (t, *J*=7.5 Hz, 3 H), 2.33 (s, 3 H), 3.27 (q, *J*=7.3 Hz, 2 H), 3.69 (s, 3 H), 7.14 (t, *J*=7.5 Hz, 1 H), 7.24 - 7.31 (m, 1 H), 7.43 (d, *J*=8.3 Hz, 1 H), 7.61 (d, *J*=8.1 Hz, 1 H), 7.84 (t, *J*=2.1 Hz, 1 H), 8.42 (d, *J*=1.8 Hz, 1 H), 8.50 (d, *J*=2.5 Hz, 1 H). HRMS: (ESI) m/z 330.1276 [(M+H)$^+$ Calcd for $C_{17}H_{19}N_3O_2S$ 330.1270].

Example 237

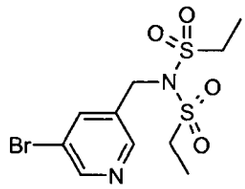
(a) *N*-((5-bromopyridin-3-yl)methyl)ethanesulfonamide



A flask is charged with 5-bromonicotinaldehyde (1.15 g, 6.18 mmol), ethanesulfonamide (1.35 g, 12.37 mmol) and toluene (120 mL), and titanium isopropoxide (2.64 g, 9.27 mmol) is added dropwise. The mixture is stirred at 120 °C overnight. The mixture is concentrated *in vacuo*. The residue is taken up in DCM (100 mL) and MeOH (100 mL) and $NaBH_4$ (0.468 g, 12.37 mmol) is added at 0 °C. The mixture is stirred at 0 °C for 30 min. Water (50 mL) is then added and the mixture is stirred for 5 min. The suspension is filtered through a pad of celite. The celite layer is washed with DCM (50 mL × 3). The filtrate is concentrated *in vacuo*. The resulting aqueous phase is extracted with DCM (500 mL) and the organic phase is dried over Na_2SO_4, silica gel (20 g) added, and concentrated *in vacuo*. The residue is purified by silica chromatography eluting with a 0

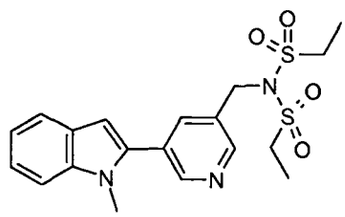
to 7% MeOH-DCM gradient to give *N*-((5-bromopyridin-3-yl)methyl)ethanesulfonamide. MS (ESI) *m/z* 278.9, 280.8, $(M+H)^+$.

(b) *N*-((5-Bromopyridin-3-yl)methyl)-l-(ethylsulfonyl)ethanesulfonamide



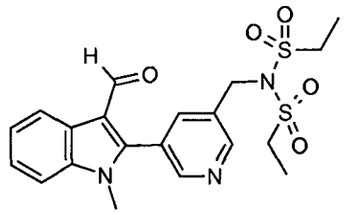
To a solution of *N*-((5-bromopyridin-3-yl)methyl)ethanesulfonamide (1.8 g, 5.55 mmol) and triethylamine (1.683 g, 16.64 mmol) in DCM (20 mL) at 0 °C is added ethanesulfonyl chloride (1.426 g, 11.09 mmol), and the mixture is stirred at 0 °C for 1h. Silica gel (10 g) is added and the mixture is concentrated *in vacuo*. The residue is purified by silica chromatography eluting with 0 to 2% MeOH-DCM to give *N*-((5-bromopyridin-3-yl)methyl)-*N*-(ethylsulfonyl)ethanesulfonamide. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.14 (t, *J*=7.3 Hz, 6 H), 3.48 (q, *J*=7.3 Hz, 4 H), 4.92 (s, 2 H), 8.0 (t, *J*=2.1 Hz, 1 H), 8.59 (d, *J*=2.0 Hz, 1 H), 8.72 (d, *J*=2.3 Hz, 1 H).

(c) *N*-(Ethylsulfonyl)-*N*-((5-(1-methyl-1H-indol-2-yl)pyridin-3-yl)methyl)ethanesulfonamide



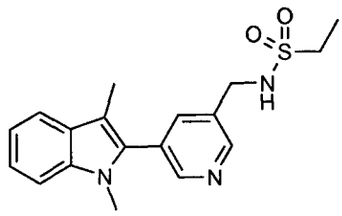
N-((5-Bromopyridin-3-yl)methyl)-l-(ethylsulfonyl)ethanesulfonamide and *N*-methyl-indole-2-boronic acid are processed according to the procedure described in Example 100 to give *N*-(ethylsulfonyl)-*N*-((5-(1-methyl-1H-indol-2-yl)pyridin-3-yl)methyl)ethanesulfonamide. MS (ESI) *m/z* 422.0 $(M+H)^+$.

(d) *N*-(Ethylsulfonyl)-*N*-((5-(3-formyl-1-methyl-1H-indol-2-yl)pyridin-3-yl)methyl)ethanesulfonamide



N-(Ethylsulfonyl)-*N*-((5-(1-methyl-1H-indol-2-yl)pyridin-3-yl)methyl)ethanesulfonamide is processed according to the procedure described in Example 235b to give *N*-(ethylsulfonyl)-*N*-((5-(3-formyl-1-methyl-1H-indol-2-yl)pyridin-3-yl)methyl)ethanesulfonamide. MS (ESI) *m/z* 450.0 $(M+H)^+$.

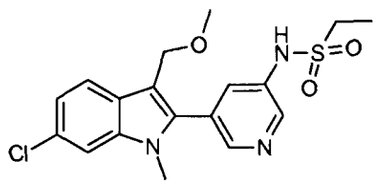
(e) *N*-((5-(1,3-Dimethyl-1H-indol-2-yl)pyridin-3-yl)methyl)ethanesulfonamide



N-(Ethylsulfonyl)-*N*-((5-(3-formyl-1-methyl-1H-indol-2-yl)pyridin-3-yl)methyl)ethanesulfonamide is processed according to the procedure described in Example 235c to give *N*-(ethylsulfonyl)-*N*-((5-(1,3-dimethyl-1H-indol-2-yl)pyridin-3-yl)methyl)ethanesulfonamide which is processed according to the procedure described in Example 225c to give *N*-((5-(1,3-dimethyl-1H-indol-2-yl)pyridin-3-yl)methyl)ethanesulfonamide. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.20 (t, *J*=7.3 Hz, 3 H), 2.24 (s, 3 H), 3.04 (q, *J*=7.3 Hz, 2 H), 3.62 (s, 3 H), 4.31 (s, 2 H), 7.10 (t, *J*=7.5 Hz, 1 H), 7.22 (ddd, *J*=8.2, 7.0, 1.3 Hz, 1 H), 7.49 (d, *J*=8.1 Hz, 1 H), 7.58 (d, *J*=7.8 Hz, 1 H), 7.72 (br. s., 1 H), 7.87 (t, *J*=2.0 Hz, 1 H), 8.61 (dd, *J*=7.2, 2.2 Hz, 2 H). HRMS: (ESI) m/z 344.1442 [(M+H)+ Calcd for $C_{18}H_{22}N_3O_2S$: 344.1427].

Example 238

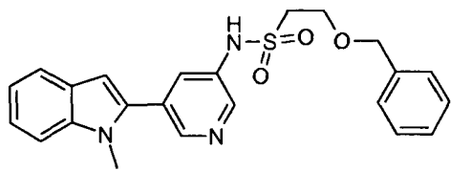
(a) Ethanesulfonic acid [5-(1-methyl-3-methoxymethyl-6-chloro-1H-indol-2-yl)-pyridin-3-yl)-amide



Bis-ethanesulfonic acid [5-(1-methyl-3-carboxaldehyde-6-chloro-1H-indol-2-yl)-pyridin-3-yl)-amide (Example 235b, 0.150 g, 0.319 mmol) is dissolved in methanol (5 mL) and cooled to 0 °C. $NaBH_4$ (0.019 g, 0.798 mmol) is added and the reaction mixture is stirred at room temperature for 2 h. 4M aqueous NaOH (1 mL) is added and the reaction is stirred at room temperature for 1 h. The methanol is then removed *in vacuo*. The crude is taken up in DCM and washed with water twice. The organic layer is dried over Na_2SO_4 and concentrated *in vacuo*. The crude is purified by silica gel flash chromatography (dichloromethane-methanol, 9:1) to afford bis-ethanesulfonic acid [5-(1-methyl-3-methoxymethyl-6-chloro-1H-indol-2-yl)-pyridin-3-yl)-amide. ^{1}H NMR (400 MHz, MeOD) δ ppm 1.41 (t, *J*=7.3 Hz, 3 H), 3.28 (q, *J*=7.3 Hz, 2 H), 3.39 (s, 3 H), 3.72 (s, 3 H), 4.54 (s, 2 H), 7.18 (dd, *J*=8.6, 1.8 Hz, 1 H), 7.56 (d, *J*=1.8 Hz, 1 H), 7.71 (d, *J*=8.6 Hz, 1 H), 7.93 (t, *J*=2.3 Hz, 1 H), 8.48 (d, *J*=1.8 Hz, 1 H), 8.54 (d, *J*=2.5 Hz, 1 H). HRMS: (ESI) m/z 394.0990 [(M+H)$^+$ Calcd for $C_{18}H_{20}N_3O_3SCl$ 394.0986].

Example 239

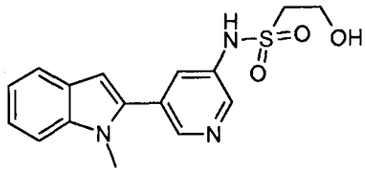
(a) 2-(Benzyloxy)-*N*-(5-(1-methyl-1H-indol-2-yl)pyridin-3-yl)ethanesulfonamide



To a solution of 5-(1-methyl-1H-indol-2-yl)pyridin-3-amine (Example 100, 150 mg, 0.672 mmol) and triethylamine (272 mg, 2.69 mmol) in DCM (6 mL) is added 2-chloroethanesulfonyl chloride (274 mg, 1.68 mmol) in DCM (2 mL) dropwise at 0 °C. The mixture is stirred at 0 °C for 1 h. Silica gel (5 g) is added and the mixture is concentrated. After elution, the fractions containing the product are concentrated to give a residue, which is redissolved in benzyl alcohol (20 mL). 60% NaH in mineral oil is added. The mixture is stirred at 70 °C for 1 day. The mixture is then filtered and the filtrate is purified on Xbridge C18 eluting with a 1:9 to 9:1 acetonitrile-water gradient to give 2-(benzyloxy)-

N-(5-(1-methyl-1H-indol-2-yl)pyridin-3-yl)ethanesulfonamide. MS (ESI) *m/z* 422.1 $(M+H)^+$.

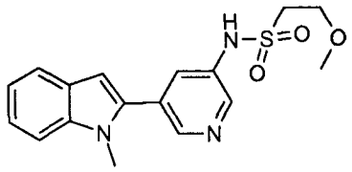
(b) 2-Hydroxy-*N*-(5-(1-methyl-1H-indol-2-yl)pyridin-3-yl)ethanesulfonamide



A flask is charged with 2-(benzyloxy)-N-(5-(1-methyl-1H-indol-2-yl)pyridin-3-yl)ethanesulfonamide (90 mg, 0.214 mmol) and MeOH (5 mL), and the flask is flushed with N_2. 10% Pd/C (22.7 mg, 0.021 mmol) is added to the mixture. The flask is flushed with H_2 and stirred under H_2 atmosphere at 50 °C overnight. The mixture is filtered and the filtrate is purified by silica chromatography eluting with a 0 to 4% methanol-DCM gradient to give 2-hydroxy-*N*-(5-(1-methyl-1H-indol-2-yl)pyridin-3-yl)ethanesulfonamide. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 3.37 (t, *J*=6.2 Hz, 2 H), 3.77 (s, 3 H), 3.80 (t, *J*=6.3 Hz, 2 H), 4.96 (br. s., 1 H), 6.70 (s, 1 H), 7.10 (t, *J*=7.1 Hz, 1 H), 7.23 (td, *J*=7.6, 1.1 Hz, 1 H), 7.53 (d, *J*=7.8 Hz, 1 H), 7.61 (d, *J*=7.8 Hz, 1 H), 7.79 (t, *J*=2.3 Hz, 1 H), 8.47 (d, *J*=2.5 Hz, 1 H), 8.55 (d, *J*=1.8 Hz, 1 H), 10.12 (br. s., 1 H). HRMS: (ESI) m/z 332.1072 [$(M+H)^+$ Calcd for $C_{16}H_{18}N_3O_3S$ 332.1063].

Example 240

2-Methoxy-*N*-(5-(1-methyl-1H-indol-2-yl)pyridin-3-yl) ethanesulfonamide

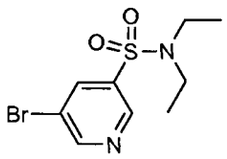


A flask is charged with 5-(1-methyl-1*H*-indol-2-yl)pyridin-3-amine (Example 100, 22 mg, 0.10 mmol), DCM (2 mL) and TEA (20 mg, 0.20 mmol). 2-Chloroethanesulfonyl chloride (16 mg, 0.10 mmol) in DCM (0.5 mL) is added dropwise at 0°C. The mixture is stirred over weekend at room temperature. The solvent is removed *in vacuo* and methanol (2 mL) and 5 M aqueous NaOH (3 mL) are added. The mixture is stirred at 60 °C overnight, concentrated *in vacuo* and the residue is extracted with DCM. The combined organic phase is dried over Na_2SO_4 and concentrated. The residue is purified on silica

chromatography eluting with a 0 to 5% methanol-DCM gradient to give 2-methoxy-*N*-(5-(1-methyl-1H-indol-2-yl)pyridin-3-yl) ethanesulfonamide. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 3.18 (s, 3 H), 3.51 (t, *J*=5.7 Hz, 2 H), 3.70 (t, *J*=5.7 Hz, 2 H), 3.77 (s, 3 H), 6.70 (d, *J*=0.5 Hz, 1 H), 7.10 (td, *J*=7.5, 1.0 Hz, 1 H), 7.23 (ddd, *J*=8.2, 7.1, 1.1 Hz, 1 H), 7.53 (d, *J*=8.3 Hz, 1 H), 7.61 (d, *J*=7.8 Hz, 1 H), 7.78 (t, *J*=2.3 Hz, 1 H), 8.46 (d, *J*=2.5 Hz, 1 H), 8.55 (d, *J*=2.0 Hz, 1 H). HRMS: (ESI) m/z 346.1251 [(M+H)+ Calcd for $C_{17}H_{20}N_3O_3S$: 346.1225].

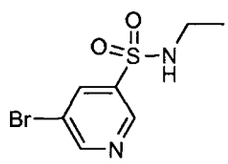
Example 241

(a) 5-bromo-*N*,*N*-diethylpyridine-3-sulfonamide



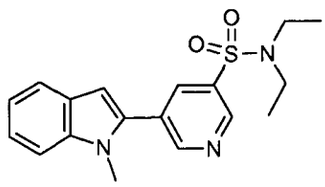
To a suspension of 5-bromopyridine-3-sulfonamide (237 mg, 1 mmol) and K_2CO_3 (276 mg, 2 mmol) in DMF (1 mL) is added iodoethane (156 mg, 1 mmol) in DMF (5 mL) via syringe pump over 2 hours. The mixture is then stirred at room temperature overnight. Iodoethane (0.020 mL, 0.2 mmol) in DMF (1 mL) is added dropwise. The mixture is stirred over the weekend and filtered. The filtrate is purified by Xterra RP18 eluting with a 1:9 to 9:1 acetonitrile-water gradient to give 5-bromo-*N*,*N*-diethylpyridine-3-sulfonamide. MS (ESI) *m/z* 293.0, 295.1 $(M+H)^+$.

(b) *N*-ethyl-5-(1-methyl-1H-indol-2-yl)pyridine-3-sulfonamide.



The method described in Example 241a also affords *N*-ethyl-5-(1-methyl-1H-indol-2-yl)pyridine-3-sulfonamide as a product of the reaction. MS (ESI) *m/z* 265.0, 267.0 $(M+H)^+$.

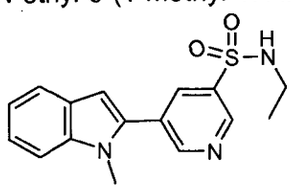
(c) *N*,*N*-diethyl-5-(1-methyl-1H-indol-2-yl)pyridine-3-sulfonamide



A flask is charged with 1-methyl-1H-indol-2-ylboronic acid (90 mg, 0.512 mmol), 5-bromo-*N*,*N*-diethylpyridine-3-sulfonamide (100 mg, 0.341 mmol) and polymer supported $Pd(PPh_3)_4$ (189 mg, 0.017 mmol), and the flask is flushed with N_2 for 5 min. 1,4-Dioxane (10 mL) and 2M K_2CO_3 in water (0.512 mL, 1.023 mmol) are added under N_2 and the mixture is stirred at 90 °C under N_2 for 2 h. The mixture is then cooled to room temperature and DMF (4 mL) is added. The mixture is concentrated *in vacuo* and the residue is filtered and the filtrate is purified by Xterra RP18 eluting with a 1:9 to 9:1 acetonitrile-water gradient to give *N*,*N*-diethyl-5-(1-methyl-1H-indol-2-yl)pyridine-3-sulfonamide. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.10 (t, *J*=7.1 Hz, 6 H), 3.29 (d, *J*=7.1 Hz, 4 H), 3.80 (s, 3 H), 6.85 (s, 1 H), 7.08 - 7.14 (m, 1 H), 7.26 (td, *J*=7.71, 1.26 Hz, 1 H), 7.56 (dd, *J*=8.3, 0.5 Hz, 1 H), 7.63 (d, *J*=7.8 Hz, 1 H), 8.33 (t, *J*=2.1 Hz, 1 H), 9.00 (d, *J*=2.0 Hz, 1 H), 9.10 (d, *J*=2.2 Hz, 1 H). HRMS: (ESI) m/z 344.1428 [$(M+H)^+$ Calcd for $C_{18}H_{22}N_3O_2S$ 344.1427].

Example 242

N-ethyl-5-(1-methyl-1H-indol-2-yl)pyridine-3-sulfonamide



N-Ethyl-5-(1-methyl-1H-indol-2-yl)pyridine-3-sulfonamide is processed according to the method described in Example 241c to give *N*-ethyl-5-(1-methyl-1H-indol-2-yl)pyridine-3-sulfonamide. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.02 (t, *J*=7.2 Hz, 3 H), 2.92 (q, *J*=7.2 Hz, 2 H), 3.81 (s, 3 H), 6.83 (s, 1 H), 7.12 (t, *J*=7.1 Hz, 1 H), 7.26 (td, *J*=7.6, 1.1 Hz, 1 H), 7.56 (d, *J*=8.3 Hz, 1 H), 7.63 (d, *J*=7.8 Hz, 1 H), 8.31 (t, *J*=2.2 Hz, 1 H), 8.97 (d, *J*=2.3 Hz, 1 H), 9.08 (d, *J*=2.2 Hz, 1 H). HRMS: (ESI) m/z 316.1126 [$(M+H)^+$ Calcd for $C_{16}H_{18}N_3O_2S$ 316.1114].

Example 243: In-vitro Assay for Aldosterone Synthase Inhibition

The activities of a compound according to the present invention can be assessed by the following *in vitro* method well-described in the art. See Fiebeler, A *et al.* (2005), "Aldosterone Synthase Inhibitor Ameliorates Angiotensin II–Induced Organ Damage," *Circulation*, 111:3087-3094.

In particular, the inhibition of aldosterone and cortisol secretion *in vitro* can be determined by the following assay.

The cell line NCI-H295R was originally isolated from an adrenocortical carcinoma and has been characterized in the literature through the stimulable secretion of steroid hormones and the presence of the enzymes essential for steroidogenesis. The cells show the physiological property of zonally undifferentiated human foetal adrenocortical cells which, however, have the capacity to produce the steroid hormones which are formed in the three phenotypically distinguishable zones in the adult adrenal cortex. Thus, the NCI-H295R cells have CYP11B2 (aldosterone synthase) and CYP11B1 (steroid 11-hydroxylase).

The human adrenocortical carcinoma NCI-H295R cell line is obtained from American Type Culture Collection (Manassas, VA). Insulin/transferrin/selenium (ITS)-A supplement (100x), DMEM/F-12, antibiotic/antimycotic (100x), and fetal calf serum (FCS) are purchased from Invitrogen (Carlsbad, CA). Anti-mouse PVT scintillation proximity assay (SPA) beads and NBS 96-well plates are obtained from Amersham (Piscataway, NJ) and Corning (Acton, MA), respectively. Clear bottom 96-well flat bottom plates are purchased from Costar (Corning, NY). Aldosterone and angiotensin (Ang II) are purchased from Sigma (St. Louis, MO). D-[1,2,6,7-3H(N)]aldosterone and [1,2,6,7-3H(N)]cortisol are acquired from PerkinElmer (Boston, MA). Nu-serum is a product of BD Biosciences (Franklin Lakes, NJ).

For in vitro measurement of aldosterone and cortisol activity, human adrenocortical carcinoma NCI-H295R cells are seeded in NBS 96-well plates at a density of 25,000 cells/well in 100 µL of a growth medium containing DMEM/F12 supplemented with 10% FCS, 2.5% Nu-serum, 1 µg ITS/ml, and 1x antibiotic/antimycotic. The medium is changed after culturing for 3 days at 37 °C under an atmosphere of 5% CO2/95% air. On the following day, cells are rinsed with 100 µL of DMEM/F12 and incubated in quadruplicate wells at 37 °C for 24 hours with 100 µL of treatment medium containing a cell stimulant and a compound at different concentrations. The test substance is added in a concentration range from 0.2

nanomolar to 16 micromolar. Cell stimulants which can be used are angiotensin-II (1 micormolar), potassium ions (16 millimolar), forskolin (10 micromolar) or a combination of two stimulants. At the end of incubation, the excretion of aldosterone and cortisol into the culture medium can be detected and quantified by commercially available, specific monoclonal antibodies in radioimmunoassays in accordance with the manufacturer's instructions.

Measurement of aldosterone can also be performed using a 96-well plate format. Each test sample is incubated with 0.02 µCi of D-[1,2,6,7-3H(N)]aldosterone and 0.3 µg of anti-aldosterone antibody in phosphate-buffered saline (PBS) containing 0.1% Triton X-100, 0.1% bovine serum albumin, and 12% glycerol in a total volume of 200 µL at room temperature for 1 hour. Anti-mouse PVT SPA beads (50 µL) are then added to each well and incubated overnight at room temperature prior to counting in a Microbeta plate counter. The amount of aldosterone in each sample is calculated by comparing with a standard curve generated using known quantities of the hormone. Measurement of cortisol can be performed in a manner similar to that of aldosterone, except that [1,2,6,7-3H(N)]cortisol is used.

Inhibition of the release of a steroid can be used as a measure of the respective enzyme inhibition by the added test compounds. The dose-dependent inhibition of enzymatic activity by a compound is calculated by means of an inhibition plot which is characterized by an IC_{50}. The IC_{50} values for active test compounds are ascertained by a simple linear regression analysis in order to construct inhibition plots without data weighting. The inhibition plot is calculated by fitting a 4-parameter logistic function to the raw data points using the least squares method. The equation of the 4-parameter logistic function is calculated as follows: Y = (d-a) / ((1 + (x/c)(b) + a) where: a = minimum, b = slope, c= IC_{50}, d = maximum, x = inhibitor concentrations.

Table 1. Inhibitory Activity of Compounds

Example	Aldosterone cell secretion IC_{50} (nM)	Cortisol cell secretion IC_{50} (nM)
6	1	7
15	27	447
33	14	662
42	30	600

65	10	240
90	40	400
101	2	37
106	85	530
107	9	220
123	78	650
138	43	326
171	3	168
180	2	3
186	21	390
192	4	20
196	3	19
206	2	213
209	23	788
214	56	377
216 (one enantiomer)	32	600
216 (other enantiomer)	35	1230
217	4	22
226	36	345
228	105	> 1000
229	5	125
231	2	51
236	21	1100
237	5	1611
238	44	> 1000
242	23	> 1000

Equivalents

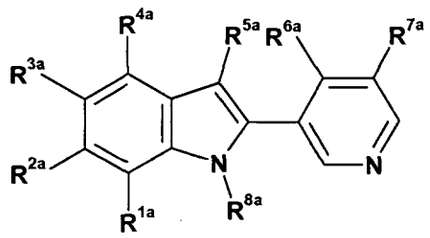
Those skilled in the art will recognize, or be able to ascertain using no more than routine experimentation, numerous equivalents to the specific procedures described herein. Such equivalents are considered to be within the scope of the present invention and are covered by the following claims. The appropriate components, processes, and

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CLAIMS

We Claim:

1. A compound of Formula I:



(I)

wherein:

R^{1a}, R^{2a}, R^{3a}, and R^{4a} are each independently hydrogen, halogen, cyano, hydroxy, alkoxy, alkyl, alkenyl, or alkoxycarbonyl;

R^{5a} is hydrogen, halogen, cyano, alkyl, alkenyl, arylalkyl, heteroarylalkyl, aminocarbonyl, alkylaminocarbonyl, carboxylate, alkoxycarbonyl, heterocyclylcarbonyl, aryl, or heteroaryl;

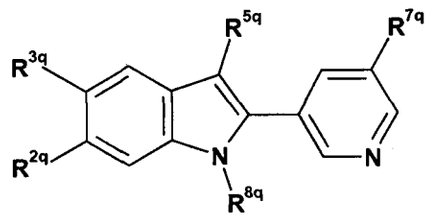
R^{6a} and R^{7a} are each independently hydrogen, halogen, hydroxy, alkoxy, amino, alkyl, sulfonyl, -O-sulfonyl, alkylamino, heterocyclyl, aminocarbonyl, carboxylate, or alkoxycarbonyl;

R^{8a} is hydrogen, alkyl, arylalkyl, heteroarylalkyl, alkoxycarbonyl, sulfonyl, aroyl, aryl, or heteroaryl; and pharmaceutically acceptable salts, polymorphs, rotamers, prodrugs, enantiomers, hydrates, and solvates thereof;

with the proviso that at least one of R^{1a}-R^{8a} is other than hydrogen; and when R^{3a} is lower alkyl or halogen, then at least one of R^{1a}, R^{2a} and R^{4a}-R^{8a} is other than hydrogen; and when R^{5a} is cyano or lower alkyl optionally substituted with cyano, -C(O)-piperidine, amino, alkylamino, dialkylamino, carboxylate, alkoxycarbonyl, aminocarbonyl, or heterocyclyl, then at least one of R^{1a}-R^{4a} and R^{6a}-R^{8a} is other than hydrogen; and when R^{7a} is imidazolyl, then at least one of R^{1a}-R^{6a} and R^{8a} is other than hydrogen; and when R^{8a} is lower alkyl, arylalkyl or alkoxycarbonyl, then at least one of R^{1a}-R^{7a} is other than hydrogen; and when R^{5a} is lower alkyl and R^{8a} is alkyl substituted with carboxylate or $PO_3R^{21}R^{22}$ wherein R^{21} and R^{22} are each independently hydrogen or lower alkyl, then at least one of R^{1a}-R^{4a} and R^{6a} and R^{7a} is other than hydrogen; and when R^{3a} is halogen and R^{5a} and R^{8a} are independently lower alkyl optionally substituted with carboxylate, alkoxycarbonyl, or -C(O)-piperidine, then at least one of R^{1a}, R^{2a}, R^{4a}, R^{6a} and R^{7a} is

other than hydrogen; and when R^{5a} is lower alkenyl substituted with heteroaryl and R^{8a} is lower alkyl, then at least one of R^{1a}-R^{4a}, R^{6a} and R^{7a} is other than hydrogen; and when R^{3a} is halogen or lower alkyl and R^{5a} is lower alkyl substituted with dialkylamino, dialkylaminocarbonyl, carboxylate, alkoxycarbonyl or aminocarbonyl, then at least one of R^{1a}, R^{2a}, R^{4a}, and R^{6a}-R^{8a} is other than hydrogen; and when R^{3a} is –O-benzyl and R^{5a} is alkyl-NH_2, then at least one of R^{1a}, R^{2a}, R^{4a}, and R^{6a}-R^{8a} is other than hydrogen; and when R^{2a} and R^{3a} are each alkoxy and R^{5a} is cyano, then at least one of R^{1a}, R^{4a}, and R^{6a}-R^{8a} is other than hydrogen; and when R^{1a} and R^{3a} are each halogen and R^{5a} is alkyl–NH_2, then at least one of R^{2a}, R^{4a}, and R^{6a}-R^{8a} is other than hydrogen; and when R^{2a} is alkoxycarbonyl and R^{4a} is halogen, then at least one of R^{1a}, R^{3a}, R^{5a} and R^{6a}-R^{8a} is other than hydrogen; and when R^{5a} is alkyl and R^{7a} is –OCH_2-(N-methyl pyrrolidine), then at least one of R^{1a}-R^{4a}, R^{6a} and R^{8a} is other than hydrogen; and when R^{3a} is cycloalkyl and R^{5a} is alkyl–NH_2, then at least one of R^{1a}, R^{2a}, R^{4a}, and R^{6a}-R^{8a} is other than hydrogen; and when R^{3a} is alkyl substituted with aroyl, and R^5 and R^8 are each independently hydrogen or lower alkyl, then at least one of R^{1a}, R^{2a}, and R^{4a} is other than hydrogen.

2. A compound of Formula II:



(II)

wherein:

R^{2q} is hydrogen or halogen;

R^{3q} is hydrogen, halogen, or cyano;

R^{5q} is hydrogen, alkyl, or cyano;

R^{7q} is hydrogen, halogen, alkoxy, -OSO_2-heterocyclyl, -O-arylalkyl, -NR'-SO_2-alkyl, -NR'-C(O)-alkyl, -NR'-C(O)-NR'-alkyl, -NR'-C(O)-O-alkyl, haloalkyl, or alkyl optionally substituted with heterocyclyl, –NR'-SO_2-alkyl, -NR'-SO_2-haloalkyl, NR'-C(O)-alkyl, NR'-C(O)-heterocyclyl, -NR'-C(O)-NR'-alkyl, or –NR'-C(O)-O-alkyl;

R^{8q} is hydrogen, alkyl, hydroxyalkyl, -alkyl-OC(O)-alkyl, carboxylate, alkoxycarbonyl, or arylalkyl substituted with alkyl, or aroyl substituted with cyano and/or alkyl, or -alkyl-O-aryl substituted with alkoxycarbonyl;

each R' is independently hydrogen, C_1-C_4-alkyl, or C_3-C_6-cycloalkyl; and pharmaceutically acceptable salts, polymorphs, rotamers, prodrugs, enantiomers, hydrates, and solvates thereof;

with the proviso that at least one of R^{2q}, R^{3q}, R^{5q}, R^{7q} and R^{8q} is other than hydrogen; and when R^{8q} is lower alkyl or alkoxycarbonyl, then at least one of R^{2q}, R^{3q}, R^{5q} and R^{7q} is other than hydrogen; and when R^{5q} is cyano, then at least one of R^{2q}, R^{3q}, and R^{8q} is other than hydrogen.

3. The compound according to claim 2, wherein R^{7q} is alkoxy or alkyl substituted with heterocyclyl and R^{8q} is alkyl.

4. The compound according to claim 2, wherein

R^{2q} is hydrogen or halogen;

R^{3q} is hydrogen, or halogen;

R^{5q} is hydrogen or cyano;

R^{7q} is alkyl optionally substituted with heterocyclyl, –NR'-SO_2-alkyl, -NR'-SO_2-haloalkyl, NR'-C(O)-alkyl, NR'-C(O)-heterocyclyl, -NR'-C(O)-NR'-alkyl, or –NR'-C(O)-O-alkyl;

R' is independently hydrogen, C_1-C_4-alkyl, or C_3-C_6-cycloalkyl; and

R^{8q} is hydrogen, or C_{1-6}alkyl.

5. The compound according to claim 2 or 4, wherein

R^{2q} is hydrogen or halogen;

R^{3q} is hydrogen, or halogen;

R^{5q} is hydrogen or cyano;

R^{7q} is C_{1-4}alkyl optionally substituted with heterocyclyl, –NR'-SO_2-C_{1-4}alkyl, -NR'-SO_2-haloC_{1-4}alkyl, NR'-C(O)- C_{1-4}alkyl, NR'-C(O)-heterocyclyl, -NR'-C(O)-NR'-C_{1-4}alkyl, or –NR'-C(O)-O-C_{1-4}alkyl;

R' is independently hydrogen, or C_1-C_4-alkyl; and

R^{8q} is hydrogen, or C_{1-6}alkyl.

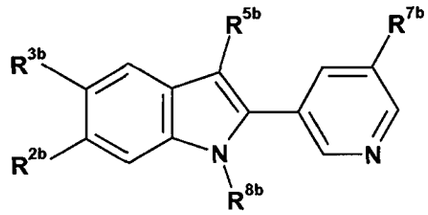
6. The compound according to claims 2 to 5, wherein

R^{7q} is C_{1-4}alkyl substituted with –NR'-SO_2-C_{1-4}alkyl, -NR'-SO_2-haloC_{1-4}alkyl, or NR'-C(O)- C_{1-4}alkyl;

R' is independently hydrogen, or C_1-C_4-alkyl; and

R^{8q} is hydrogen, methyl, or ethyl.

7. A compound of Formula III:



(III)

wherein:

R^{2b} is hydrogen or halogen;

R^{3b} is hydrogen, halogen, or cyano;

R^{5b} is alkyl;

R^{7b} is hydrogen, halogen, alkoxy, -OSO_2-heterocyclyl, -O-arylalkyl, -NR'-SO_2-alkyl, -NR'-C(O)-alkyl, -NR'-C(O)-NR'-alkyl, -NR'-C(O)-O-alkyl, haloalkyl, or alkyl optionally substituted with heterocyclyl, –NR'-SO_2-alkyl, -NR'-SO_2-haloalkyl, NR'-C(O)-alkyl, -NR'-C(O)-NR'-alkyl, NR'-C(O)-heterocyclyl, or –NR'-C(O)-O-alkyl;

R^{8b} is hydrogen, alkyl, hydroxyalkyl, -alkyl-OC(O)-alkyl, carboxylate, alkoxycarbonyl, or arylalkyl substituted with alkyl, or aroyl substituted with cyano and/or alkyl, or -alkyl-O-aryl substituted with alkoxycarbonyl;

each R' is independently hydrogen, C_1-C_4-alkyl, or C_3-C_6-cycloalkyl; and pharmaceutically acceptable salts, polymorphs, rotamers, prodrugs, enantiomers, hydrates, and solvates thereof.

8. The compound according to claim 7, wherein

R^{2b} is hydrogen or halogen;

R^{3b} is hydrogen, halogen, or cyano;

R^{5b} is C_{1-4}alkyl;

R^{7b} is hydrogen, halogen, C_{1-4}alkoxy, -OSO_2-heterocyclyl, -O-arylalkyl, -NR'-SO_2-C_{1-4}alkyl, -NR'-C(O)- C_{1-4}alkyl, -NR'-C(O)-NR'- C_{1-4}alkyl, -NR'-C(O)-O-alkyl, haloalkyl, or C_{1-4}alkyl optionally substituted with heterocyclyl, –NR'-SO_2- C_{1-4}alkyl, -NR'-SO_2-halo C_{1-4}alkyl, NR'-C(O)- C_{1-4}alkyl, -NR'-C(O)-NR'- C_{1-4}alkyl, NR'-C(O)-heterocyclyl, or –NR'-C(O)-O- C_{1-4}alkyl;

R^{8b} is hydrogen, C_{1-4}alkyl, hydroxyalkyl, - C_{1-4}alkyl-OC(O)- C_{1-4}alkyl, carboxylate, alkoxycarbonyl, or arylalkyl substituted with C_{1-4}alkyl, or aroyl substituted with cyano and/or C_{1-4}alkyl, or - C_{1-4}alkyl-O-aryl substituted with alkoxycarbonyl;

each R' is independently hydrogen, C_1-C_4-alkyl, or C_3-C_6-cycloalkyl; and pharmaceutically acceptable salts, polymorphs, rotamers, prodrugs, enantiomers, hydrates, and solvates thereof.

9. The compound according to claim 7 or 8, wherein

R^{2b} is hydrogen or halogen;

R^{3b} is hydrogen, halogen, or cyano;

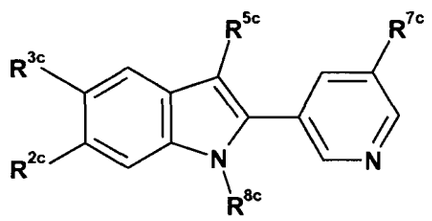
R^{5b} is methyl, ethyl or isopropyl;

R^{7b} is C_{1-4}alkyl substituted with –NR'-SO_2- C_{1-4}alkyl, -NR'-SO_2-haloC_{1-4}alkyl, NR'-C(O)- C_{1-4}alkyl, or -NR'-C(O)-NR'- C_{1-4}alkyl;

R^{8b} is hydrogen, methyl or ethyl;

each R' is independently hydrogen, or C_1-C_4-alkyl.

10. A compound of Formula IV:



(IV)

wherein:

R^{2c} is hydrogen or halogen;

R^{3c} is hydrogen, halogen, or cyano;

R^{5c} is cyano; and

R^{7c} is hydrogen, halogen alkoxy, -OSO_2-heterocyclyl, -O-arylalkyl, -NR'-SO_2-alkyl, -NR'-C(O)-alkyl, -NR'-C(O)-NR'-alkyl, -NR'-C(O)-O-alkyl or alkyl optionally substituted with heterocyclyl, –NR'-SO_2-alkyl, -NR'-SO_2-haloalkyl, NR'-C(O)-alkyl, NR'-C(O)-heterocyclyl, -NR'-C(O)-NR'-alkyl, or –NR'-C(O)-O-alkyl;

R^{8c} is alkyl;

each R' is independently hydrogen, C_1-C_4-alkyl, or C_3-C_6-cycloalkyl; and pharmaceutically acceptable salts, polymorphs, rotamers, prodrugs, enantiomers, hydrates, and solvates thereof.

11. The compound according to claim 10, wherein

R^{2c} is hydrogen or halogen;

R^{3c} is hydrogen, halogen, or cyano;

R^{5c} is cyano; and

R^{7c} is hydrogen, halogen, C_{1-4}alkoxy, -OSO_2-heterocyclyl, -O-arylalkyl, -NR'-SO_2-C_{1-4} alkyl, -NR'-C(O)- C_{1-4} alkyl, -NR'-C(O)-NR'- C_{1-4} alkyl, -NR'-C(O)-O- C_{1-4} alkyl or C_{1-4} alkyl optionally substituted with heterocyclyl, –NR'-SO_2- C_{1-4} alkyl, -NR'-SO_2-halo C_{1-4} alkyl, NR'-C(O)- C_{1-4} alkyl, NR'-C(O)-heterocyclyl, -NR'-C(O)-NR'- C_{1-4} alkyl, or –NR'-C(O)-O- C_{1-4} alkyl;

R^{8c} is C_{1-4} alkyl; and

each R' is independently hydrogen, C_1-C_4-alkyl, or C_3-C_6-cycloalkyl.

12. The compound according to claim 10 or 11, wherein

R^{2c} is hydrogen or halogen;

R^{3c} is hydrogen, or halogen;

R^{5c} is cyano; and

R^{7c} is C_{1-4} alkyl optionally substituted with –NR'-SO_2- C_{1-4} alkyl, -NR'-SO_2-halo C_{1-4} alkyl, NR'-C(O)- C_{1-4} alkyl;

R^{8c} is C_{1-4} alkyl;

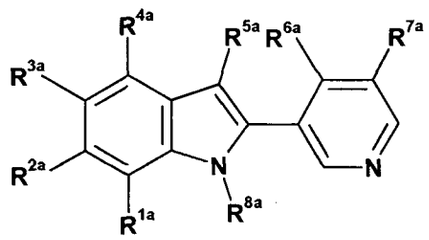
each R' is independently hydrogen, methyl, ethyl or propyl.

13. The compound according to claims 10, 11 or 12, wherein

R^{7c} is C_{1-4} alkyl substituted with –NR'-SO_2- C_{1-4} alkyl, -NR'-SO_2-halo C_{1-4} alkyl, NR'-C(O)- C_{1-4} alkyl; and

each R' is independently hydrogen or C_1-C_4-alkyl.

14. A compound of Formula I:



(I)

wherein:

R^{1a}, R^{2a}, R^{3a}, and R^{4a} are each independently hydrogen, halogen, cyano, hydroxy, alkoxy, alkyl, alkenyl, or alkoxycarbonyl;

R^{5a} is hydrogen halogen, cyano, alkyl, alkenyl, arylalkyl, heteroarylalkyl, aminocarbonyl, alkylaminocarbonyl, carboxylate, alkoxycarbonyl, heterocyclylcarbonyl, aryl, or heteroaryl;

R^{6a} and R^{7a} are each independently hydrogen, halogen, hydroxy, alkoxy, amino, alkyl, sulfonyl, -O-sulfonyl, alkylamino, heterocyclyl, aminocarbonyl, carboxylate, or alkoxycarbonyl;

R^{8a} is hydrogen, alkyl, arylalkyl, heteroarylalkyl, alkoxycarbonyl, sulfonyl, aroyl, aryl, or heteroaryl; and pharmaceutically acceptable salts, polymorphs, rotamers, prodrugs, enantiomers, hydrates, and solvates thereof;

with the proviso that at least one of R^{1a}-R^{8a} is other than hydrogen; and when R^{5a} is cyano or lower alkyl optionally substituted with cyano, -C(O)-piperidine, amino, alkylamino, dialkylamino, carboxylate, alkoxycarbonyl, aminocarbonyl, or heterocyclyl, then at least one of R^{1a}-R^{4a} and R^{6a}-R^{8a} is other than hydrogen; and when R^{7a} is imidazolyl, then at least one of R^{1a}-R^{6a} and R^{8a} is other than hydrogen; and when R^{8a} is alkyl, arylalkyl or alkoxycarbonyl, then at least one of R^{1a}-R^{7a} is other than hydrogen; and when R^{5a} is lower alkyl and R^{8a} is alkyl substituted with carboxylate or $PO_3R^{21}R^{22}$ wherein R^{21} and R^{22} are each independently hydrogen or lower alkyl, then at least one of R^{1a}-R^{4a} and R^{6a} and R^{7a} is other than hydrogen; and when R^{3a} is halogen and R^{5a} and R^{8a} are independently lower alkyl optionally substituted with carboxylate, alkoxycarbonyl, or -C(O)-piperidine, then at least one of R^{1a}, R^{2a}, R^{4a}, R^{6a} and R^{7a} is other than hydrogen; and when R^{3a} is halogen or lower alkyl and R^{5a} is lower alkyl substituted with dialkylamino, dialkylaminocarbonyl, carboxylate, alkoxycarbonyl or aminocarbonyl, then at least one of R^{1a}, R^{2a}, R^{4a}, and R^{6a}-R^{8a} is other than hydrogen; and when R^{2a} and R^{3a} are each alkoxy and R^{5a} is cyano, then at least one of R^{1a}, R^{4a}, and R^{6a}-R^{8a} is other than hydrogen; and when R^{3a} is alkyl substituted with aroyl, and R^5 and R^8 are each

independently hydrogen or lower alkyl, then at least one of R^{1a}, R^{2a}, and R^{4a} is other than hydrogen, for use in therapy.

15. A method of treating an aldosterone synthase associated state in a subject, comprising administering to said subject a therapeutically effective amount of the compound of Formulae I, II, III or IV according to claims 1-13 such that said aldosterone synthase associated state in said subject is treated.

16. The method of claim 15, wherein said aldosterone synthase associated state in a subject is characterized by an abnormal activity of aldosterone synthase.

17. The method of claim 15, wherein said aldosterone synthase associated state in a subject is characterized by an abnormal expression of aldosterone synthase.

18. The method of claim 15, wherein said aldosterone synthase associated state is a cardiovascular disease selected from heart failure, congestive heart failure, arrhythmia, diastolic dysfunction, left ventricular diastolic dysfunction, diastolic heart failure, impaired diastolic filling, systolic dysfunction, ischemia, hypertropic cardiomyopathy, sudden cardiac death, myocardial and vascular fibrosis, impaired arterial compliance, myocardial necrotic lesions, vascular damage, myocardial infarction, left ventricular hypertrophy, decreased ejection fraction, cardiac lesions, vascular wall hypertrophy, endothelial thickening, or fibrinoid necrosis of coronary arteries.

19. The method of claim 15, wherein said aldosterone synthase associated state is selected from renal dysfunction, liver diseases, cerebrovascular diseases, vascular diseases, retinopathy, neuropathy, insulinopathy, edema, endothelial dysfunction, baroreceptor dysfunction, migraine headaches, and hypertension.

20. A method for treating a subject for heart failure, congestive heart failure, arrhythmia, diastolic dysfunction, left ventricular diastolic dysfunction, diastolic heart failure, impaired diastolic filling, systolic dysfunction, ischemia, hypertropic cardiomyopathy, sudden cardiac death, myocardial and vascular fibrosis, impaired arterial compliance, myocardial necrotic lesions, vascular damage, myocardial infarction, left ventricular hypertrophy, decreased ejection fraction, cardiac lesions, vascular wall hypertrophy, endothelial

thickening, fibrinoid necrosis of coronary arteries, renal dysfunction, liver diseases, cerebrovascular diseases, vascular diseases, retinopathy, neuropathy, insulinopathy, edema, endothelial dysfunction, baroreceptor dysfunction, migraine headaches, or hypertension, comprising:

administering to said subject an effective amount of the compound of Formula I, II, III, or IV according to claims 1-13 such that said subject is treated.

21. The method of any one of claims 15-20, wherein said subject is human.

22. The method of any one of claims 15-21, wherein said compound is administered in combination with a second agent.

23. The method of claim 22, wherein said second agent is an HMG-Co-A reductase inhibitor, an angiotensin II receptor antagonist, angiotensin converting enzyme (ACE) Inhibitor, a calcium channel blocker (CCB), a dual angiotensin converting enzyme/neutral endopeptidase (ACE/NEP) inhibitor, an endothelin antagonist, a renin inhibitor, a diuretic, an ApoA-I mimic, an anti-diabetic agent, an obesity-reducing agent, an aldosterone receptor blocker, an endothelin receptor blocker, or a CETP inhibitor.

24. A pharmaceutical composition, comprising

an effective amount of the compound of Formulae I, II, III, or IV according to claims 1-13, and

a pharmaceutically acceptable carrier or diluent.

25. The pharmaceutical composition of claim 24, further comprising a second agent.

26. The pharmaceutical composition of claim 25, wherein said second agent is an HMG-Co-A reductase inhibitor, an angiotensin II receptor antagonist, angiotensin converting enzyme (ACE) Inhibitor, a calcium channel blocker (CCB), a dual angiotensin converting enzyme/neutral endopeptidase (ACE/NEP) inhibitor, an endothelin antagonist, a renin inhibitor, a diuretic, an ApoA-I mimic, an anti-diabetic agent, an obesity-reducing agent, an aldosterone receptor blocker, an endothelin receptor blocker, or a CETP inhibitor

27. Use of a compound of Formula (I), (II), (III) or (IV) according to claims 1-13, for the preparation of a pharmaceutical composition for the treatment of a disorder or disease in a subject mediated by the inhibition of aldosterone synthase.

28. A compound of Formula (I), (II), (III) or (IV) according to claims 1-13, for use as a medicament.

29. The pharmaceutical composition of any one of claims 24-26, for use as a medicament.

30. A method of treating a disorder or disease mediated by aldosterone synthase in a mammal, comprising:

administering to the mammal in need thereof a therapeutically effective amount of a compound of Formula (I), (II), (III) or (IV) according to claims 1-13.

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(81) **Estados (Países) Designados** *(a menos que se indique de otra manera, para cada tipo de protección nacional disponible)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PE, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

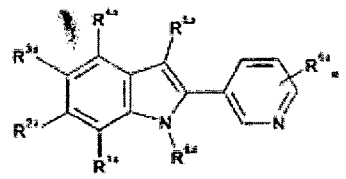
(84) **Estados (Países) Designados** *(a menos que se indique de otra manera, para cada tipo de protección regional disponible)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasiáticos (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), Europeos (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

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(54) **Título : COMPUESTOS ORGÁNICOS**



(I)

(57) **Resumen:**

La presente invención proporciona compuestos orgánicos novedosos de la fórmula I); métodos de uso, y composiciones farmacéuticas de los mismos.

COMPUESTOS ORGÁNICOS

La hormona mineralocorticoide aldosterona es producida por la glándula suprarrenal, y actúa sobre los túbulos distales y los ductos de recolección del riñón para aumentar la reabsorción de los iones y el agua en el riñón. La aldosterona provoca la conservación del sodio, la secreción del potasio, el aumento en la retención de agua, y el aumento en la presión sanguínea.

La aldosterona se ha implicado en la patogénesis de las enfermedades cardiovasculares, tales como hipertensión e insuficiencia cardíaca. En los estudios clínicos, el tratamiento con el antagonista no selectivo de los receptores de mineralocorticoides (MRA) espironolactona, o con el antagonista no selectivo de los receptores de mineralocorticoides (MRA) eplerenona, reduce de una manera significativa la patología y mortalidad entre los pacientes con insuficiencia cardíaca o infarto de miocardio que ya están tomando un inhibidor de la enzima convertidora de angiotensina o un bloqueador-ß. Sin embargo, se observaron efectos secundarios significativos, tales como ginecomastia e impotencia, en los pacientes masculinos que recibieron espironolactona, mientras que se vio hipercalemia en los pacientes que tomaron cualquiera de los fármacos.

La invención pertenece a los compuestos y a los métodos para utilizarlos como se describe en la presente. Los ejemplos de los compuestos de la invención incluyen los compuestos de las fórmulas

I a IV, y los compuestos de los Ejemplos.

En otra modalidad, la invención pertenece, cuando menos en parte, a un método para el tratamiento de un trastorno o enfermedad mediada por la sintasa de aldosterona en un sujeto, mediante la administración al sujeto, de una cantidad terapéuticamente efectiva de un compuesto de las fórmulas I a IV, de tal manera que se trata el trastorno o enfermedad mediada por la sintasa de aldosterona en el sujeto.

En todavía otra modalidad, la invención pertenece, cuando menos en parte, a un método para el tratamiento de un sujeto para hipocalemia, hipertensión, enfermedad de Conn, insuficiencia renal, en particular, insuficiencia renal crónica, restenosis, ateroesclerosis, síndrome X, obesidad, nefropatía, enfermedad posterior a infarto de miocardio, enfermedades cardíacas coronarias, mayor formación de colágeno, fibrosis y remodelación en seguida de hipertensión y disfunción endotelial, enfermedades cardiovasculares, disfunción renal, enfermedades hepáticas, enfermedades cerebrovasculares, enfermedades vasculares, retinopatía, neuropatía, insulinopatía, edema, disfunción endotelial, disfunción de barorreceptor, migraña, dolores de cabeza, insuficiencia cardíaca, tal como insuficiencia cardíaca congestiva, arritmia, disfunción diastólica, disfunción diastólica de ventrículo izquierdo, insuficiencia cardíaca diastólica, llenado diastólico deteriorado, disfunción sistólica, isquemia, cardiomiopatía hipertrófica, muerte cardíaca repentina, fibrosis de miocardio y vascular, funcionamiento arterial deteriorado, lesiones

necróticas de miocardio, daño vascular, infarto de miocardio, hipertrofia de ventrículo izquierdo, fracción de expulsión reducida, lesiones cardíacas, hipertrofia de las paredes vasculares, engrosamiento endotelial, o necrosis fibrinoide de las arterias coronarias, el cual comprende administrar al sujeto una cantidad terapéuticamente efectiva de un compuesto de las fórmulas I a IV, de tal manera que se trate al sujeto.

En todavía otra modalidad, la invención pertenece, cuando menos en parte, a composiciones farmacéuticas, las cuales comprenden una cantidad efectiva de un compuesto de las fórmulas 1, II, III o IV, en donde esta cantidad efectiva es efectiva para tratar un estado asociado con la sintasa de aldosterona.

Un planteamiento alternativo para aminorar los efectos perjudiciales de la aldosterona, es suprimir su producción mediante los inhibidores de la sintasa de aldosterona, una enzima responsable de los pasos finales de la biosíntesis de la aldosterona a partir de la desoxicorticosterona, por medio de la conversión de la corticosterona para formar 18-OH-corticosterona, la cual entonces se convierte hasta aldosterona.

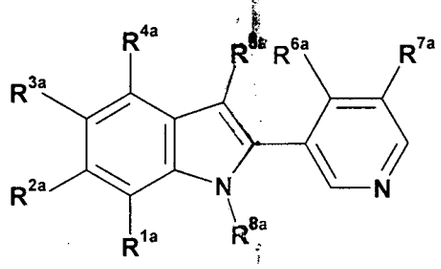
La invención pertenece, cuando menos en parte, a compuestos, a composiciones farmacéuticas que contienen a los compuestos, y a métodos de uso de los mismos. La presente invención también se refiere a compuestos novedosos que se pueden utilizar, por ejemplo, como moduladores de la sintasa de aldosterona, o como inhibidores de la síntesis de aldosterona.

Los compuestos de la presente invención, por ejemplo, se pueden utilizar para tratar diferentes estados asociados con la sintasa de aldosterona, tales como hipocalemia, hipertensión, enfermedad de Conn, insuficiencia renal, en particular, insuficiencia renal crónica, restenosis, ateroesclerosis, síndrome X, obesidad, nefropatía, enfermedad posterior a infarto de miocardio, enfermedades cardíacas coronarias, mayor formación de colágeno, fibrosis y remodelación en seguida de hipertensión y disfunción endotelial, enfermedades cardiovasculares, disfunción renal, enfermedades hepáticas, enfermedades cerebrovasculares, enfermedades vasculares, retinopatía, neuropatía, insulinopatía, edema, disfunción endotelial, disfunción de barorreceptor, migraña, dolores de cabeza, insuficiencia cardíaca, tal como insuficiencia cardíaca congestiva, arritmia, disfunción diastólica, disfunción diastólica de ventrículo izquierdo, insuficiencia cardíaca diastólica, llenado diastólico deteriorado, disfunción sistólica, isquemia, cardiomiopatía hipertrófica, muerte cardíaca repentina, fibrosis de miocardio y vascular, funcionamiento arterial deteriorado, lesiones necróticas de miocardio, daño vascular, infarto de miocardio, hipertrofia de ventrículo izquierdo, fracción de expulsión reducida, lesiones cardíacas, hipertrofia de las paredes vasculares, engrosamiento endotelial, y necrosis fibrinoide de las arterias coronarias.

Compuestos de la Invención

La presente invención pertenece, cuando menos en parte, a los

compuestos de la fórmula I:



(I)

en donde:

R^{1a}, R^{2a}, R^{3a}, y R^{4a} son cada uno independientemente hidrógeno, halógeno, ciano, hidroxilo, alcoxilo, alquilo, alquenilo, o alcoxi-carbonilo;

R^{5a} es hidrógeno halógeno, ciano, alquilo, alquenilo, aril-alquilo, heteroaril-alquilo, amino-carbonilo, alquil-amino-carbonilo, carboxilato, alcoxi-carbonilo, heterociclil-carbonilo, arilo, o heteroarilo;

R^{6a} y R^{7a} son cada uno independientemente hidrógeno, halógeno, hidroxilo, alcoxilo, amino, alquilo, sulfonilo, -O-sulfonilo, alquil-amino, heterociclilo, amino-carbonilo, carboxilato, o alcoxi-carbonilo;

R^{8a} es hidrógeno, alquilo, aril-alquilo, heteroaril-alquilo, alcoxi-carbonilo, sulfonilo, aroílo, arilo, o heteroarilo;

y las sales farmacéuticamente aceptables, polimorfos, rotámeros, pro-fármacos, enantiómeros, hidratos, y solvatos de los mismos;

con la condición de que cuando menos uno de R^{1a}-R^{8a} es diferente de hidrógeno; y cuando R^{3a} es alquilo inferior o halógeno,

entonces cuando menos uno de R^{1a}, R^{2a} y R^{4a}-R^{8a} es diferente de hidrógeno; y cuando R^{5a} es ciano o alquilo inferior opcionalmente sustituido con ciano, -C(O)-piperidina, amino, alquil-amino, dialquil-amino, carboxilato, alcoxi-carbonilo, amino-carbonilo, o heterociclilo, entonces cuando menos uno de R^{1a}-R^{4a} y R^{6a}-R^{8a} es diferente de hidrógeno; y cuando R^{7a} es imidazolilo, entonces cuando menos uno de R^{1a}-R^{6a} y R^{8a} es diferente de hidrógeno; y cuando R^{8a} es alquilo inferior, aril-alquilo o alcoxi-carbonilo, entonces cuando menos uno de R^{1a}-R^{7a} es diferente de hidrógeno; y cuando R^{5a} es alquilo inferior, y R^{8a} es alquilo sustituido con carboxilato o $PO_3R^{21}R^{22}$ en donde R^{21} y R^{22} son cada uno independientemente hidrógeno o alquilo inferior, entonces cuando menos uno de R^{1a}-R^{4a} y R^{6a} y R^{7a} es diferente de hidrógeno; y cuando R^{3a} es halógeno y R^{5a} y R^{8a} son independientemente alquilo inferior opcionalmente sustituido con carboxilato, alcoxi-carbonilo, o -C(O)-piperidina, entonces cuando menos uno de R^{1a}, R^{2a}, R^{4a}, R^{6a} y R^{7a} es diferente de hidrógeno; y cuando R^{5a} es alquenilo inferior sustituido con heteroarilo, y R^{8a} es alquilo inferior, entonces cuando menos uno de R^{1a}-R^{4a}, R^{6a} y R^{7a} es diferente de hidrógeno; y cuando R^{3a} es halógeno, o alquilo inferior, y R^{5a} es alquilo inferior sustituido con dialquil-amino, dialquil-amino-carbonilo, carboxilato, alcoxi-carbonilo o amino-carbonilo, entonces cuando menos uno de R^{1a}, R^{2a}, R^{4a}, y R^{6a}-R^{8a} es diferente de hidrógeno; y cuando R^{3a} es -O-bencilo y R^{5a} es alquil-NH_2, entonces cuando menos uno de R^{1a}, R^{2a}, R^{4a}, y R^{6a}-R^{8a} es diferente de hidrógeno; y cuando R^{2a} y R^{3a} son cada uno alcoxilo y R^{5a} es ciano,

entonces cuando menos uno de R^{1a}, R^{4a}, y R^{6a}-R^{8a} es diferente de hidrógeno; y cuando R^{1a} y R^{3a} son cada uno halógeno y R^{5a} es alquil–NH_2, entonces cuando menos uno de R^{2a}, R^{4a}, y R^{6a}-R^{8a} es diferente de hidrógeno; y cuando R^{2a} es alcoxi-carbonilo y R^{4a} es halógeno, entonces cuando menos uno de R^{1a}, R^{3a}, R^{5a} y R^{6a}-R^{8a} es diferente de hidrógeno; y cuando R^{5a} es alquilo y R^{7a} es -OCH_2-(N-metil-pirrolidina), entonces cuando menos uno de R^{1a}-R^{4a}, R^{6a} y R^{8a} es diferente de hidrógeno; y cuando R^{3a} es cicloalquilo y R^{5a} es alquil–NH_2, entonces cuando menos uno de R^{1a}, R^{2a}, R^{4a}, y R^{6a}-R^{8a} es diferente de hidrógeno; y cuando R^{3a} es alquilo sustituido con aroílo, y R^5 y R^8 son cada uno independientemente hidrógeno o alquilo inferior, entonces cuando menos uno de R^{1a}, R^{2a}, y R^{4a} es diferente de hidrógeno.

Los ejemplos de R^{1a} incluyen hidrógeno, halógeno (por ejemplo, cloro o flúor), hidroxilo, y alcoxilo (por ejemplo, metoxilo).

En una modalidad adicional, R^{1a} es alquilo opcionalmente sustituido (por ejemplo, metilo, etilo, o propilo), el cual puede estar sustituido con grupos tales como carboxilato, hidroxilo, alquil-amino (por ejemplo, etil-amino) el cual puede estar adicionalmente sustituido con hidroxilo, y arilo (por ejemplo, fenilo) el cual puede estar adicionalmente sustituido con carboxilato.

En todavía una modalidad adicional, R^{1a} es alquenilo opcionalmente sustituido (por ejemplo, alquenilo es etenilo o propenilo), el cual puede estar sustituido con grupos tales como hidroxilo, alcoxi-carbonilo (por ejemplo, butoxi-carbonilo), y arilo (por

ejemplo, fenilo) el cual puede estar adicionalmente sustituido con alcoxi-carbonilo (por ejemplo, metoxi-carbonilo).

En una modalidad, R^{2a} incluye hidrógeno, halógeno (por ejemplo, cloro o flúor), hidroxilo, alquilo (por ejemplo, metilo), y alcoxilo (por ejemplo, metoxilo).

Los ejemplos de R^{3a} incluyen hidrógeno, halógeno (por ejemplo, cloro o flúor), alcoxilo (por ejemplo, metoxilo), ciano, y alcoxi-carbonilo (por ejemplo, metoxi-carbonilo).

En una modalidad adicional, R^{3a} es alquilo opcionalmente sustituido (por ejemplo, metilo, o etilo), el cual puede estar sustituido con grupos tales como carboxilato, alcoxi-carbonilo (por ejemplo, etoxi-carbonilo), hidroxilo, y halógeno. Este alquilo opcionalmente sustituido puede ser, por ejemplo trifluoro-metilo.

Los ejemplos de R^{4a} incluyen hidrógeno, halógeno (por ejemplo, flúor), y ciano.

En una modalidad, R^{5a} incluye hidrógeno, halógeno (por ejemplo, bromo), alquenilo (por ejemplo, propenilo), ciano, $-C(O)NH_2$, carboxilato, alcoxi-carbonilo (por ejemplo, metoxi-carbonilo o isopropoxi-carbonilo), aril-alquilo (por ejemplo, bencilo), heteroaril-alquilo (por ejemplo, imidazolil-metilo), heterociclil-carbonilo (por ejemplo, pirrolidinil-carbonilo), alquil-amino-carbonilo (por ejemplo, etil-amino-carbonilo), y arilo (por ejemplo, fenilo).

En otra modalidad, R^{5a} incluye alquilo opcionalmente sustituido (por ejemplo, metilo, etilo, propilo o butilo), el cual puede estar sustituido con grupos tales como hidroxilo, alcoxilo (por ejemplo,

etoxilo), y carboxilato.

En todavía otra modalidad, R^{5a} incluye heteroarilo opcionalmente sustituido (por ejemplo, 1,2,4-oxadiazolilo), el cual puede estar sustituido con grupos tales como alquilo (por ejemplo, metilo).

Los ejemplos de R^{6a} y R^{7a} incluyen alcoxilo (por ejemplo, metoxilo, etoxilo, o benciloxilo), el cual puede estar sustituido con hidroxilo o arilo (por ejemplo, fenilo); halógeno (por ejemplo, cloro o flúor); hidroxilo; sulfonilo, el cual puede estar sustituido con arilo (por ejemplo, fenil-sulfonilo) o alquilo (por ejemplo, butil-sulfonilo); alquil-amino (por ejemplo, etil-amino); carboxilato; alcoxi-carbonilo (por ejemplo, etoxi-carbonilo); amino-carbonilo; y amino (por ejemplo, $-NH(S(O)_2(CH_3)_2$, $-NR'-S(O)_2$-alquilo, -NR'-C(O)-alquilo, -NR'-C(O)-NR'-alquilo, y -NR'-C(O)-O-alquilo, en donde cada R' es independientemente hidrógeno, alquilo de 1 a 4 átomos de carbono, o cicloalquilo de 3 a 6 átomos de carbono). En otra modalidad, R^{6a} es $-NH-S(O)_2-CH_3$.

En una modalidad, R^{6a} y R^{7a} incluye heterociclilo opcionalmente sustituido (por ejemplo, piperazinilo), el cual puede estar sustituido con grupos tales como alquilo (por ejemplo, metilo).

En otra modalidad, R^{6a} y R^{7a} incluye alquilo opcionalmente sustituido (por ejemplo, metilo, o etilo), el cual puede estar sustituido con grupos tales como heterociclilo (por ejemplo, morfolinilo, piperazinilo, pirrolidinilo, o dióxido de tiomorfolinilo), el cual por sí mismo puede estar sustituido con alquilo (por ejemplo, metilo) o

$-NH_2$; hidroxilo; alcoxilo (por ejemplo, metoxilo); o halógeno. Este alquilo opcionalmente sustituido puede ser, por ejemplo, trifluoro-metilo.

En otra modalidad, R^{6a} y R^{7a} incluye alquilo opcionalmente sustituido (por ejemplo, metilo, o etilo), el cual puede estar sustituido con amino (por ejemplo, $-NR^{30b}R^{31b}$). Los ejemplos de R^{30b} incluyen hidrógeno y metilo. Los ejemplos de R^{31b} incluyen alcoxi-carbonilo (por ejemplo, etoxi-carbonilo); alquil-amino-carbonilo (por ejemplo, etil-amino-carbonilo); heterociclil-carbonilo (por ejemplo, morfolinilo); acilo (por ejemplo, $-C(O)-(CH_2)_2CH_3$); alquilo (por ejemplo, etilo), el cual puede estar opcionalmente sustituido con hidroxilo; sulfonilo, el cual puede estar sustituido con bencilo; dialquil-amino (por ejemplo, dietil-amino-sulfonilo); alquilo (por ejemplo, metil-sulfonilo, etil-sulfonilo, propil-sulfonilo, butil-sulfonilo, o trifluoro-metil-sulfonilo); o arilo (por ejemplo, fenil-sulfonilo). Este fenil-sulfonilo puede estar, por ejemplo, adicionalmente sustituido con halógeno (por ejemplo, flúor).

En otra modalidad, R^{6a} y R^{7a} incluyen -O-sulfonilo opcionalmente sustituido, el cual puede estar sustituido con grupos tales como alquilo (por ejemplo, metilo); amino (por ejemplo, dimetil-amino, dietil-amino, o -N(Et)-(bencilo)); o heterociclilo (por ejemplo, morfolinilo, piperazinilo, N-metil-piperazinilo, o pirrolidinilo).

En una modalidad, R^{8a} incluye hidrógeno, heteroarilo (por ejemplo, 3-piridinilo), y alcoxi-carbonilo (por ejemplo, isopropoxi-carbonilo o butoxi-carbonilo).

En otra modalidad, R^{8a} incluye aril-alquilo opcionalmente sustituido (por ejemplo, bencilo), el cual puede estar sustituido con grupos en la posición *para* y/o en la posición *meta*. Los ejemplos de estos grupos incluyen alcoxi-carbonilo (por ejemplo, metoxi-carbonilo); carboxilato; alquilo (por ejemplo, metilo); ciano; alcoxilo (por ejemplo, metoxilo); halógeno (por ejemplo, flúor); sulfonilo que está opcionalmente sustituido con alquilo (por ejemplo, metil-sulfonilo); heteroarilo (por ejemplo, tetrazolilo); alcoxilo (por ejemplo, metoxilo o benciloxilo); o combinaciones de los mismos.

En todavía otra modalidad, R^{8a} incluye heteroaril-alquilo opcionalmente sustituido (por ejemplo, benzo-imidazolil-metilo, 1,2,3-triazolil-metilo, o isoxazolil-metilo), el cual puede estar sustituido con alquilo (por ejemplo, metilo), el cual opcionalmente puede estar adicionalmente sustituido con arilo (por ejemplo, fenilo) de tal manera que R^{8a} es heteroaril-alquilo sustituido con bencilo.

En otra modalidad, R^{8a} incluye aroílo opcionalmente sustituido (por ejemplo, benzoílo), el cual puede estar sustituido con grupos en la posición *para* y/o en la posición *meta*. Los ejemplos de estos grupos incluyen ciano, alquilo (por ejemplo, metilo, o etilo), alcoxilo (por ejemplo, metoxilo o dimetoxilo), alcoxi-carbonilo (por ejemplo, butoxi-carbonilo), carboxilato, o combinaciones de los mismos.

En otra modalidad, R^{8a} incluye alquilo opcionalmente sustituido (por ejemplo, metilo, etilo, propilo, isopropilo o butilo), el cual puede estar sustituido con grupos tales como $-NHC(O)R^{20a}$ y $-OC(O)R^{20a}$, en donde R^{20a} es alquilo (por ejemplo, butilo).

En todavía otra modalidad, R^{8a} incluye alquilo opcionalmente sustituido (por ejemplo, metilo, etilo, propilo, isopropilo o butilo), el cual puede estar sustituido con grupos tales como cicloalquilo (por ejemplo, ciclohexilo); carboxilato; hidroxilo; alcoxi-carbonilo (por ejemplo, butoxi-carbonilo); y sulfonilo que está opcionalmente sustituido con arilo (por ejemplo, fenil-sulfonilo).

En todavía otra modalidad, R^{8a} incluye alquilo opcionalmente sustituido (por ejemplo, metilo, etilo, propilo, isopropilo o butilo), el cual puede estar sustituido con grupos tales como heterociclilo (por ejemplo, piperazinilo o azetidilo), el cual por sí mismo puede estar sustituido con grupos tales como alquilo, dialquilo (por ejemplo, dimetilo), y =O.

En todavía otra modalidad, R^{8a} incluye alquilo opcionalmente sustituido (por ejemplo, metilo, etilo, propilo, isopropilo o butilo), el cual puede estar sustituido con grupos tales como heterociclil-carbonilo (por ejemplo, piperazinil-carbonilo), el cual por sí mismo puede estar sustituido con grupos tales como alquilo o dialquilo (por ejemplo, dimetilo); arilo (por ejemplo, fenilo), el cual por sí mismo puede estar sustituido con grupos tales como carboxilato; y alcoxilo (por ejemplo, metoxilo, etoxilo, propoxilo, butoxilo, pentoxilo, o fenoxilo), el cual por sí mismo puede estar sustituido con grupos tales como alcoxi-carbonilo (por ejemplo, metoxi-carbonilo o etoxi-carbonilo), carboxilato, e hidroxilo.

En una modalidad, R^{8a} es fenoxi-alquilo sustituido (por ejemplo, metilo, etilo, propilo, isopropilo o butilo), y este fenoxilo

está opcionalmente sustituido en la posición *para* y/o en la posición *meta* con grupos tales como alcoxi-carbonilo (por ejemplo, metoxi-carbonilo o etoxi-carbonilo), carboxilato, e hidroxilo.

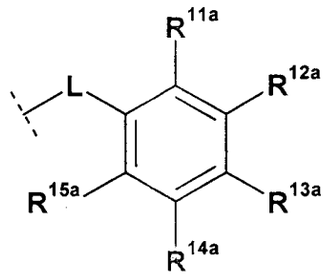
Otro ejemplo de R^{8a} incluye arilo opcionalmente sustituido (por ejemplo, fenilo), el cual puede estar sustituido en la posición *para* y/o en la posición *meta* con grupos tales como ciano, alcoxilo (por ejemplo, metoxilo), o combinaciones de los mismos.

Otro ejemplo de R^{8a} incluye sulfonilo opcionalmente sustituido, el cual puede estar sustituido con grupos tales como arilo (por ejemplo, fenilo), el cual por sí mismo puede estar sustituido con grupos tales como alquilo (por ejemplo, metilo), carboxilato, o combinaciones de los mismos.

En una modalidad de la presente invención R^{5a} es hidrógeno, metilo, etilo, ciano, carboxilato, o alcoxi-carbonilo.

En otra modalidad de la presente invención R^{8a} es hidrógeno, metilo, etilo, bencil-CO_2H, o bencil-CO_2Me.

En todavía otra modalidad, R^{8a} es:



L es alquilo, carbonilo, sulfonilo, o $-(CH_2)_2-O-$; y

R^{11a}, R^{12a}, R^{13a}, R^{14a}, y R^{15a} son cada uno independientemente hidrógeno, alquilo, ciano, halógeno, alcoxilo, alcoxi-carbonilo,

carboxilato, heteroarilo, o sulfonilo.

Cada uno de los grupos anteriormente mencionados R^{1a}, R^{2a}, R^{3a}, R^{4a}, R^{5a}, R^{6a} y R^{8a} puede estar opcionalmente sustituido.

Otra modalidad de la fórmula (I), en donde:

R^{1a} es hidrógeno, halógeno, hidroxilo, alcoxilo, alquilo, o alquenilo;

R^{2a} es hidrógeno, halógeno, alquilo, hidroxilo, o alcoxilo;

R^{3a} es hidrógeno, halógeno, ciano, alcoxilo, alquilo, o alcoxi-carbonilo;

R^{4a} es hidrógeno, halógeno, o ciano;

R^{5a} es hidrógeno, halógeno, ciano, alquilo, alquenilo, aril-alquilo, heteroaril-alquilo, amino-carbonilo, alquil-amino-carbonilo, carboxilato, alcoxi-carbonilo, heterociclil-carbonilo, arilo, o heteroarilo;

R^{6a} y R^{7a} son cada uno independientemente hidrógeno, halógeno, hidroxilo, alcoxilo, amino, alquilo, sulfonilo, -O-sulfonilo, alquil-amino, heterociclilo, amino-carbonilo, carboxilato, o alcoxi-carbonilo; y

R^{8a} es hidrógeno, alquilo, aril-alquilo, heteroaril-alquilo, alcoxi-carbonilo, sulfonilo, aroílo, arilo, o heteroarilo.

Otra modalidad de la fórmula (I), en donde:

R^{5a} es hidrógeno, ciano, metilo, etilo, carboxilato, o metoxi-carbonilo.

Otra modalidad de la fórmula (I), en donde:

R^{8a} es hidrógeno, metilo, etilo, bencil-CO_2H, o bencil-CO_2Me.

Otra modalidad de la fórmula (I), en donde:

R^{1a} es hidrógeno;

R^{2a} es hidrógeno, halógeno, o hidroxilo;

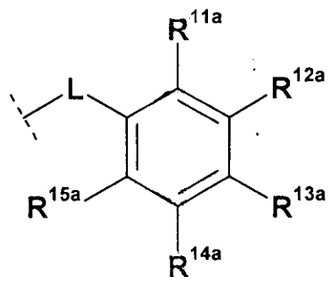
R^{3a} es hidrógeno, halógeno, ciano, o alcoxilo;

R^{4a} es hidrógeno o halógeno;

R^{5a} es hidrógeno o alquilo;

R^{6a} y R^{7a} son hidrógeno;

R^{8a} es:



L es alquilo, carbonilo, sulfonilo, o $-(CH_2)_2-O-$; y

R^{11a}, R^{12a}, R^{13a}, R^{14a}, y R^{15a} son cada uno independientemente hidrógeno, alquilo, ciano, halógeno, alcoxilo, alcoxi-carbonilo, carboxilato, heteroarilo, o sulfonilo.

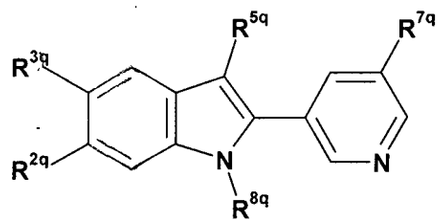
Otra modalidad de la fórmula (I), en donde:

R^{11a} y R^{15a} son cada uno independientemente hidrógeno, alquilo, ciano, halógeno, o alcoxilo;

R^{12a} y R^{14a} son cada uno independientemente hidrógeno, alquilo, ciano, halógeno, alcoxilo, alcoxi-carbonilo, carboxilato, heteroarilo, o sulfonilo; y

R^{13a} es hidrógeno, alquilo, ciano, alcoxilo, alcoxi-carbonilo, carboxilato, heteroarilo, o sulfonilo.

En todavía otra modalidad, la invención pertenece, cuando menos en parte, a los compuestos de la fórmula II:



(II)

en donde:

R^{2q} es hidrógeno o halógeno;

R^{3q} es hidrógeno, halógeno, o ciano;

R^{5q} es hidrógeno, alquilo, o ciano;

R^{7q} es hidrógeno, halógeno, alcoxilo, -OSO_2-heterociclilo, -O-aril-alquilo, -NR'-SO_2-alquilo, -NR'-C(O)-alquilo, -NR'-C(O)-NR'-alquilo, -NR'-C(O)-O-alquilo, halo-alquilo, o alquilo opcionalmente sustituido con heterociclilo, –NR'-SO_2-alquilo, -NR'-SO_2-halo-alquilo, NR'-C(O)-alquilo, NR'-C(O)-heterociclilo, -NR'-C(O)-NR'-alquilo, o –NR'-C(O)-O-alquilo;

R^{8q} es hidrógeno, alquilo, hidroxi-alquilo, -alquil-OC(O)-alquilo, carboxilato, alcoxi-carbonilo, o aril-alquilo sustituido con alquilo, o aroílo sustituido con ciano y/o alquilo, o -alquil-O-arilo sustituido con alcoxi-carbonilo;

cada R' es independientemente hidrógeno, alquilo de 1 a 4 átomos de carbono, o cicloalquilo de 3 a 6 átomos de carbono;

y las sales farmacéuticamente aceptables, polimorfos, rotámeros, pro-fármacos, enantiómeros, hidratos, y solvatos de los mismos,

con la condición de que cuando menos uno de R^{2q}, R^{3q}, R^{5q}, R^{7q} y R^{8q} es diferente de hidrógeno; y cuando R^{8q} es alquilo inferior o alcoxi-carbonilo, entonces cuando menos uno de R^{2q}, R^{3q}, R^{5q} y R^{7q} es diferente de hidrógeno; y cuando R^{5q} es ciano, entonces cuando menos uno de R^{2q}, R^{3q}, y R^{8q} es diferente de hidrógeno.

En otra modalidad, R^{7q} es alcoxilo o alquilo sustituido con heterociclilo, y R^{8q} es alquilo.

Otra modalidad de la fórmula (II), en donde R^{7q} es alcoxilo o alquilo sustituido con heterociclilo, y R^{8q} es alquilo.

Otra modalidad de la fórmula (II), en donde:

R^{2q} es hidrógeno o halógeno;

R^{3q} es hidrógeno, o halógeno;

R^{5q} es hidrógeno o ciano;

R^{7q} es alquilo opcionalmente sustituido con heterociclilo, –NR'-SO_2-alquilo, -NR'-SO_2-halo-alquilo, NR'-C(O)-alquilo, NR'-C(O)-heterociclilo, -NR'-C(O)-NR'-alquilo, o -NR'-C(O)-O-alquilo;

R' es independientemente hidrógeno, alquilo de 1 a 4 átomos de carbono, o cicloalquilo de 3 a 6 átomos de carbono; y

R^{8q} es hidrógeno, o alquilo de 1 a 6 átomos de carbono.

Otra modalidad de la fórmula (II), en donde:

R^{2q} es hidrógeno o halógeno;

R^{3q} es hidrógeno, o halógeno;

R^{5q} es hidrógeno o ciano;

R^{7q} es alquilo de 1 a 4 átomos de carbono opcionalmente sustituido con heterociclilo, –NR'-SO_2-alquilo de 1 a 4 átomos de

carbono, -NR'-SO_2-haloalquilo de 1 a 4 átomos de carbono, NR'-C(O)-alquilo de 1 a 4 átomos de carbono, NR'-C(O)-heterociclilo, -NR'-C(O)-NR'-alquilo de 1 a 4 átomos de carbono, o -NR'-C(O)-O-alquilo de 1 a 4 átomos de carbono;

R' es independientemente hidrógeno, o alquilo de 1 a 4 átomos de carbono; y

R^{8q} es hidrógeno, o alquilo de 1 a 6 átomos de carbono.

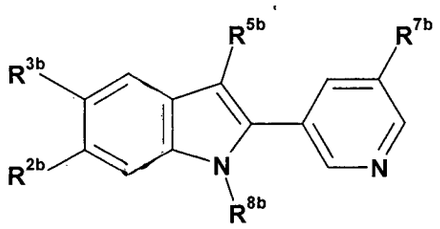
Otra modalidad de la fórmula (II), en donde:

R^{7q} es alquilo de 1 a 4 átomos de carbono sustituido con –NR'-SO_2-alquilo de 1 a 4 átomos de carbono, -NR'-SO_2-haloalquilo de 1 a 4 átomos de carbono, o NR'-C(O)-alquilo de 1 a 4 átomos de carbono;

R' es independientemente hidrógeno, o alquilo de 1 a 4 átomos de carbono; y

R^{8q} es hidrógeno, metilo, o etilo.

En todavía otra modalidad, la invención pertenece, cuando menos en parte, a los compuestos de la fórmula III:



(III)

en donde:

R^{2b} es hidrógeno o halógeno;

R^{3b} es hidrógeno, halógeno, o ciano;

R^{5b} es alquilo;

R^{7b} es hidrógeno, halógeno, alcoxilo, -OSO_2-heterociclilo, -O-aril-alquilo, -NR'-SO_2-alquilo, -NR'-C(O)-alquilo, -NR'-C(O)-NR'-alquilo, -NR'-C(O)-O-alquilo, halo-alquilo, o alquilo opcionalmente sustituido con heterociclilo, –NR'-SO_2-alquilo, -NR'-SO_2-halo-alquilo, NR'-C(O)-alquilo, -NR'-C(O)-NR'-alquilo, NR'-C(O)-heterociclilo, o –NR'-C(O)-O-alquilo;

R^{8b} es hidrógeno, alquilo, hidroxi-alquilo, -alquil-OC(O)-alquilo, carboxilato, alcoxi-carbonilo, o aril-alquilo sustituido con alquilo, o aroílo sustituido con ciano y/o alquilo, o -alquil-O-arilo sustituido con alcoxi-carbonilo;

cada R' es independientemente hidrógeno, alquilo de 1 a 4 átomos de carbono, o cicloalquilo de 3 a 6 átomos de carbono;

y las sales farmacéuticamente aceptables, polimorfos, rotámeros, pro-fármacos, enantiómeros, hidratos, y solvatos de los mismos.

Otra modalidad de la fórmula (III), en donde:

R^{2b} es hidrógeno o halógeno;

R^{3b} es hidrógeno, halógeno, o ciano;

R^{5b} es alquilo de 1 a 4 átomos de carbono;

R^{7b} es hidrógeno, halógeno, alcoxilo de 1 a 4 átomos de carbono, -OSO_2-heterociclilo, -O-aril-alquilo, -NR'-SO_2-alquilo de 1 a 4 átomos de carbono, -NR'-C(O)-alquilo de 1 a 4 átomos de carbono, -NR'-C(O)-NR'-alquilo de 1 a 4 átomos de carbono, -NR'-C(O)-O-alquilo, halo-alquilo, o alquilo de 1 a 4 átomos de carbono opcionalmente sustituido con heterociclilo, –NR'-SO_2-alquilo de 1 a 4

átomos de carbono, -NR'-SO_2-halo-alquilo de 1 a 4 átomos de carbono, NR'-C(O)-alquilo de 1 a 4 átomos de carbono, -NR'-C(O)-NR'-alquilo de 1 a 4 átomos de carbono, NR'-C(O)-heterociclilo, o –NR'-C(O)-O-alquilo de 1 a 4 átomos de carbono;

R^{8b} es hidrógeno, alquilo de 1 a 4 átomos de carbono, hidroxi-alquilo, -alquilo de 1 a 4 átomos de carbono-OC(O)-alquilo de 1 a 4 átomos de carbono, carboxilato, alcoxi-carbonilo, o aril-alquilo sustituido con alquilo de 1 a 4 átomos de carbono, o aroílo sustituido con ciano y/o alquilo de 1 a 4 átomos de carbono, o -alquilo de 1 a 4 átomos de carbono-O-arilo sustituido con alcoxi-carbonilo;

cada R' es independientemente hidrógeno, alquilo de 1 a 4 átomos de carbono, o cicloalquilo de 3 a 6 átomos de carbono;

y las sales farmacéuticamente aceptables, polimorfos, rotámeros, pro-fármacos, enantiómeros, hidratos, y solvatos de los mismos.

Otra modalidad de la fórmula (III), en donde:

R^{2b} es hidrógeno o halógeno;

R^{3b} es hidrógeno, halógeno, o ciano;

R^{5b} es metilo, etilo, o isopropilo;

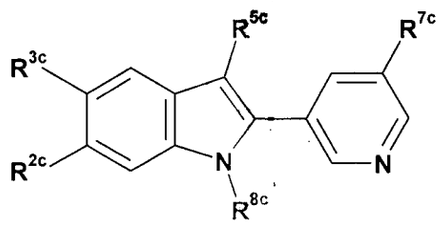
R^{7b} es alquilo de 1 a 4 átomos de carbono sustituido con –NR'-SO_2-alquilo de 1 a 4 átomos de carbono, -NR'-SO_2-haloalquilo de 1 a 4 átomos de carbono, NR'-C(O)-alquilo de 1 a 4 átomos de carbono, o -NR'-C(O)-NR'-alquilo de 1 a 4 átomos de carbono;

R^{8b} es hidrógeno, metilo, o etilo;

cada R' es independientemente hidrógeno, o alquilo de 1 a 4

átomos de carbono.

En todavía otra modalidad, la invención pertenece, cuando menos en parte, a los compuestos de la fórmula IV:



(IV)

en donde:

R^{2c} es hidrógeno o halógeno;

R^{3c} es hidrógeno, halógeno, o ciano;

R^{5c} es ciano; y

R^{7c} es hidrógeno, halógeno alcoxilo, -OSO_2-heterociclilo, -O-aril-alquilo, -NR'-SO_2-alquilo, -NR'-C(O)-alquilo, -NR'-C(O)-NR'-alquilo, -NR'-C(O)-O-alquilo o alquilo opcionalmente sustituido con heterociclilo, –NR'-SO_2-alquilo, -NR'-SO_2-halo-alquilo, NR'-C(O)-alquilo, NR'-C(O)-heterociclilo, -NR'-C(O)-NR'-alquilo, o -NR'-C(O)-O-alquilo;

R^{8c} es alquilo;

cada R' es independientemente hidrógeno, alquilo de 1 a 4 átomos de carbono, o cicloalquilo de 3 a 6 átomos de carbono;

y las sales farmacéuticamente aceptables, polimorfos, rotámeros, pro-fármacos, enantiómeros, hidratos, y solvatos de los mismos.

Otra modalidad de la fórmula (IV), en donde:

R^{2c} es hidrógeno o halógeno;

R^{3c} es hidrógeno, halógeno, o ciano;

R^{5c} es ciano; y

R^{7c} es hidrógeno, halógeno, alcoxilo de 1 a 4 átomos de carbono, -OSO_2-heterociclilo, -O-aril-alquilo, -NR'-SO_2-alquilo de 1 a 4 átomos de carbono, -NR'-C(O)-alquilo de 1 a 4 átomos de carbono, -NR'-C(O)-NR'-alquilo de 1 a 4 átomos de carbono, -NR'-C(O)-O-alquilo de 1 a 4 átomos de carbono o alquilo de 1 a 4 átomos de carbono opcionalmente sustituido con heterociclilo, –NR'-SO_2-alquilo de 1 a 4 átomos de carbono, -NR'-SO_2-halo-alquilo de 1 a 4 átomos de carbono, NR'-C(O)-alquilo de 1 a 4 átomos de carbono, NR'-C(O)-heterociclilo, -NR'-C(O)-NR'-alquilo de 1 a 4 átomos de carbono, o -NR'-C(O)-O-alquilo de 1 a 4 átomos de carbono;

R^{8c} es alquilo de 1 a 4 átomos de carbono;

cada R' es independientemente hidrógeno, alquilo de 1 a 4 átomos de carbono, o cicloalquilo de 3 a 6 átomos de carbono;

y las sales farmacéuticamente aceptables, polimorfos, rotámeros, pro-fármacos, enantiómeros, hidratos, y solvatos de los mismos.

Otra modalidad de la fórmula (IV), en donde:

R^{2c} es hidrógeno o halógeno;

R^{3c} es hidrógeno, o halógeno;

R^{5c} es ciano; y

R^{7c} es alquilo de 1 a 4 átomos de carbono opcionalmente sustituido con –NR'-SO_2-alquilo de 1 a 4 átomos de carbono, -NR'-SO_2-halo-alquilo de 1 a 4 átomos de carbono, NR'-C(O)-alquilo de 1

a 4 átomos de carbono;

R^{8c} es alquilo de 1 a 4 átomos de carbono;

cada R' es independientemente hidrógeno o alquilo de 1 a 4 átomos de carbono.

Otra modalidad de la fórmula (IV), en donde:

R^{7c} es alquilo de 1 a 4 átomos de carbono sustituido con –NR'-SO_2-alquilo de 1 a 4 átomos de carbono, -NR'-SO_2-halo-alquilo de 1 a 4 átomos de carbono, NR'-C(O)-alquilo de 1 a 4 átomos de carbono; y

cada R' es independientemente hidrógeno, metilo, etilo, o propilo.

Definiciones

El término "alquilo" incluye a los grupos alifáticos saturados, incluyendo los grupos alquilo de cadena recta (por ejemplo, metilo, etilo, propilo, butilo, pentilo, hexilo, heptilo, octilo, nonilo, decilo, etc.), los grupos alquilo de cadena ramificada (isopropilo, butilo terciario, isobutilo, etc.), los grupos cicloalquilo-(alicíclico) (ciclopropilo, ciclopentilo, ciclohexilo, cicloheptilo, y ciclo-octilo), los grupos alquil-cicloalquilo sustituidos, y los grupos cicloalquil-alquilo sustituidos. El término alquilo incluye además a los grupos alquilo, los cuales pueden incluir además átomos de oxígeno, nitrógeno, azufre o fósforo reemplazando a uno o más átomos de carbono de la estructura base del hidrocarburo. En ciertas modalidades, un grupo alquilo de cadena recta o de cadena ramificada tiene 6 o menos átomos de carbono en su estructura base (por ejemplo, de 1 a 6

átomos de carbono para la cadena recta, y de 3 a 6 átomos de carbono para la cadena ramificada), y de una manera muy preferible 4 o menos. De la misma manera, los cicloalquilos preferidos tienen de 3 a 8 átomos de carbono en su estructura de anillo, y de una manera muy preferible, tienen 5 ó 6 átomos de carbono en la estructura del anillo. El término C_1-C_6 incluye a los grupos alquilo que contienen de 1 a 6 átomos de carbono.

Más aún, el término alquilo incluye tanto a los "alquilos insustituidos" como a los "alquilos sustituidos", el último de los cuales se refiere a las fracciones de alquilo que tienen sustituyentes reemplazando a hidrógeno sobre uno o más átomos de carbono de la estructura base del hidrocarburo. Estos sustituyentes pueden incluir, por ejemplo, alquenilo, alquinilo, halógeno, hidroxilo, alquil-carboniloxilo, aril-carboniloxilo, alcoxi-carboniloxilo, ariloxi-carboniloxilo, carboxilato, alquil-carbonilo, aril-carbonilo, alcoxi-carbonilo, amino-carbonilo, alquil-amino-carbonilo, dialquil-amino-carbonilo, tioalquil-carbonilo, alcoxilo, fosfato, fosfonato, fosfinato, ciano, amino (incluyendo alquil-amino, dialquil-amino, aril-amino, diaril-amino, y alquil-aril-amino), acil-amino (incluyendo alquil-carbonil-amino, aril-carbonil-amino, carbamoílo y ureido), amidino, imino, sulfhidrilo, tioalquilo, tioarilo, tiocarboxilato, sulfatos, alquil-sulfinilo, sulfonato, sulfamoílo, sulfonamido, nitro, trifluoro-metilo, ciano, azido, heterociclilo, alquil-arilo, o una fracción aromática o heteroaromática. Los cicloalquilos pueden estar adicionalmente sustituido, por ejemplo, con los sustituyentes descritos

anteriormente. Una fracción de "alquil-arilo" o de "aril-alquilo" es un alquilo sustituido con un arilo (por ejemplo, fenil-metilo (bencilo)). El término "alquilo" también incluye las cadenas laterales de los aminoácidos naturales y no naturales.

El término "arilo" incluye a los grupos que incluyen grupos aromáticos de un solo anillo de 5 y 6 miembros que pueden incluir desde cero hasta cuatro heteroátomos, por ejemplo, benceno, fenilo, pirrol, furano, tiofeno, tiazol, isotiazol, imidazol, triazol, tetrazol, pirazol, oxazol, iso-oxazol, piridina, pirazina, piridazina, y pirimidina, etc. Adicionalmente, el término "arilo" incluye a los grupos arilo multicíclicos, por ejemplo, tricíclicos o bicíclicos, por ejemplo, naftaleno, benzoxazol, benzodioxazol, benzotiazol, benzo-imidazol, benzotiofeno, metilendioxi-fenilo, quinolina, isoquinolina, naftiridina, indol, benzofurano, purina, benzofurano, desazapurina, o indolizina. Estos grupos arilo que tienen heteroátomos en la estructura del anillo también pueden ser referidos como "aril-heterociclos" "heterociclos," "heteroarilos" o "heteroaromáticos".

Los grupos heteroarilo típicos incluyen 2- o 3-tienilo, 2- o 3-furilo, 2- o 3-pirrolilo, 2-, 4-, o 5-imidazolilo, 3-, 4-, o 5-pirazolilo, 2-, 4-, o 5-tiazolilo, 3-, 4-, o 5-isotiazolilo, 2-, 4-, o 5-oxazolilo, 3-, 4-, o 5-isoxazolilo, 3- ó 5-1,2,4-triazolilo, 4- o 5-1,2,3-triazolilo, tetrazolilo, 2-, 3-, ó 4-piridilo, 3- o 4-piridazinilo, 3-, 4-, o 5-pirazinilo, 2-pirazinilo, 2-, 4-, o 5-pirimidinilo. Un grupo heteroarilo puede ser mono-, bi-, tri-, o poli-cíclico.

El término "heteroarilo" también se refiere a un grupo en donde

el anillo heteroaromático está fusionado con uno o más anillos de arilo, cicloalifáticos, o de heterociclilo, en donde el radical o el punto de unión está sobre el anillo heteroaromático. Los ejemplos no limitantes incluyen, pero no se limitan a, 1-, 2-, 3-, 5-, 6-, 7-, u 8-indolizinilo, 1-, 3-, 4-, 5-, 6-, ó 7-isoindolilo, 2-, 3-, 4-, 5-, 6-, ó 7-indolilo, 2-, 3-, 4-, 5-, 6-, ó 7-indazolilo, 2-, 4-, 5-, 6-, 7-, u 8-purinilo, 1-, 2-, 3-, 4-, 6-, 7-, 8-, ó 9-quinolizinilo, 2-, 3-, 4-, 5-, 6-, 7-, u 8-quinolinilo, 1-, 3-, 4-, 5-, 6-, 7-, u 8-isoquinolinilo, 1-, 4-, 5-, 6-, 7-, u 8-ftalazinilo, 2-, 3-, 4-, 5-, o 6-naftiridinilo, 2-, 3-, 5-, 6-, 7-, u 8-quinazolinilo, 3-, 4-, 5-, 6-, 7-, u 8-cinolinilo, 2-, 4-, 6-, ó 7-pteridinilo, 1-, 2-, 3-, 4-, 5-, 6-, 7-, u 8-4aH carbazolilo, 1-, 2-, 3-, 4-, 5-, 6-, 7-, u 8-carbazolilo, 1-, 3-, 4-, 5-, 6-, 7-, 8-, ó 9-carbolinilo, 1-, 2-, 3-, 4-, 6-, 7-, 8-, 9-, ó 10-fenantridinilo, 1- , 2-, 3-, 4-, 5-, 6-, 7-, 8-, ó 9-acridinilo, 1-, 2-, 4-, 5-, 6-, 7-, 8-, ó 9-perimidinilo, 2-, 3-, 4-, 5-, 6-, 8-, 9-, ó 10-fenantrolinilo, 1-, 2-, 3-, 4-, 6-, 7-, 8-, ó 9-fenazinilo, 1-, 2-, 3-, 4-, 6-, 7-, 8-, 9-, ó 10-fenotiazinilo,1-, 2-, 3-, 4-, 6-, 7-, 8-, 9-, ó 10-fenoxazinilo, 2-, 3-, 4-, 5-, 6-, ó 1-, 3-, 4-, 5-, 6-, 7-, 8-, 9-, ó 10- bencisoquinolinilo, 2-, 3-, 4-, o tieno[2,3-b]furanilo, 2-, 3-, 5-, 6-, 7-, 8-, 9-, 10 -, u 11-7H-pirazino[2,3-c]carbazolilo, 2-, 3-, 5-, 6-, ó 7-2H-furo[3,2-b]-piranilo, 2-, 3-, 4-, 5-, 7-, u 8-5H-pirido[2,3-d]-o-oxazinilo, 1-, 3-, o 5-1H-pirazolo-[4,3-d]-oxazolilo, 2-, 4-, o 5-4H-imidazo-[4,5-d]-tiazolilo, 3-, 5-, u 8-pirazino[2,3-d]piridazinilo, 2-, 3-, 5-, o 6- imidazo[2,1-b]tiazolilo, 1-, 3-, 6-, 7-, 8-, ó 9-furo[3,4-c]cinolinilo, 1-, 2-, 3-, 4-, 5-, 6-, 8-, 9-, 10, u 11-4H-pirido[2,3-c]carbazolilo, 2-, 3-, 6-, ó 7-imidazo[1,2-b][1,2,4]triazinilo,

7-benzo[b]tienilo, 2-, 4-, 5- , 6-, ó 7-benzoxazolilo, 2-, 4-, 5-, 6-, ó 7-bencimidazolilo, 2-, 4-, 4-, 5-, 6-, ó 7-benzotiazolilo, 1-, 2-, 4-, 5-, 6-, 7-, 8-, ó 9- benzoxapinilo, 2-, 4-, 5-, 6-, 7-, u 8-benzoxazinilo, 1-, 2-, 3-, 5-, 6-, 7-, 8-, 9-, 10-, u 11-1H-pirrolo[1,2-b][2]benzazapinilo. Los grupos heteroarilo fusionados típicos incluyen, pero no se limitan a 2-, 3-, 4-, 5-, 6-, 7-, u 8-quinolinilo, 1-, 3-, 4-, 5-, 6-, 7-, u 8-isoquinolinilo, 2-, 3-, 4-, 5-, 6-, ó 7-indolilo, 2-, 3-, 4-, 5-, 6-, ó 7-benzo[b]tienilo, 2-, 4-, 5-, 6-, ó 7-benzoxazolilo, 2-, 4-, 5-, 6-, ó 7-bencimidazolilo, 2-, 4-, 5-, 6-, ó 7-benzotiazolilo.

El anillo aromático de un grupo "arilo" o "heteroarilo" puede estar sustituido en una o más posiciones del anillo con estos sustituyentes, como se describe anteriormente, como por ejemplo, halógeno, hidroxilo, alcoxilo, alquil-carboniloxilo, aril-carboniloxilo, alcoxi-carboniloxilo, ariloxi-carboniloxilo, carboxilato, alquil-carbonilo, alquil-amino-carbonilo, aril-alquil-amino-carbonilo, alquenil-amino-carbonilo, alquil-carbonilo, aril-carbonilo, aril-alquil-carbonilo, alquenil-carbonilo, alcoxi-carbonilo, amino-carbonilo, tioalquil-carbonilo, fosfato, fosfonato, fosfinato, ciano, amino (incluyendo alquil-amino, dialquil-amino, aril-amino, diaril-amino, y alquil-aril-amino), acil-amino (incluyendo alquil-carbonil-amino, aril-carbonil-amino, carbamoílo y ureido), amidino, imino, sulfhidrilo, tioalquilo, tioarilo, tiocarboxilato, sulfatos, alquil-sulfinilo, sulfonato, sulfamoílo, sulfonamido, nitro, trifluoro-metilo, ciano, azido, heterociclilo, alquil-arilo, o una fracción aromática o heteroaromática. Los grupos arilo también se pueden fusionar o puentear con anillos

alicíclico o heterocíclico que no sean aromáticos, como para para formar un policiclo (por ejemplo, tetralina).

El término "alquenilo" incluye a los grupos alifáticos insaturados análogos en longitud y en la posible sustitución a los alquilos descritos anteriormente, pero que contienen cuando menos un doble enlace.

Por ejemplo, el término "alquenilo" incluye a los grupos alquenilo de cadena recta (por ejemplo, etilenilo, propenilo, butenilo, pentenilo, hexenilo, heptenilo, octenilo, nonenilo, decenilo, etc.), los grupos alquenilo de cadena ramificada, los grupos cicloalquenilo (alicíclicos) (ciclopropenilo, ciclopentenilo, ciclohexenilo, ciclo-heptenilo, y ciclo-octenilo), los grupos cicloalquenilo sustituido por alquilo o alquenilo, y los grupos alquenilo sustituido por cicloalquilo o cicloalquenilo. El término "alquenilo" incluye además los grupos alquenilo que incluyen átomos de oxígeno, nitrógeno, azufre, o fósforo reemplazando a uno o más átomos de carbono de la estructura base de hidrocarburo. En ciertas modalidades, un grupo alquenilo de cadena recta o de cadena ramificada tiene 6 ó menos átomos de carbono en su estructura base (por ejemplo, de 2 a 6 átomos de carbono para la cadena recta, y de 3 a 6 átomos de carbono para la cadena ramificada). De la misma manera, los grupos cicloalquenilo pueden tener de 3 a 8 átomos de carbono en su estructura de anillo, y más preferiblemente tienen 5 ó 6 átomos de carbono en su estructura de anillo. El término "de 2 a 6 átomos de carbono" incluye los grupos alquenilo que contienen de 2 a 6 átomos

de carbono.

Más aún, el término "alquenilo" incluye tanto a los "alquenilos insustituidos" como a los "alquenilos sustituidos", los últimos de los cuales se refieren a las fracciones de alquenilo que tienen sustituyentes reemplazando a un hidrógeno sobre uno o más átomos de carbono de la estructura base de hidrocarburo. Estos sustituyentes pueden incluir, por ejemplo, grupos alquilo, grupos alquinilo, halógenos, hidroxilo, alquil-carboniloxilo, aril-carboniloxilo, alcoxi-carboniloxilo, ariloxi-carboniloxilo, carboxilato, alquil-carbonilo, aril-carbonilo, alcoxi-carbonilo, amino-carbonilo, alquil-amino-carbonilo, dialquil-amino-carbonilo, tioalquil-carbonilo, alcoxilo, fosfato, fosfonato, fosfinato, ciano, amino (incluyendo alquil-amino, dialquil-amino, aril-amino, diaril-amino, y alquil-aril-amino), acil-amino (incluyendo alquil-carbonil-amino, aril-carbonil-amino, carbamoílo, y ureido), amidino, imino, sulfhidrilo, tioalquilo, tioarilo, tiocarboxilato, sulfatos, alquil-sulfinilo, sulfonato, sulfamoílo, sulfonamido, nitro, trifluoro-metilo, ciano, azido, heterociclilo, alquil-arilo, o una fracción aromática o heteroaromática.

El término "alquinilo" incluye a los grupos alifáticos insaturados análogos en longitud y en posibles sustitución a los grupos alquilo descritos anteriormente, pero que contienen cuando menos un triple enlace.

Por ejemplo, el término "alquinilo" incluye a los grupos alquinilo de cadena recta (por ejemplo, etinilo, propinilo, butinilo, pentinilo, hexinilo, heptinilo, octinilo, noninilo, decinilo, etc.), a los grupos

alquinilo de cadena ramificada, y a los grupos alquinilo sustituido por cicloalquilo o cicloalquenilo. El término "alquinilo" incluye además a los grupos alquinilo que incluyen átomos de oxígeno, nitrógeno, azufre, o fósforo, reemplazando a uno o más átomos de carbono de la estructura base de hidrocarburo. En ciertas modalidades, un grupo alquinilo de cadena recta o de cadena ramificada tiene 6 ó menos átomos de carbono en su estructura base (por ejemplo, de 2 a 6 átomos de carbono para la cadena recta, y de 3 a 6 átomos de carbono para la cadena ramificada). El término " de 2 a 6 átomos de carbono" incluye los grupos alquinilo que contienen de 2 a 6 átomos de carbono.

Mas aún, el término "alquinilo" incluye tanto a los "alquinilos insustituidos" como a los "alquinilos sustituidos", los últimos de los cuales se refieren a las fracciones de alquinilo que tienen sustituyentes reemplazando a un hidrógeno sobre uno o más átomos de carbono de la estructura base de hidrocarburo. Estos sustituyentes pueden incluir, por ejemplo, grupos alquilo, grupos alquinilo, halógenos, hidroxilo, alquil-carboniloxilo, aril-carboniloxilo, alcoxi-carboniloxilo, ariloxi-carboniloxilo, carboxilato, alquil-carbonilo, aril-carbonilo, alcoxi-carbonilo, amino-carbonilo, alquil-amino-carbonilo, dialquil-amino-carbonilo, tioalquil-carbonilo, alcoxilo, fosfato, fosfonato, fosfinato, ciano, amino (incluyendo alquil-amino, dialquil-amino, aril-amino, diaril-amino, y alquil-aril-amino), aril-amino (incluyendo alquil-carbonil-amino, aril-carbonil-amino, carbamoílo, y ureido), amidino, imino, sulfhidrilo, tioalquilo,

tioarilo, tiocarboxilato, sulfatos, alquil-sulfinilo, sulfonato, sulfamoílo, sulfonamido, nitro, trifluoro-metilo, ciano, azido, heterociclilo, alquil-arilo, o una fracción aromática o hetero-aromática.

A menos que el número de átomos de carbono se especifique de otra manera, el término "alquilo inferior" significa un grupo alquilo, como se define anteriormente, pero que tiene de uno a cinco átomos de carbono en su estructura base. "Alquenilo inferior" y "alquinilo inferior" tienen longitudes de cadena, por ejemplo, de 2 a 5 átomos de carbono.

El término "alcoxilo" incluye los grupos alquilo, alquenilo, y alquinilo sustituidos e insustituidos covalentemente enlazados a un átomo de oxígeno. Los ejemplos de los grupos alcoxilo incluyen a los grupos metoxilo, etoxilo, isopropiloxilo, propoxilo, butoxilo, y pentoxilo. Los ejemplos de los grupos alcoxilo sustituido incluyen a los grupos alcoxilo halogenado. Los grupos alcoxilo pueden estar sustituidos con grupos tales como alquenilo, alquinilo, halógeno, hidroxilo, alquil-carboniloxilo, aril-carboniloxilo, alcoxi-carboniloxilo, ariloxi-carboniloxilo, carboxilato, alquil-carbonilo, aril-carbonilo, alcoxi-carbonilo, amino-carbonilo, alquil-amino-carbonilo, dialquil-amino-carbonilo, tioalquil-carbonilo, alcoxilo, fosfato, fosfonato, fosfinato, ciano, amino (incluyendo alquil-amino, dialquil-amino, aril-amino, diaril-amino, y alquil-aril-amino), acil-amino (incluyendo alquil-carbonil-amino, aril-carbonil-amino, carbamoílo, y ureido), amidino, imino, sulfhidrilo, tioalquilo, tioarilo, tiocarboxilato, sulfatos, alquil-sulfinilo, sulfonato, sulfamoílo, sulfonamido, nitro, trifluoro-

metilo, ciano, azido, heterociclilo, alquil-arilo, o una fracción aromática o heteroaromática. Los ejemplos de los grupos alcoxilo sustituidos por halógeno incluyen, pero no se limitan a, fluoro-metoxilo, difluoro-metoxilo, trifluoro-metoxilo, cloro-metoxilo, dicloro-metoxilo, tricloro-metoxilo, etc.

El término "acilo" incluye a los compuestos y fracciones que contienen al radical de acilo (CH_3-CO-), o un grupo carbonilo. Incluye las fracciones de acilo sustituido. El término "acilo sustituido" incluye a los grupos acilo en donde uno o más de los átomos de hidrógeno son reemplazados, por ejemplo, por grupos alquilo, grupos alquinilo, halógenos, hidroxilo, alquil-carboniloxilo, aril-carboniloxilo, alcoxi-carboniloxilo, ariloxi-carboniloxilo, carboxilato, alquil-carbonilo, aril-carbonilo, alcoxi-carbonilo, amino-carbonilo, alquil-amino-carbonilo, dialquil-amino-carbonilo, tioalquil-carbonilo, alcoxilo, fosfato, fosfonato, fosfinato, ciano, amino (incluyendo alquil-amino, dialquil-amino, aril-amino, diaril-amino, y dialquil-aril-amino), acil-amino (incluyendo alquil-carbonil-amino, aril-carbonil-amino, carbamoílo, y ureido), amidino, imino, sulfhidrilo, tioalquilo, tioarilo, tiocarboxilato, sulfatos, alquil-sulfinilo, sulfonato, sulfamoílo, sulfonamido, nitro, trifluoro-metilo, ciano, azido, heterociclilo, alquil-arilo, o una fracción aromática o hetero-aromática.

El término "acil-amino" incluye las fracciones en donde una fracción de acilo se enlaza a un grupo amino. Por ejemplo, el término incluye a los grupos alquil-carbonil-amino, aril-carbonil-amino, carbamoílo y ureido.

El término "aroílo" incluye los compuestos y fracciones con una fracción de arilo o heteroaromática enlazada a un grupo carbonilo. Los ejemplos de los grupos aroílo incluyen fenil-carboxilo, naftil-carboxilo, etc. Incluyen las fracciones de aroílo sustituido. El término "aroílo sustituido" incluye los grupos aroílo en donde uno o más de los átomos de hidrógeno son reemplazados, por ejemplo, por grupos alquilo, grupos alquinilo, halógenos, hidroxilo, alquil-carboniloxilo, aril-carboniloxilo, alcoxi-carboniloxilo, ariloxi-carboniloxilo, carboxilato, alquil-carbonilo, aril-carbonilo, alcoxi-carbonilo, amino-carbonilo, alquil-amino-carbonilo, dialquil-amino-carbonilo, tioalquil-carbonilo, alcoxilo, fosfato, fosfonato, fosfinato, ciano, amino (incluyendo alquil-amino, dialquil-amino, aril-amino, diaril-amino, y alquil-aril-amino), acil-amino (incluyendo alquil-carbonil-amino, aril-carbonil-amino, carbamoílo y ureido), amidino, imino, sulfhidrilo, tioalquilo, tioarilo, tiocarboxilato, sulfatos, alquil-sulfinilo, sulfonato, sulfamoílo, sulfonamido, nitro, trifluoro-metilo, ciano, azido, heterociclilo, alquil-arilo, o una fracción aromática o heteroaromática.

Los términos "alcoxi-alquilo," "alquil-amino-alquilo" y "tioalcoxi-alquilo" incluyen a los grupos alquilo, como se describen anteriormente, los cuales incluyen además átomos de oxígeno, nitrógeno o azufre reemplazando a uno o más átomos de carbono de la estructura base del hidrocarburo, por ejemplo, átomos de oxígeno, nitrógeno o azufre.

El término "carbamoílo" incluye $H_2NC(O)$-, alquil-NHC(O)-, $(alquil)_2NC(O)$-, aril-NHC(O)-, alquil-(aril)-NC(O)-, heteroaril-

NHC(O)-, alquil-(heteroaril)-NC(O)-, aril-alquil-NHC(O)-, alquil-(aril-alquil)-NC(O)-, etc. El término incluye las fracciones de carbamoílo sustituido.

El término "sulfonilo" incluye R-SO_2--, en donde R es hidrógeno, alquilo, arilo, heteroarilo, aril-alquilo, heteroaril-alquilo, alcoxilo, ariloxilo, cicloalquilo, o heterociclilo.

El término "sulfonamido" incluye alquil-$S(O)_2$-NH-, aril-$S(O)_2$-NH-, aril-alquil-$S(O)_2$-NH-, heteroaril-$S(O)_2$-NH-, heteroaril-alquil-$S(O)_2$-NH-, alquil-$S(O)_2$-N(alquil)-, aril-$S(O)_2$-N(alquil)-, aril-alquil-$S(O)_2$-N(alquil)-, heteroaril-$S(O)_2$-N(alquil)-, heteroaril-alquil-$S(O)_2$-N(alquil)-, etc. El término incluye las fracciones de carbamoílo sustituido

El término "heterociclilo" o "heterociclo" incluye un anillo o sistema de anillos no aromático saturado o insaturado, opcionalmente sustituido, por ejemplo, el cual es un sistema de anillos monocíclico de 4, 5, 6, ó 7 miembros, bicíclico de 7, 8, 9, 10, 11, ó 12 miembros,, o tricíclico de 10, 11, 12, 13, 14, ó 15 miembros, y contiene cuando menos un heteroátomo seleccionado a partir de O, S y N, en donde los átomos de N y S también pueden ser opcionalmente oxidados hasta diferentes estados de oxidación. El grupo heterocíclico se puede unir en un heteroátomo o en un átomo de carbono. El heterociclilo pueden incluir anillos fusionados o puenteados, así como anillos espirocíclicos. Los ejemplos de heterociclos incluyen tetrahidrofurano (THF), dihidrofurano, 1,4-dioxano, morfolina, 1,4-ditiano, piperazina, piperidina, 1,3-dioxolano,

imidazolidina, imidazolina, pirrolina, pirrolidina, tetrahidropirano, dihidropirano, oxatiolano, ditiolano, 1,3-dioxano, 1,3-ditiano, oxatiano, tiomorfolina, etc.

El término "heterociclilo" incluye a los grupos heterocíclicos como se definen en la presente, sustituidos con 1, 2 ó 3 sustituyentes tales como alquilo, hidroxilo (o hidroxilo protegido), halógeno, oxo (por ejemplo, =O), amino, alquil-amino, o dialquil-amino, alcoxilo, cicloalquilo, carboxilo, heterociclo-oxilo, en donde heterociclo-oxilo denota un grupo heterocíclico enlazado a través de un puente de oxígeno, alquil-O-C(O)--, mercapto, nitro, ciano, sulfamoílo o sulfonamida, arilo, alquil-C(O)-O--, aril-C(O)-O--, aril-S-, ariloxilo, alquil-S--, formilo (por ejemplo, HC(O)--), carbamoílo, aril-alquil--, y arilo sustituido con alquilo, cicloalquilo, alcoxilo, hidroxilo, amino, alquil-C(O)-NH--, alquil-amino, dialquil-amino, o halógeno.

El término "sulfamoílo" incluye $H_2NS(O)_2$-, alquil-$NHS(O)_2$-, $(alquil)_2NS(O)_2$-, aril-$NHS(O)_2$-, alquil-(aril)-$NS(O)_2$-, $(aril)_2NS(O)_2$-, heteroaril-$NHS(O)_2$-, (aril-alquil)-$NHS(O)_2$-, (heteroaril-alquil)-$NHS(O)_2$-, etc. El término incluye las fracciones de sulfamoílo sustituido.

El término "ariloxilo" incluye tanto un grupo --O-arilo, como un grupo --O-heteroarilo, en donde arilo y heteroarilo se definen en la presente. El término incluye las fracciones de ariloxilo sustituido.

El término "amina" o "amino" incluye los compuestos en donde un átomo de nitrógeno se enlaza covalentemente a cuando menos un átomo de carbono o heteroátomo. El término incluye "alquil-amino" el

cual comprende a los grupos y compuestos en donde el nitrógeno se enlaza a cuando menos un grupo alquilo adicional. El término "dialquil-amino" incluye a los grupos en donde el átomo de nitrógeno se enlaza a cuando menos dos grupos alquilo adicionales. Los términos "aril-amino" y "diaril-amino" incluyen a los grupos en donde el nitrógeno se enlaza a cuando menos uno o dos grupos arilo, respectivamente. El término "alquil-aril-amino," "alquil-amino-arilo" o "aril-amino-alquilo" se refiere a un grupo amino que se enlaza a cuando menos un grupo alquilo y cuando menos un grupo arilo. El término "alcamino-alquilo" se refiere a un grupo alquilo, alquenilo, o alquinilo enlazado a un átomo de nitrógeno, el cual también se enlaza a un grupo alquilo. El término "amina" o "amino" también incluye las fracciones sustituidas.

El término "amida," "amido" o "amino-carbonilo" incluye a los compuestos o fracciones que contienen un átomo de nitrógeno que se enlaza al átomo de carbono de un grupo carbonilo o tiocarbonilo. El término incluye a los grupos "alcamino-carbonilo" o "alquil-amino-carbonilo", los cuales incluyen a los grupos alquilo, alquenilo, arilo o alquinilo enlazados a un grupo amino enlazado a un grupo carbonilo. Incluye a los grupos aril-amino-carbonilo y aril-carbonil-amino, los cuales incluyen las fracciones de arilo o heteroarilo enlazadas a un grupo amino, el cual se enlaza al átomo de carbono de un grupo carbonilo o tiocarbonilo. Los términos "alquil-amino-carbonilo", "alquenil-amino-carbonilo", "alquinil-amino-carbonilo", "aril-amino-carbonilo", "alquil-carbonil-amino", "alquenil-carbonil-amino",

"alquinil-carbonil-amino", y "aril-carbonil-amino" se incluyen en el término "amida". Las amidas también incluyen a los grupos urea (amino-carbonil-amino), y carbamatos (oxi-carbonil-amino). El término "amida," "amido" o "amino-carbonilo" también incluye las fracciones sustituidas.

El término "carbonilo" o "carboxilo" incluye a los compuestos y fracciones que contienen un átomo de carbono conectado con un doble enlace a un átomo de oxígeno. El carbonilo puede estar adicionalmente sustituido con cualquier fracción que permita que los compuestos de la invención lleven a cabo su función pretendida. Por ejemplo, las fracciones de carbonilo pueden estar sustituidas con alquilos, alquenilos, alquinilos, arilos, alcoxilos, aminos, etc. Los ejemplos de las fracciones que contienen un carbonilo incluyen aldehídos, cetonas, ácidos carboxílicos, amidas, ésteres, anhídridos, etc.

El término "tiocarbonilo" o "tiocarboxilo" incluye a los compuestos y fracciones que contienen un átomo de carbono conectado con un doble enlace a un átomo de azufre. El término también incluye las fracciones sustituidas.

El término "éter" incluye a los compuestos o fracciones que contienen un oxígeno enlazado a dos átomos de carbono o heteroátomos diferentes. Por ejemplo, el término incluye "alcoxi-alquilo", que se refiere a un grupo alquilo, alquenilo, o alquinilo covalentemente enlazado a un átomo de oxígeno que está covalentemente enlazado a otro grupo alquilo. El término también

incluye las fracciones sustituidas.

El término "éster" incluye a los compuestos y fracciones que contienen un átomo de carbono o un heteroátomo enlazado a un átomo de oxígeno que está enlazado al átomo de carbono de un grupo carbonilo. El término "éster" incluye a los grupos alcoxi-carboxilo, tales como metoxi-carbonilo, etoxi-carbonilo, propoxi-carbonilo, butoxi-carbonilo, pentoxi-carbonilo, etc. Los grupos alquilo, alquenilo, o alquinilo son como se definen anteriormente. El término también incluye las fracciones sustituidas.

El término "tioéter" incluye a los compuestos y fracciones que contienen un átomo de azufre enlazado a dos átomos o heteroátomos diferentes. Los ejemplos de los tioéteres incluyen, pero no se limitan a, alktioalquilos, alktioalquenilos, y alktioalquinilos. El término "alktioalquilos" incluye a los compuestos con un grupo alquilo, alquenilo, o alquinilo enlazado a un átomo de azufre que está enlazado a un grupo alquilo. De una manera similar, el término "alktioalquenilos" y "alktioalquinilos" se refiere a los compuestos o fracciones en donde un grupo alquilo, alquenilo, o alquinilo está enlazado a un átomo de azufre que está covalentemente enlazado a un grupo alquinilo. El término también incluye las fracciones sustituidas.

El término "hidroxi" o "hidroxilo" incluye grupos con un -OH u $-O^-$.

El término "halógeno" incluye flúor, bromo, cloro, yodo, etc. El término "perhalogenado" se refiere en general a una fracción en

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donde todos los hidrógenos son reemplazados por átomos de halógeno.

Los términos "policiclilo" o "radical policíclico" se refieren a dos o más anillos cíclicos (por ejemplo, cicloalquilos, cicloalquenilos, cicloalquinilos, arilos, y/o heterociclilos) en donde dos o más átomos de carbono son comunes a dos anillos adjuntos, por ejemplo los anillos son "anillos fusionados". Los anillos que están unidos a través de átomos no adyacentes se denominan como anillos "puenteados". Cada uno de los anillos del policiclo puede estar sustituido con sustituyentes tales como los descritos anteriormente, como por ejemplo, halógeno, hidroxilo, alquil-carboniloxilo, aril-carboniloxilo, alcoxi-carboniloxilo, ariloxi-carboniloxilo, carboxilato, alquil-carbonilo, alcoxi-carbonilo, alquil-amino-carbonilo, aril-alquil-amino-carbonilo, alquenil-amino-carbonilo, alquil-carbonilo, aril-carbonilo, aril-alquil-carbonilo, alquenil-carbonilo, amino-carbonilo, tioalquil-carbonilo, alcoxilo, fosfato, fosfonato, fosfinato, ciano, amido, amino (incluyendo alquil-amino, dialquil-amino, aril-amino, diaril-amino, y alquil-aril-amino), acil-amino (incluyendo alquil-carbonil-amino, aril-carbonil-amino, carbamoílo, y ureido), amidino, imino, sulfhidrilo, tioalquilo, tioarilo, tiocarboxilato, sulfatos, alquil-sulfinilo, sulfonato, sulfamoílo, sulfonamido, nitro, trifluoro-metilo, ciano, azido, heterociclilo, alquilo, alquil-arilo, o una fracción aromática o heteroaromática.

El término "heteroátomo" incluye a los átomos de cualquier elemento diferente de carbono o hidrógeno. Los heteroátomos

preferidos son nitrógeno, oxígeno, azufre, y fósforo.

Se observará que la estructura de algunos de los compuestos de esta invención incluye átomos de carbono asimétricos. De conformidad con lo anterior, se debe entender que los isómeros que se presenten de esta asimetría (por ejemplo, todos los enantiómeros y estereoisómeros) están incluidos dentro del alcance de esta invención, a menos que se indique de otra manera. Estos isómeros se pueden obtener en una forma sustancialmente pura mediante técnicas de separación clásicas y mediante síntesis estereo-químicamente controlada. Adicionalmente, las estructuras y otros compuestos y fracciones discutidos en esta solicitud también incluyen a todos los tautómeros de los mismos.

El término "isómeros" se refiere a diferentes compuestos que tienen la misma fórmula molecular, pero que difieren en el arreglo y configuración de los átomos. Más aún, el término "un isómero óptico" o "un estereoisómero" se refiere a cualquiera de las diferentes configuraciones estereoisoméricas que pueden existir para un compuesto dado de la presente invención, e incluye a los isómeros geométricos. Se entiende que un sustituyente se puede unir en un centro quiral de un átomo de carbono. Por consiguiente, la invención incluye a los enantiómeros, diaestereómeros o racematos del compuesto. Los "enantiómeros" son un par de estereoisómeros que no son imágenes de espejo que se puedan sobreponer uno sobre el otro. Una mezcla de 1:1 de un par de enantiómeros es una mezcla "racémica". El término se utiliza para designar una mezcla racémica

donde sea apropiado. Los "diaestereoisómeros" son los estereoisómeros que tienen cuando menos dos átomos asimétricos, pero que no son imágenes de espejo uno del otro. La estereoquímica absoluta se especifica de acuerdo con el sistema de Cahn-Ingold-Prelog R-S. Cuando un compuesto es un enantiómero puro, la estereoquímica en cada átomo de carbono quiral se puede especificar mediante *R* o *S*. Los compuestos resueltos cuya configuración absoluta se desconozca, se pueden designar como (+) o (-), dependiendo de la dirección (dextrógira o levógira) en la que gire la luz polarizada en el plano a la longitud de onda de la línea D de sodio. Algunos de los compuestos descritos en la presente contienen uno o más centros asimétricos, y por lo tanto, pueden dar lugar a enantiómeros, diaestereómeros, y otras formas estereoisoméricas que puedan definirse, en términos de estereoquímica absoluta, como (*R*) o (*S*). La presente invención pretende incluir todos los posibles isómeros, incluyendo las mezclas racémicas, las formas ópticamente puras, y las mezclas de intermediarios. Los isómeros (R) y (S) ópticamente activos se pueden preparar utilizando sintones quirales o reactivos quirales, o se pueden resolver empleando técnicas convencionales. Si el compuesto contiene un doble enlace, el sustituyente puede estar en la configuración E ó Z. Si el compuesto contiene un cicloalquilo disustituido, el sustituyente de cicloalquilo puede tener una configuración *cis* o *trans*. También se pretende incluir a todas las formas tautoméricas.

La relación de intervalos de valores en la presente solicitud meramente pretende servir como un método resumido para referirse individualmente a cada valor separado que caiga dentro del intervalo.

Cualquier átomo de carbono asimétrico sobre los compuestos de la presente invención puede estar presente en la configuración (*R*), (*S*) o (*R,S*), de preferencia en la configuración (*R*) o (*S*). Los sustituyentes en átomos con enlaces insaturados, si es posible, pueden estar presentes en la forma *cis* (*Z*) o *trans* (*E*). Por consiguiente, los compuestos de la presente invención pueden estar en la forma de uno de los posibles isómeros o mezclas de los mismos, por ejemplo, as isómeros geométricos sustancialmente puros (*cis* o *trans*), diaestereómeros, isómeros ópticos (antípodas), racematos, o mezclas de los mismos.

Cualesquiera mezclas de isómeros resultantes se pueden separar con base en las diferencias fisicoquímicas de los constituyentes, en los isómeros geométricos u ópticos puros, diaestereómeros, racematos, por ejemplo mediante cromatografía y/o cristalización fraccionaria.

Cualesquiera racematos resultantes de los productos finales o de los intermediarios se pueden resolver en los antípodas ópticos mediante métodos conocidos, por ejemplo mediante la separación de las sales diaestereoméricas de los mismos, obtenidas con un ácido o base ópticamente activos, y liberando el compuesto ácido o básico ópticamente activo. En particular, la fracción de imidazolilo se puede

emplear de esta manera para resolver los compuestos de la presente invención en sus antípodas ópticos, por ejemplo mediante cristalización fraccionaria de una sal formada con un ácido ópticamente activo, por ejemplo, ácido tartárico, ácido dibenzoil-tartárico, ácido diacetil-tartárico, ácido di-O,O'-p-toluoil-tartárico, ácido mandélico, ácido málico, o ácido canfor-10-sulfónico. Los productos racémicos también se pueden resolver mediante cromatografía quiral, por ejemplo cromatografía de líquidos a alta presión (HPLC) utilizando un adsorbente quiral.

Los compuestos de la presente invención se obtienen en la forma libre, como una sal de los mismos, o como derivados de pro-fármaco de los mismos.

El término "sales farmacéuticamente aceptables" incluye las sales que retienen la efectividad biológica y las propiedades de los compuestos de esta invención, y que no son biológicamente o de otra manera indeseables. En muchos casos, los compuestos de la presente invención son capaces de formar sales de ácido y/o de base en virtud de la presencia de grupos amino y/o carboxilo, o grupos similares a los mismos. Las sales de adición de ácido farmacéuticamente aceptables se pueden formar con ácidos inorgánicos y ácidos orgánicos. Los ácidos inorgánicos a partir de los cuales se pueden derivar las sales incluyen, por ejemplo, ácido clorhídrico, ácido bromhídrico, ácido sulfúrico, ácido nítrico, ácido fosfórico, etc. Los ácidos orgánicos a partir de los cuales se pueden derivar las sales incluyen, por ejemplo, ácido acético, ácido

propiónico, ácido glicólico, ácido pirúvico, ácido oxálico, ácido maleico, ácido malónico, ácido succínico, ácido fumárico, ácido tartárico, ácido cítrico, ácido benzoico, ácido cinámico, ácido mandélico, ácido metan-sulfónico, ácido etan-sulfónico, ácido p-toluen-sulfónico, ácido salicílico, etc. Las sales de adición de base farmacéuticamente aceptables se pueden formar con bases inorgánicas y orgánicas. Las bases inorgánicas a partir de las cuales se pueden derivar las sales incluyen, por ejemplo, sodio, potasio, litio, amonio, calcio, magnesio, hierro, zinc, cobre, manganeso, aluminio, etc.; se prefieren en particular las sales de amonio, potasio, sodio, calcio y magnesio. Las bases orgánicas a partir de las cuales se pueden derivar las sales incluyen, por ejemplo, aminas primarias, secundarias, y terciarias, aminas sustituidas incluyendo aminas sustituidas que se presentan naturalmente, aminas cíclicas, resinas básicas de intercambio de iones, etc., específicamente tales como isopropil-amina, trimetil-amina, dietil-amina, trietil-amina, tripropil-amina, y etanolamina. Las sales farmacéuticamente aceptables de la presente invención se pueden sintetizar a partir de un compuesto progenitor, una fracción básica o ácida, mediante métodos químicos convencionales. En términos generales, estas sales se pueden preparar mediante la reacción de las formas del ácido libre de estos compuestos con una cantidad estequiométrica de la base apropiada (tales como hidróxido, carbonato, o bicarbonato de Na, Ca, Mg, o K, o similares), o mediante la reacción de las formas de base libre de estos compuestos con una cantidad estequiométrica

del ácido apropiado. Estas reacciones típicamente se llevan a cabo en agua o en un solvente orgánico, o en una mezcla de los dos. En términos generales, se prefieren los medios no acuosos como éter, acetato de etilo, etanol, isopropanol, o acetonitrilo, cuando sea practicable. Las listas de las sales adecuadas adicionales se pueden encontrar, por ejemplo, en *Remington's Pharmaceutical Sciences,* 20ª Edición, Mack Publishing Company, Easton, Pa. (1985).

Cuando está presente un grupo básico en los compuestos de la presente invención, los compuestos se pueden convertir en las sales de adición de ácido de los mismos, en particular, en las sales de adición de ácido con la fracción de piridinilo de la estructura, de preferencia las sales farmacéuticamente aceptables de los mismos. Éstas se forman con ácidos inorgánicos o con ácidos orgánicos. Los ácidos inorgánicos adecuados incluyen, pero no se limitan a, ácido clorhídrico, ácido sulfúrico, un ácido fosfórico o halohídrico. Los ácidos orgánicos adecuados incluyen, pero no se limitan a, ácidos carboxílicos, tales como ácidos alcano (de 1 a 4 átomos de carbono)-carboxílicos, los cuales, por ejemplo, están insustituidos o sustituidos por halógeno, por ejemplo ácido acético; tales como los ácidos dicarboxílicos saturados o insaturados, por ejemplo ácido oxálico, succínico, maleico o fumárico; tales como los ácidos hidroxi-carboxílicos, por ejemplo ácido glicólico, láctico, málico, tartárico, o cítrico; tales como los aminoácidos, por ejemplo ácido aspártico o glutámico; los ácidos sulfónicos orgánicos, tales como los ácidos alquilo (de 1 a 4 átomos de carbono)-sulfónicos, por ejemplo ácido

metan-sulfónico; o los ácidos aril-sulfónicos que están insustituidos o sustituidos, por ejemplo por halógeno. Se prefieren las sales formadas con ácido clorhídrico, ácido metan-sulfónico, y ácido maleico.

Cuando está presente un grupo ácido en los compuestos de la presente invención, los compuestos se pueden convertir en sales con bases farmacéuticamente aceptables. Estas sales incluyen las sales de metales alcalinos, como las sales de sodio, litio y potasio; las sales de metales alcalinotérreos, como las sales de calcio y magnesio; las sales de amonio con bases orgánicas, por ejemplo las sales de trimetil-amina, las sales de dietil-amina, las sales de tris-(hidroxi-metil)-metil-amina, las sales de diciclohexil-amina, y las sales de N-metil-D-glucamina; las sales con aminoácidos como arginina, lisina, etc. Las sales se pueden formar empleando métodos convencionales, convenientemente en la presencia de un solvente etéreo o alcohólico, tal como un alcanol inferior. A partir de las soluciones del último, las sales se pueden precipitar con éteres, por ejemplo dietil-éter. Las sales resultantes se pueden convertir en los compuestos libres mediante su tratamiento con ácidos. Éstas u otras sales también se pueden utilizar para la purificación de los compuestos obtenidos.

Cuando están presentes tanto un grupo básico como un grupo ácido en la misma molécula, los compuestos de la presente invención también pueden formar sales internas.

Las sales de los compuestos de la presente invención que

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tengan cuando menos un grupo formador de sal, se pueden preparar de una manera conocida por sí misma. Por ejemplo, las sales de los compuestos de la presente invención que tengan grupos ácidos se pueden formar, por ejemplo, mediante el tratamiento de los compuestos con compuestos de metales, tales como sales de metales alcalinos de los ácidos carboxílicos orgánicos adecuados, por ejemplo la sal sódica del ácido 2-etil-hexanoico, con compuestos de metales alcalinos o de metales alcalinotérreos orgánicos, tales como los hidróxidos, carbonatos, o carbonatos ácidos correspondientes, tales como hidróxido, carbonato, o carbonato ácido de sodio o de potasio, con los compuestos de calcio correspondientes, o con amoniaco o una amina orgánica adecuada, utilizándose de preferencia cantidades estequiométricas o solamente un pequeño exceso del agente formador de sal. Las sales de adición de ácido de los compuestos de la presente invención se obtienen de la manera acostumbrada, por ejemplo mediante el tratamiento de los compuestos con un ácido o con un reactivo de intercambio de aniones adecuado. Se pueden formar las sales internas de los compuestos de la presente invención que contengan grupos formadores de sales ácidos y básicos, por ejemplo un grupo carboxilo libre y un grupo amino libre, por ejemplo, mediante la neutralización de las sales, tales como las sales de adición de ácido, hasta el punto isoeléctrico, por ejemplo con bases débiles, o mediante su tratamiento con intercambiadores de iones.

Las sales se pueden convertir de la manera acostumbrada en

los compuestos libres; las sales de metales y de amonio se pueden convertir, por ejemplo, mediante su tratamiento con ácidos adecuados, y las sales de adición de ácido, por ejemplo, mediante su tratamiento con un agente básico adecuado.

La presente invención incluye todos los compuestos isotópicamente marcados farmacéuticamente aceptables de la invención, es decir, los Agentes de la Invención, en donde: (1) uno o más átomos son reemplazados por átomos que tienen el mismo número atómico, pero una masa atómica o número de masa diferente de la masa atómica o número de masa usualmente encontrado en la naturaleza, y/o (2) la proporción isotópica de uno o más átomos es diferente de la proporción que se presenta naturalmente.

Los ejemplos de los isótopos adecuados para incluirse en los compuestos de la invención comprenden los isótopos de hidrógeno, tales como ^{2}H y ^{3}H, carbono, tales como ^{11}C, ^{13}C y ^{14}C, cloro, tal como ^{36}Cl, flúor, tal como ^{18}F, yodo, tales como ^{123}I y ^{125}I, nitrógeno, tales como ^{13}N y ^{15}N, oxígeno, tales como ^{15}O, ^{17}O y ^{18}O, fósforo, tal como ^{32}P, y azufre, tal como ^{35}S.

Ciertos Agentes de la Invención isotópicamente marcados, por ejemplo, aquéllos que incorporan un isótopo radioactivo, son útiles en los estudios de distribución del fármaco y/o de sustrato en el tejido. Los isótopos radioactivos de tritio, es decir, ^{3}H, y de carbono-14, es decir, ^{14}C, son particularmente útiles para este propósito en vista de su facilidad de incorporación y fáciles medios de detección.

La sustitución con isótopos más pesados, tales como deuterio,

es decir, ^{2}H, puede proporcionar ciertas ventajas terapéuticas resultantes de la mayor estabilidad metabólica, por ejemplo, una mayor vida media *in vivo*, o requerimientos de dosificación reducida, y por consiguiente, se puede preferir en algunas circunstancias.

La sustitución con isótopos emisores de positrones, tales como ^{11}C, ^{18}F, ^{15}O y ^{13}N, puede ser útil en los estudios de Tomografía de Emisión de Positrones (PET) para examinar la ocupación de sustrato del receptor.

Los Agentes de la Invención isotópicamente marcados se pueden preparar, en términos generales, mediante técnicas convencionales conocidos por los expertos en este campo, o mediante procesos análogos a aquéllos descritos en los Ejemplos y Preparaciones acompañantes, utilizando reactivos isotópicamente marcados apropiados en lugar del reactivo no marcado anteriormente empleado.

La presente invención también proporciona fracciones de pro-fármaco de los compuestos de la presente invención, que se convierten *in vivo* hasta los compuestos de la presente invención. Una fracción de pro-fármaco es un compuesto activo o inactivo que se modifica químicamente a través de la acción fisiológica *in vivo*, tal como hidrólisis, el metabolismo, etc., en un compuesto de esta invención en seguida de la administración del pro-fármaco a un sujeto. El término "fracción de pro-fármaco" incluye las fracciones que se pueden metabolizar *in vivo* hasta un grupo hidroxilo, y las fracciones que pueden permanecer convenientemente esterificadas

in vivo. De preferencia, las fracciones de pro-fármaco se metabolizan *in vivo* mediante las esterasas o mediante otros mecanismos hasta los grupos hidroxilo u otros grupos convenientes. Los ejemplos de los pro-fármacos y sus usos son bien conocidos en la materia (véase, por ejemplo, Berge y colaboradores, (1977) "Pharmaceutical Salts" *J. Pharm. Sci.* 66:1-19). Los pro-fármacos se pueden preparar *in situ* durante el aislamiento y purificación final de los compuestos, o haciendo reaccionar por separado el compuesto purificado en su forma de ácido libre o hidroxilo con un agente esterificante adecuado. Los grupos hidroxilo se pueden convertir en ésteres por medio del tratamiento con un ácido carboxílico. Los ejemplos de las fracciones de pro-fármaco incluyen las fracciones de éster de alquilo inferior ramificado o no ramificado, sustituido e insustituido (por ejemplo, los ésteres de ácido propiónico), ésteres de alquenilo inferior, ésteres de di-alquilo inferior-amino-alquilo inferior (por ejemplo, dimetil-amino-etil-éster), ésteres de acil-amino-alquilo inferior (por ejemplo, acetiloxi-metil-éster), ésteres de aciloxi-alquilo inferior (por ejemplo, pivaloiloxi-metil-éster), ésteres de arilo (fenil-éster), ésteres de aril-alquilo inferior (por ejemplo, bencil-éster), ésteres de arilo y de aril-alquilo inferior sustituidos (por ejemplo, con sustituyentes de metilo, halógeno, o metoxilo), amidas, amidas de alquilo inferior, amidas de di-alquilo inferior, e hidroxilamidas. Las fracciones de pro-fármaco preferidas son los ésteres de ácido propiónico y los acil-ésteres.

La idoneidad y las técnicas involucradas en la elaboración y

utilización de pro-fármacos son bien conocidas por los expertos en la materia. Los pro-fármacos se pueden dividir conceptualmente en dos categorías no exclusivas: pro-fármacos bioprecursores y pro-fármacos portadores. Véase *The Practice of Medicinal Chemistry*, Capítulos 31-32 (Ed. Wermuth, Academic Press, San Diego, Calif., 2001). En general, los pro-fármacos bioprecursores son compuestos que son inactivos o que tienen una baja actividad, comparándose con el compuesto de fármaco activo correspondiente, que contienen uno o más grupos protectores, y se convierten hasta la forma activa mediante el metabolismo o solvólisis. Tanto la forma del fármaco activo como cualesquiera productos metabólicos liberados deben tener una toxicidad aceptablemente baja. Típicamente, la formación del compuesto de fármaco activo involucra un proceso metabólico o una reacción que es una de los siguientes tipos:

1. Reacciones de oxidación, tales como la oxidación de alcohol, carbonilo, y funciones de ácido, hidroxilación de átomos de carbono alifáticos, hidroxilación de átomos de carbono alicíclicos, oxidación de átomos de carbono aromáticos, oxidación de dobles enlaces de carbono-carbono, oxidación de grupos funcionales que contienen nitrógeno, oxidación de silicio, fósforo, arsénico, y azufre, N-desalquilación oxidativa, O- y S-desalquilación oxidativa, desaminación oxidativa, así como otras reacciones oxidativas.

2. Reacciones de reducción, tales como la reducción de grupos carbonilo, la reducción de grupos alcohólicos y de dobles enlaces de carbono-carbono, la reducción de grupos de función que

contienen nitrógeno, y otras reacciones de reducción.

3. Reacciones sin cambiar el estado de oxidación, tales como la hidrólisis de ésteres y éteres, la disociación hidrolítica de enlaces individuales de carbono-nitrógeno, la disociación hidrolítica de heterociclos no aromáticos, la hidratación y deshidratación en múltiples enlaces, nuevos enlaces atómicos resultantes de las reacciones de deshidratación, deshalogenación hidrolítica, remoción de la molécula de haluro de hidrógeno, y otras de tales reacciones.

Los pro-fármacos portadores son compuestos de fármaco que contienen una fracción de transporte, por ejemplo que mejoran la absorción y/o el suministro localizado a los sitios de acción. Deseablemente, para este pro-fármaco portador, el enlace entre la fracción de fármaco y la fracción de transporte es un enlace covalente, el pro-fármaco es inactivo o menos activo que el compuesto de fármaco, y cualquier fracción de transporte liberada es aceptablemente no tóxica. Para los pro-fármacos en donde la fracción de transporte se pretenda para mejorar la absorción, típicamente la liberación de la fracción de transporte debe ser rápida. En otros casos, es deseable utilizar una fracción que proporcione una liberación lenta, por ejemplo ciertos polímeros u otras fracciones, tales como ciclodextrinas. Véase Cheng y colaboradores, Patente de los Estados Unidos de Norteamérica Número US20040077595, incorporada a la presente como referencia. Estos pro-fármacos portadores con frecuencia son convenientes para los fármacos oralmente administrados. Los pro-fármacos portadores,

por ejemplo, se pueden utilizar para mejorar una o más de las siguientes propiedades: mayor lipofilicidad, mayor duración de los efectos farmacológicos, mayor especificidad del sitio, menor toxicidad y reacciones adversas, y/o mejora en la formulación del fármaco (por ejemplo, estabilidad, solubilidad en agua, supresión de una propiedad organoléptica o fisicoquímica indeseable). Por ejemplo, se puede aumentar la lipofilicidad mediante la esterificación de los grupos hidroxilo con ácidos carboxílicos lipofílicos, o de los grupos de ácido carboxílico con alcoholes, por ejemplo alcoholes alifáticos. Wermuth, *The Practice of Medicinal Chemistry*, Capítulos 31-32, Ed. Wermuth, Academic Press, San Diego, Calif., 2001.

Los pro-fármacos de ejemplo son, por ejemplo, los ésteres de ácidos carboxílicos y los derivados S-acílicos y O-acílicos de tioles, alcoholes o fenoles, en donde el acilo tiene el significado como se define en la presente. Se prefieren los derivados de éster farmacéuticamente aceptables que se pueden convertir mediante solvólisis bajo condiciones fisiológicas hasta el ácido carboxílico progenitor, por ejemplo los ésteres de alquilo inferior, ésteres de cicloalquilo, ésteres de alquenilo inferior, ésteres de bencilo, ésteres de alquilo inferior mono- o di-sustituidos, tales como los ésteres de ω-(amino, mono- o di-alquilo inferior-amino, carboxilo, alcoxilo inferior-carbonilo)-alquilo inferior, los ésteres de α-(alcanoiloxilo inferior, alcoxilo inferior-carbonilo, o di-alquilo inferior-amino-carbonilo)-alquilo inferior, tales como el pivaloiloxi-metil-éster, etc., convencionalmente utilizados en la técnica. En adición, las aminas

se han enmascarado como derivados sustituidos por aril-carboniloxi-metilo que se disocian mediante las esterasas *in vivo*, liberando el fármaco libre y formaldehído (Bundgaard, *J. Med. Chem.* 2503 (1989)). Más aún, los fármacos que contienen un grupo NH ácido, tal como imidazol, imida, indol, etc., se han enmascarado con grupos N-aciloxi-metilo (Bundgaard, *Design of Prodrugs*, Elsevier (1985)). Los grupos hidroxilo se han enmascarado como ésteres y éteres. La Patente Europea Número EP 039,051 (Sloan y Little) da a conocer pro-fármacos de ácido hidroxámico de base de Mannich, su preparación, y su uso.

En vista de la estrecha relación entre los compuestos, los compuestos en la forma de sus sales, y los pro-fármacos, cualquier referencia a los compuestos de la presente invención se debe entender para referirse también a los pro-fármacos correspondientes de los compuestos de la presente invención, como sea apropiado y conveniente.

Adicionalmente, los compuestos de la presente invención, incluyendo sus sales, también se pueden obtener en la forma de sus hidratos, o pueden incluir otros solventes utilizados para su cristalización.

Los compuestos de la presente invención se preparan a partir de los compuestos comúnmente disponibles, empleando los procedimientos conocidos por los expertos en este campo, incluyendo cualquiera o más de las siguientes condiciones, sin limitación:

Dentro del alcance de este texto, solamente un grupo fácilmente removible que no sea un constituyente del producto final deseado particular de los compuestos de la presente invención, se designa como un "grupo protector", a menos que el contexto lo indique de otra manera. La protección de los grupos funcionales por parte de estos grupos protectores, los grupos protectores mismos, y sus reacciones de disociación, 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 y P. G. M. Wuts, "Protective Groups in Organic Synthesis", Tercera Edición, Wiley, Nueva York 1999.

Las mezclas de isómeros que se pueden obtener de acuerdo con la invención se pueden separar de una manera conocida por sí misma en los isómeros individuales; los diaestereoisómeros se pueden separar, por ejemplo, mediante división entre mezclas de solventes polifásicas, recristalización, y/o separación cromatográfica, por ejemplo sobre gel de sílice, o, por ejemplo, mediante cromatografía de líquidos a presión media sobre una columna de fase inversa, y los racematos se pueden separar, por ejemplo, mediante la formación de sales con reactivos formadores de sales ópticamente puros y la separación de la mezcla de diaestereoisómeros que se puede obtener de esta manera, por ejemplo por medio de cristalización fraccionaria, o mediante cromatografía sobre materiales de columna ópticamente activos.

Los intermediarios y los productos finales se pueden procesar y/o purificar de acuerdo con los métodos convencionales, por ejemplo empleando métodos cromatográficos, métodos de distribución, (re-)cristalización, etc.

Lo siguiente se aplica en general a todos los procesos mencionados anteriormente en la presente y más adelante en la presente.

Todos los pasos del proceso anteriormente mencionado se pueden llevar a cabo bajo condiciones de reacción que son conocidas por sí mismas, incluyendo las mencionadas de una manera específica, en ausencia, o por costumbre en la presencia de solventes o diluyentes, incluyendo, por ejemplo, los solventes o diluyentes que sean inertes hacia los reactivos utilizados y los disuelvan, en ausencia o en la presencia de catalizadores, agentes de condensación o neutralizantes, por ejemplo intercambiadores de iones, tales como intercambiadores de cationes, por ejemplo en la forma de H^+, dependiendo de la naturaleza de la reacción, y/o de los reactivos, a temperatura reducida, normal, o elevada, por ejemplo en un intervalo de temperatura de aproximadamente -100°C a aproximadamente 190°C, incluyendo, por ejemplo, de aproximadamente -80°C a aproximadamente 150°C, por ejemplo de -80°C a -60°C, a temperatura ambiente, de -20°C a 40°C, o a la temperatura de reflujo, bajo presión atmosférica o en un recipiente cerrado, donde sea apropiado bajo presión, y/o en una atmósfera inerte, por ejemplo bajo una atmósfera de argón o de nitrógeno.

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En todas las etapas de las reacciones, las mezclas de isómeros que se formen se pueden separar en los isómeros individuales, por ejemplo diaestereoisómeros o enantiómeros, o en cualesquiera mezclas de isómeros deseadas, por ejemplo racematos, o mezclas de diaestereoisómeros.

Los solventes a partir de los cuales se pueden seleccionar los solventes que son adecuados para cualquier reacción particular incluyen los mencionados de una manera específica, o, por ejemplo, agua, ésteres, tales como alcanoatos inferiores de alquilo inferior, por ejemplo acetato de etilo, éteres, tales como éteres alifáticos, por ejemplo dietil-éter, o éteres cíclicos, por ejemplo tetrahidrofurano o dioxano, hidrocarburos aromáticos líquidos, tales como benceno o tolueno, alcoholes, tales como metanol, etanol, o 1- ó 2-propanol, nitrilos, tales como acetonitrilo, hidrocarburos halogenados, tales como cloruro de metileno o cloroformo, amidas de ácido, tales como dimetil-formamida o dimetil-acetamida, bases, tales como bases de nitrógeno heterocíclico, por ejemplo piridina ó N-metil-pirrolidin-2-ona, anhídridos de ácido carboxílico, tales como anhídridos de ácido alcanoico inferior, por ejemplo anhídrido acético, hidrocarburos cíclicos, lineales o ramificados, tales como ciclohexano, hexano, o isopentano, o mezclas de estos solventes, por ejemplo soluciones acuosas, a menos que se indique de otra manera en la descripción de los procesos. Estas mezclas de solventes también se pueden utilizar en el procesamiento, por ejemplo mediante cromatografía o división.

Los compuestos, incluyendo sus sales, también se pueden obtener en la forma de hidratos, o, por ejemplo, sus cristales pueden incluir al solvente utilizado para la cristalización. Puede haber diferentes formas cristalinas presentes.

La invención se refiere también a las formas del proceso en donde un compuesto que se pueda obtener como un intermediario en cualquier etapa del proceso, se utiliza como material de partida, y se llevan a cabo los pasos restantes del proceso, o en donde se forma un material de partida bajo las condiciones de reacción, o se utiliza en la forma de un derivado, por ejemplo en una forma protegida o en la forma de una sal, o un compuesto que se pueda obtener mediante el proceso de acuerdo con la invención se produce bajo las condiciones del proceso, y se procesa adicionalmente *in situ*.

Todos los materiales de partida, bloques de construcción, reactivos, ácidos, bases, agentes deshidratantes, solventes, y catalizadores utilizados para la síntesis de los compuestos de la presente invención, están comercialmente disponibles, o se pueden producir mediante los métodos de síntesis orgánica conocidos por un experto ordinario en este campo (Houben-Weyl, 4ª Edición, 1952, Methods of Organic Synthesis, Thieme, Volumen 21).

En términos generales, los enantiómeros de los compuestos de la presente invención se pueden preparar mediante los métodos conocidos para los expertos en este campo para resolver las mezclas racémicas, tales como mediante la formación y recristalización de las sales diaestereoméricas, o mediante cromatografía quiral o HPLC de

separación, utilizando fases estacionarias quirales.

En los compuestos de partida y en los intermediarios, los cuales se convierten hasta los compuestos de la invención de una manera descrita en la presente, los grupos funcionales presentes, tales como los grupos amino, tiol, carboxilo, e hidroxilo, opcionalmente se protegen mediante grupos protectores convencionales que son comunes en la química orgánica de preparación. Los grupos amino, tiol, carboxilo, e hidroxilo protegidos son aquéllos que se pueden convertir, bajo condiciones ligeras, en los grupos amino, tiol, carboxilo, e hidroxilo libres, sin que se destruya la estructura base molecular, o sin que tengan lugar otras reacciones secundarias indeseadas.

El propósito de introducir grupos protectores es proteger a los grupos funcionales de las reacciones indeseadas con los componentes de la reacción, bajo las condiciones empleadas para llevar a cabo una transformación química deseada. La necesidad y elección de los grupos protectores para una reacción particular es conocida por los expertos en la materia, y depende de la naturaleza del grupo funcional que se vaya a proteger (grupo hidroxilo, grupo amino, etc.), de la estructura y estabilidad de la molécula de la que sea parte el sustituyente, y de las condiciones de reacción.

Los grupos protectores bien conocidos que satisfacen estas condiciones, y su introducción y remoción, se describen, por ejemplo, en McOmie, "Protective Groups in Organic Chemistry", Plenum Press, Londres, NY (1973); y en Greene y Wuts, "Protective

Groups in Organic Synthesis", John Wiley and Sons, Inc., NY (1999).

Las reacciones anteriormente mencionadas se llevan a cabo de acuerdo con los métodos convencionales, en la presencia o en ausencia de diluyentes, de preferencia tales como los que sean inertes para los reactivos y que sean solventes de los mismos, de catalizadores, agentes de condensación u otros agentes, respectivamente, y/o atmósferas inertes, a bajas temperaturas, a temperatura ambiente, o a temperaturas elevadas, de preferencia en o cerca del punto de ebullición de los solventes utilizados, y a presión atmosférica o súper-atmosférica. Los solventes, catalizadores, y condiciones de reacción preferidos se estipulan en los Ejemplos ilustrativos adjuntos.

La invención incluye además cualquier variante de los presentes procesos, en donde se utilice un producto intermediario que se pueda obtener en cualquier etapa de los mismos como material de partida y se lleven a cabo los pasos restantes, o en donde se formen los materiales de partida *in situ* bajo las condiciones de reacción, o en donde se utilicen los componentes de4 la reacción en la forma de sus sales o de sus antípodas ópticamente puros.

Abreviaturas:

ATP: 5'-trifosfato de adenosina	BINAP: 2,2'-bis-(difenil-fosfino)-1,1'-binaftilo racémico
BOC: terbutil-carboxilo	br: amplia

bs: amplia singulete	calcd: calculado
d: doblete	DAST: trifluoruro de (dietil-amino)-azufre
dd: doblete de dobletes	DCM: dicloro-metano
DIEA: dietil-isopropil-amina	DME: 1,4-dimetoxi-etano
DMF: *N*,*N*-dimetil-formamida	DMSO: sulfóxido de dimetilo
DPPA: difenil-fosforil-azida	DTT: ditioeritritol
EDTA: ácido-etilen-diamina-tetra-acético	ESI: ionización por electroaspersión
EtOAc: acetato de etilo	h: hora(s)
HATU: hexafluorofosfato de *O*-(7-azobenzotriazol-1-il)-1,1,3,3-tetrametil-uronio	HOBt: 1-hidroxi-7-azabenzotriazol
HPLC: cromatografía de líquidos a alta presión	LCMS: cromatografía de líquidos y espectrometría de masas
MeOD: metanol-d4	MeOH: metanol
MS: espectrometría de masas	m: multiplete
min: minutos	m/z: proporción de la masa a la carga

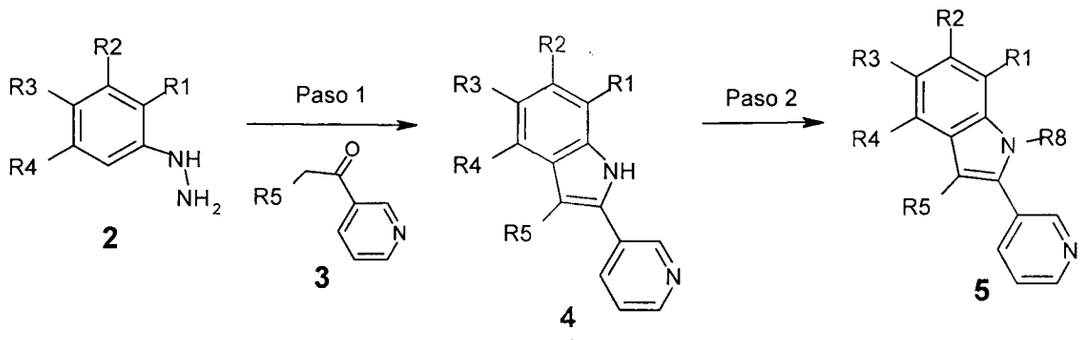
n.d.: no determinado	RMN: resonancia magnética nuclear
ppm: partes por millón	Pr: propilo
PyBOP: hexafluorofosfato de benzotriazol-1-il-oxi-tri-pirrolidino-fosfonio	rt: temperatura ambiente
s: singulete	t: triplete
TFA: ácido trifluoro-acético	THF: tetrahidrofurano
TLC: cromatografía de capa delgada	Tris·HCl: clorhidrato de amino-tris-(hidroxi-metil)-metano

Métodos para Sintetizar los Compuestos de la Invención

Los compuestos de la invención se pueden sintetizar empleando los métodos descritos en los siguientes esquemas, ejemplos, y empleando las técnicas reconocidas en este campo. Todos los compuestos descritos en la presente se incluyen en la invención como compuestos.

Los compuestos de la invención se pueden sintetizar de acuerdo con cuando menos uno de los métodos descritos en los Esquemas 1 a 7.

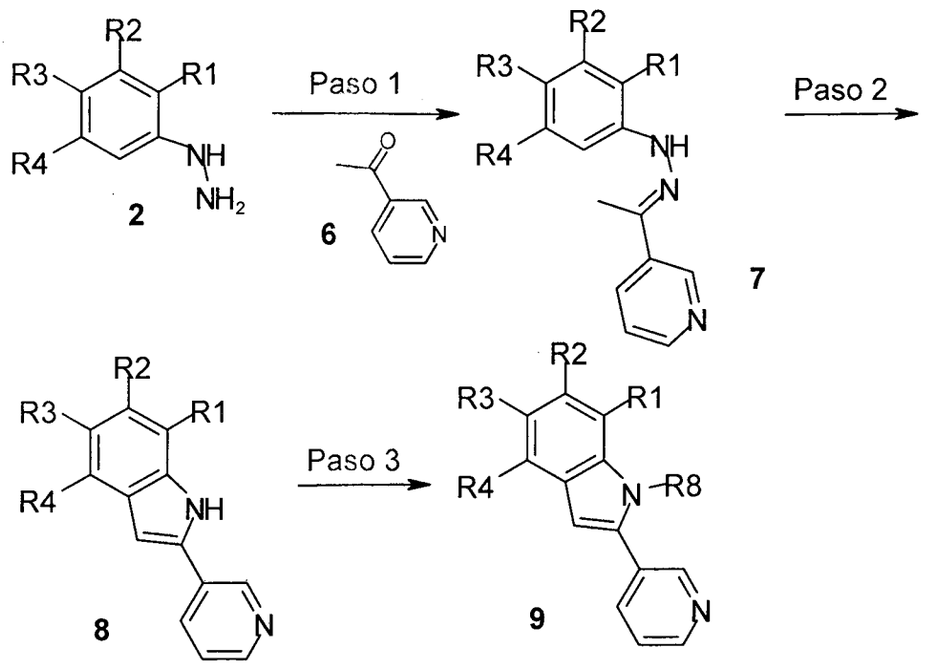
Esquema 1.



En el Paso 1, el derivado de hidrazina apropiado 2 se calienta con el derivado de 3 acetil-piridina 3 en un solvente, por ejemplo, etanol, dando como resultado la formación de la hidrazona correspondiente, la cual, después de la adición de un ácido, por ejemplo, cloruro de hidrógeno, se somete a reacción de Fisher para dar el indol 4. La piridina 3 se puede preparar convenientemente a partir del ácido nicotínico, por medio de la formación de la amida de Weinreb y la subsiguiente adición del reactivo de Grignard apropiado, por ejemplo, bromuro de n-propil-magnesio. En el Paso 2, el indol 4 se desprotona con una base fuerte, tal como hexametil-disilamida de potasio, y el anión resultante se atrapa con el reactivo electrofílico apropiado, por ejemplo, un cloruro de ácido, un cloroformato, un bromuro de alquilo, un cloruro de alquilo o un yoduro de alquilo, para dar el indol 5. La transformación apropiada del R8 en 5 conduce a análogos adicionales. Por ejemplo, si R8 contiene un éster, el éster se puede hidrolizar hasta el ácido carboxílico correspondiente. En otro ejemplo, si R8 contiene un nitrilo, el nitrilo se puede hacer reaccionar con azida para dar el

tetrazol correspondiente.

Esquema 2.

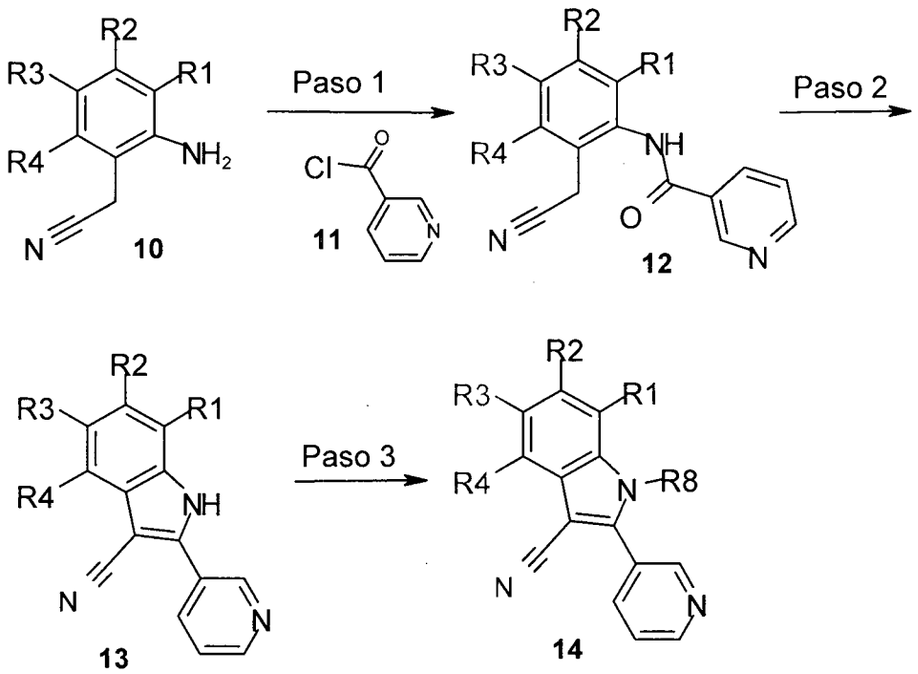


En el Paso 1, el derivado de hidrazina apropiado 2 se calienta con 3-acetil-piridina 6 en un solvente, por ejemplo, etanol, dando como resultado la formación de la hidrazona correspondiente 7. En el Paso 2, el 7 se calienta, puro, con poli-ácido fosfórico, de preferencia entre 160°C y 220°C, para dar el indol 8. En el Paso 3, el indol 4 se desprotona con una base fuerte, por ejemplo, hexametil-disilamida de potasio, y el anión resultante se atrapa con el reactivo electrofílico apropiado, por ejemplo, un cloruro de ácido, un cloroformato, una cetona o éster alfa,beta-insaturado, un bromuro de alquilo, un cloruro de alquilo, o un yoduro de alquilo, para dar el indol 9. La transformación apropiada del R8 en 9 conduce a análogos adicionales. Por ejemplo, si R8 contiene un éster, el éster se puede

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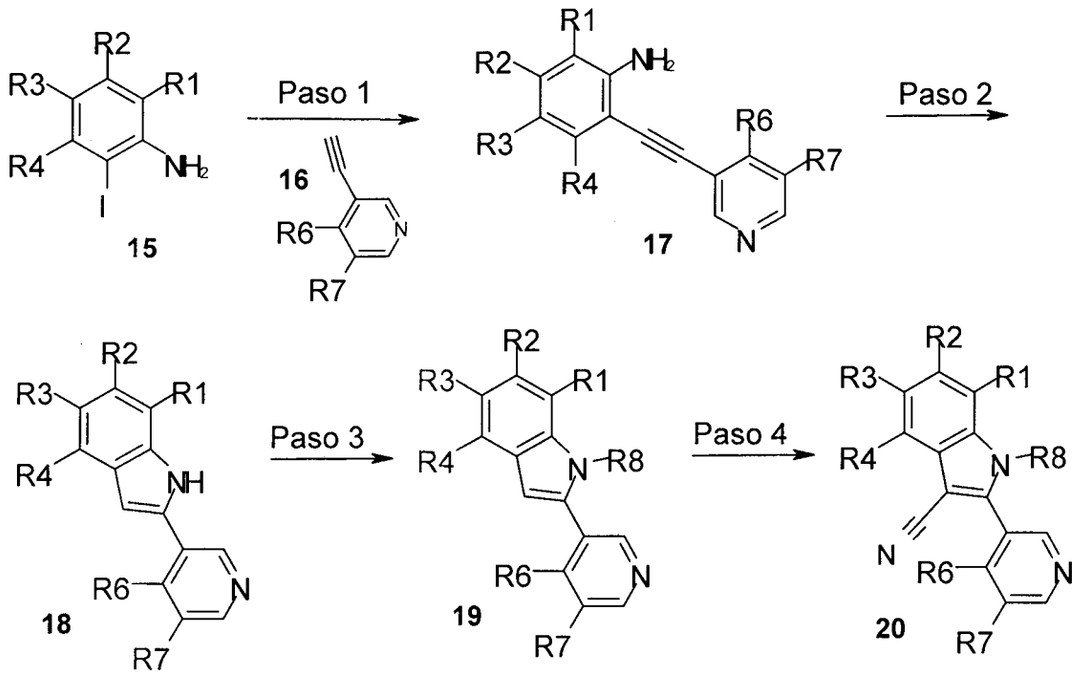
hidrolizar hasta el ácido carboxílico correspondiente. En otro ejemplo, si R8 contiene un nitrilo, el nitrilo se puede hacer reaccionar con azida para dar el tetrazol correspondiente.

Esquema 3.



En el Paso 1, el derivado de la anilina apropiado 10 se acopla con cloruro de nicotinilo en la presencia de una base de amina, por ejemplo, di-isopropil-etil-amina, para dar la amida 12. En el Paso 2, el calentamiento del 12 en la presencia de una base fuerte, por ejemplo, hidruro de sodio, da el indol 13. En el Paso 3, el indol 13 se desprotona con una base fuerte, por ejemplo, hidruro de sodio, y el anión resultante se atrapa con el reactivo electrofílico apropiado, por ejemplo, yoduro de metilo, para dar el indol 14.

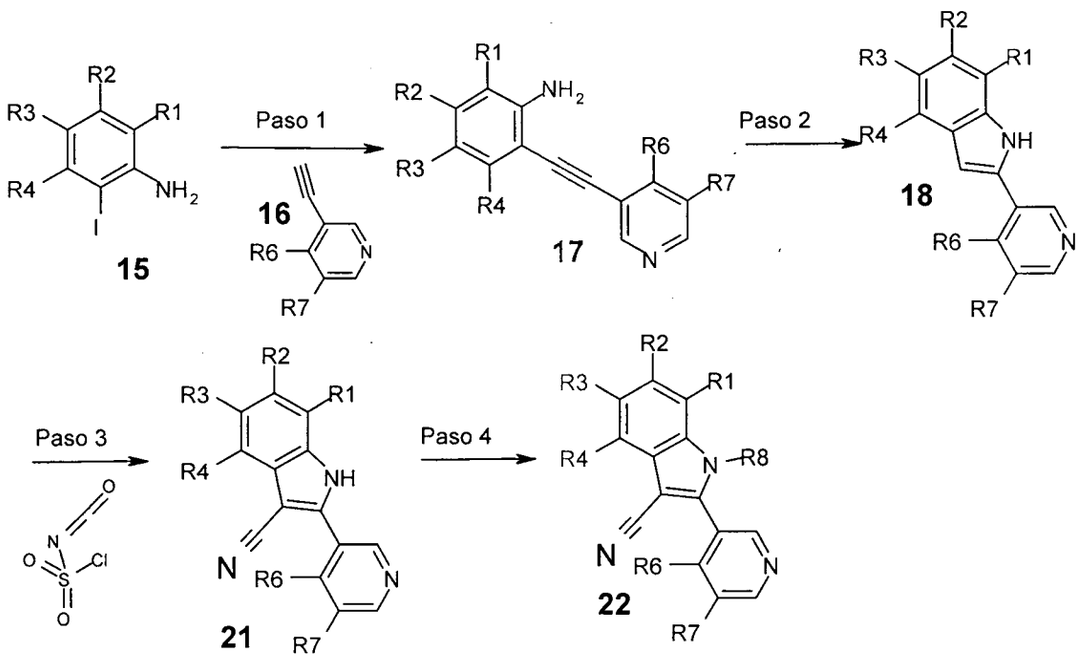
Esquema 4.



El Paso 1 involucra la reacción de un derivado de yodo-anilina 15 y el derivado de acetileno 16 en la presencia de sales de paladio, por ejemplo, $PdCl_2(PPh_3)_2$, sales de cobre, de preferencia yoduro de cobre, en un solvente de amina, de preferencia trietil-amina, para dar el alquino 17. En el Paso 2, el tratamiento de la anilina 17 con una base, por ejemplo, terbutóxido de potasio, en un solvente polar, de preferencia N-metil-pirrolidinona, da el indol 18. En el Paso 3, el indol 18 se desprotona con una base fuerte, por ejemplo, hidruro de sodio, y el anión resultante se atrapa con el reactivo electrofílico apropiado, por ejemplo, un cloruro de alquilo, o una cetona alfa,beta-

insaturada, para dar el indol 19. Opcionalmente, el indol 19 se puede hacer reaccionar con isocianato de cloro-sulfonilo, seguido por dimetil-formamida, como en el Paso 4, para dar el indol 20. Las transformaciones apropiadas del R8 en 19 conducen a análogos adicionales. Por ejemplo, si R8 contiene un éster, el éster se puede hidrolizar hasta el ácido carboxílico correspondiente.

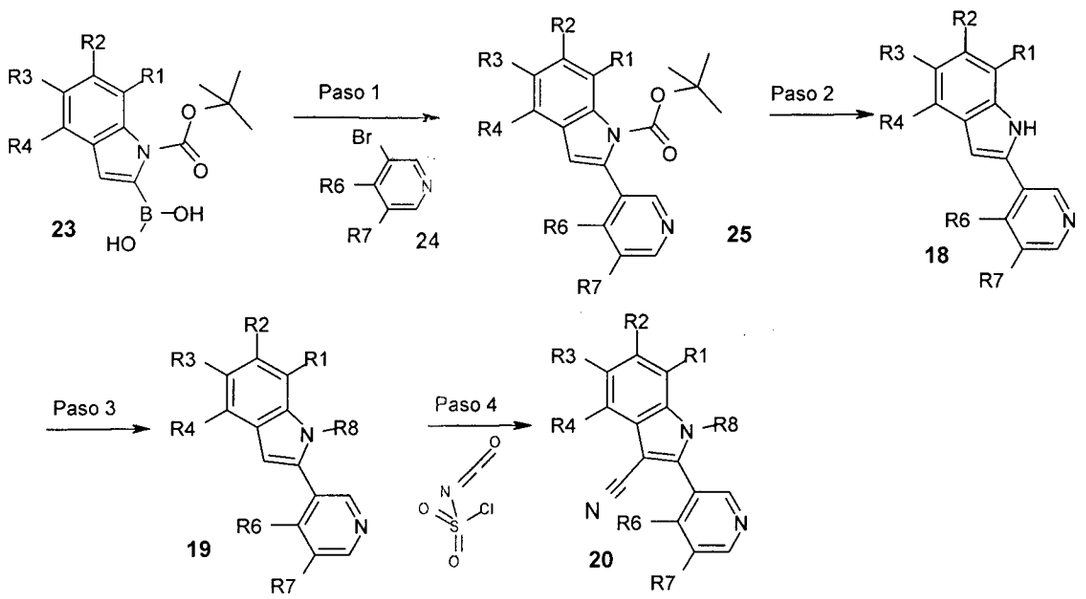
Esquema 5.



El Paso 1 involucra la reacción de un derivado de yodo-anilina 15 y el derivado de acetileno 16 en la presencia de sales de paladio, por ejemplo, $PdCl_2(PPh_3)_2$, sales de cobre, por ejemplo, yoduro de cobre, en un solvente de amina, por ejemplo, trietil-amina, para dar el alquino 17. En el Paso 2, el tratamiento de la anilina 17 con una base, por ejemplo, terbutóxido de potasio, en un solvente polar, por

ejemplo, N-metil-pirrolidinona, da el indol 18. En el Paso 3, el indol 18 se puede hacer reaccionar con isocianato de cloro-sulfonilo, seguido por dimetil-formamida, para dar el indol 21. En el Paso 4, el indol 21 se desprotona con una base fuerte, por ejemplo, hidruro de sodio, y el anión resultante se atrapa con el reactivo electrofílico apropiado, por ejemplo, yoduro de metilo, para dar el indol 22.

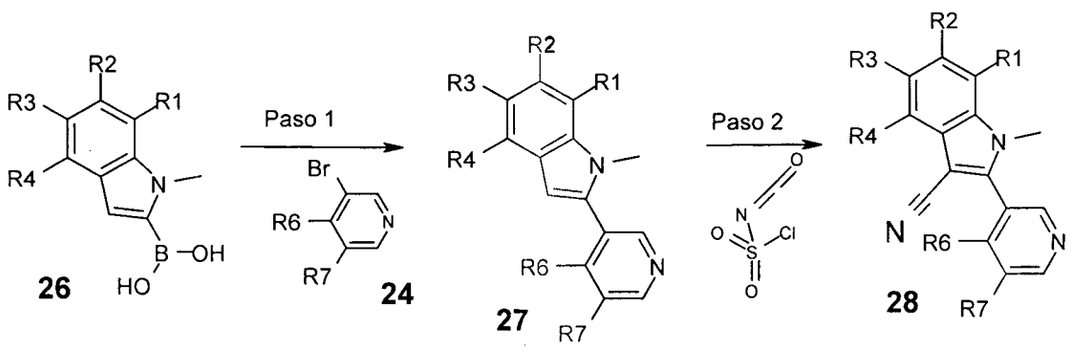
Esquema 6.



En el Paso 1, el ácido N-Boc-2-indol-borónico apropiado 23 se hace reaccionar con la 3-bromo-piridina apropiada 24 en la presencia de sales de paladio, por ejemplo, Pd_2dba_3, ligandos, por ejemplo, s-Phos, y una base, por ejemplo, fosfato de potasio, en un solvente orgánico, por ejemplo, tolueno, para dar el indol 25. En el Paso 2, el carbamato se disocia, por ejemplo, utilizando ácido trifluoro-acético o gel de sílice. En el Paso 3, el indol 18 se desprotona con una base

fuerte, por ejemplo, hidruro de sodio, y el anión resultante se atrapa con el reactivo electrofílico apropiado, por ejemplo, yoduro de metilo, para dar el indol 19. De una manera alternativa, el indol 18 se puede calentar con carbonato de dimetilo en la presencia de una base, por ejemplo, carbonato de potasio, para dar el indol 19, en donde R8 es metilo. Opcionalmente, el indol 19 se puede hacer reaccionar con isocianato de cloro-sulfonilo, seguido por dimetil-formamida, como en el Paso 4, para dar el indol 20. Las transformaciones apropiadas de R6 y R7 en 19 ó 20 conducen a análogos adicionales.

Esquema 7.

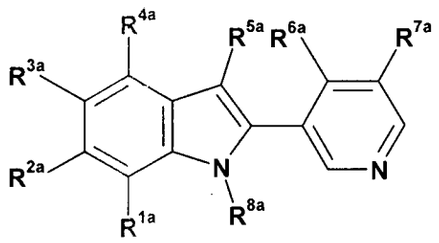


En el Paso 1, el ácido N-metil-2-indol-borónico apropiado 26 se hace reaccionar con el heterociclo apropiado 24 en la presencia de sales de paladio, por ejemplo, Pd_2dba_3, ligandos, por ejemplo, s-Phos, y una base, por ejemplo, fosfato de potasio, en un solvente orgánico, por ejemplo, tolueno, para dar el indol 27. Opcionalmente, el indol 27 se puede hacer reaccionar con isocianato de cloro-sulfonilo, seguido por dimetil-formamida, como en el Paso 2, para dar el indol 28. Las transformaciones apropiadas de R6 y R7 en 27 ó

28 conducen a análogos adicionales.

Métodos de la Invención

La invención pertenece, cuando menos en parte, a métodos para el tratamiento de un sujeto para un trastorno o enfermedad, mediante la administración a un sujeto, de una cantidad terapéuticamente efectiva de un compuesto de la fórmula I:



(I)

en donde:

R^{1a}, R^{2a}, R^{3a}, y R^{4a} son cada uno independientemente hidrógeno, halógeno, ciano, hidroxilo, alcoxilo, alquilo, alquenilo, o alcoxi-carbonilo;

R^{5a} es hidrógeno halógeno, ciano, alquilo, alquenilo, aril-alquilo, heteroaril-alquilo, amino-carbonilo, alquil-amino-carbonilo, carboxilato, alcoxi-carbonilo, heterociclil-carbonilo, arilo, o heteroarilo;

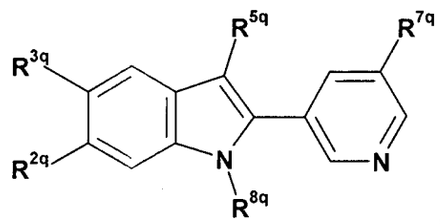
R^{6a} y R^{7a} son cada uno independientemente hidrógeno, halógeno, hidroxilo, alcoxilo, amino, alquilo, sulfonilo, -O-sulfonilo, alquil-amino, heterociclilo, amino-carbonilo, carboxilato, o alcoxi-carbonilo;

R^{8a} es hidrógeno, alquilo, aril-alquilo, heteroaril-alquilo, alcoxi-carbonilo, sulfonilo, aroílo, arilo, o heteroarilo;

y las sales farmacéuticamente aceptables, polimorfos, rotámeros, pro-fármacos, enantiómeros, hidratos, y solvatos del mismo, con la condición de que cuando menos uno de R^{1a}-R^{8a} es diferente de hidrógeno; y cuando R^{5a} es ciano o alquilo inferior opcionalmente sustituido con ciano, -C(O)-piperidina, amino, alquil-amino, dialquil-amino, carboxilato, alcoxi-carbonilo, amino-carbonilo, o heterociclilo, entonces cuando menos uno de R^{1a}-R^{4a} y R^{6a}-R^{8a} es diferente de hidrógeno; y cuando R^{7a} es imidazolilo, entonces cuando menos uno de R^{1a}-R^{6a} y R^{8a} es diferente de hidrógeno; y cuando R^{8a} es alquilo, aril-alquilo o alcoxi-carbonilo, entonces cuando menos uno de R^{1a}-R^{7a} es diferente de hidrógeno; y cuando R^{5a} es alquilo inferior, y R^{8a} es alquilo sustituido con carboxilato o $PO_3R^{21}R^{22}$ en donde R^{21} y R^{22} son cada uno independientemente hidrógeno o alquilo inferior, entonces cuando menos uno de R^{1a}-R^{4a} y R^{6a} y R^{7a} es diferente de hidrógeno; y cuando R^{3a} es halógeno y R^{5a} y R^{8a} son independientemente alquilo inferior opcionalmente sustituido con carboxilato, alcoxi-carbonilo, o -C(O)-piperidina, entonces cuando menos uno de R^{1a}, R^{2a}, R^{4a}, R^{6a} y R^{7a} es diferente de hidrógeno; y cuando R^{3a} es halógeno, o alquilo inferior, y R^{5a} es alquilo inferior sustituido con dialquil-amino, dialquil-amino-carbonilo, carboxilato, alcoxi-carbonilo o amino-carbonilo, entonces cuando menos uno de R^{1a}, R^{2a}, R^{4a}, y R^{6a}-R^{8a} es diferente de hidrógeno; y cuando R^{2a} y R^{3a} son cada uno alcoxilo y R^{5a} es ciano, entonces cuando menos uno de R^{1a}, R^{4a}, y R^{6a}-R^{8a} es diferente de hidrógeno; y cuando R^{3a} es alquilo

sustituido con aroílo, y R^5 y R^8 son cada uno independientemente hidrógeno o alquilo inferior, entonces cuando menos uno de R^{1a}, R^{2a}, y R^{4a} es diferente de hidrógeno, de tal manera que se trata el trastorno o la enfermedad en el sujeto.

En una modalidad, la invención pertenece, cuando menos en parte, a métodos para el tratamiento de un sujeto para un trastorno o enfermedad, mediante la administración a un sujeto, de una cantidad terapéuticamente efectiva de un compuesto de la fórmula II:



(II)

en donde:

R^{2q} es hidrógeno o halógeno;

R^{3q} es hidrógeno, halógeno, o ciano;

R^{5q} es hidrógeno, alquilo, o ciano;

R^{7q} es hidrógeno, halógeno, alcoxilo, -OSO_2-heterociclilo, -O-aril-alquilo, -NR'-SO_2-alquilo, -NR'-C(O)-alquilo, -NR'-C(O)-NR'-alquilo, -NR'-C(O)-O-alquilo, halo-alquilo, o alquilo opcionalmente sustituido con heterociclilo, –NR'-SO_2-alquilo, -NR'-SO_2-halo-alquilo, NR'-C(O)-alquilo, NR'-C(O)-heterociclilo, -NR'-C(O)-NR'-alquilo, o -NR'-C(O)-O-alquilo;

R^{8q} es hidrógeno, alquilo, hidroxi-alquilo, -alquil-OC(O)-alquilo, carboxilato, alcoxi-carbonilo, o aril-alquilo sustituido con alquilo, o

aroílo sustituido con ciano y/o alquilo, o -alquil-O-arilo sustituido con alcoxi-carbonilo;

cada R' es independientemente hidrógeno, alquilo de 1 a 4 átomos de carbono, o cicloalquilo de 3 a 6 átomos de carbono;

y sales farmacéuticamente aceptables, polimorfos, rotámeros, pro-fármacos, enantiómeros, hidratos, y solvatos del mismo, con la condición de que cuando menos uno de R^{2q}, R^{3q}, R^{5q}, R^{7q} y R^{8q} es diferente de hidrógeno, de tal manera que se trata el trastorno o la enfermedad en el sujeto.

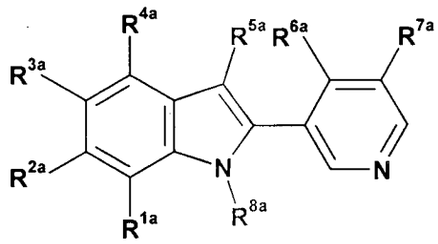
En otra modalidad, la invención pertenece, cuando menos en parte, a métodos para el tratamiento de un sujeto para un trastorno o enfermedad, mediante la administración a un sujeto, de una cantidad terapéuticamente efectiva de un compuesto de las fórmulas III o IV, y las sales farmacéuticamente aceptables, polimorfos, rotámeros, pro-fármacos, enantiómeros, hidratos, y solvatos del mismo, de tal manera que se trata el trastorno o la enfermedad en el sujeto.

El término "trastorno" o "enfermedad" incluye cualquier condición patológica, desarreglo, o anormalidad de la función de una parte, órgano, o sistema de un organismo, resultante de distintas causas, tales como infección, defecto genético, o tensión medio-ambiental, y caracterizado por un grupo identificable de signos o síntomas; y cualquier estado físico o mental patológico. Véase *Dorland's Illustrated Medical Dictionary,* (W.B. Saunders Co. 27ª Edición, 1988).

En otra modalidad, el trastorno o enfermedad es una

enfermedad seleccionada a partir de, hipocalemia, hipertensión, enfermedad de Conn, insuficiencia renal, en particular, insuficiencia renal crónica, restenosis, ateroesclerosis, síndrome X, obesidad, nefropatía, enfermedad posterior a infarto de miocardio, enfermedades cardíacas coronarias, mayor formación de colágeno, fibrosis y remodelación en seguida de hipertensión y disfunción endotelial, enfermedades cardiovasculares, disfunción renal, enfermedades hepáticas, enfermedades cerebrovasculares, enfermedades vasculares, retinopatía, neuropatía, insulinopatía, edema, disfunción endotelial, disfunción de barorreceptor, migraña, dolores de cabeza, insuficiencia cardíaca, tal como insuficiencia cardíaca congestiva, arritmia, disfunción diastólica, disfunción diastólica de ventrículo izquierdo, insuficiencia cardíaca diastólica, llenado diastólico deteriorado, disfunción sistólica, isquemia, cardiomiopatía hipertrófica, muerte cardíaca repentina, fibrosis de miocardio y vascular, funcionamiento arterial deteriorado, lesiones necróticas de miocardio, daño vascular, infarto de miocardio, hipertrofia de ventrículo izquierdo, fracción de expulsión reducida, lesiones cardíacas, hipertrofia de las paredes vasculares, engrosamiento endotelial, o necrosis fibrinoide de las arterias coronarias.

La invención también pertenece, cuando menos en parte, a métodos para inhibir la actividad de la sintasa de aldosterona en un sujeto, mediante la administración a un sujeto, de una cantidad terapéuticamente efectiva de un compuesto de la fórmula I:



(I)

en donde:

R^{1a}, R^{2a}, R^{3a}, y R^{4a} son cada uno independientemente hidrógeno, halógeno, ciano, hidroxilo, alcoxilo, alquilo, alquenilo, o alcoxi-carbonilo;

R^{5a} es hidrógeno halógeno, ciano, alquilo, alquenilo, aril-alquilo, heteroaril-alquilo, amino-carbonilo, alquil-amino-carbonilo, carboxilato, alcoxi-carbonilo, heterociclil-carbonilo, arilo, o heteroarilo;

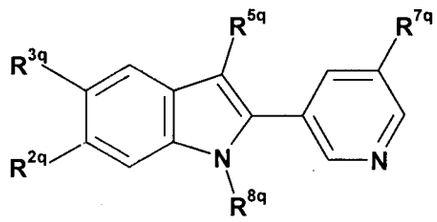
R^{6a} y R^{7a} son cada uno independientemente hidrógeno, halógeno, hidroxilo, alcoxilo, amino, alquilo, sulfonilo, -O-sulfonilo, alquil-amino, heterociclilo, amino-carbonilo, carboxilato, o alcoxi-carbonilo;

R^{8a} es hidrógeno, alquilo, aril-alquilo, heteroaril-alquilo, alcoxi-carbonilo, sulfonilo, aroílo, arilo, o heteroarilo;

y las sales farmacéuticamente aceptables, polimorfos, rotámeros, pro-fármacos, enantiómeros, hidratos, y solvatos del mismo, de tal manera que se inhibe la actividad de la sintasa de aldosterona.

La invención también pertenece, cuando menos en parte, a métodos para inhibir la actividad de la sintasa de aldosterona en un

sujeto, mediante la administración a un sujeto, de una cantidad terapéuticamente efectiva de un compuesto de la fórmula II:



(II)

en donde:

R^{2q} es hidrógeno o halógeno;

R^{3q} es hidrógeno, halógeno, o ciano;

R^{5q} es hidrógeno, alquilo, o ciano;

R^{7q} es hidrógeno, halógeno, alcoxilo, -OSO_2-heterociclilo, -O-aril-alquilo, -NR'-SO_2-alquilo, -NR'-C(O)-alquilo, -NR'-C(O)-NR'-alquilo, -NR'-C(O)-O-alquilo, halo-alquilo, o alquilo opcionalmente sustituido con heterociclilo, –NR'-SO_2-alquilo, -NR'-SO_2-halo-alquilo, NR'-C(O)-alquilo, NR'-C(O)-heterociclilo, -NR'-C(O)-NR'-alquilo, o -NR'-C(O)-O-alquilo;

R^{8q} es hidrógeno, alquilo, hidroxi-alquilo, -alquil-OC(O)-alquilo, carboxilato, alcoxi-carbonilo, o aril-alquilo sustituido con alquilo, o aroílo sustituido con ciano y/o alquilo, o -alquil-O-arilo sustituido con alcoxi-carbonilo;

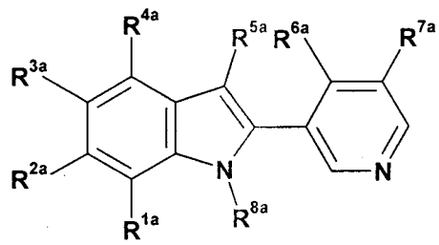
cada R' es independientemente hidrógeno, alquilo de 1 a 4 átomos de carbono, o cicloalquilo de 3 a 6 átomos de carbono;

y las sales farmacéuticamente aceptables, polimorfos, rotámeros, pro-fármacos, enantiómeros, hidratos, y solvatos del mismo, de tal manera que se inhibe la actividad de la sintasa de

aldosterona.

En una modalidad, la invención pertenece, cuando menos en parte, a métodos para inhibir la actividad de la sintasa de aldosterona en un sujeto, mediante la administración a un sujeto, de una cantidad terapéuticamente efectiva de un compuesto de las fórmulas III o IV, de tal manera que se inhibe la actividad de la sintasa de aldosterona.

Otra modalidad de la presente invención incluye métodos para el tratamiento de un estado asociado con la sintasa de aldosterona, mediante la administración a un sujeto, de una cantidad terapéuticamente efectiva de un compuesto de la fórmula I:



(I)

en donde:

R^{1a}, R^{2a}, R^{3a}, y R^{4a} son cada uno independientemente hidrógeno, halógeno, ciano, hidroxilo, alcoxilo, alquilo, alquenilo, o alcoxi-carbonilo;

R^{5a} es hidrógeno halógeno, ciano, alquilo, alquenilo, aril-alquilo, heteroaril-alquilo, amino-carbonilo, alquil-amino-carbonilo, carboxilato, alcoxi-carbonilo, heterociclil-carbonilo, arilo, o heteroarilo;

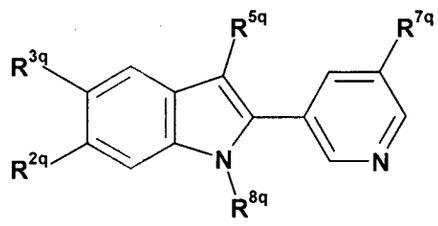
R^{6a} y R^{7a} son cada uno independientemente hidrógeno,

halógeno, hidroxilo, alcoxilo, amino, alquilo, sulfonilo, -O-sulfonilo, alquil-amino, heterociclilo, amino-carbonilo, carboxilato, o alcoxi-carbonilo;

R^{8a} es hidrógeno, alquilo, aril-alquilo, heteroaril-alquilo, alcoxi-carbonilo, sulfonilo, aroílo, arilo, o heteroarilo;

y las sales farmacéuticamente aceptables, polimorfos, rotámeros, pro-fármacos, enantiómeros, hidratos, y solvatos del mismo, de tal manera que se trata dicho estado asociado con la sintasa de aldosterona en el sujeto.

Todavía otra modalidad de la presente invención incluye métodos para el tratamiento de un estado asociado con la sintasa de aldosterona, mediante la administración a un sujeto, de una cantidad terapéuticamente efectiva de un compuesto de la fórmula II:



(II)

en donde:

R^{2q} es hidrógeno o halógeno;

R^{3q} es hidrógeno, halógeno, o ciano;

R^{5q} es hidrógeno, alquilo, o ciano;

R^{7q} es hidrógeno, halógeno, alcoxilo, $-OSO_2$-heterociclilo, -O-aril-alquilo, $-NR'-SO_2$-alquilo, -NR'-C(O)-alquilo, -NR'-C(O)-NR'-alquilo, -NR'-C(O)-O-alquilo, halo-alquilo, o alquilo opcionalmente

sustituido con heterociclilo, –NR'-SO_2-alquilo, -NR'-SO_2-halo-alquilo, NR'-C(O)-alquilo, NR'-C(O)-heterociclilo, -NR'-C(O)-NR'-alquilo, o -NR'-C(O)-O-alquilo;

R^{8q} es hidrógeno, alquilo, hidroxi-alquilo, -alquil-OC(O)-alquilo, carboxilato, alcoxi-carbonilo, o aril-alquilo sustituido con alquilo, o aroílo sustituido con ciano y/o alquilo, o -alquil-O-arilo sustituido con alcoxi-carbonilo;

cada R' es independientemente hidrógeno, alquilo de 1 a 4 átomos de carbono, o cicloalquilo de 3 a 6 átomos de carbono;

y las sales farmacéuticamente aceptables, polimorfos, rotámeros, pro-fármacos, enantiómeros, hidratos, y solvatos del mismo, de tal manera que se trata dicho estado asociado con la sintasa de aldosterona en el sujeto.

Todavía otra modalidad de la presente invención incluye métodos para el tratamiento de un estado asociado con la sintasa de aldosterona, mediante la administración a un sujeto, de una cantidad terapéuticamente efectiva de un compuesto de la fórmula III o IV, de tal manera que se trata dicho estado asociado con la sintasa de aldosterona en el sujeto.

El término "estado asociado con la sintasa de aldosterona" se refiere a un estado, enfermedad, o trastorno que se puede tratar mediante la modulación (por ejemplo, la inhibición) de la sintasa de aldosterona. La sintasa de aldosterona es una enzima mitocondrial del citocromo 450 que cataliza el último paso de la producción de aldosterona en la corteza suprarrenal, es decir, la conversión de la

11-desoxi-corticosterona hasta aldosterona. Se ha demostrado que la sintasa de aldosterona se expresa en todos los tejidos cardiovasculares, tales como el corazón, cordón umbilical, arterias mesentéricas y pulmonares, aorta, endotelio, y células vasculares. Más aún, la expresión de la sintasa de aldosterona está estrechamente correlacionada con la producción de aldosterona en las células. Se ha observado que las elevaciones de la actividad de aldosterona inducen diferentes enfermedades, tales como insuficiencia cardíaca congestiva, fibrosis de miocardio, arritmia ventricular, y otros efectos adversos, etc.

Los ejemplos de la sintasa de los estados asociados con aldosterona incluyen hipocalemia, hipertensión, enfermedad de Conn, insuficiencia renal, en particular, insuficiencia renal crónica, restenosis, ateroesclerosis, síndrome X, obesidad, nefropatía, enfermedad posterior a infarto de miocardio, enfermedades cardíacas coronarias, mayor formación de colágeno, fibrosis y remodelación en seguida de hipertensión y disfunción endotelial, enfermedades cardiovasculares, disfunción renal, enfermedades hepáticas, enfermedades cerebrovasculares, enfermedades vasculares, retinopatía, neuropatía, insulinopatía, edema, disfunción endotelial, disfunción de barorreceptor, migraña, dolores de cabeza, insuficiencia cardíaca, tal como insuficiencia cardíaca congestiva, arritmia, disfunción diastólica, disfunción diastólica de ventrículo izquierdo, insuficiencia cardíaca diastólica, llenado diastólico deteriorado, disfunción sistólica, isquemia, cardiomiopatía

hipertrófica, muerte cardíaca repentina, fibrosis de miocardio y vascular, funcionamiento arterial deteriorado, lesiones necróticas de miocardio, daño vascular, infarto de miocardio, hipertrofia de ventrículo izquierdo, fracción de expulsión reducida, lesiones cardíacas, hipertrofia de las paredes vasculares, engrosamiento endotelial, y necrosis fibrinoide de las arterias coronarias.

En una modalidad, el estado asociado con la sintasa de aldosterona se caracteriza por una actividad anormal de la sintasa de aldosterona y/o por una expresión anormal de la sintasa de aldosterona.

El término "anormal" incluye una actividad o característica que difiere de una actividad o característica normal.

El término "actividad anormal" incluye una actividad que difiere de la actividad del gen o de la proteína de tipo silvestre o nativos, o que difiere de la actividad del gen o de la proteína en un sujeto sano. La actividad anormal puede ser más fuerte o más débil que la actividad normal.

En una modalidad, la "actividad anormal" incluye la producción anormal (ya sea la sobre o sub)-producción del ARNm transcrito a partir de un gen. En otra modalidad, la "actividad anormal" incluye la producción anormal (ya sea la sobre o sub)-producción del polipéptido a partir de un gen. En otra modalidad, la actividad anormal se refiere a un nivel de un ARNm o polipéptido que es diferente de un nivel normal de este ARNm o polipéptido por aproximadamente el 15 por ciento, aproximadamente el 25 por

ciento, aproximadamente el 35 por ciento, aproximadamente el 50 por ciento, aproximadamente el 65 por ciento, aproximadamente el 85 por ciento, aproximadamente el 100 por ciento o más. De preferencia, el nivel anormal de ARNm o polipéptido puede ser ya sea más alto o más bajo que el nivel normal de este ARNm o polipéptido. Todavía en otra modalidad, la actividad anormal se refiere a la actividad funcional de una proteína que es diferente de una actividad normal de la proteína de tipo silvestre. De preferencia, la actividad anormal puede ser más fuerte o más débil que la actividad normal. De preferencia, la actividad anormal se debe a las mutaciones en el gen correspondiente, y las mutaciones pueden estar en la región codificante del gen, o en las regiones no codificantes, tales como las regiones promotoras de transcripción. Las mutaciones pueden ser sustituciones, supresiones, o inserciones.

Los compuestos de la presente invención, como compuestos inhibidores de la sintasa de aldosterona, son útiles para el tratamiento de un trastorno o enfermedad mediada por la sintasa de aldosterona o que responda a la inhibición de la sintasa de aldosterona. En particular, los compuestos de la presente invención son útiles para el tratamiento de un estado asociado con la sintasa de aldosterona, incluyendo hipocalemia, hipertensión, enfermedad de Conn, insuficiencia renal, en particular, insuficiencia renal crónica, restenosis, ateroesclerosis, síndrome X, obesidad, nefropatía, enfermedad posterior a infarto de miocardio, enfermedades

cardíacas coronarias, mayor formación de colágeno, fibrosis y remodelación en seguida de hipertensión y disfunción endotelial, enfermedades cardiovasculares, disfunción renal, enfermedades hepáticas, enfermedades cerebrovasculares, enfermedades vasculares, retinopatía, neuropatía, insulinopatía, edema, disfunción endotelial, disfunción de barorreceptor, migraña, dolores de cabeza, insuficiencia cardíaca, tal como insuficiencia cardíaca congestiva, arritmia, disfunción diastólica, disfunción diastólica de ventrículo izquierdo, insuficiencia cardíaca diastólica, llenado diastólico deteriorado, disfunción sistólica, isquemia, cardiomiopatía hipertrófica, muerte cardíaca repentina, fibrosis de miocardio y vascular, funcionamiento arterial deteriorado, lesiones necróticas de miocardio, daño vascular, infarto de miocardio, hipertrofia de ventrículo izquierdo, fracción de expulsión reducida, lesiones cardíacas, hipertrofia de las paredes vasculares, engrosamiento endotelial, y necrosis fibrinoide de las arterias coronarias.

El término "compuesto inhibidor de la sintasa de aldosterona" incluye los compuestos que reducen la actividad de la sintasa de aldosterona, por ejemplo, la capacidad de la sintasa de aldosterona para sintetizar la aldosterona, *in vivo* o *in vitro*. En una modalidad, los compuestos inhibidores de las sintasas de aldosterona son los compuestos inhibidores de la síntesis de aldosterona.

El término "inhibición" o "inhibir" incluye la reducción o supresión de una condición, síntoma, o trastorno o enfermedad dados, o una disminución significativa en la actividad de la línea

base de una actividad o proceso biológico. En una modalidad, la condición o síntoma o trastorno o enfermedad es mediada por la actividad de la sintasa de aldosterona. En otra modalidad, la condición o el síntoma o el trastorno o enfermedad está asociada con la actividad anormal de la sintasa de aldosterona, o la condición o el síntoma o el trastorno o la enfermedad está asociada con la expresión anormal de la sintasa de aldosterona.

El término "sujeto" incluye animales (por ejemplo, mamíferos). Un sujeto también se refiere, por ejemplo, a primates (por ejemplo, seres humanos, incluyendo hombres y mujeres), vacas, ovejas, cabras, caballos, perros, gatos, conejos, ratas, ratones, peces, aves, etc.

El término "una cantidad terapéuticamente efectiva" de un compuesto de la presente invención se refiere a una cantidad del compuesto de la presente invención que provocará la respuesta biológica o médica de un sujeto, por ejemplo, la reducción o inhibición de la actividad de una enzima o de una proteína, o que aminorará los síntomas, aliviará las condiciones, hará más lento o retardará el progreso de la enfermedad, o prevendrá una enfermedad, etc. En una modalidad no limitante, el término "una cantidad terapéuticamente efectiva" se refiere a la cantidad del compuesto de la presente invención que, cuando se administra a un sujeto, es efectiva para: (1) cuando menos aliviar parcialmente, inhibir, prevenir y/o aminorar una condición o un trastorno o una enfermedad (i) mediada por la sintasa de aldosterona, o (ii) asociada

con la actividad de la sintasa de aldosterona, o (iii) caracterizada por una actividad anormal de la sintasa de aldosterona; o (2) reducir o inhibir la actividad de la sintasa de aldosterona; o (3) reducir o inhibir la expresión de la sintasa de aldosterona. En otra modalidad no limitante, el término "una cantidad terapéuticamente efectiva" se refiere a la cantidad del compuesto de la presente invención que, cuando se administra a una célula, o a un tejido, o a un material biológico no celular, o a un medio, es efectiva para cuando menos reducir o inhibir parcialmente la actividad de la sintasa de aldosterona; o para cuando menos reducir o inhibir parcialmente la expresión de la sintasa de aldosterona.

La cantidad efectiva puede variar dependiendo de factores tales como el tamaño y el peso del sujeto, el tipo de enfermedad, o el compuesto orgánico particular. Por ejemplo, la elección del compuesto orgánico puede afectar lo que constituya una "cantidad efectiva". Un experto ordinario en la materia será capaz de estudiar los factores anteriormente mencionados, y de tomar la determinación con respecto a la cantidad efectiva del compuesto orgánico sin una indebida experimentación.

El término "tratar" o "tratamiento" de cualquier enfermedad o trastorno, incluye curar, así como aminorar cuando menos un síntoma del estado, enfermedad, o trastorno (por ejemplo, el estado asociado con la sintasa de aldosterona). El término también incluye aliviar o aminorar cuando menos un parámetro físico, incluyendo aquéllos que puedan no ser discernibles por el paciente; o modular

la enfermedad o el trastorno, ya sea físicamente (por ejemplo, la estabilización de un síntoma discernible), fisiológicamente (por ejemplo, la estabilización de un parámetro físico), o ambos. Los términos también pueden incluir la prevención o demora del establecimiento o desarrollo o progreso de la enfermedad o del trastorno.

Una modalidad adicional incluye métodos para el tratamiento de un trastorno o enfermedad asociada con la sintasa de aldosterona en un sujeto, mediante la administración a un sujeto, de una cantidad efectiva de un compuesto de la invención (por ejemplo, un compuesto de las fórmulas I a IV, o un compuesto descrito de otra manera en la presente) en combinación con un segundo agente, de tal manera que se trate al sujeto para este trastorno asociado con la sintasa de aldosterona.

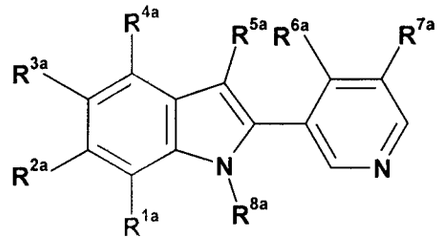
El trastorno o enfermedad se puede caracterizar por una actividad anormal de la sintasa de aldosterona o una expresión anormal de la sintasa de aldosterona.

En una modalidad, el trastorno o enfermedad incluye, pero no se limita a, hipocalemia, hipertensión, enfermedad de Conn, insuficiencia renal, en particular, insuficiencia renal crónica, restenosis, ateroesclerosis, síndrome X, obesidad, nefropatía, enfermedad posterior a infarto de miocardio, enfermedades cardíacas coronarias, mayor formación de colágeno, fibrosis y remodelación en seguida de hipertensión y disfunción endotelial, enfermedades cardiovasculares, disfunción renal, enfermedades

hepáticas, enfermedades cerebrovasculares, enfermedades vasculares, retinopatía, neuropatía, insulinopatía, edema, disfunción endotelial, disfunción de barorreceptor, migraña, dolores de cabeza, insuficiencia cardíaca, tal como insuficiencia cardíaca congestiva, arritmia, disfunción diastólica, disfunción diastólica de ventrículo izquierdo, insuficiencia cardíaca diastólica, llenado diastólico deteriorado, disfunción sistólica, isquemia, cardiomiopatía hipertrófica, muerte cardíaca repentina, fibrosis de miocardio y vascular, funcionamiento arterial deteriorado, lesiones necróticas de miocardio, daño vascular, infarto de miocardio, hipertrofia de ventrículo izquierdo, fracción de expulsión reducida, lesiones cardíacas, hipertrofia de las paredes vasculares, engrosamiento endotelial, y necrosis fibrinoide de las arterias coronarias.

En una modalidad, la invención pertenece, cuando menos en parte, a métodos para el tratamiento de un sujeto para insuficiencia cardíaca, insuficiencia cardíaca congestiva, arritmia, disfunción diastólica, disfunción diastólica de ventrículo izquierdo, insuficiencia cardíaca diastólica, llenado diastólico deteriorado, disfunción sistólica, isquemia, cardiomiopatía hipertrófica, muerte cardíaca repentina, fibrosis de miocardio y vascular, funcionamiento arterial deteriorado, lesiones necróticas de miocardio, daño vascular, infarto de miocardio, hipertrofia de ventrículo izquierdo, fracción de expulsión reducida, lesiones cardíacas, hipertrofia de las paredes vasculares, engrosamiento endotelial, necrosis fibrinoide de las arterias coronarias, disfunción renal, enfermedades hepáticas,

enfermedades cerebrovasculares, enfermedades vasculares, retinopatía, neuropatía, insulinopatía, edema, disfunción endotelial, disfunción de barorreceptor, migraña, dolores de cabeza, o hipertensión, los cuales comprenden administrar a este sujeto, una cantidad efectiva de un compuesto de la fórmula I:



(I)

en donde:

R^{1a}, R^{2a}, R^{3a}, y R^{4a} son cada uno independientemente hidrógeno, halógeno, ciano, hidroxilo, alcoxilo, alquilo, alquenilo, o alcoxi-carbonilo;

R^{5a} es hidrógeno halógeno, ciano, alquilo, alquenilo, aril-alquilo, heteroaril-alquilo, amino-carbonilo, alquil-amino-carbonilo, carboxilato, alcoxi-carbonilo, heterociclil-carbonilo, arilo, o heteroarilo;

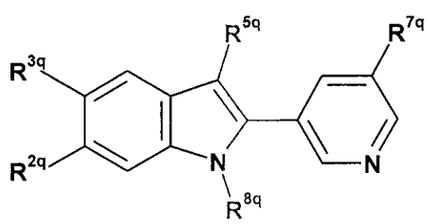
R^{6a} y R^{7a} son cada uno independientemente hidrógeno, halógeno, hidroxilo, alcoxilo, amino, alquilo, sulfonilo, -O-sulfonilo, alquil-amino, heterociclilo, amino-carbonilo, carboxilato, o alcoxi-carbonilo;

R^{8a} es hidrógeno, alquilo, aril-alquilo, heteroaril-alquilo, alcoxi-carbonilo, sulfonilo, aroílo, arilo, o heteroarilo;

y las sales farmacéuticamente aceptables, polimorfos,

rotámeros, pro-fármacos, enantiómeros, hidratos, y solvatos del mismo, de tal manera que se trata al sujeto.

En otra modalidad, la invención pertenece, cuando menos en parte, a métodos para el tratamiento de un sujeto para insuficiencia cardíaca, insuficiencia cardíaca congestiva, arritmia, disfunción diastólica, disfunción diastólica de ventrículo izquierdo, insuficiencia cardíaca diastólica, llenado diastólico deteriorado, disfunción sistólica, isquemia, cardiomiopatía hipertrófica, muerte cardíaca repentina, fibrosis de miocardio y vascular, funcionamiento arterial deteriorado, lesiones necróticas de miocardio, daño vascular, infarto de miocardio, hipertrofia de ventrículo izquierdo, fracción de expulsión reducida, lesiones cardíacas, hipertrofia de las paredes vasculares, engrosamiento endotelial, necrosis fibrinoide de las arterias coronarias, disfunción renal, enfermedades hepáticas, enfermedades cerebrovasculares, enfermedades vasculares, retinopatía, neuropatía, insulinopatía, edema, disfunción endotelial, disfunción de barorreceptor, migraña, dolores de cabeza, o hipertensión, el cual comprende administrar a este sujeto, una cantidad efectiva de un compuesto de la fórmula II:



(II)

en donde:

R^{2q} es hidrógeno o halógeno;

R^{3q} es hidrógeno, halógeno, o ciano;

R^{5q} es hidrógeno, alquilo, o ciano;

R^{7q} es hidrógeno, halógeno, alcoxilo, -OSO_2-heterociclilo, -O-aril-alquilo, -NR'-SO_2-alquilo, -NR'-C(O)-alquilo, -NR'-C(O)-NR'-alquilo, -NR'-C(O)-O-alquilo, halo-alquilo, o alquilo opcionalmente sustituido con heterociclilo, –NR'-SO_2-alquilo, -NR'-SO_2-halo-alquilo, NR'-C(O)-alquilo, NR'-C(O)-heterociclilo, -NR'-C(O)-NR'-alquilo, o -NR'-C(O)-O-alquilo;

R^{8q} es hidrógeno, alquilo, hidroxi-alquilo, -alquil-OC(O)-alquilo, carboxilato, alcoxi-carbonilo, o aril-alquilo sustituido con alquilo, o aroílo sustituido con ciano y/o alquilo, o -alquil-O-arilo sustituido con alcoxi-carbonilo;

cada R' es independientemente hidrógeno, alquilo de 1 a 4 átomos de carbono, o cicloalquilo de 3 a 6 átomos de carbono;

y las sales farmacéuticamente aceptables, polimorfos, rotámeros, pro-fármacos, enantiómeros, hidratos, y solvatos del mismo, de tal manera que se trata al sujeto.

En todavía otra modalidad, la invención pertenece, cuando menos en parte, a métodos para el tratamiento de un sujeto para insuficiencia cardíaca, insuficiencia cardíaca congestiva, arritmia, disfunción diastólica, disfunción diastólica de ventrículo izquierdo, insuficiencia cardíaca diastólica, llenado diastólico deteriorado, disfunción sistólica, isquemia, cardiomiopatía hipertrófica, muerte cardíaca repentina, fibrosis de miocardio y vascular, funcionamiento arterial deteriorado, lesiones necróticas de miocardio, daño vascular,

infarto de miocardio, hipertrofia de ventrículo izquierdo, fracción de expulsión reducida, lesiones cardíacas, hipertrofia de las paredes vasculares, engrosamiento endotelial, necrosis fibrinoide de las arterias coronarias, disfunción renal, enfermedades hepáticas, enfermedades cerebrovasculares, enfermedades vasculares, retinopatía, neuropatía, insulinopatía, edema, disfunción endotelial, disfunción de barorreceptor, migraña, dolores de cabeza, o hipertensión, el cual comprende administrar a este sujeto, una cantidad efectiva de un compuesto de la fórmula III o IV, y las sales farmacéuticamente aceptables, polimorfos, rotámeros, pro-fármacos, enantiómeros, hidratos, y solvatos del mismo, de tal manera que se trata al sujeto.

En todavía otra modalidad, la invención pertenece, cuando menos en parte, a métodos en donde el compuesto de la invención (por ejemplo, un compuesto de las fórmulas I a IV o un compuesto descrito de otra manera en la presente) se administra en combinación con un segundo agente.

El término "en combinación con" un segundo agente o tratamiento incluye la co-administración del compuesto de la invención (por ejemplo, un compuesto de las fórmulas I a IV o un compuesto descrito de otra manera en la presente) con el segundo agente o tratamiento, la administración del compuesto de la invención primero, seguido por el segundo agente o tratamiento, y la administración del segundo agente o tratamiento primero, seguido por el compuesto de la invención.

El término "segundo agente" incluye cualquier agente que se conozca en la materia para tratar, prevenir, o reducir los síntomas de una enfermedad o trastorno descrito en la presente, por ejemplo, un trastorno asociado con la sintasa de aldosterona, tal como, por ejemplo, hipocalemia, hipertensión, enfermedad de Conn, insuficiencia renal, en particular, insuficiencia renal crónica, restenosis, ateroesclerosis, síndrome X, obesidad, nefropatía, enfermedad posterior a infarto de miocardio, enfermedades cardíacas coronarias, mayor formación de colágeno, fibrosis y remodelación en seguida de hipertensión y disfunción endotelial, enfermedades cardiovasculares, disfunción renal, enfermedades hepáticas, enfermedades cerebrovasculares, enfermedades vasculares, retinopatía, neuropatía, insulinopatía, edema, disfunción endotelial, disfunción de barorreceptor, migraña, dolores de cabeza, insuficiencia cardíaca, tal como insuficiencia cardíaca congestiva, arritmia, disfunción diastólica, disfunción diastólica de ventrículo izquierdo, insuficiencia cardíaca diastólica, llenado diastólico deteriorado, disfunción sistólica, isquemia, cardiomiopatía hipertrófica, muerte cardíaca repentina, fibrosis de miocardio y vascular, funcionamiento arterial deteriorado, lesiones necróticas de miocardio, daño vascular, infarto de miocardio, hipertrofia de ventrículo izquierdo, fracción de expulsión reducida, lesiones cardíacas, hipertrofia de las paredes vasculares, engrosamiento endotelial, y necrosis fibrinoide de las arterias coronarias. Adicionalmente, el segundo agente puede ser cualquier agente que

beneficie al paciente cuando se administre en combinación con la administración de un compuesto de la invención.

Los ejemplos de los segundos agentes incluyen inhibidores de HMG-Co-A-reductasa, antagonistas de los receptores de angiotensina II, inhibidores de la enzima convertidora de angiotensina (ACE), bloqueadores del canal de calcio (CCB), inhibidores dobles de la enzima convertidora de angiotensina / endopeptidasa neutra (ACE / NEP), antagonistas de endotelina, inhibidores de renina, diuréticos, miméticos de ApoA-I, agentes anti-diabéticos, agentes reductores de la obesidad, bloqueadores de los receptores de aldosterona, bloqueadores de los receptores de endotelina, e inhibidores de CETP.

El término "inhibidor de HMG-Co-A-reductasa" (también denominados como inhibidores de beta-hidroxi-beta-metil-glutaril-co-enzima-A-reductasa) incluye a los agentes activos que se pueden utilizar para reducir los niveles de lípidos, incluyendo el colesterol en sangre. Los ejemplos incluyen atorvastatina, cerivastatina, compactina, dalvastatina, dihidrocompactina, fluindostatina, fluvastatina, lovastatina, pitavastatina, mevastatina, pravastatina, rivastatina, simvastatina, y velostatina, o sales farmacéuticamente aceptables de las mismas.

El término "inhibidor de ACE" (también denominados como inhibidores de las enzimas convertidoras de angiotensina) incluye moléculas que interrumpen la degradación enzimática de la angiotensina I hasta la angiotensina II. Estos compuestos se pueden

utilizar para la regulación de la presión sanguínea y para el tratamiento de insuficiencia cardíaca congestiva. Los ejemplos incluyen alacepril, benazepril, benazeprilato, captopril, ceronapril, cilazapril, delapril, enalapril, enaprilato, fosinopril, imidapril, lisinopril, moveltopril, perindopril, quinapril, ramipril, espirapril, temocapril, y trandolapril, o las sales farmacéuticamente aceptables de los mismos.

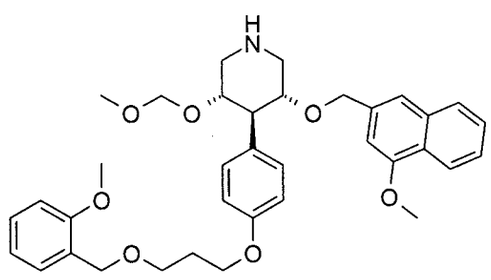
El término "un bloqueador del canal de calcio (CCB)" incluye dihidro-piridinas (DHPs), y no dihidro-piridinas (por ejemplo, bloqueadores del canal de calcio del tipo diltiazem y del tipo verapamil). Los ejemplos incluyen amlodipina, felodipina, riosidina, isradipina, lacidipina, nicardipina, nifedipina, niguldipina, niludipina, nimodipina, nisoldipina, nitrendipina, y nivaldipina, y es de preferencia una no dihidro-piridina representativa seleccionada a partir del grupo que consiste en flunarizina, prenilamina, diltiazem, fendilina, galopamil, mibefradil, anipamil, tiapamil, y verapamil, o las sales farmacéuticamente aceptables de los mismos. Los bloqueadores del canal de calcio se pueden utilizar como fármacos contra la hipertensión, contra la angina de pecho, o anti-arrítmicos.

El término "inhibidor doble de la enzima convertidora de angiotensina / endopeptidasa neutra (ACE /NEP)" incluye omapatrilato (véase la Patente Europea Número EP 629627), fasidotril o fasidotrilato, o las sales farmacéuticamente aceptables de los mismos.

El término "antagonista de endotelina" incluye bosentan (véase

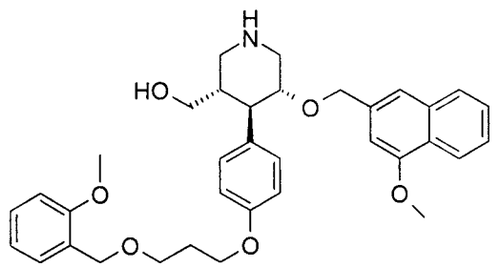
la Patente Europea Número EP 526708 A), tezosentan (véase la Publicación Internacional Número WO 96/19459), o las sales farmacéuticamente aceptables de los mismos.

El término "inhibidor de renina" incluye ditequireno (nombre químico: [1*S*-[1*R**,2*R**,4*R**(1*R**,2*R**)]]-1-[(1,1-dimetil-etoxi)-carbonil]-L-prolil-L-fenilalanil-N-[2-hidroxi-5-metil-1-(2-metil-propil)-4-[[[2-metil-1-[[(2-piridinil-metil)-amino]-carbonil]-butil]-amino]-carbonil]-hexil]-*N*-alfa-metil-L-histidinamida); terlaquireno (nombre químico: [*R*-(*R**,*S**)]-N-(4-morfolinil-carbonil)-1-fenilalanil-N-[1-(ciclohexil-metil)-2-hidroxi-3-(1-metil-etoxi)-3-oxopropil]-S-metil-L-cistein-amida); y zanquireno (nombre químico: [1*S*-[1*R**[*R**(*R**)],2*S**,3*R**]]-*N*-[1-(ciclohexil-metil)-2,3-dihidroxi-5-metil-hexil]-alfa-[[2-[[(4-metil-1-piperazinil)-sulfonil]-metil]-1-oxo-3-fenil-propil]-amino]-4-tiazol-propanamida), o las sales de clorhidrato de los mismos, o SPP630, SPP635 y SPP800, como son desarrollados por Speedel, o RO 66-1132 y RO 66-1168 de las fórmulas (A) y (B):



(A)

y



(B)

,

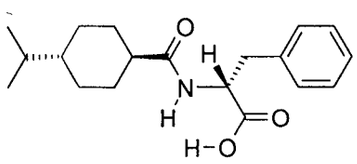
o las sales farmacéuticamente aceptables de los mismos.

El término "diurético" incluye a los derivados de tiazida (por ejemplo, cloro-tiazida, hidrocloro-tiazida, metil-clotiazida, y

clorotalidona).

El término "mimético de ApoA-I" incluye a los péptidos D4F (por ejemplo, de la fórmula D-W-F-K-A-F-Y-D-K-V-A-E-K-F-K-E-A-F).

El término "agente anti-diabético" incluye a los potenciadores de la secreción de insulina que promueven la secreción de insulina a partir de las células-ß pancreáticas. Los ejemplos incluyen a los derivados de biguanida (por ejemplo, metformina), sulfonil-ureas (SU) (por ejemplo, tolbutamida, clorpropamida, tolazamida, acetohexamida, 4-cloro-*N*-[(1-pirrolidinil-amino)-carbonil]-bencen-sulfonamida (glicopiramida), glibenclamida (gliburida), gliclazida, 1-butil-3-metanilil-urea, carbutamida, glibonurida, glipizida, gliquidona, glisoxepida, glibutiazol, glibuzol, glihexamida, glimidina, glipinamida, fenbutamida, y tolil-ciclamida), o las sales farmacéuticamente aceptables de las mismas. Otros ejemplos incluyen a los derivados de fenilalanina (por ejemplo, nateglinida [*N*-(*trans*-4-isopropil-ciclohexil-carbonil)-*D*-fenilalanina] (véanse las Patentes Europeas Números EP 196222 y EP 526171) de la fórmula:



;

repaglinida [(*S*)-ácido 2-etoxi-4-{2-[[3-metil-1-[2-(1-piperidinil)-fenil]-butil]-amino]-2-oxo-etil}-benzoico] (véanse las Patentes Europeas Números EP 589874, EP 147850 A2, en particular el Ejemplo 11 de la página 61, y EP 207331 A1); dihidrato de (2*S*)-2-bencil-3-(*cis*-hexahidro-2-isoindolinil-carbonil)-propionato de calcio (por ejemplo,

metiglinida (véase la Patente Europea Número EP 507534)); y glimepirida (véase la Patente Europea Número EP 31058). Otros ejemplos incluyen a los inhibidores de DPP-IV, GLP-1, y agonistas de GLP-1.

DPP-IV es responsable de la inactivación de GLP-1. De una manera más particular, DPP-IV genera un antagonista de los receptores de GLP-1, y de esta manera, reduce la respuesta fisiológica al GLP-1. GLP-1 es un estimulante mayor de la secreción de la insulina pancreática, y tiene efectos benéficos directos sobre la eliminación de la glucosa.

El inhibidor de DPP-IV puede ser peptídico o, de preferencia, no peptídico. Los inhibidores de DPP-IV se dan a conocer en cada caso de una manera genérica y específica, por ejemplo, en las Patentes Números WO 98/19998, DE 196 16 486 A1, WO 00/34241 y WO 95/15309, en cada caso en particular en las reivindicaciones de compuestos; y los productos finales de los ejemplos de procesamiento, el asunto objeto de los productos finales, las preparaciones farmacéuticas, y las reivindicaciones, se incorporan a la presente solicitud por referencia a estas publicaciones. Se prefieren los compuestos que se dan a conocer específicamente en el Ejemplo 3 de la Publicación Internacional Número WO 98/19998, y en el Ejemplo 1 de la Publicación Internacional Número WO 00/34241, respectivamente.

GLP-1 es una proteína insulinotrópica que es descrita, por ejemplo, por W.E. Schmidt y colaboradores, en *Diabetologia*, 28,

1985, 704-707 y en la Patente de los Estados Unidos de Norteamérica Número US 5,705,483.

El término "agonistas de GLP-1" incluye las variantes y los análogos de GLP-1(7-36)NH_2 los cuales se dan a conocer en particular en las Patentes de los Estados Unidos de Norteamérica Números US 5,120,712, US 5,118666, y US 5,512,549, en la Publicación Internacional Número WO 91/11457, y por C. Orskov y colaboradores, en J. Biol. Chem. 264 (1989) 12826. Otros ejemplos incluyen GLP-1(7-37), en cuyo compuesto, la funcionalidad de amida carboxi-terminal de Arg^{36} es desplazada con Gly en la posición 37 de la molécula de GLP-1(7-36)NH_2 y las variantes y los análogos de la misma, incluyendo GLN^9-GLP-1(7-37), D-GLN^9-GLP-1(7-37), acetil-LYS^9-GLP-1(7-37), LYS^{18}-GLP-1(7-37) y, en particular, GLP-1(7-37)OH, VAL^8-GLP-1(7-37), GLY^8-GLP-1(7-37), THR^8-GLP-1(7-37), MET^8-GLP-1(7-37), y 4-imidazo-propionil-GLP-1. También se da una preferencia especial al análogo del agonista de GLP exendina-4, descrita por Greig y colaboradores en *Diabetologia* 1999, 42, 45-50.

En la definición de un "agente anti-diabético" están los potenciadores de la sensibilidad a la insulina que restablecen la función deteriorada de los receptores de insulina para reducir la resistencia a la insulina y, en consecuencia, para potenciar la sensibilidad a la insulina. Los ejemplos incluyen a los derivados de tiazolidinadiona hipoglicémicos (por ejemplo, glitazona, (*S*)-((3,4-dihidro-2-(fenil-metil)-2H-1-benzopiran-6-il)-metil-tiazolidina-2,4-diona (englitazona), 5-{[4-(3-(5-metil-2-fenil-4-oxazolil)-1-oxopropil)-

fenil]-metil}-tiazolidina-2,4-diona (darglitazona), 5-{[4-(1-metil-ciclohexil)-metoxi)-fenil]metil}-tiazolidina-2,4-diona (ciglitazona), 5-{[4-(2-(1-indolil)-etoxi)-fenil]metil}-tiazolidina-2,4-diona (DRF2189), 5-{4-[2-(5-metil-2-fenil-4-oxazolil)-etoxi)]-bencil}-tiazolidina-2,4-diona (BM-13.1246), 5-(2-naftil-sulfonil)-tiazolidina-2,4-diona (AY-31637), bis-{4-[(2,4-dioxo-5-tiazolidinil)-metil]-fenil}-metano (YM268), 5-{4-[2-(5-metil-2-fenil-4-oxazolil)-2-hidroxi-etoxi]-bencil}-tiazolidina-2,4-diona (AD-5075), 5-[4-(1-fenil-1-ciclopropan-carbonil-amino)-bencil]-tiazolidina-2,4-diona (DN-108) 5-{[4-(2-(2,3-dihidro-indol-1-il)-etoxi)-fenil]metil}-tiazolidina-2,4-diona, 5-[3-(4-cloro-fenil])-2-propinil]-5-fenil-sulfonil)-tiazolidina-2,4-diona, 5-[3-(4-cloro-fenil])-2-propinil]-5-(4-fluoro-fenil-sulfonil)-tiazolidina-2,4-diona, 5-{[4-(2-(metil-2-piridinil-amino)-etoxi)-fenil]metil}-tiazolidina-2,4-diona (rosiglitazona), 5-{[4-(2-(5-etil-2-piridil)-etoxi)-fenil]-metil}-tiazolidina-2,4-diona (pioglitazona), 5-{[4-((3,4-dihidro-6-hidroxi-2,5,7,8-tetrametil-2H-1-benzopiran-2-il)-metoxi)-fenil]-metil}-tiazolidina-2,4-diona (troglitazona), 5-[6-(2-fluoro-benciloxi)naftalen-2-il-metil]-tiazolidina-2,4-diona (MCC555), 5-{[2-(2-naftil)-benzoxazol-5-il]-metil}-tiazolidina-2,4-diona (T-174), y 5-(2,4-dioxo-tiazolidin-5-il-metil)-2-metoxi-N-(4-trifluoro-metil-bencil)-benzamida (KRP297)).

Otros agentes anti-diabéticos incluyen a los moduladores de la senda de señalización de insulina, como los inhibidores de fosfatasas de proteína tirosina (PTPasas), compuestos miméticos de moléculas no pequeñas anti-diabéticos, e inhibidores de amido-transferasa de glutamina-fructosa-6-fosfato (GFAT); compuestos que

tienen influencia sobre la producción desregulada de la glucosa hepática, como los inhibidores de glucosa-6-fosfatasa (G6Pasa), los inhibidores de fructosa-1,6-bisfosfatasa (F-1,6-BPasa), los inhibidores de fosforilasa de glicógeno (GP), antagonistas de los receptores de glucagon, e inhibidores de carboxicinasa de piruvato de fosfoenol (PEPCK); inhibidores de cinasa de deshidrogenasa de piruvato (PDHK); inhibidores del vaciado gástrico; insulina; inhibidores de GSK-3; agonistas del receptor retinoide X (RXR); agonistas de Beta-3 AR; agonistas de las proteínas de desacoplamiento (UCPs); agonistas de PPARγ no de tipo glitazona; agonistas dobles de PPARα/PPARγ; compuestos anti-diabéticos que contienen vanadio; hormonas de incretina, como el péptido tipo glucagon-1 (GLP-1), y los agonistas de GLP-1; antagonistas de los receptores de imidazolina de las células-beta; miglitol; antagonistas α_2-adrenérgicos; y las sales farmacéuticamente aceptables de los mismos.

El término "agente reductor de la obesidad" incluye a los inhibidores de lipasa (por ejemplo, orlistato), y a los supresores del apetito (por ejemplo, sibutramina y fentermina).

El término "bloqueador de los receptores de aldosterona" incluye espironolactona y eplerenona.

El término "bloqueador de los receptores de endotelina" incluye bosentan.

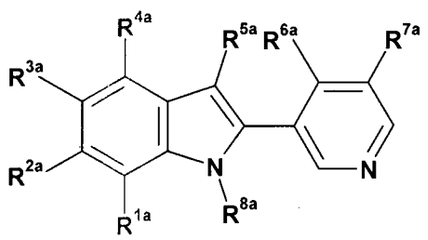
El término "inhibidor de CETP" se refiere a un compuesto que inhibe el transporte mediado por la proteína de transferencia de

colesteril-éster (CETP), de diferentes colesteril-ésteres y triglicéridos desde HDL hasta LDL y VLDL. Esta actividad de inhibición de la proteína de transferencia de colesteril-éster es fácilmente determinada por los expertos en este campo, de acuerdo con los ensayos convencionales (por ejemplo, la Patente de los Estados Unidos de Norteamérica Número 6,140,343). Los ejemplos incluyen a los compuestos que se dan a conocer en la Patente de los Estados Unidos de Norteamérica Número 6,140,343 y en la Patente de los Estados Unidos de Norteamérica Número 6,197,786 (por ejemplo, el [2R,4S]-etil-éster del ácido 4-[(3,5-bis-trifluoro-metil-bencil)-metoxi-carbonil-amino]-2-etil-6-trifluoro-metil-3,4-dihidro-2H-quinolin-1-carboxílico (torcetrapib); los compuestos que se dan a conocer en la Patente de los Estados Unidos de Norteamérica Número 6,723,752 (por ejemplo, (2R)-3-{[3-(4-cloro-3-etil-fenoxi)-fenil]-[[3-(1,1,2,2-tetrafluoro-etoxi)-fenil]-metil]-amino}-1,1,1-trifluoro-2-propanol; los compuestos que se dan a conocer en la Solicitud de Patente de los Estados Unidos de Norteamérica con Número de Serie 10/807,838; los derivados de polipéptido que se dan a conocer en la Patente de los Estados Unidos de Norteamérica Número 5,512,548; los derivados de rosenonolactona, y los análogos de colesteril-éster que contienen fosfato que se dan a conocer en *J. Antibiot.,* 49(8): 815-816 (1996), y en *Bioorg. Med. Chem. Lett.;* 6: 1951-1954 (1996), respectivamente. Adicionalmente, los inhibidores de la proteína de transferencia de colesteril-éster también incluyen aquéllos que se dan a conocer en las Publicaciones Internacionales Números

WO2000/017165, WO2005/095409 y WO2005/097806.

Composiciones Farmacéuticas de la Invención

La invención también pertenece a composiciones farmacéuticas que comprenden una cantidad efectiva de un compuesto de la fórmula I:



(I)

en donde:

R^{1a}, R^{2a}, R^{3a}, y R^{4a} son cada uno independientemente hidrógeno, halógeno, ciano, hidroxilo, alcoxilo, alquilo, alquenilo, o alcoxi-carbonilo;

R^{5a} es hidrógeno halógeno, ciano, alquilo, alquenilo, aril-alquilo, heteroaril-alquilo, amino-carbonilo, alquil-amino-carbonilo, carboxilato, alcoxi-carbonilo, heterociclil-carbonilo, arilo, o heteroarilo;

R^{6a} y R^{7a} son cada uno independientemente hidrógeno, halógeno, hidroxilo, alcoxilo, amino, alquilo, sulfonilo, -O-sulfonilo, alquil-amino, heterociclilo, amino-carbonilo, carboxilato, o alcoxi-carbonilo;

R^{8a} es hidrógeno, alquilo, aril-alquilo, heteroaril-alquilo, alcoxi-carbonilo, sulfonilo, aroílo, arilo, o heteroarilo;

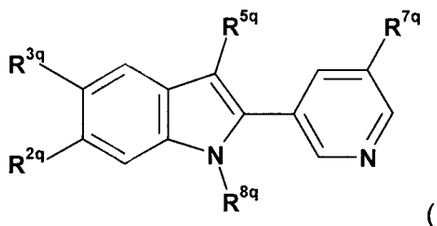
y las sales farmacéuticamente aceptables, polimorfos,

rotámeros, pro-fármacos, enantiómeros, hidratos, y solvatos del mismo;

con la condición de que cuando menos uno de R^{1a}-R^{8a} es diferente de hidrógeno; y cuando R^{5a} es ciano o alquilo inferior opcionalmente sustituido con ciano, -C(O)-piperidina, amino, alquil-amino, dialquil-amino, carboxilato, alcoxi-carbonilo, amino-carbonilo, o heterociclilo, entonces cuando menos uno de R^{1a}-R^{4a} y R^{6a}-R^{8a} es diferente de hidrógeno; y cuando R^{7a} es imidazolilo, entonces cuando menos uno de R^{1a}-R^{6a} y R^{8a} es diferente de hidrógeno; y cuando R^{8a} es alquilo, aril-alquilo o alcoxi-carbonilo, entonces cuando menos uno de R^{1a}-R^{7a} es diferente de hidrógeno; y cuando R^{5a} es alquilo inferior, y R^{8a} es alquilo sustituido con carboxilato o $PO_3R^{21}R^{22}$ en donde R^{21} y R^{22} son cada uno independientemente hidrógeno o alquilo inferior, entonces cuando menos uno de R^{1a}-R^{4a} y R^{6a} y R^{7a} es diferente de hidrógeno; y cuando R^{3a} es halógeno y R^{5a} y R^{8a} son independientemente alquilo inferior opcionalmente sustituido con carboxilato, alcoxi-carbonilo, o -C(O)-piperidina, entonces cuando menos uno de R^{1a}, R^{2a}, R^{4a}, R^{6a} y R^{7a} es diferente de hidrógeno; y cuando R^{3a} es halógeno, o alquilo inferior, y R^{5a} es alquilo inferior sustituido con dialquil-amino, dialquil-amino-carbonilo, carboxilato, alcoxi-carbonilo o amino-carbonilo, entonces cuando menos uno de R^{1a}, R^{2a}, R^{4a}, y R^{6a}-R^{8a} es diferente de hidrógeno; y cuando R^{2a} y R^{3a} son cada uno alcoxilo y R^{5a} es ciano, entonces cuando menos uno de R^{1a}, R^{4a}, y R^{6a}-R^{8a} es diferente de hidrógeno; y cuando R^{3a} es alquilo sustituido con aroílo, y R^5 y R^8 son cada uno independientemente

hidrógeno o alquilo inferior, entonces cuando menos uno de R^{1a}, R^{2a}, y R^{4a} es diferente de hidrógeno, en donde esta cantidad efectiva es efectiva para tratar un estado asociado con la sintasa de aldosterona.

En otra modalidad, la invención pertenece a composiciones farmacéuticas que comprenden una cantidad efectiva de un compuesto de la fórmula II:



(II)

en donde:

R^{2q} es hidrógeno o halógeno;

R^{3q} es hidrógeno, halógeno, o ciano;

R^{5q} es hidrógeno, alquilo, o ciano;

R^{7q} es hidrógeno, halógeno, alcoxilo, -OSO_2-heterociclilo, -O-aril-alquilo, -NR'-SO_2-alquilo, -NR'-C(O)-alquilo, -NR'-C(O)-NR'-alquilo, -NR'-C(O)-O-alquilo, halo-alquilo, o alquilo opcionalmente sustituido con heterociclilo, –NR'-SO_2-alquilo, -NR'-SO_2-halo-alquilo, NR'-C(O)-alquilo, NR'-C(O)-heterociclilo, -NR'-C(O)-NR'-alquilo, o -NR'-C(O)-O-alquilo;

R^{8q} es hidrógeno, alquilo, hidroxi-alquilo, -alquil-OC(O)-alquilo, carboxilato, alcoxi-carbonilo, o aril-alquilo sustituido con alquilo, o aroílo sustituido con ciano y/o alquilo, o -alquil-O-arilo sustituido con alcoxi-carbonilo;

cada R' es independientemente hidrógeno, alquilo de 1 a 4 átomos de carbono, o cicloalquilo de 3 a 6 átomos de carbono,

con la condición de que cuando menos uno de R^{2q}, R^{3q}, R^{5q}, R^{7q} y R^{8q} es diferente de hidrógeno, en donde esta cantidad efectiva es efectiva para tratar un estado asociado con la sintasa de aldosterona.

En todavía otra modalidad, la invención pertenece a composiciones farmacéuticas que comprenden una cantidad efectiva de un compuesto de la fórmula III o IV, en donde esta cantidad efectiva es efectiva para tratar un estado asociado con la sintasa de aldosterona.

La composición o combinación farmacéutica de la presente invención puede estar en una dosificación unitaria de aproximadamente 1 a 1,000 miligramos de ingredientes activos para un sujeto de aproximadamente 50 a 70 kilogramos, de preferencia de aproximadamente 1 a 500 miligramos, o de aproximadamente 1 a 250 miligramos, o de aproximadamente 1 a 150 miligramos, o de aproximadamente 0.5 a 100 miligramos, o de aproximadamente 1 a 50 miligramos de ingredientes activos. La dosificación terapéuticamente efectiva de un compuesto, la composición farmacéutica, o las combinaciones de la misma, dependen de la especie del sujeto, del peso corporal, de la edad y la condición individual, del trastorno o enfermedad o de la gravedad de la misma que sea tratada. Un médico, clínico, o veterinario de una experiencia ordinaria puede determinar fácilmente la cantidad efectiva de cada

uno de los ingredientes activos necesarios para prevenir, tratar, o inhibir el progreso del trastorno o enfermedad.

Las propiedades de dosificación anteriormente citadas se pueden demostrar en pruebas *in vitro* e *in vivo* utilizando convenientemente mamíferos, por ejemplo ratones, ratas, perros, monos, u órganos aislados, tejidos, y preparaciones de los mismos. Los compuestos de la presente invención se pueden aplicar *in vitro* en la forma de soluciones, por ejemplo de preferencia soluciones acuosas, e *in vivo* ya sea enteralmente, parenteralmente, de una manera conveniente intravenosamente, por ejemplo como una suspensión o en una solución acuosa. La dosificación *in vitro* puede estar en el intervalo de concentraciones de entre aproximadamente 10^{-3} molar y aproximadamente 10^{-9} molar, o en el intervalo de concentraciones de entre aproximadamente 10^{-6} molar y aproximadamente 10^{-9} molar.

Las actividades de un compuesto de acuerdo con la presente invención se pueden evaluar mediante métodos tanto *in vitro* como *in vivo*.

El término "vehículo farmacéuticamente aceptable" incluye cualquiera y todos los solventes, medios de dispersión, recubrimientos, tensoactivos, antioxidantes, conservadores (por ejemplo, agentes antibacterianos, agentes antifúngicos), agentes isotónicos, agentes demoradores de absorción, sales, conservadores, fármacos, estabilizantes de fármacos, aglutinantes, excipientes, agentes humectantes, emulsionantes, reguladores del

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pH, agentes de desintegración, lubricantes, recubrimientos, agentes edulcorantes, agentes saborizantes, colorantes, materiales similares, y combinaciones de los mismos, como sería conocido por un experto ordinario en la materia (véase, por ejemplo, Remington's Pharmaceutical Sciences, 18ª Edición, Mack Printing Company, 1990, páginas 1289-1329, incorporado a la presente como referencia). Excepto hasta donde cualquier vehículo convencional sea incompatible con el ingrediente activo, se contempla su uso en las composiciones terapéuticas o farmacéuticas. Los vehículos farmacéuticamente aceptables adecuados incluyen, pero no se limitan a, agua, soluciones de sal, alcohol, aceites vegetales, polietilenglicoles, gelatina, lactosa, amilasa, estearato de magnesio, talco, ácido silícico, parafina viscosa, aceite de perfume, monoglicéridos y diglicéridos de ácidos grasos, ésteres de ácidos grasos de petroetral, hidroxi-metil-celulosa, polivinil-pirrolidona, etc.

Las composiciones farmacéuticas de la invención se pueden formular para vías de administración particulares, tales como administración oral, administración parenteral, y administración rectal, etc. En adición, las composiciones farmacéuticas de la presente invención se pueden hacer en una forma sólida, incluyendo cápsulas, tabletas, píldoras, gránulos, polvos o supositorios, o en una forma líquida, incluyendo soluciones, suspensiones o emulsiones. Las composiciones farmacéuticas se pueden someter a las operaciones farmacéuticas convencionales, tales como esterilización y/o pueden contener diluyentes inertes convencionales,

agentes lubricantes, o agentes reguladores, así como adyuvantes, tales como conservadores, estabilizantes, agentes humectantes, emulsionantes y reguladores del pH, etc.

En ciertas modalidades, las composiciones farmacéuticas son tabletas y cápsulas de gelatina, las cuales comprenden al ingrediente activo junto con:

a) diluyentes, por ejemplo, lactosa, dextrosa, sacarosa, manitol, sorbitol, celulosa y/o glicina;

b) lubricantes, por ejemplo, sílice, talco, ácido esteárico, su sal de magnesio o de calcio y/o polietilenglicol; para tabletas también,

c) aglutinantes, por ejemplo, silicato de magnesio y aluminio, pasta de almidón, gelatina, tragacanto, metil-celulosa, carboxi-metil-celulosa de sodio y/o polivinil-pirrolidona; si se desea,

d) desintegrantes, por ejemplo, almidones, agar, ácido algínico o su sal sódica, o mezclas efervescentes; y/o

e) absorbentes, colorantes, saborizantes y edulcorantes.

Las tabletas pueden tener recubrimiento de película o recubrimiento entérico de acuerdo con los métodos conocidos en este campo.

Las composiciones adecuadas para administración oral incluyen una cantidad efectiva de un compuesto de la invención en la forma de tabletas, grageas, suspensiones acuosas u oleosas, polvos o gránulos dispersables, emulsión, cápsulas duras o blandas, o jarabes o elíxires. Las composiciones pretendidas para uso oral se

preparan de acuerdo con cualquier método conocido en la técnica para la fabricación de composiciones farmacéuticas, y estas composiciones pueden contener uno o más agentes seleccionados a partir del grupo que consiste en agentes edulcorantes, agentes saborizantes, agentes colorantes, y agentes conservadores, con el objeto de proporcionar preparaciones farmacéuticamente elegantes y de buen sabor. Las tabletas contienen al ingrediente activo mezclado con excipientes farmacéuticamente aceptables no tóxicos que sean adecuados para la fabricación de tabletas. Estos excipientes son, por ejemplo, diluyentes inertes, tales como carbonato de calcio, carbonato de sodio, lactosa, fosfato de calcio, o fosfato de sodio; agentes de granulación o desintegrantes, por ejemplo almidón de maíz, o ácido algínico; agentes aglutinantes, por ejemplo almidón, gelatina, o acacia; y agentes lubricantes, por ejemplo estearato de magnesio, ácido esteárico, o talco. Las tabletas no se recubren, o bien se recubren mediante técnicas conocidas para demorar la desintegración y absorción en el tracto gastrointestinal y de esta manera proporcionar una acción sostenida durante un período más largo. Por ejemplo, se puede emplear un material de demora de tiempo tal como monestearato de glicerilo o diestearato de glicerilo. Las formulaciones para uso oral se pueden presentar como cápsulas de gelatina dura en donde se mezcla el ingrediente activo con un diluyente sólido inerte, por ejemplo carbonato de calcio, fosfato de calcio, o caolín, o como cápsulas de gelatina blanda en donde se mezcla el ingrediente activo con agua o con un medio oleoso, por

ejemplo aceite de cacahuate, parafina líquida, o aceite de oliva.

Las composiciones inyectables son de preferencia soluciones o suspensiones isotónicas acuosas, y los supositorios convenientemente se preparan a partir de emulsiones o suspensiones grasas. Estas composiciones se pueden esterilizar y/o pueden contener adyuvantes, tales como agentes conservadores, estabilizantes, humectantes, o emulsionantes, promotores de solución, sales para regular la presión osmótica, y/o reguladores del pH. En adición, también pueden contener otras sustancias terapéuticamente valiosas. Estas composiciones se preparan de acuerdo con los métodos convencionales de mezcla, granulación, o recubrimiento, respectivamente, y pueden contener de aproximadamente el 0.1 al 75 por ciento, de preferencia de aproximadamente el 1 al 50 por ciento del ingrediente activo.

Las composiciones adecuadas para aplicación transdérmica incluyen una cantidad efectiva de un compuesto de la invención con un vehículo. Los vehículos convenientes incluyen solventes farmacológicamente aceptables absorbibles para ayudar al paso a través de la piel del huésped. Por ejemplo, los dispositivos transdérmicos están en la forma de un parche, el cual comprende un miembro de respaldo, un depósito que contiene al compuesto opcionalmente con vehículos, opcionalmente una barrera de control de velocidad para suministrar el compuesto a la piel del huésped a una velocidad controlada y previamente determinada durante un período de tiempo prolongado, y elementos para asegurar el

dispositivo a la piel.

Las composiciones adecuadas para aplicación tópica, por ejemplo a la piel y a los ojos, incluyen soluciones acuosas, suspensiones, ungüentos, cremas, geles, o formulaciones rociables, por ejemplo para suministrarse en aerosol o similar. Estos sistemas de suministro tópico serán apropiados en particular para aplicación dérmica, por ejemplo para el tratamiento de cáncer de piel, por ejemplo para uso profiláctico en cremas para el sol, lociones, aerosoles, etc. De esta manera, son particularmente adecuadas para utilizarse en formulaciones tópicas, incluyendo cosméticas, bien conocidas en este campo. Éstas pueden contener solubilizantes, estabilizantes, agentes mejoradores de tonicidad, reguladores del pH, y conservadores.

La presente invención proporciona además composiciones farmacéuticas anhidras y formas de dosificación que comprenden los compuestos de la presente invención como ingredientes activos, debido a que el agua puede facilitar la degradación de algunos compuestos. Por ejemplo, la adición de agua (por ejemplo, al 5 por ciento) es ampliamente aceptada en la técnica farmacéutica como un medio para simular el almacenamiento a largo plazo, con el objeto de determinar las características, tales como la vida de anaquel o la estabilidad de las formulaciones a través del tiempo. Véase, por ejemplo, Jens T. Carstensen, *Drug Stability: Principles & Practice,* 2ª Edición, Marcel Dekker, NY, N.Y., 1995, páginas 379-80. En efecto, el agua y el calor aceleran la descomposición de algunos

compuestos. Por consiguiente, el efecto del agua sobre una formulación puede ser de un gran significado, debido a que el agua y/o la humedad son comúnmente encontradas durante la fabricación, manejo, empaque, almacenamiento, embarque, y uso de las formulaciones.

Se pueden preparar composiciones farmacéuticas anhidras y formas de dosificación de la invención utilizando ingredientes anhidros o que contengan una baja humedad, y condiciones de baja humedad. Las composiciones farmacéuticas y las formas de dosificación que comprenden lactosa y cuando menos un ingrediente activo que comprende una amina primaria o secundaria de preferencia son anhidras si se espera un contacto sustancial con la humedad durante la fabricación, empaque, y/o almacenamiento.

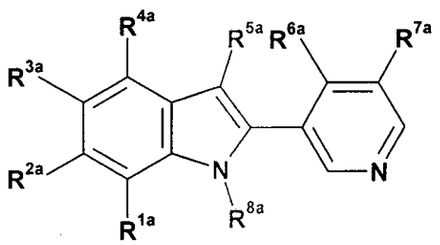
Una composición farmacéutica anhidra se debe preparar y almacenar de tal manera que se mantenga su naturaleza anhidra. De conformidad con lo anterior, las composiciones anhidras de preferencia se empacan utilizando materiales que se sepa que previenen la exposición al agua, de tal forma que se puedan incluir en kits de formulación adecuados. Los ejemplos del empaque adecuado incluyen, pero no se limitan a, láminas herméticamente selladas, plásticos, recipientes de dosis unitaria (por ejemplo, frascos), paquetes de burbuja, y paquetes de tiras.

La invención proporciona además composiciones farmacéuticas y formas de dosificación que comprenden uno o más agentes que reducen la velocidad a la cual se descompondrá el compuesto de la

presente invención como un ingrediente activo. Estos agentes, los cuales son referidos en la presente como "estabilizantes", incluyen, pero no se limitan a, antioxidantes, tales como ácido ascórbico, reguladores del pH, o reguladores de sales, etc.

Una modalidad de la invención incluye una composición farmacéutica como se describe anteriormente en combinación con un segundo agente y un vehículo farmacéutico.

En todavía otra modalidad, la invención pertenece, cuando menos en parte, a los compuestos de la fórmula I:



(I)

en donde:

R^{1a}, R^{2a}, R^{3a}, y R^{4a} son cada uno independientemente hidrógeno, halógeno, ciano, hidroxilo, alcoxilo, alquilo, alquenilo, o alcoxi-carbonilo;

R^{5a} es hidrógeno halógeno, ciano, alquilo, alquenilo, aril-alquilo, heteroaril-alquilo, amino-carbonilo, alquil-amino-carbonilo, carboxilato, alcoxi-carbonilo, heterociclil-carbonilo, arilo, o heteroarilo;

R^{6a} y R^{7a} son cada uno independientemente hidrógeno, halógeno, hidroxilo, alcoxilo, amino, alquilo, sulfonilo, -O-sulfonilo, alquil-amino, heterociclilo, amino-carbonilo, carboxilato, o alcoxi-

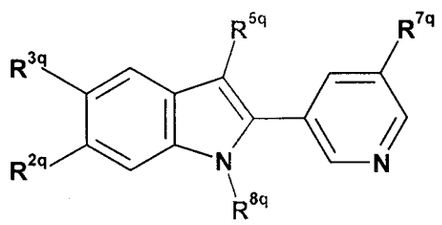
carbonilo;

R^{8a} es hidrógeno, alquilo, aril-alquilo, heteroaril-alquilo, alcoxi-carbonilo, sulfonilo, aroílo, arilo, o heteroarilo; y las sales farmacéuticamente aceptables, polimorfos, rotámeros, pro-fármacos, enantiómeros, hidratos, y solvatos de los mismos;

con la condición de que cuando menos uno de R^{1a}-R^{8a} es diferente de hidrógeno; y cuando R^{5a} es ciano o alquilo inferior opcionalmente sustituido con ciano, -C(O)-piperidina, amino, alquil-amino, dialquil-amino, carboxilato, alcoxi-carbonilo, amino-carbonilo, o heterociclilo, entonces cuando menos uno de R^{1a}-R^{4a} y R^{6a}-R^{8a} es diferente de hidrógeno; y cuando R^{7a} es imidazolilo, entonces cuando menos uno de R^{1a}-R^{6a} y R^{8a} es diferente de hidrógeno; y cuando R^{8a} es alquilo, aril-alquilo o alcoxi-carbonilo, entonces cuando menos uno de R^{1a}-R^{7a} es diferente de hidrógeno; y cuando R^{5a} es alquilo inferior, y R^{8a} es alquilo sustituido con carboxilato o $PO_3R^{21}R^{22}$ en donde R^{21} y R^{22} son cada uno independientemente hidrógeno o alquilo inferior, entonces cuando menos uno de R^{1a}-R^{4a} y R^{6a} y R^{7a} es diferente de hidrógeno; y cuando R^{3a} es halógeno y R^{5a} y R^{8a} son independientemente alquilo inferior opcionalmente sustituido con carboxilato, alcoxi-carbonilo, o -C(O)-piperidina, entonces cuando menos uno de R^{1a}, R^{2a}, R^{4a}, R^{6a} y R^{7a} es diferente de hidrógeno; y cuando R^{3a} es halógeno, o alquilo inferior, y R^{5a} es alquilo inferior sustituido con dialquil-amino, dialquil-amino-carbonilo, carboxilato, alcoxi-carbonilo o amino-carbonilo, entonces cuando menos uno de R^{1a}, R^{2a}, R^{4a}, y R^{6a}-R^{8a} es diferente de hidrógeno; y cuando R^{2a} y R^{3a}

son cada uno alcoxilo y R^{5a} es ciano, entonces cuando menos uno de R^{1a}, R^{4a}, y R^{6a}-R^{8a} es diferente de hidrógeno; y cuando R^{3a} es alquilo sustituido con aroílo, y R^5 y R^8 son cada uno independientemente hidrógeno o alquilo inferior, entonces cuando menos uno de R^{1a}, R^{2a}, y R^{4a} es diferente de hidrógeno, para utilizarse en terapia.

En todavía otra modalidad, la invención pertenece, cuando menos en parte, a los compuestos de la fórmula II:



(II)

en donde:

R^{2q} es hidrógeno o halógeno;

R^{3q} es hidrógeno, halógeno, o ciano;

R^{5q} es hidrógeno, alquilo, o ciano;

R^{7q} es hidrógeno, halógeno, alcoxilo, -OSO_2-heterociclilo, -O-aril-alquilo, -NR'-SO_2-alquilo, -NR'-C(O)-alquilo, -NR'-C(O)-NR'-alquilo, -NR'-C(O)-O-alquilo, halo-alquilo, o alquilo opcionalmente sustituido con heterociclilo, –NR'-SO_2-alquilo, -NR'-SO_2-halo-alquilo, NR'-C(O)-alquilo, NR'-C(O)-heterociclilo, -NR'-C(O)-NR'-alquilo, o -NR'-C(O)-O-alquilo;

R^{8q} es hidrógeno, alquilo, hidroxi-alquilo, -alquil-OC(O)-alquilo, carboxilato, alcoxi-carbonilo, o aril-alquilo sustituido con alquilo, o aroílo sustituido con ciano y/o alquilo, o -alquil-O-arilo sustituido con

alcoxi-carbonilo;

cada R' es independientemente hidrógeno, alquilo de 1 a 4 átomos de carbono, o cicloalquilo de 3 a 6 átomos de carbono,

con la condición de que cuando menos uno de R^{2q}, R^{3q}, R^{5q}, R^{7q} y R^{8q} es diferente de hidrógeno, para utilizarse en terapia.

Otra modalidad de la invención pertenece, cuando menos en parte, a los compuestos de la fórmula III o IV, para utilizarse en terapia.

Todavía otra modalidad de la invención pertenece, cuando menos en parte, al uso de los compuestos de la fórmula (I), (II), (III) o (IV), como se describen anteriormente, y a los compuestos de los Ejemplos, para la preparación de una composición farmacéutica para el tratamiento de un trastorno o enfermedad en un sujeto, mediada por la inhibición de la sintasa de aldosterona.

En todavía otra modalidad, la invención pertenece, cuando menos en parte, a los compuestos de la fórmula (I), (II), (III) o (IV), como se describen anteriormente, y a los compuestos de los Ejemplos, para utilizarse como un medicamento.

Otra modalidad de la invención pertenece, cuando menos en parte, a composiciones farmacéuticas, como se describen anteriormente, para utilizarse como un medicamento.

En otra modalidad, la invención pertenece, cuando menos en parte, al uso de composiciones farmacéuticas, como se describen anteriormente, para la preparación de un medicamento para el tratamiento de un trastorno o enfermedad en un sujeto, mediada por

la inhibición de la sintasa de aldosterona.

Otra modalidad de la invención pertenece, cuando menos en parte, a métodos para el tratamiento de un trastorno o enfermedad mediada por la sintasa de aldosterona en un mamífero, mediante la administración al mamífero que lo necesite, de una cantidad terapéuticamente efectiva de un compuesto de la fórmula (I), (II), (III) o (IV), como se describen anteriormente, y en los Ejemplos.

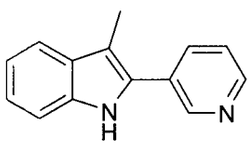
Otra modalidad de la invención pertenece a kits, los cuales comprenden una composición farmacéutica como se describe anteriormente, empacada con instrucciones para el uso de la composición farmacéutica en el tratamiento de un estado asociado con la sintasa de aldosterona, en un sujeto que lo necesite.

Ejemplificación de la Invención

Los siguientes ejemplos pretenden ilustrar la invención y no deben interpretarse como limitaciones sobre la misma. Las temperaturas se dan en grados centígrados. Si no se menciona de otra manera, todas las evaporaciones se llevan a cabo bajo presión reducida, de preferencia entre aproximadamente 15 mm Hg y 100 mm Hg (= de 20 a 133 mbar). La estructura de los productos finales, intermediarios y materiales de partida se confirma mediante métodos analíticos convencionales, por ejemplo, microanálisis y características espectroscópicas, por ejemplo, MS, IR, RMN. Las abreviaturas empleadas son las convencionales en la técnica.

Ejemplo 1

Clorhidrato de 3-metil-2-piridin-3-il-1H-indol

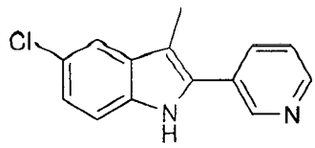


El clorhidrato de 3-metil-2-piridin-3-il-1H-indol se sintetiza basándose en el método descrito en la Patente de los Estados Unidos de Norteamérica Número US3468894. Un matraz se carga con 3-propionil-piridina (1.004 gramos, 7.279 milimoles),clorhidrato de fenil-hidrazina (1.010 gramos, 6.915 milimoles), y etanol (15 mililitros). La mezcla se calienta a reflujo durante 1 hora, y se enfría a temperatura ambiente. A una porción de la mezcla de reacción (2.5 mililitros), se le agrega HCl (4M en dioxano, 1 mililitro, 4 milimoles), y la mezcla se calienta a reflujo. Después de 3 horas, la mezcla se concentra al vacío. El sólido se disuelve en una cantidad mínima de metanol en ebullición (17 mililitros), y se deja enfriar lentamente a temperatura ambiente. Se precipita un sólido y, después de enfriar a 0°C, durante 30 minutos, el sólido amarillo se filtra, se lava con porciones de metanol frío, y se seca bajo un alto vacío, para dar el clorhidrato de 3-metil-2-piridin-3-il-1H-indol como agujas amarillas.

^{1}H RMN (400 MHz, MeOD) δ ppm (sal de HCl) 2.56 (s, 3 H), 7.09 - 7.13 (m, 1 H), 7.23 - 7.26 (m, 1 H), 7.43 (d, *J*=8.1 Hz, 1 H), 7.63 (d, *J*=8.1 Hz, 1 H), 8.14 - 8.18 (m, 1 H), 8.74 (d, *J*=5.8 Hz, 1 H), 8.83-8.85 (m, 1 H), 9.08 (s, 1 H).

Ejemplo 2

Clorhidrato de 5-cloro-3-metil-2-piridin-3-il-1H-indol

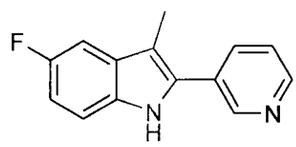


El clorhidrato de 5-cloro-3-metil-2-piridin-3-il-1H-indol se sintetiza basándose en el método descrito en la Patente de los Estados Unidos de Norteamérica Número US3468894. El clorhidrato de (4-cloro-fenil)-hidrazina (3.0 gramos, 16.8 milimoles), y 3-propionil-piridina (2.4 gramos, 17.6 milimoles) en etanol (45 mililitros), se calienta a reflujo durante 6 horas. La mezcla se enfría entonces a temperatura ambiente, y, se agrega a HCl (4M en 1,4-dioxano, 17.6 mililitros). La mezcla resultante se calienta a reflujo durante 24 horas. La mezcla se enfría entonces a temperatura ambiente, y el precipitado amarillo se filtra y se lava con metanol (10 mililitros) tres veces, para dar el clorhidrato de 5-cloro-3-metil-2-piridin-3-il-1H-indol como un sólido amarillo.

MS (ESI) *m/z* 243.0 y 244.9 $(M+H)^+$.

Ejemplo 3

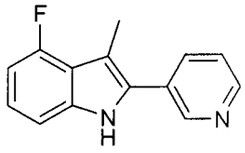
clorhidrato de 5-fluoro-3-metil-2-piridin-3-il-1H-indol

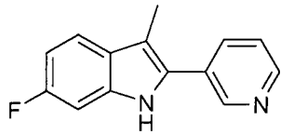


(4-fluoro-fenil)-hidrazina clorhidrato se procesa de acuerdo con el procedimiento descrito en el Ejemplo 2 para dar el clorhidrato de 5-fluoro-3-metil-2-piridin-3-il-1H-indol. MS (ESI) *m/z* 227.0 $(M+H)^+$.

Ejemplo 4

clorhidrato de 4- y 6-fluoro-3-metil-2-piridin-3-il-1H-indol



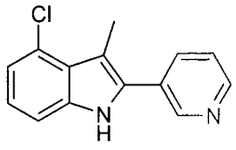


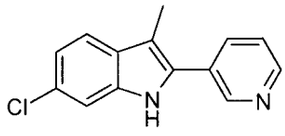
El clorhidrato de (3-fluoro-fenil)-hidrazina se procesa de acuerdo con el procedimiento descrito en el Ejemplo 2, para dar una mezcla de clorhidrato de 4-fluoro-3-metil-2-piridin-3-il-1H-indol y clorhidrato de 6-fluoro-3-metil-2-piridin-3-il-1H-indol.

MS (ESI) *m/z* 227.0 $(M+H)^+$.

Ejemplo 5

clorhidrato de 4- y 6-cloro-3-metil-2-piridin-3-il-1H-indol



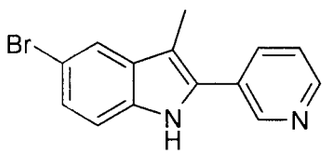


El clorhidrato de (3-cloro-fenil)-hidrazina se procesa de acuerdo con el procedimiento descrito en el Ejemplo 2, para dar una mezcla de clorhidrato de 4-cloro-3-metil-2-piridin-3-il-1H-indol y clorhidrato de 6-cloro-3-metil-2-piridin-3-il-1H-indol.

MS (ESI) *m/z* 242.96 y 244.98 $(M+H)^+$.

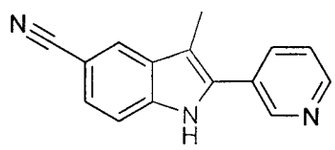
Ejemplo 6

(a) 5-bromo-3-metil-2-piridin-3-il-1H-indol



A una suspensión de clorhidrato de 4-bromo-fenil-hidrazina (10.00 gramos, 42.95 milimoles) en etanol anhidro (200 mililitros), se le agrega 3-propionil-piridina (7.51 gramos, 42.95 milimoles), y la mezcla se agita a reflujo durante 30 minutos. a la solución amarilla se le agrega HCl 4M en 1,4-dioxano (42.9 mililitros), y la agitación se continúa a reflujo durante la noche. La mezcla de reacción se enfría con un baño de agua helada, y el precipitado amarillo se filtra a través de un embudo sinterizado, para dar el clorhidrato de 5-bromo-3-metil-2-piridin-3-il-1H-indol como un sólido amarillo. El producto se disuelve en metanol (100 mililitros), y se trata con metóxido de sodio, para dar la base libre, la cual se utiliza en el siguiente paso sin mayor purificación.

(b) 3-metil-2-piridin-3-il-1H-indol-5-carbonitrilo



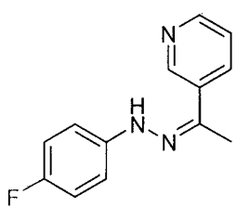
El 5-bromo-3-metil-2-piridin-3-il-1H-indol (5.0 gramos, 16.7 milimoles), y cianuro de cobre (I) (1.9 gramos, 20.1 milimoles) se colocan en un matraz de fondo redondo, el cual se inunda con N_2. Se agrega *N*-metil-pirrolidinona (40 mililitros) mediante una jeringa. La mezcla resultante se calienta a 200°C bajo N_2 con agitación vigorosa durante la noche. La mezcla se enfría a temperatura ambiente, y se agrega dicloro-metano (200 mililitros). La mezcla se filtra a través de un cojín de Celite. El filtrado se lava con amoníaco acuoso al 10 por ciento en cloruro de amonio acuoso saturado. La fase acuosa se

extrae con dicloro-metano. La fase orgánica combinada se seca sobre sulfato de sodio, y se concentra. El residuo se purifica mediante cromatografía por evaporación instantánea en gel de sílice (acetato de etilo-heptano, 0:1 a 1:0), para dar el 3-metil-2-piridin-3-il-1H-indol-5-carbonitrilo.

^{1}H RMN (400 MHz, DMSO-d_6) δ ppm 2.45 (s, 3 H), 7.45 - 7.60 (m, 3 H), 8.06 - 8.11 (m, 1 H), 8.15 (s, 1 H), 8.60 (dd, *J*=4.8, 1.5 Hz, 1 H), 8.91 (d, *J*=1.5 Hz, 1 H), 11.94 (br. s., 1 H). HRMS (ESI) m/z 234.1031 [$(M+H)^+$ Calculado para $C_{15}H_{11}N_3$, 234.1031].

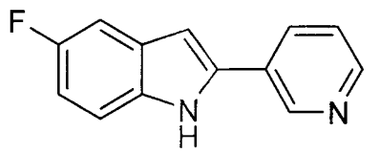
Ejemplo 7

(a) *N*-(4-fluoro-fenil)-*N'*-[1-piridin-3-il-et-(Z)-iliden]-hidrazina



La 3-acetil-piridina (5.00 gramos, 40.45 milimoles), y clorhidrato de 4-fluoro-fenil-hidrazina (6.44 gramos, 38.43 milimoles) se suspenden en etanol (70 mililitros), y se calienta a reflujo. Después de 1 hora, se agrega HCl (4M en dioxano, 150 mililitros, 600 milimoles), y la mezcla se calienta a reflujo durante 16 horas. La mezcla se concentra al vacío y se absorbe en un poco de etanol. El sólido se filtra y se lava con etanol, para dar el un sólido amarillo. El filtrado se concentra a sequedad. El sólido resultante se lava con pequeñas cantidades de etanol helado, y se filtra. Las dos fracciones se combinan y se utilizan en el siguiente paso sin mayor purificación.

(b) 5-fluoro-2-piridin-3-il-indol

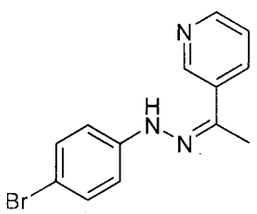


Un matraz se carga con poli-ácido fosfórico (1.2 gramos), y se agrega *N*-(4-fluoro-fenil)-*N*'-[1-piridin-3-il-et-(Z)-ilidén]-hidrazina (1.0 gramos). La mezcla se agita con un termómetro y se calienta a 160°C (temperatura interna), sobre lo cual, la pasta se deja enfriar a 100°C. Se agregan agua (90 mililitros) y acetato de etilo, y la mezcla se agita vigorosamente hasta que se obtiene un precipitado amarillo separado. El precipitado se filtra y las dos fases se separan. La fase de acetato de etilo se desecha. Los sólidos y la fase acuosa se combinan, y se agrega NaOH 1M acuoso, seguido por cloroformo, y la mezcla se agita vigorosamente hasta la disolución completa. La fase acuosa se extrae con cloroformo y la fase orgánica combinada se seca sobre $MgSO_4$ y se concentra al vacío. El residuo se purifica mediante cromatografía por evaporación instantánea en gel de sílice (acetato de etilo-heptano, 7:3 a 9:1), para dar el compuesto como un sólido color café.

MS (ESI) *m/z* 213 $(M+H)^+$.

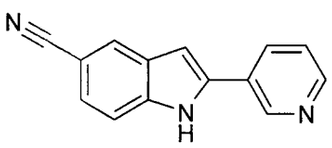
Ejemplo 8

(a) Clorhidrato de *N*-(4-bromo-fenil)-*N*'-[1-piridin-3-il-et-(Z)-ilidén]-hidrazina



A una solución de clorhidrato de 4-bromo-fenil-hidrazina (11.5 gramos, 50 milimoles) en etanol anhidro (200 mililitros), se le agrega 3-acetil-piridina (6.1 gramos, 50 milimoles). La mezcla se calienta a 90°C, y se agita durante 3 horas, se enfría a temperatura ambiente, y se filtra a través de un embudo de vidrio sinterizado. El sólido se lava con etanol, y se coloca bajo un alto vacío durante la noche, para dar el clorhidrato de *N*-(4-bromo-fenil)-*N*'-[1-piridin-3-il-et-(Z)-iliden]-hidrazina como un sólido amarillo.

(b) 2-piridin-3-il-1H-indol-5-carbonitrilo



Un matraz adaptado con un agitador mecánico, se carga con poli-ácido fosfórico (15 gramos), y clorhidrato de *N*-(4-bromo-fenil)-*N*'-[1-piridin-3-il-et-(Z)-iliden]-hidrazina (18 gramos), y se calienta a 210°C (temperatura del baño de aceite) durante 1 hora. La pasta se deja enfriar a temperatura ambiente y se agrega NaOH 1M acuoso, seguido por cloroformo, y la mezcla se agita vigorosamente hasta la disolución completa. La fase acuosa se extrae con cloroformo y la fase orgánica combinada se seca sobre $MgSO_4$ y se concentra al vacío, para dar el 5-bromo-2-piridin-3-il-1H-indol como un sólido

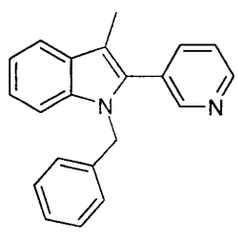
color café, el cual se utiliza sin mayor purificación.

El 5-bromo-2-piridin-3-il-1H-indol (7.0 gramos, 21.8 milimoles), y cianuro de cobre (I) (2.3 gramos, 26.1 milimoles) se colocan en un matraz de fondo redondo, el cual se inunda con N_2. Se agrega *N*-metil-pirrolidinona (40 mililitros) mediante una jeringa. La mezcla resultante se calienta a 160°C bajo N_2 con agitación vigorosa durante la noche. La mezcla se enfría a temperatura ambiente, y se vierte en amoníaco acuoso al 10 por ciento en cloruro de amonio acuoso saturado (300 mililitros). La fase acuosa se extrae con diclorometano (100 mililitros) cinco veces. La fase orgánica combinada se seca sobre sulfato de sodio, y se concentra. El residuo se purifica mediante cromatografía por evaporación instantánea en gel de sílice (acetato de etilo-heptano, 0:1 a 1:0), para dar el 2-piridin-3-il-1H-indol-5-carbonitrilo.

^{1}H RMN (400 MHz, DMSO-d_6) δ ppm 7.20 (s, 1 H), 7.48 (dd, *J*=8.3, 1.5 Hz, 1 H), 7.51 - 7.55 (m, 1 H), 7.59 (d, *J*=8.6 Hz, 1 H), 8.12 (s, 1 H), 8.25 - 8.29 (m, 1 H), 8.56 (dd, *J*=4.8, 1.5 Hz, 1 H), 9.14 (d, *J*=1.8 Hz, 1 H), 12.27 (s, 1 H). HRMS (ESI) m/z 220.0869 [$(M+H)^+$ Calculado para $C_{14}H_9N_3$, 220.0875].

Ejemplo 9

1-bencil-3-metil-2-piridin-3-il-1H-indol

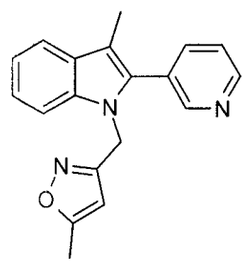


El clorhidrato de 3-metil-2-piridin-3-il-1H-indol (Ejemplo 1, 0.110 gramos, 0.445 milimoles) se suspende en tetrahidrofurano (3 mililitros), y se enfría a 0°C. Se agrega por goteo KHMDS (0.5M en tolueno, 2 mililitros, 1 milimol), se baja el baño de enfriamiento, y la mezcla se agita a temperatura ambiente durante 15 minutos, después de lo cual, se baja al baño de agua helada. Se agrega por goteo bromuro de bencilo (0.093 gramos, 0.534 milimoles). Después de 3 horas, se agrega bromuro de bencilo adicional (0.046 gramos, 0.267 milimoles), y, después de completarse la reacción, la mezcla se apaga con HCl acuoso 1M y se diluye con acetato de etilo. La fase acuosa se extrae y la fase orgánica combinada se seca sobre $MgSO_4$, se filtra, y se concentra al vacío. La purificación del residuo mediante cromatografía por evaporación instantánea en gel de sílice (dicloro-metano : metanol, 99:1), proporciona el 1-bencil-3-metil-2-piridin-3-il-1H-indol como un sólido amarillo pálido.

^{1}H RMN (400 MHz, MeOD) δ ppm 2.18 (s, 3 H), 5.19 (s, 2 H), 6.69 - 6.71 (m, 2 H), 7.01 - 7.11 (m, 5 H), 7.21 (d, *J*=8.1 Hz, 1 H), 7.37 - 7.41 (m, 1 H), 7.52 (d, *J*=7.8 Hz, 1 H), 7.67 - 7.70 (m, 1 H), 8.36 (s, 1 H), 8.43 - 8.45 (m, 1 H). MS (ESI) *m/z* 299 $(M+H)^+$.

Ejemplo 10

Clorhidrato de 3-metil-1-(5-metil-isoxazol-3-il-metil)-2-piridin-3-il-1H-indol

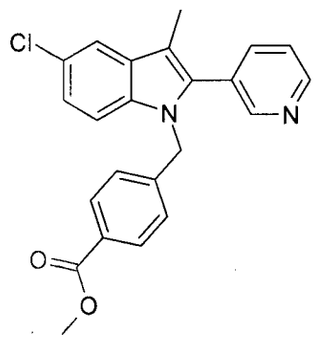


Un matraz se carga con clorhidrato de 3-metil-2-piridin-3-il-1H-indol (Ejemplo 1, 0.100 gramos, 0.408 milimoles) en tetrahidrofurano (2.5 mililitros), y se enfría a 0°C. Se agrega KHMDS (0.5 M en tolueno, 1.8 mililitros, 0.898 milimoles), y la mezcla se agita a temperatura ambiente durante 30 minutos, seguido por la adición de 3-bromo-metil-5-metil-isoxazol (0.144 gramos, 0.817 milimoles). La mezcla de reacción se agita durante 0.5 horas, entonces se apaga con una solución saturada de cloruro de amonio, y se extrae con acetato de etilo. La capa orgánica se seca sobre sulfato de sodio, y se concentra al vacío. El residuo se purifica mediante HPLC en fase inversa con una columna XBridge Shield RP18 y un gradiente de NH_4OH acuoso al 0.1 por ciento en acetonitrilo, para proporcionar el producto de 3-metil-1-(5-metil-isoxazol-3-il-metil)-2-piridin-3-il-1H-indol como un aceite incoloro. El aceite se disuelve en dietil-éter y se agregan unas cuantas gotas de HCl concentrado. Los volátiles se remueven al vacío, y el residuo se liofiliza para proporcionar el producto como un sólido amarillo.

^{1}H RMN (400 MHz, MeOD) δ ppm (sal de HCl) 2.30 (s, 3 H), 2.31 (s, 3 H), 5.30 (s, 2 H), 5.67 (s, 1 H), 7.18 (t, *J*=8.0 Hz, 1 H), 7.27 (ddd, *J*=7.6, 1.1 Hz, 1 H), 7.45 (d, *J*=8.1 Hz, 1 H), 7.56 - 7.69 (m, 2 H), 7.99 (dt, *J*=8.0, 1.9, 1.8 Hz, 1 H), 8.56 - 8.68 (m, 2 H). HRMS (ESI) m/z 304.1440 [$(M+H)^+$ Calculado para $C_{19}H_{18}N_3O$, 304.1450].

Ejemplo 11

Metil-éster del ácido 4-(5-cloro-3-metil-2-piridin-3-il-1H-indol-1-il-metil)-benzoico

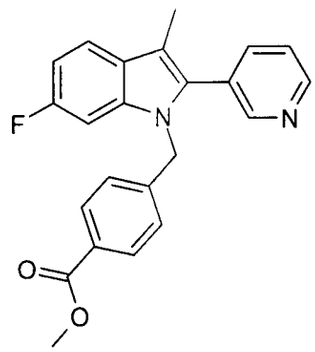


A una solución de clorhidrato de 5-cloro-3-metil-2-piridin-3-il-1H-indol (Ejemplo 2, 558 miligramos, 2.0 milimoles) en tetrahidrofurano (20 mililitros), se le agrega KHMDS 0.5 M en tolueno (8.8 mililitros, 4.4 milimoles), y la mezcla se agita a temperatura ambiente durante 30 minutos, sobre lo cual, se agrega el metil-éster del ácido 4-bromo-metil-benzoico (916 miligramos, 4.0 milimoles). La mezcla de reacción se agita durante 3 horas. Se agrega metanol para apagar la reacción, y los solventes se remueven al vacío. El residuo se purifica mediante cromatografía por evaporación instantánea con del 1 al 3 por ciento de metanol en dicloro-metano, para dar el metil-éster del ácido 4-(5-cloro-3-metil-2-piridin-3-il-1H-indol-1-il-metil)-benzoico.

MS (ESI) *m/z* 391.3 y 393.3 $(M+H)^+$.

Ejemplo 12

Metil-éster del ácido 4-(6-fluoro-3-metil-2-piridin-3-il-1H-indol-1-il-metil)-benzoico

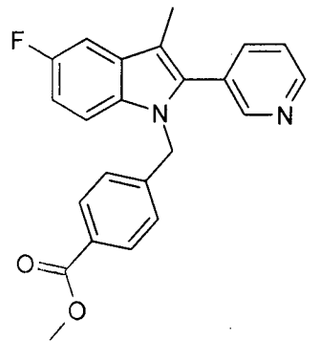


La mezcla de clorhidrato de 4- y 6-fluoro-3-metil-2-piridin-3-il-1H-indol (Ejemplo 4), y metil-éster del ácido 4-bromo-metil-benzoico se procesan de acuerdo con el método descrito en el Ejemplo 11. La separación de los regioisómeros se hace en una X-Bridge RP18 eluyendo con un gradiente del 30 al 70 por ciento de acetonitrilo en NH_4OH al 0.1 por ciento, para dar el metil-éster del ácido 4-(6-fluoro-3-metil-2-piridin-3-il-1H-indol-1-il-metil)-benzoico.

^{1}H RMN (400 MHz, $CDCl_3$) δ ppm 2.30 (s, 3 H), 3.90 (s, 3 H), 5.22 (s, 2 H), 6.86 (dd, *J*=9.8, 2.1 Hz, 1 H), 6.93 - 7.00 (m, 3 H), 7.34 - 7.38 (m, 1 H), 7.55 - 7.61 (m, 2 H), 7.90 - 7.92 (m, 1 H), 7.92 - 7.94 (m, 1 H), 8.59 (dd, *J*=2.3, 0.9 Hz, 1 H), 8.63 (dd, *J*=4.9, 1.6 Hz, 1 H). HRMS (ESI) m/z 375.1498 [$(M+H)^+$ Calculado para $C_{23}H_{20}FN_2O_2$, 375.1509].

Ejemplo 13

Metil-éster del ácido 4-(4-fluoro-3-metil-2-piridin-3-il-1H-indol-1-il-metil)-benzoico

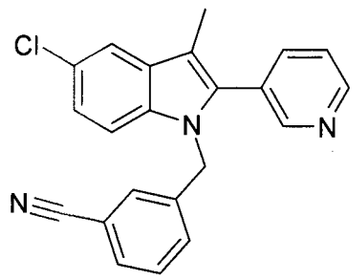


El método descrito en el Ejemplo 12 también proporciona el metil-éster del ácido 4-(4-fluoro-3-metil-2-piridin-3-il-1H-indol-1-il-metil)-benzoico.

MS (ESI) *m/z* 375.2 $(M+H)^+$.

Ejemplo 14

3-(5-cloro-3-metil-2-piridin-3-il-1H-indol-1-il-metil)-benzonitrilo



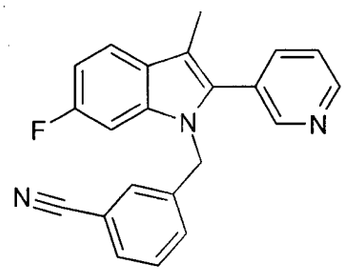
El clorhidrato de 5-cloro-3-metil-2-piridin-3-il-1H-indol (Ejemplo 2), y 3-bromo-metil-benzonitrilo se procesan de acuerdo con el método descrito en el Ejemplo 11, para dar el 3-(5-cloro-3-metil-2-piridin-3-il-1H-indol-1-il-metil)-benzonitrilo.

^{1}H RMN (400 MHz, MeOD) δ ppm 2.25 (s, 3 H), 5.36 (s, 2 H), 7.03 (d, *J*=7.8 Hz, 1 H), 7.14 (s, 1 H), 7.18 (dd, *J*=8.6, 2.0 Hz, 1 H), 7.33 (d, *J*=8.6 Hz, 1 H), 7.36 (t, *J*=7.7 Hz, 1 H), 7.49 - 7.56 (m, 2 H), 7.62 (d, *J*=2.0 Hz, 1 H), 7.81 (dt, *J*=7.8, 1.9 Hz, 1 H), 8.47 (d, *J*=2.3

Hz, 1 H), 8.58 (dd, *J*=5.1, 1.8 Hz, 1 H). HRMS (ESI) m/z 358.1102 [(M+H)$^+$ Calculado para $C_{22}H_{17}ClN_3$, 358.1111].

Ejemplo 15

Clorhidrato de 3-(6-fluoro-3-metil-2-piridin-3-il-1H-indol-1-il-metil)-benzonitrilo

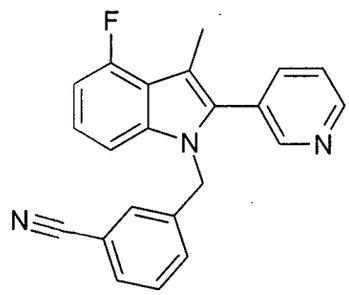


La mezcla de clorhidrato de 4- y 6-fluoro-3-metil-2-piridin-3-il-1H-indol (Ejemplo 4), y 3-bromo-metil-benzonitrilo se procesan de acuerdo con el método descrito en el Ejemplo 11. La separación de los regioisómeros se hace en una Chiralcel® OD, eluyendo con heptano-isopropanol, 4:1, para dar el 3-(6-fluoro-3-metil-2-piridin-3-il-1H-indol-1-il-metil)-benzonitrilo.

^{1}H RMN (400 MHz, DMSO-d_6) δ ppm (sal de HCl) 2.23 (s, 3 H), 5.41 (s, 2 H), 6.96 - 7.06 (m, 2 H), 7.27 (s, 1 H), 7.37 - 7.43 (m, 2 H), 7.62 - 7.69 (m, 2 H), 7.81 (t, *J*=6.3 Hz, 1 H), 8.17 (d, *J*=7.3 Hz, 1 H), 8.75 - 8.82 (m, 2 H). HRMS (ESI) m/z 342.1405 [(M+H)$^+$ Calculado para $C_{22}H_{17}FN_3$: 342.1407]

Ejemplo 16

Clorhidrato de 3-(4-fluoro-3-metil-2-piridin-3-il-1H-indol-1-il-metil)-benzonitrilo

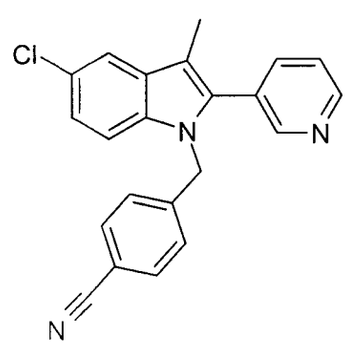


La mezcla de clorhidrato de 4- y 6-fluoro-3-metil-2-piridin-3-il-1H-indol (Ejemplo 4), y 3-bromo-metil-benzonitrilo se procesan de acuerdo con el método descrito en el Ejemplo 11. La separación de los regioisómeros se hace en una Chiralcel® OD eluyendo con heptano-isopropanol, 4:1, para dar el 3-(4-fluoro-3-metil-2-piridin-3-il-1H-indol-1-il-metil)-benzonitrilo.

^{1}H RMN (400 MHz, DMSO-d_6) δ ppm (sal de HCl) 2.33 (s, 3 H), 5.41 (s, 2 H), 6.87 (dd, *J*=11.4, 7.8 Hz, 1 H), 7.06 (d, *J*=7.1 Hz, 1 H), 7.12 - 7.21 (m, 1 H), 7.26 - 7.34 (m, 2 H), 7.42 (t, *J*=7.7 Hz, 1 H), 7.66 (d, *J*=7.6 Hz, 1 H), 7.81 (dd, *J*=7.2, 5.2 Hz, 1 H), 8.18 (d, *J*=7.3 Hz, 1 H), 8.79 (br. s., 2 H). HRMS (ESI) m/z 342.1407 [$(M+H)^+$ Calculado para $C_{22}H_{17}FN_3$: 342.1407].

Ejemplo 17

4-(5-cloro-3-metil-2-piridin-3-il-1H-indol-1-il-metil)-benzonitrilo

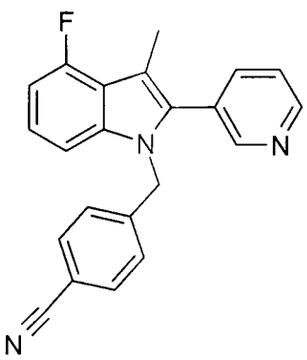


El clorhidrato de 5-cloro-3-metil-2-piridin-3-il-1H-indol (Ejemplo 2), y 4-bromo-metil-benzonitrilo se procesan de acuerdo con el método descrito en el Ejemplo 11, para dar el 4-(5-cloro-3-metil-2-piridin-3-il-1H-indol-1-il-metil)-benzonitrilo.

^{1}H RMN (400 MHz, MeOD) δ ppm 2.28 (s, 3 H), 5.42 (s, 2 H), 6.98 (d, *J*=8.3 Hz, 1 H), 7.20 (dd, *J*=8.6, 2.0 Hz, 1 H), 7.34 (d, *J*=8.8 Hz, 1 H), 7.55 (dd, *J*=7.8, 5.1 Hz, 1 H), 7.57 - 7.62 (m, 2 H), 7.66 (d, *J*=2.0 Hz, 1 H), 7.84 (dt, *J*=7.8, 1.9 Hz, 1 H), 8.50 (d, *J*=2.0 Hz, 1 H), 8.60 (dd, *J*=4.9, 1.6 Hz, 1 H). HRMS (ESI) m/z 358.1120 [$(M+H)^+$ Calculado para $C_{22}H_{17}ClN_3$: 358.1111].

Ejemplo 18

Clorhidrato de 4-(4-fluoro-3-metil-2-piridin-3-il-1H-indol-1-il-metil)-benzonitrilo

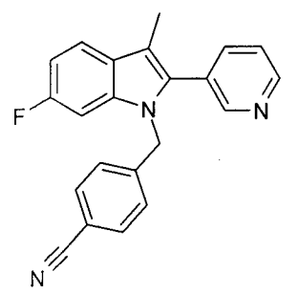


La mezcla de clorhidrato de 4- y 6-fluoro-3-metil-2-piridin-3-il-1H-indol (Ejemplo 4), y 4-bromo-metil-benzonitrilo se procesa de acuerdo con el método descrito en el Ejemplo 11. La separación de los regioisómeros se hace en una Chiralcel® OD eluyendo con heptano-isopropanol, 4:1, para dar el 4-(4-fluoro-3-metil-2-piridin-3-il-1H-indol-1-il-metil)-benzonitrilo.

^{1}H RMN (400 MHz, DMSO-d_6) δ ppm (sal de HCl) 2.34 (s, 3 H), 5.46 (s, 2 H), 6.87 (dd, *J*=11.4, 7.8 Hz, 1 H), 6.96 (d, *J*=8.6 Hz, 2 H), 7.11 - 7.20 (m, 1 H), 7.29 (d, *J*=8.1 Hz, 1 H), 7.68 (d, *J*=8.3 Hz, 2 H), 7.72 - 7.80 (m, 1 H), 8.05 - 8.14 (m, 1 H), 8.71 - 8.79 (m, 2 H). HRMS (ESI) m/z 342.1407 [(M+H)$^+$ Calculado para $C_{22}H_{17}FN_3$: 342.1407].

Ejemplo 19

4-(6-fluoro-3-metil-2-piridin-3-il-1H-indol-1-il-metil)-benzonitrilo

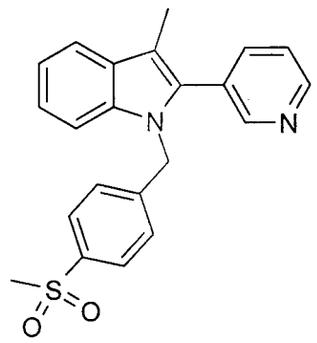


La mezcla de clorhidrato de 4- y 6-fluoro-3-metil-2-piridin-3-il-1H-indol (Ejemplo 4), y 4-bromo-metil-benzonitrilo se procesa de acuerdo con el método descrito en el Ejemplo 11. La separación de los regioisómeros se hace en una Chiralcel® OD eluyendo con heptano-isopropanol, 4:1, para dar el 4-(6-fluoro-3-metil-2-piridin-3-il-1H-indol-1-il-metil)-benzonitrilo.

^{1}H RMN (400 MHz, $CDCl_3$) δ ppm 2.30 (s, 3 H), 5.22 (s, 2 H), 6.83 (dd, *J*=9.7, 2.1 Hz, 1 H), 6.93 - 7.01 (m, 3 H), 7.36 (dd, *J*=7.6, 5.1 Hz, 1 H), 7.49 - 7.63 (m, 4 H), 8.56 (d, *J*=1.3 Hz, 1 H), 8.64 (d, *J*=3.5 Hz, 1 H). HRMS (ESI) m/z 342.1390 [(M+H)$^+$ Calculado para $C_{22}H_{17}FN_3$: 342.1407].

Ejemplo 20

1-(4-metan-sulfonil-bencil)-3-metil-2-piridin-3-il-1H-indol

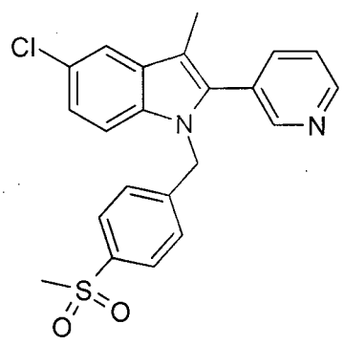


El clorhidrato de 3-metil-2-piridin-3-il-1H-indol (Ejemplo 1), y 1-bromo-metil-4-metan-sulfonil-benceno se procesan de acuerdo con el método descrito en el Ejemplo 11, para dar el 1-(4-metan-sulfonil-bencil)-3-metil-2-piridin-3-il-1H-indol.

^{1}H RMN (400 MHz, MeOD) δ ppm 2.33 (s, 3 H), 3.08 (s, 3 H), 5.46 (s, 2 H), 7.08 (d, *J*=8.1 Hz, 2 H), 7.18 (t, *J*=7.3 Hz, 1 H), 7.24 (t, *J*=7.6 Hz, 1 H), 7.34 (d, *J*=8.1 Hz, 1 H), 7.55 (dd, *J*=7.8, 4.8 Hz, 1 H), 7.68 (d, *J*=7.8 Hz, 1 H), 7.81 (d, *J*=8.3 Hz, 2 H), 7.85 (dt, *J*=7.8, 1.9 Hz, 1 H), 8.52 (d, *J*=2.3 Hz, 1 H), 8.59 (dd, *J*=4.9, 1.6 Hz, 1 H). HRMS (ESI) m/z 377.1318 [$(M+H)^+$ Calculado para $C_{22}H_{21}N_2O_2S$: 377.1324].

Ejemplo 21

5-cloro-1-(4-metan-sulfonil-bencil)-3-metil-2-piridin-3-il-1H-indol

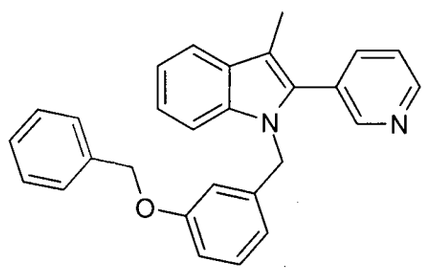


El clorhidrato de 5-cloro-3-metil-2-piridin-3-il-1H-indol (Ejemplo 2), y 1-bromo-metil-4-metan-sulfonil-benceno se procesan de acuerdo con el método descrito en el Ejemplo 11, para dar el 5-cloro-1-(4-metan-sulfonil-bencil)-3-metil-2-piridin-3-il-1H-indol.

^{1}H RMN (400 MHz, MeOD) δ ppm 2.29 (s, 3 H), 3.09 (s, 3 H), 5.46 (s, 2 H), 7.20 (dd, *J*=8.6, 2.0 Hz, 1 H), 7.34 (d, *J*=8.8 Hz, 1 H), 7.53 – 7.57 (m, 1 H), 7.66 (d, *J*=1.8 Hz, 1 H), 7.79 - 7.84 (m, 1 H), 7.86 (dt, *J*=7.9, 2.0 Hz, 1 H), 8.52 (dd, *J*=2.3, 1.0 Hz, 1 H), 8.61 (dd, *J*=5.1, 1.8 Hz, 1 H). HRMS (ESI) m/z 411.0927 [(M+H)$^+$ Calculado para $C_{22}H_{20}N_2O_2SCl$: 411.0934].

Ejemplo 22

1-(3-benciloxi-bencil)-clorhidrato de 3-metil-2-piridin-3-il-1H-indol



El clorhidrato de 3-metil-2-piridin-3-il-1H-indol (Ejemplo 1), y 1-benciloxi-4-bromo-metil-benceno se procesan de acuerdo con el método descrito en el Ejemplo 11, para dar el 1-(3-benciloxi-bencil)-3-metil-2-piridin-3-il-1H-indol.

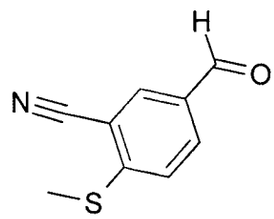
^{1}H RMN (400 MHz, MeOD) δ ppm (sal de HCl) 2.31 (s, 3 H), 4.91 (s, 2 H), 5.28 (s, 2 H), 6.37 (s, 1 H), 6.45 (d, *J*=7.6 Hz, 1 H), 6.82 (dd, *J*=8.2, 2.1 Hz, 1 H), 7.12 (t, *J*=7.8 Hz, 1 H), 7.16 - 7.22 (m, 1 H), 7.22 - 7.38 (m, 7 H), 7.61 (dd, *J*=8.0, 5.2 Hz, 1 H), 7.68 (d,

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J=7.8 Hz, 1 H), 7.85 (dt, *J*=8.0, 1.8 Hz, 1 H), 8.46 (d, *J*=1.3 Hz, 1 H), 8.60 (dd, *J*=5.1, 1.5 Hz, 1 H). HRMS (ESI) m/z 405.1969 [$(M+H)^+$ Calculado para $C_{28}H_{25}N_2O$: 405.1967].

Ejemplo 23

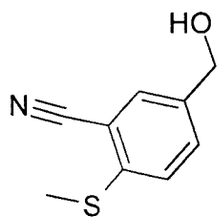
(a) 5-formil-2-metil-sulfanil-benzonitrilo



Un matraz se carga con 5-fluoro-2-formil-benzonitrilo (0.200 gramos, 1.34 milimoles), carbonato de potasio (0.371 gramos, 0.268 milimoles), tiometóxido de sodio (0.142 gramos, 2.01 milimoles), y dimetil-formamida (20 mililitros). La mezcla se agita a temperatura ambiente durante 10 minutos, entonces se diluye con acetato de etilo y se lava con agua. La capa orgánica se seca sobre sulfato de sodio, y se concentra al vacío, para proporcionar el 5-formil-2-metil-sulfanil-benzonitrilo como un sólido color amarillo.

^{1}H RMN (400 MHz, $CDCl_3$) δ ppm 2.64 (s, 3 H), 7.41 (d, *J*=8.3 Hz, 1 H), 8.01 (dd, *J*=8.5, 1.9 Hz, 1 H), 8.07 (d, *J*=1.8 Hz, 1 H), 9.95 (s, 1 H).

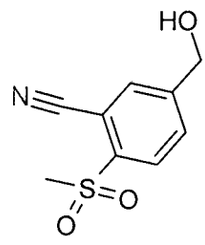
(b) 5-hidroxi-metil-2-metil-sulfanil-benzonitrilo



Un matraz se carga con 5-formil-2-metil-sulfanil-benzonitrilo (1.0 gramos, 5.68 milimoles) en metanol (20 mililitros), y se enfría a 0°C. Se agrega borohidruro de sodio (1.07 gramos, 28.40 milimoles), y la mezcla se agita a temperatura ambiente durante 2 horas, seguido por la remoción del solvente al vacío. El residuo se vuelve a disolver en dicloro-metano y se lava con agua dos veces. La capa orgánica se seca sobre sulfato de sodio, y se concentra al vacío, para proporcionar el 5-hidroxi-metil-2-metil-sulfanil-benzonitrilo como un sólido blanco.

^{1}H RMN (400 MHz, $CDCl_3$) δ ppm 2.57 (s, 3 H), 4.70 (d, *J*=5.1 Hz, 2 H), 7.33 (d, *J*=8.3 Hz, 1 H), 7.53 (dd, *J*=8.3, 1.0 Hz, 1 H), 7.62 (s, 1 H).

(c) 5-hidroxi-metil-2-metan-sulfonil-benzonitrilo



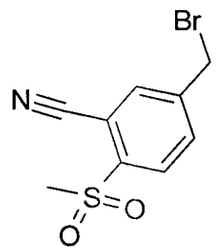
Un matraz se carga con 5-hidroxi-metil-2-metil-sulfanil-benzonitrilo (0.866 gramos, 4.86 milimoles) en una mezcla de metanol (10 mililitros), y agua (10 mililitros). Se agrega oxono (7.47 gramos, 12.16 milimoles), y la mezcla se agita a temperatura ambiente durante 16 horas. El residuo se acidifica a un pH de 1 utilizando HCl 1M acuoso, y entonces se extrae con dicloro-metano

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dos veces. La capa orgánica se seca sobre sulfato de sodio, y se concentra al vacío, para proporcionar el 5-hidroxi-metil-2-metan-sulfonil-benzonitrilo como un sólido blanco.

^{1}H RMN (400 MHz, $CDCl_3$) δ ppm 3.28 (s, 3 H), 4.89 (s, 2 H), 7.80 (d, *J*=8.1 Hz, 1 H), 7.95 (s, 1 H), 8.18 (d, *J*=8.1 Hz, 1 H).

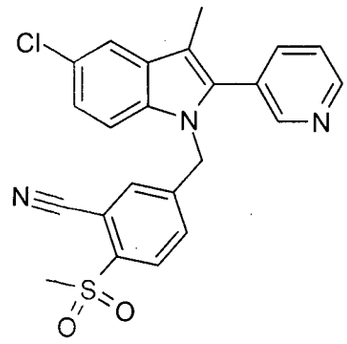
(d) 5-bromo-metil-2-metan-sulfonil-benzonitrilo



Un matraz se carga con el 5-hidroxi-metil-2-metil-sulfonil-benzonitrilo (0.788 gramos, 3.73 milimoles) en tolueno (5 mililitros), y se calienta a 40°C. Se agrega PBr_3 (0.175 mililitros, 1.86 milimoles), y la reacción se pone a reflujo durante 0.5 horas. Se enfría entonces a temperatura ambiente, se diluye con dicloro-metano, y se lava con agua. La capa acuosa se extrae con dicloro-metano. La capa orgánica combinada se seca sobre sulfato de sodio, y se concentra al vacío, para proporcionar el 5-bromo-metil-2-metan-sulfonil-benzonitrilo como un sólido blanco.

^{1}H RMN (400 MHz, $CDCl_3$) δ ppm 3.28 (s, 3 H), 4.89 (s, 2 H), 7.80 (d, *J*=8.3 Hz, 1 H), 7.94 (s, 1 H), 8.18 (d, *J*=8.1 Hz, 1 H).

(e) 2-metan-sulfonil-5-(3-metil-2-piridin-3-il-indol-1-il-metil)-benzonitrilo

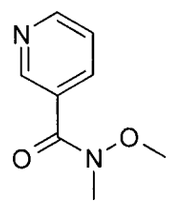


El producto del Ejemplo 1 se procesa de acuerdo con el método descrito en el Ejemplo 11, para dar el 2-metan-sulfonil-5-(3-metil-2-piridin-3-il-indol-1-il-metil)-benzonitrilo.

^{1}H RMN (400 MHz, MeOD) δ ppm 2.35 (s, 3 H), 3.27 (s, 3 H), 5.53 (s, 2 H), 7.19 - 7.31 (m, 3 H), 7.37 (d, *J*=8.1 Hz, 1 H), 7.51 (d, *J*=1.3 Hz, 1 H), 7.65 (dd, *J*=7.8, 5.1 Hz, 1 H), 7.71 (d, *J*=7.6 Hz, 1 H), 7.98 (d, *J*=7.6 Hz, 1 H), 8.02 (d, *J*=8.1 Hz, 1 H), 8.60 (d, *J*=1.8 Hz, 1 H), 8.65 (dd, *J*=5.1, 1.5 Hz, 1 H). HRMS (ESI) m/z 402.1269 [(M+H)$^+$ Calculado para $C_{23}H_{20}N_3O_2S$: 402.1276].

Ejemplo 24

(a) *N*-metil-*N*-metoxi-nicotinamida

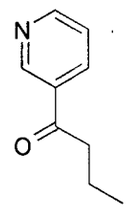


Un matraz se carga con el ácido nicotínico (5.0 gramos, 40.6 milimoles). Se agrega cloruro de tionilo (30.0 mililitros), y la reacción se pone a reflujo durante 1 hora. Se enfría entonces a temperatura ambiente, y se concentra al vacío. El residuo se disuelve en dicloro-

metano anhidro (30 mililitros), y se agrega *O*,*N*-dimetil-hidroxilamina (4.35 gramos, 44.0 milimoles), seguida por la adición de trietil-amina (14.15 gramos, 100.0 milimoles). La mezcla de reacción se agita a temperatura ambiente durante 1.5 horas. Luego se lava con agua, y la fase acuosa se extrae con dicloro-metano. La capa orgánica combinada se seca sobre sulfato de sodio, y se concentra al vacío, para proporcionar la *N*-metil-*N*-metoxi-nicotinamida como un aceite color café.

MS (ESI) *m/z* 167.0 $(M+H)^+$.

(b) 1-piridin-3-il-butan-1-ona

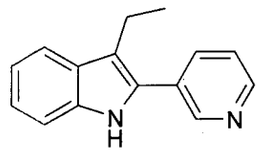


Un matraz se carga con *N*-metil-*N*-metoxi-nicotinamida (1.0 gramos, 6.02 milimoles), y tetrahidrofurano (10 mililitros). Se agrega cloruro de propil-magnesio (2M en tetrahidrofurano, 3.31 mililitros, 6.62 milimoles), y la mezcla se agita a temperatura ambiente durante la noche. Se apaga con una solución saturada de bicarbonato de sodio, y se extrae con dicloro-metano. La capa orgánica combinada se seca sobre sulfato de sodio, y se concentra al vacío, para proporcionar la 1-piridin-3-il-butan-1-ona como un aceite color amarillo.

^{1}H RMN (400 MHz, $CDCl_3$) δ ppm 1.03 (t, *J*=7.5 Hz, 3 H), 1.74 - 1.87 (m, 2 H), 2.97 (t, *J*=7.3 Hz, 2 H), 7.42 (dd, *J*=8.0, 4.9 Hz, 1 H),

8.24 (dt, *J*=8.0, 2.0, 1.9 Hz, 1 H), 8.78 (dd, *J*=4.9, 2.0 Hz, 1 H), 9.18 (d, *J*=2.0 Hz, 1 H).

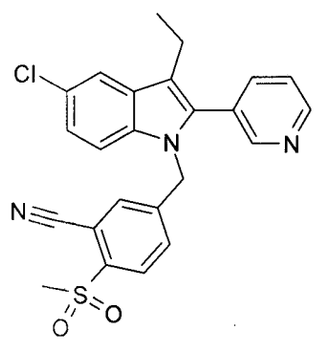
(c) 3-etil-2-piridin-3-il-1H-indol



Un matraz se carga con fenil-hidrazina (0.873 gramos, 6.46 milimoles), y EtOH (14 mililitros). Se agrega 1-piridin-3-il-butan-1-ona (0.914 gramos, 6.13 milimoles), y la reacción se pone a reflujo durante 1 hora. Después de enfriar a temperatura ambiente, se agrega HCl (4M en 1,4-dioxano, 6.45 mililitros, 25.83 milimoles). La mezcla de reacción se pone a reflujo durante 4 horas. Después de enfriar a temperatura ambiente, el precipitado formado se filtra para proporcionar el 3-etil-2-piridin-3-il-1H-indol como un sólido amarillo.

MS (ESI) *m/z* 223.0 $(M+H)^+$.

(d) 2-metan-sulfonil-5-(3-etil-2-piridin-3-il-indol-1-il-metil)-benzonitrilo



El 3-etil-2-piridin-3-il-1H-indol y 2-metan-sulfonil-5-(3-etil-2-piridin-3-il-indol-1-il-metil)-benzonitrilo (Ejemplo 23d) se procesan de

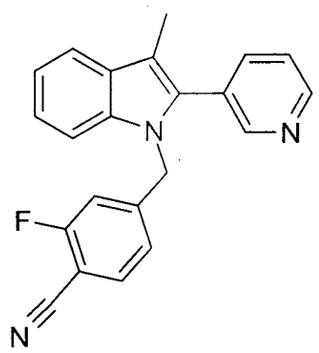
acuerdo con el método descrito en el Ejemplo 11, para dar el 2-metan-sulfonil-5-(3-etil-2-piridin-3-il-indol-1-il-metil)-benzonitrilo.

^{1}H RMN (400 MHz, MeOD) δ ppm 1.27 (t, *J*=7.6 Hz, 3 H), 2.77 (q, *J*=7.6 Hz, 2 H), 3.27 (s, 3 H), 5.49 (s, 2 H), 7.14 - 7.31 (m, 3 H), 7.37 (d, *J*=8.1 Hz, 1 H), 7.49 (s, 1 H), 7.57 (dd, *J*=7.8, 5.1 Hz, 1 H), 7.74 (d, *J*=7.8 Hz, 1 H), 7.86 (dt, *J*=7.8, 1.8 Hz, 1 H), 8.03 (d, *J*=8.3 Hz, 1 H), 8.51 (d, *J*=2.0 Hz, 1 H), 8.62 (dd, *J*=4.9, 1.4 Hz, 1 H).

HRMS (ESI) m/z 416.1424 [$(M+H)^+$ Calculado para $C_{24}H_{22}N_3O_2S$: 416.1433].

Ejemplo 25

3-fluoro-4-(3-metil-2-piridin-3-il-1H-indol-1-il-metil)-benzonitrilo



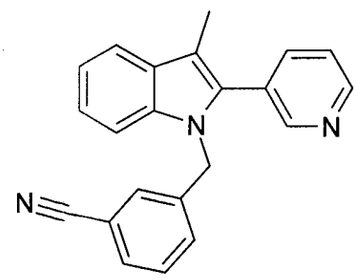
Un matraz se carga con clorhidrato de 3-metil-2-piridin-3-il-1H-indol (Ejemplo 1, 0.080 gramos, 0.326 milimoles), y dimetil-formamida (1.5 mililitros), y se agrega NaH al 60 por ciento en aceite mineral (0.028 gramos, 0.719 milimoles). La mezcla se agita a temperatura ambiente durante 20 minutos, seguido por la adición de 4-bromo-metil-3-fluoro-benzonitrilo (0.175 gramos, 0.817 milimoles). La mezcla de reacción se agita a temperatura ambiente durante 30 minutos. El residuo se diluye con dimetil-formamida (1.5 mililitros),

se filtra, y se purifica mediante HPLC en fase inversa con una columna XBridge Shield RP18 y un gradiente de NH_4OH acuoso al 0.1 por ciento en acetonitrilo, para proporcionar el 3-fluoro-4-(3-metil-2-piridin-3-il-indol-1-il-metil)-benzonitrilo como un sólido amarillo.

^{1}H RMN (400 MHz, MeOD) δ ppm 2.32 (s, 3 H), 5.47 (s, 2 H), 6.62 (t, *J*=7.6 Hz, 1 H), 7.20 (t, *J*=7.5 Hz, 1 H), 7.27 (t, *J*=7.6 Hz, 1 H), 7.38 (d, *J*=8.1 Hz, 2 H), 7.50 (d, *J*=9.9 Hz, 1 H), 7.56 (dd, *J*=7.8, 4.8 Hz, 1 H), 7.68 (d, *J*=7.8 Hz, 1 H), 7.86 (dd, *J*=7.8, 1.8 Hz, 1 H), 8.52 (s, 1 H), 8.60 (dd, *J*=4.9, 1.6 Hz, 1 H). HRMS (ESI) m/z 342.1394 [$(M+H)^+$ Calculado para $C_{22}H_{17}FN_3$: 342.1407].

Ejemplo 26

3-(3-metil-2-piridin-3-il-1H-indol-1-il-metil)-benzonitrilo



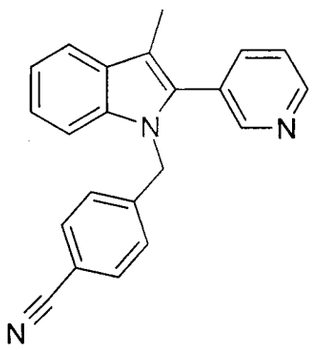
El clorhidrato de 3-metil-2-piridin-3-il-1H-indol (Ejemplo 1), y 3-bromo-metil-benzonitrilo se procesan de acuerdo con el método descrito en el Ejemplo 25, para dar el 3-(3-metil-2-piridin-3-il-1H-indol-1-il-metil)-benzonitrilo.

^{1}H RMN (400 MHz, MeOD) δ ppm 2.33 (s, 3 H), 5.41 (s, 2 H), 7.08 (d, *J*=8.1 Hz, 1 H), 7.16 (s, 1 H), 7.20 (t, *J*=7.2 Hz, 1 H), 7.27 (ddd, *J*=7.6, 1.0 Hz, 1 H), 7.37 (d, *J*=5.8 Hz, 1 H), 7.38 - 7.42 (m, 1

H), 7.54 - 7.57 (m, 1 H), 7.57 (s, 1 H), 7.68 (d, *J*=7.8 Hz, 1 H), 7.85 (dt, *J*=7.8, 1.9 Hz, 1 H), 8.50 (d, *J*=2.0 Hz, 1 H), 8.60 (dd, *J*=4.8, 1.5 Hz, 1 H). HRMS (ESI) m/z 324.1491 [$(M+H)^+$ Calculado para $C_{22}H_{18}N_3$: 324.1501].

Ejemplo 27

4-(3-metil-2-piridin-3-il-1H-indol-1-il-metil)-benzonitrilo

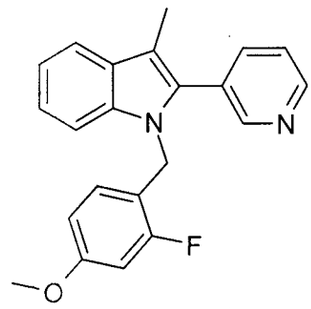


El clorhidrato de 3-metil-2-piridin-3-il-1H-indol (Ejemplo 1), y 4-bromo-metil-benzonitrilo se procesan de acuerdo con el método descrito en el Ejemplo 25, para dar el 4-(3-metil-2-piridin-3-il-1H-indol-1-il-metil)-benzonitrilo.

^{1}H RMN (400 MHz, MeOD) δ ppm 2.32 (s, 3 H), 5.43 (s, 2 H), 6.99 (d, *J*=8.6 Hz, 2 H), 7.13 - 7.21 (m, 1 H), 7.25 (ddd, *J*=7.6, 1.3 Hz, 1 H), 7.34 (d, *J*=8.1 Hz, 1 H), 7.54 (dd, *J*=8.0, 4.9 Hz, 2 H), 7.58 (d, *J*=8.3 Hz, 1 H), 7.67 (d, *J*=7.6 Hz, 1 H), 7.84 (dt, *J*=7.9, 2.0 Hz, 1 H), 8.50 (d, *J*=1.5 Hz, 1 H), 8.59 (dd, *J*=4.9, 1.6 Hz, 1 H). HRMS (ESI) m/z 324.1501 [$(M+H)^+$ Calculado para $C_{22}H_{18}N_3$: 324.1501].

Ejemplo 28

1-(2-fluoro-4-metoxi-bencil)-clorhidrato de 3-metil-2-piridin-3-il-1H-indol

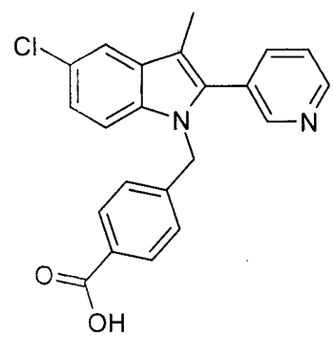


El clorhidrato de 3-metil-2-piridin-3-il-1H-indol (Ejemplo 1), y 4-bromo-metil-2-fluoro-1-metoxi-benceno se procesan de acuerdo con el método descrito en el Ejemplo 25, para dar el 1-(2-fluoro-4-metoxi-bencil)-clorhidrato de 3-metil-2-piridin-3-il-1H-indol.

^{1}H RMN (400 MHz, MeOD) δ ppm (sal de HCl) 2.38 (s, 3 H), 3.82 (s, 3 H), 5.35 (s, 2 H), 6.54 - 6.62 (m, 2 H), 6.94 (t, *J*=8.6 Hz, 1 H), 7.22 (ddd, *J*=7.5, 0.9 Hz, 1 H), 7.33 (ddd, *J*=7.6, 1.1 Hz, 1 H), 7.45 (d, *J*=8.3 Hz, 1 H), 7.72 (d, *J*=7.8 Hz, 1 H), 8.12 (dd, *J*=8.2, 5.7 Hz, 1 H), 8.54 (dt, *J*=8.1, 1.6 Hz, 1 H), 8.80 - 8.89 (m, 2 H). HRMS (ESI) m/z 347.1568 [$(M+H)^+$ Calculado para $C_{22}H_{20}FN_2O$: 347.1560].

Ejemplo 29

Ácido 4-(5-cloro-3-metil-2-piridin-3-il-1H-indol-1-il-metil)-benzoico



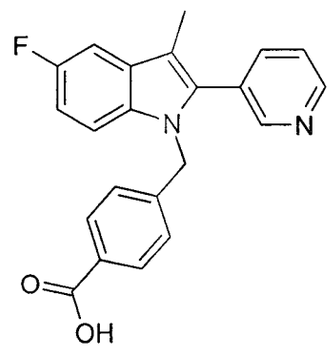
El metil-éster del ácido 4-(5-cloro-3-metil-2-piridin-3-il-1H-

indol-1-il-metil)-benzoico (Ejemplo 11, 200 miligramos, 0.51 milimoles) en metanol (5 mililitros) se agrega al NaOH acuoso 5M (1 mililitro, 5 milimoles), y la mezcla se agita a temperatura ambiente durante 5 horas. Se agrega HCl concentrado (4.4 mililitros) para neutralizar la mezcla de reacción, y los solventes se remueven al vacío. El residuo se vuelve a disolver en metanol, y se purifica mediante HPLC en fase inversa con una columna XBridge Shield RP18 y un gradiente de NH_4OH al 0.1 por ciento en acetonitrilo, para proporcionar el ácido 4-(5-cloro-3-metil-2-piridin-3-il-1H-indol-1-il-metil)-benzoico.

^{1}H RMN (400 MHz, MeOD) δ ppm 2.25 (s, 3 H), 5.34 (s, 2 H), 6.82 (d, *J*=8.1 Hz, 2 H), 7.15 (dd, *J*=8.6, 2.0 Hz, 1 H), 7.31 (d, *J*=8.6 Hz, 1 H), 7.50 (dd, *J*=7.7, 4.9 Hz, 1 H), 7.61 (d, *J*=2.0 Hz, 1 H), 7.78 - 7.80 (m, 1 H), 7.81 (d, *J*=8.1 Hz, 2 H), 8.50 (s, 1 H), 8.56 (br. s, 1 H). HRMS (ESI) m/z 377.1072 [$(M+H)^+$ Calculado para $C_{22}H_{18}ClN_2O_2$: 377.1057].

Ejemplo 30

Ácido 4-(5-fluoro-3-metil-2-piridin-3-il-1H-indol-1-il-metil)-benzoico



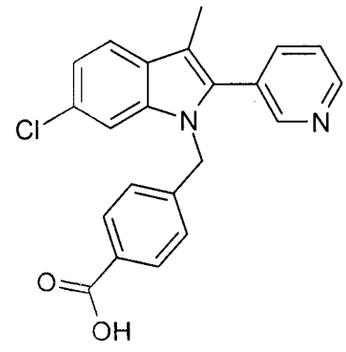
El 5-fluoro-3-metil-2-piridin-3-il-1H-indol (Ejemplo 3) se

procesa de acuerdo con el método del Ejemplo 11, para dar el metil-éster del ácido 4-(5-fluoro-3-metil-2-piridin-3-il-1H-indol-1-il-metil)-benzoico. El metil-éster del ácido 4-(5-fluoro-3-metil-2-piridin-3-il-1H-indol-1-il-metil)-benzoico se procesa de acuerdo con el método descrito en el Ejemplo 29, para dar el ácido 4-(5-fluoro-3-metil-2-piridin-3-il-1H-indol-1-il-metil)-benzoico.

^{1}H RMN (400 MHz, MeOD) δ ppm 2.25 (s, 3 H), 5.36 (s, 2 H), 6.88 (d, *J*=8.6 Hz, 2 H), 6.94 - 7.00 (m, 1 H), 7.28 - 7.29 (m, 1 H), 7.30 - 7.32 (m, 1 H), 7.49 - 7.53 (m, 1 H), 7.78 - 7.82 (m, 1 H), 7.82 - 7.86 (m, 2 H), 8.47 - 8.49 (m, 1 H), 8.56 (dd, *J*=4.9, 1.6 Hz, 1 H). HRMS (ESI) m/z 361.1360 [$(M+H)^+$ Calculado para $C_{22}H_{18}FN_2O_2$: 361.1352].

Ejemplo 31

Ácido 4-(6-cloro-3-metil-2-piridin-3-il-1H-indol-1-il-metil)-benzoico



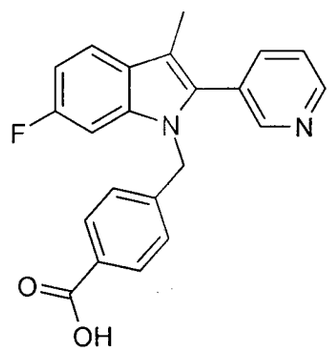
Una mezcla de 4- y 6-cloro-3-metil-2-piridin-3-il-1H-indol (Ejemplo 5) se procesa de acuerdo con el método del Ejemplo 11, para dar el metil-éster del ácido 4-(6-cloro-3-metil-2-piridin-3-il-1H-indol-1-il-metil)-benzoico y el metil-éster del ácido 4-(4-cloro-3-metil-2-piridin-3-il-1H-indol-1-il-metil)-benzoico. Esta mezcla se procesa

de acuerdo con el método descrito en el Ejemplo 29, para dar el ácido 4-(6-cloro-3-metil-2-piridin-3-il-1H-indol-1-il-metil)-benzoico después de la purificación mediante HPLC en fase inversa.

^{1}H RMN (400 MHz, MeOD) δ ppm (sal de TFA) 2.30 (s, 3 H), 5.41 (s, 2 H), 6.89 (d, *J*=8.6 Hz, 2 H), 7.15 (dd, *J*=8.3, 1.8 Hz, 1 H), 7.44 (d, *J*=1.8 Hz, 1 H), 7.64 (d, *J*=8.6 Hz, 1 H), 7.81 - 7.88 (m, 3 H), 8.20 - 8.27 (m, 1 H), 8.68 (br. s., 1 H), 8.70 - 8.73 (m, 1 H). HRMS (ESI) m/z 377.1050 [(M+H)$^+$ Calculado para $C_{22}H_{18}ClN_2O_2$: 377.1057].

Ejemplo 32

Ácido 4-(6-fluoro-3-metil-2-piridin-3-il-1H-indol-1-il-metil)-benzoico



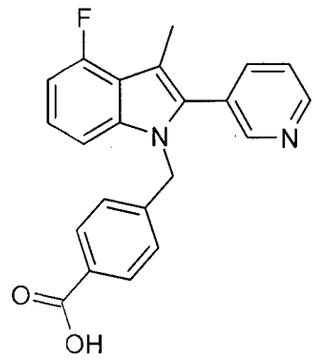
El metil-éster del ácido 4-(6-fluoro-3-metil-2-piridin-3-il-1H-indol-1-il-metil)-benzoico (Ejemplo 12) se procesa de acuerdo con el método descrito en el Ejemplo 29, para dar el ácido 4-(6-fluoro-3-metil-2-piridin-3-il-1H-indol-1-il-metil)-benzoico.

^{1}H RMN (400 MHz, MeOD) δ ppm (sal de TFA) 2.31 (s, 3 H), 5.40 (s, 2 H), 6.90 (d, *J*=8.6 Hz, 2 H), 6.93 - 7.00 (m, 1 H), 7.15 (dd, *J*=10.0, 2.1 Hz, 1 H), 7.65 (dd, *J*=8.8, 5.3 Hz, 1 H), 7.86 (d, *J*=8.6 Hz, 2 H), 7.88 - 7.92 (m, 1 H), 8.27 - 8.31 (m, 1 H), 8.70 (d, *J*=1.8 Hz, 1 H), 8.72 (dd, *J*=5.6, 1.5 Hz, 1 H). HRMS (ESI) m/z 361.1360 [(M+H)$^+$

Calculado para $C_{22}H_{18}FN_2O_2$: 361.1352].

Ejemplo 33

Ácido 4-(4-fluoro-3-metil-2-piridin-3-il-1H-indol-1-il-metil)-benzoico

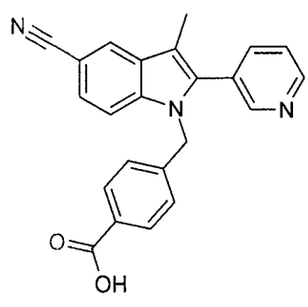


El metil-éster del ácido 4-(4-fluoro-3-metil-2-piridin-3-il-1H-indol-1-il-metil)-benzoico (Ejemplo 13) se procesa de acuerdo con el método descrito en el Ejemplo 29, para dar el ácido 4-(4-fluoro-3-metil-2-piridin-3-il-1H-indol-1-il-metil)-benzoico.

^{1}H RMN (400 MHz, DMSO-d_6) δ ppm 2.32 (s, 3 H), 5.37 (s, 2 H), 6.81 - 6.88 (m, 3 H), 7.08 - 7.15 (m, 1 H), 7.26 (d, *J*=8.1 Hz, 1 H), 7.50 (dd, *J*=7.8, 4.8 Hz, 1 H), 7.74 (d, *J*=8.3 Hz, 2 H), 7.77 - 7.81 (m, 1 H), 8.55 (d, *J*=1.5 Hz, 1 H), 8.62 (dd, *J*=4.9, 1.6 Hz, 1 H). MS (ESI) *m/z* 361.09 $(M+H)^+$.

Ejemplo 34

Ácido 4-(5-ciano-3-metil-2-piridin-3-il-1H-indol-1-il-metil)-benzoico



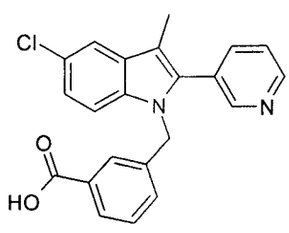
El 5-ciano-3-metil-2-piridin-3-il-indol (Ejemplo 6) se procesa de acuerdo con el método descrito en el Ejemplo 11, para dar el metil-éster del ácido 4-(5-ciano-3-metil-2-piridin-3-il-indol-1-il-metil)-benzoico. A una solución del metil-éster del ácido 4-(5-ciano-3-metil-2-piridin-3-il-indol-1-il-metil)-benzoico (80 miligramos, 0.21 milimoles) en metanol (5 mililitros), y tetrahidrofurano (5 mililitros), se le agrega hidróxido de litio acuoso 1M (2.5 mililitros, 2.5 milimoles), y la mezcla se agita durante la noche a temperatura ambiente. Los volátiles se remueven al vacío, y el residuo se vuelve a disolver en N,N-dimetil-formamida, y se purifica mediante XBridge RP18 con un gradiente de hidróxido de amonio acuoso al 0.1 por ciento en acetonitrilo, para dar el ácido 4-(5-ciano-3-metil-2-piridin-3-il-indol-1-il-metil)-benzoico.

^{1}H RMN (400 MHz, DMSO-d_6) δ ppm 2.25 (s, 3 H), 5.40 (s, 2 H), 6.71 (d, *J*=8.1 Hz, 2 H), 7.47 - 7.55 (m, 2 H), 7.66 (t, *J*=8.6 Hz, 3 H), 7.79 - 7.83 (m, 1 H), 8.20 (d, *J*=1.3 Hz, 1 H), 8.58 (d, *J*=1.5 Hz, 1 H), 8.64 (dd, *J*=4.8, 1.5 Hz, 1 H).

HRMS (ESI) m/z 368.1396 [$(M+H)^+$ Calculado para $C_{23}H_{18}N_3O_2$: 368.1399].

Ejemplo 35

Ácido 3-(5-cloro-3-metil-2-piridin-3-il-indol-1-il-metil)-benzoico

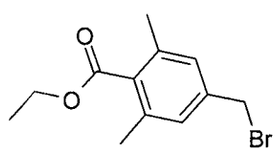


El 3-(5-cloro-3-metil-2-piridin-3-il-indol-1-il-metil)-benzonitrilo (Ejemplo 14, 200 miligramos, 0.56 milimoles) en ácido acético (3 mililitros) se agrega a una solución acuosa de HCl al 20 por ciento (3 mililitros). La mezcla de reacción se pone a reflujo durante 3 días. Los volátiles se remueven al vacío, y el residuo se vuelve a disolver en metanol, y se purifica mediante HPLC en fase inversa con XBridge Shield RP18 y un gradiente de NH_4OH al 0.1 por ciento en acetonitrilo, para dar el ácido 3-(5-cloro-3-metil-2-piridin-3-il-indol-1-il-metil)-benzoico.

^1H RMN (400 MHz, DMSO-d_6) δ ppm 2.21 (s, 3 H), 5.36 (s, 2 H), 6.83 (d, *J*=7.1 Hz, 1 H), 7.13 - 7.23 (m, 2 H), 7.43 - 7.52 (m, 3 H), 7.64 - 7.70 (m, 2 H), 7.74 - 7.81 (m, 1 H), 8.55 (s, 1 H), 8.61 - 8.62 (m, 1 H). HRMS (ESI) m/z 377.1058 [$(M+H)^+$ Calculado para $C_{22}H_{18}ClN_2O_2$: 377.1057].

Ejemplo 36

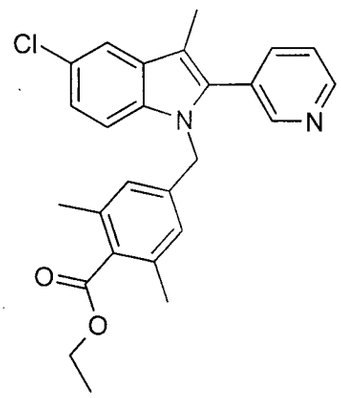
(a) Etil-éster del ácido 4-bromo-metil-2,6-dimetil-benzoico



El etil-2,4,6-trimetil-benceno (4.20 gramos, 21.41 milimoles), y *N*-bromo-succinimida (4.23 gramos, 23.55 milimoles) se absorben en tetracloruro de carbono (200 mililitros), y se agrega peróxido de benzoílo (0.53 gramos, 2.14 milimoles). La suspensión se calienta a reflujo. Después de 4 horas, la mezcla se diluye con dicloro-metano, se lava con bicarbonato de sodio acuoso saturado, agua y salmuera,

se seca y se concentra al vacío. El residuo se purifica mediante cromatografía por evaporación instantánea en gel de sílice (heptano-acetato de etilo, del 1 al 5 por ciento), para dar el etil-éster del ácido 4-bromo-metil-2,6-dimetil-benzoico parcialmente purificado, el cual se lleva al siguiente paso sin mayor purificación.

(b) Etil-éster del ácido 2,6-dimetil-4-(5-cloro-3-metil-2-piridin-3-il-indol-1-il-metil)-benzoico

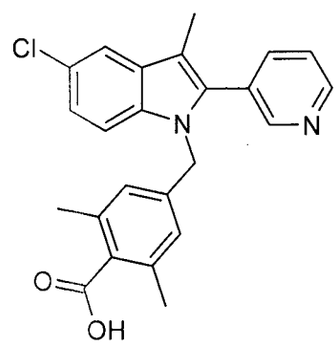


El 5-cloro-3-metil-2-piridin-3-il-1H-indol (Ejemplo 2, 1.350 gramos, 4.659 milimoles) se suspende en tetrahidrofurano (40 mililitros), y se enfría a 0°C. Se agrega por goteo KHMDS (0.5M en tolueno, 32.6 mililitros, 16.3 milimoles). Después de 1 hora, se agrega por goteo el etil-éster del ácido 4-bromo-metil-2,6-dimetil-benzoico (4.95 gramos, 18.2 milimoles) en tetrahidrofurano (10 mililitros). La mezcla se deja calentar a temperatura ambiente durante la noche. La mezcla entonces se apaga con cloruro de amonio acuoso saturado y se diluye con dicloro-metano. La fase acuosa se extrae con acetato de etilo, se seca sobre $MgSO_4$, se filtra, y se concentra al vacío. La purificación del residuo mediante

cromatografía en gel de sílice (dicloro-metano : metanol, de 1:0 a 99:1 a 49:1 a 97:3), proporciona el etil-éster del ácido 2,6-dimetil-4-(5-cloro-3-metil-2-piridin-3-il-indol-1-il-metil)-benzoico como un sólido color naranja.

MS (ESI) *m/z* 399 $(M+H)^+$.

(c) Ácido 2,6-dimetil-4-(5-cloro-3-metil-2-piridin-3-il-indol-1-il-metil)-benzoico



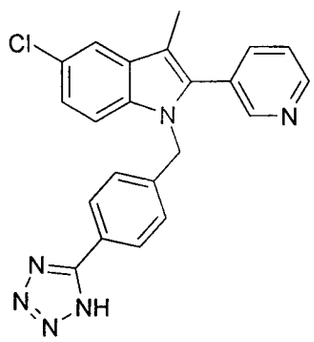
A una solución a reflujo de yoduro de litio (0.218 gramos, 1.626 milimoles) en 2,6-lutidina (5 mililitros), se le agrega el etil-éster del ácido 2,6-dimetil-4-(5-cloro-3-metil-2-piridin-3-il-indol-1-il-metil)-benzoico (0.176 gramos, 0.407 milimoles). La reacción se pone a reflujo durante la noche. Se enfría a temperatura ambiente, se acidifica a un pH de 1 utilizando una solución acuosa de HCl 1M, y se extrae con dicloro-metano. La capa orgánica se seca sobre sulfato de sodio, y se concentra al vacío. El residuo se purifica mediante HPLC en fase inversa con una columna XBridge Shield RP18 y un gradiente de NH_4OH acuoso al 0.1 por ciento en acetonitrilo, para proporcionar ácido 2,6-dimetil-4-(5-cloro-3-metil-2-piridin-3-il-indol-1-

il-metil)-benzoico como un sólido.

^{1}H RMN (400 MHz, MeOD) δ ppm 2.22 (s, 6 H), 2.28 (s, 3 H), 5.22 (s, 2 H), 6.49 (s, 2 H), 7.15 (dd, *J*=8.6, 2.0 Hz, 1 H), 7.30 (d, *J*=8.8 Hz, 1 H), 7.51 - 7.57 (m, 1 H), 7.61 (d, *J*=1.8 Hz, 1 H), 7.81 (dt, *J*=8.1, 2.0, 1.8 Hz, 1 H), 8.58 (d, *J*=1.3 Hz, 1 H), 8.61 (dd, *J*=4.9, 1.6 Hz, 1 H). HRMS (ESI) m/z 405.1379 [(M+H)$^+$ Calculado para $C_{24}H_{21}ClN_2O_2$: 405.1370].

Ejemplo 37

5-cloro-3-metil-2-piridin-3-il-1-[4-(2H-tetrazol-5-il)-bencil]-1H-indol



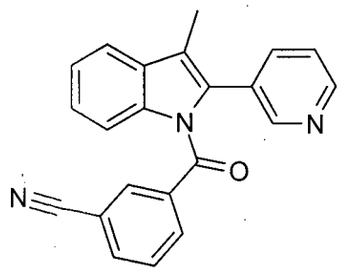
A una solución de 4-(5-cloro-3-metil-2-piridin-3-il-indol-1-il-metil)-benzonitrilo (Ejemplo 17, 179 miligramos, 0.5 milimoles) en N,N-dimetil-formamida (5 mililitros), se le agregan azida de sodio (97 miligramos, 1.5 milimoles), y cloruro de amonio (80 miligramos, 1.5 milimoles), y la mezcla se calienta a 120°C. La mezcla de reacción se enfría a temperatura ambiente, y se filtra. El filtrado se purifica mediante HPLC en fase inversa con XBridge C18 y un gradiente de NH_4OH al 0.1 por ciento en acetonitrilo, para dar el 5-cloro-3-metil-2-piridin-3-il-1-[4-(2H-tetrazol-5-il)-bencil]-1H-indol.

^{1}H RMN (400 MHz, DMSO-d_6) δ ppm 2.21 (s, 3 H), 5.34 (s, 2

H), 6.81 (d, *J*=8.1 Hz, 2 H), 7.11 (br. s., 1 H), 7.17 (dd, *J*=8.7, 2.1 Hz, 1 H), 7.48 - 7.53 (m, 2 H), 7.67 (d, *J*=2.0 Hz, 1 H), 7.77 (d, *J*=8.3 Hz, 2 H), 7.80 - 7.84 (m, 1 H), 8.60 (d, *J*=1.5 Hz, 1 H), 8.62 (dd, *J*=4.8, 1.5 Hz, 1 H). HRMS (ESI) m/z 401.1276 [$(M+H)^+$ Calculado para $C_{22}H_{18}N_6Cl$: 401.1281].

Ejemplo 38

3-(3-metil-2-piridin-3-il-indol-1-carbonil)-benzonitrilo



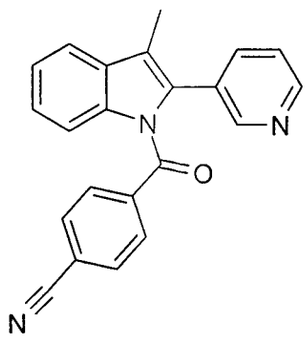
Un matraz se carga con clorhidrato de 3-metil-2-piridin-3-il-1H-indol (Ejemplo 1, 0.100 gramos, 0.408 milimoles) en tetrahidrofurano (2.5 mililitros), y se enfría a 0°C. Se agrega KHMDS (0.5 M en tolueno, 1.8 mililitros, 0.898 milimoles), y la mezcla se agita a temperatura ambiente durante 30 minutos, seguido por la adición de cloruro de 3-ciano-benzoílo (0.135 gramos, 0.817 milimoles). La mezcla de reacción se agita durante 0.5 horas, entonces se apaga con cloruro de amonio saturado, y se extrae con acetato de etilo. La capa orgánica se seca sobre sulfato de sodio, y se concentra al vacío. El residuo se purifica mediante HPLC en fase inversa con una columna XBridge Shield RP18 y un gradiente de NH_4OH acuoso al 0.1 por ciento en acetonitrilo, para proporcionar el producto de 3-(3-metil-2-piridin-3-il-indol-1-carbonil)-benzonitrilo como un sólido

amarillo.

^{1}H RMN (400 MHz, MeOD) δ ppm 2.31 (s, 3 H), 7.32 (ddd, *J*=7.9, 4.9, 0.9 Hz, 1 H), 7.37 - 7.44 (m, 2 H), 7.66 - 7.70 (m, 4 H), 7.71 - 7.76 (m, 2 H), 7.85 - 7.91 (m, 1 H), 8.37 (dd, *J*=5.1, 1.5 Hz, 1 H), 8.46 (dd, *J*=2.3, 0.8 Hz, 1 H). HRMS (ESI) m/z 338.1293 [(M+H)$^+$ Calculado para $C_{22}H_{16}N_3O$: 338.1293].

Ejemplo 39

4-(3-metil-2-piridin-3-il-indol-1-carbonil)-benzonitrilo

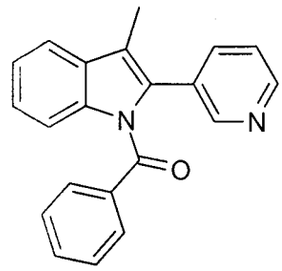


El cloruro de 4-ciano-benzoílo se procesa de acuerdo con el método descrito en el Ejemplo 38, para dar el 4-(3-metil-2-piridin-3-il-indol-1-carbonil)-benzonitrilo.

^{1}H RMN (400 MHz, MeOD) δ ppm 2.32 (s, 3 H), 7.32 (dd, *J*=7.8, 5.1 Hz, 1 H), 7.37 - 7.45 (m, 2 H), 7.49 (t, *J*=7.8 Hz, 1 H), 7.66 - 7.79 (m, 3 H), 7.79 - 7.83 (m, 1 H), 7.86 - 7.93 (m, 2 H), 8.34 (dd, *J*=4.8, 1.5 Hz, 1 H), 8.47 (d, *J*=1.5 Hz, 1 H). HRMS (ESI) m/z 338.1292 [(M+H)$^+$ Calculado para $C_{22}H_{16}N_3O$: 338.1293].

Ejemplo 40

(3-metil-2-piridin-3-il-indol-1-il)-fenil-metanona

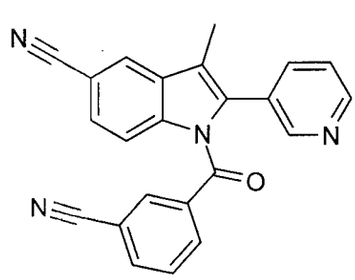


El clorhidrato de 3-metil-2-piridin-3-il-1H-indol y cloruro de benzoílo se procesan de acuerdo con el método descrito en el Ejemplo 38, para dar la (3-metil-2-piridin-3-il-indol-1-il)-fenil-metanona.

^{1}H RMN (400 MHz, MeOD) δ ppm 2.33 (s, 3 H), 7.26 - 7.40 (m, 5 H), 7.45 - 7.52 (m, 1 H), 7.57 (d, *J*=1.3 Hz, 1 H), 7.59 (s, 1 H), 7.63 (dd, *J*=7.1, 1.3 Hz, 1 H), 7.68 - 7.73 (m, 1 H), 7.75 (dt, *J*=7.8, 1.9 Hz, 1 H), 8.33 (dd, *J*=5.1, 1.5 Hz, 1 H), 8.47 (d, *J*=1.3 Hz, 2 H). HRMS (ESI) m/z 313.1337 [$(M+H)^+$ Calculado para $C_{21}H_{17}N_2O$: 313.1341].

Ejemplo 41

3-(5-ciano-3-metil-2-piridin-3-il-indol-1-carbonil)-benzonitrilo



Se agrega KHMDS (0.5 M en tolueno, 1.46 mililitros, 0.73 milimoles) a una solución de 3-metil-2-piridin-3-il-1H-indol-5-carbonitrilo (Ejemplo 6, 122 miligramos, 0.480 milimoles) en tetrahidrofurano (10 mililitros) a temperatura ambiente. Después de 5

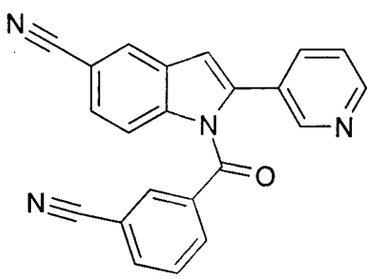
minutos, se agrega cloruro de 3-ciano-benzoílo (178 miligramos, 1.08 milimoles). La mezcla se agita bajo N_2 durante 1 hora, sobre lo cual, se agrega cloruro de amonio acuoso (0.5 mililitros). Los solventes se remueven al vacío, y el residuo se purifica mediante XBridge RP18 con un gradiente de hidróxido de amonio acuoso al 0.1 por ciento en acetonitrilo, para dar el 1-(3-ciano-benzoil)-3-metil-2-piridin-3-il-1H-indol-5-carbonitrilo.

^{1}H RMN (400 MHz, $CDCl_3$) δ ppm 2.35 (s, 3 H), 7.37 - 7.44 (m, 1 H), 7.47 - 7.52 (m, 1 H), 7.60 - 7.64 (m, 1 H), 7.68 - 7.83 (m, 5 H), 8.01 (d, *J*=1.5 Hz, 1 H), 8.51 (d, *J*=4.5 Hz, 1 H), 8.53 (s, 1 H).

HRMS (ESI) m/z 363.1247 [$(M+H)^+$ Calculado para $C_{23}H_{15}N_4O$: 363.1246].

Ejemplo 42

1-(3-ciano-benzoil)-2-piridin-3-il-1H-indol-5-carbonitrilo



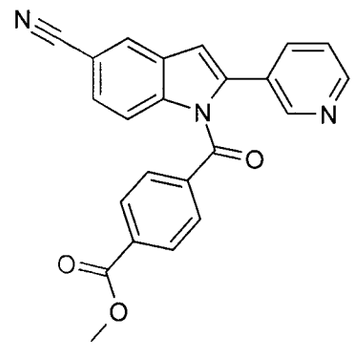
A una solución de 2-piridin-3-il-1H-indol-5-carbonitrilo (Ejemplo 8, 210 miligramos, 0.96 milimoles) en tetrahidrofurano (20 mililitros) a temperatura ambiente, se le agrega KHMDS 0.5 M en tolueno (4.10 mililitros, 2.05 milimoles). Después de 30 minutos, se agrega cloruro de 3-ciano-benzoílo (510 miligramos, 3.08 milimoles). La mezcla se agita bajo N_2 durante la noche. La reacción se apaga con cloruro de

amonio acuoso, y los volátiles se remueven al vacío. El residuo se vuelve a disolver en dicloro-metano y se vierte en bicarbonato de sodio acuoso saturado (100 mililitros). La extracción con dicloro-metano, el secado sobre sulfato de sodio, seguido por concentración, proporcionan un residuo, el cual se purifica en una XBridge RP18, utilizando un gradiente de hidróxido de amonio al 0.1 por ciento en acetonitrilo. La purificación adicional mediante cromatografía por evaporación instantánea en gel de sílice (heptano-acetato de etilo, de 3:2 a 2:3), proporciona el 1-(3-ciano-benzoil)-2-piridin-3-il-1H-indol-5-carbonitrilo.

^{1}H RMN (400 MHz, DMSO-d_6) δ ppm 7.20 (d, J=0.5 Hz, 1 H), 7.22 - 7.26 (m, 1 H), 7.55 (t, J=7.8 Hz, 1 H), 7.73 - 7.79 (m, 2 H), 7.84 (d, 1 H), 7.92 - 7.98 (m, 2 H), 8.11 (t, J=1.5 Hz, 1 H), 8.29 - 8.33 (m, 1 H), 8.39 (dd, J=4.8, 1.5 Hz, 1 H), 8.60 (dd, J=2.3, 0.8 Hz, 1 H). HRMS (ESI) m/z 349.1106 [(M+H)$^+$ Calculado para $C_{22}H_{13}N_4O$: 349.1089].

Ejemplo 43

Metil-éster del ácido 4-(5-ciano-2-piridin-3-il-indol-1-carbonil)-benzoico

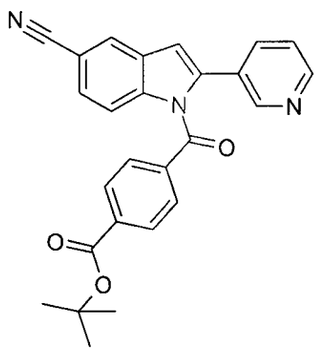


A una solución de 2-piridin-3-il-1H-indol-5-carbonitrilo (Ejemplo 8, 240 miligramos, 1.09 milimoles) en tetrahidrofurano (10 mililitros) a temperatura ambiente, se le agrega KHMDS 0.5 M en tolueno (4.0 mililitros, 2.0 milimoles). Después de 30 minutos, se agrega el metil-éster del ácido 4-cloro-carbonil-benzoico (400 miligramos, 2.0 milimoles). La mezcla se agita bajo N_2 durante 1 hora. La reacción se apaga con bicarbonato de sodio acuoso, y los volátiles se remueven al vacío. La purificación mediante cromatografía por evaporación instantánea en gel de sílice utilizando un gradiente de heptano-acetato de etilo proporciona el metil-éster del ácido 4-(5-ciano-2-piridin-3-il-indol-1-carbonil)-benzoico.

^{1}H RMN (400 MHz, MeOD) δ ppm 3.90 (s, 3 H), 7.12 (s, 1 H), 7.26 (dd, *J*=8.0, 4.9 Hz, 1 H), 7.63 - 7.72 (m, 3 H), 7.77 - 7.81 (m, 1 H), 7.91 - 7.96 (m, 3 H), 8.17 (d, *J*=1.5 Hz, 1 H), 8.32 (dd, *J*=4.8, 1.5 Hz, 1 H), 8.56 (d, *J*=2.3 Hz, 1 H). HRMS (ESI) m/z 382.1186 [$(M+H)^+$ Calculado para $C_{23}H_{16}N_3O_3$: 382.1192].

Ejemplo 44

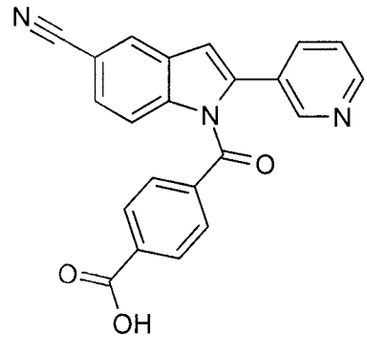
(a) Terbutil-éster del ácido 4-(5-ciano-2-piridin-3-il-indol-1-carbonil)-benzoico



Al 2-piridin-3-il-1H-indol-5-carbonitrilo (575 miligramos, 2.62 milimoles), ácido 4-(butoxi-carbonil)-benzoico (700 miligramos, 3.15 milimoles), y DMAP (780 miligramos, 3.93 milimoles) en N,N-dimetil-formamida (30 mililitros), se le agrega DCC (811 miligramos, 3.93 milimoles). La reacción se agita durante 3 días y la mezcla se vierte en agua (50 mililitros), y se extrae con acetato de etilo, se seca sobre Na_2SO_4 y se concentra. El residuo se purifica mediante cromatografía por evaporación instantánea en gel de sílice (gradiente de acetato de etilo-heptano), para dar el terbutil-éster del ácido 4-(5-ciano-2-piridin-3-il-indol-1-carbonil)-benzoico como un sólido blanco.

MS (ESI) *m/z* 424 $(M+H)^+$.

(b) ácido 4-(5-ciano-2-piridin-3-il-indol-1-carbonil)-benzoico



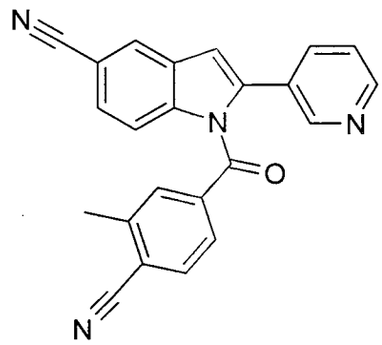
El terbutil-éster del ácido 4-(5-ciano-2-piridin-3-il-indol-1-carbonil)-benzoico (100 miligramos) se disuelve en ácido trifluoro-acético (3 mililitros), y se agita a temperatura ambiente durante 1 hora. El solvente se remueve al vacío, y el residuo se tritura con dietil-éter dos veces. El residuo se purifica mediante HPLC en fase inversa con Sunfire C18 y un gradiente de acetonitrilo en ácido

trifluoro-acético acuoso al 0.1 por ciento, para proporcionar el ácido 4-(5-ciano-2-piridin-3-il-indol-1-carbonil)-benzoico como un sólido blanco.

^{1}H RMN (400 MHz, DMSO-d_6) δ ppm (sal de TFA) 7.24 (s, 1 H), 7.28 (dd, *J*=7.9, 4.9 Hz, 1 H), 7.73 - 7.77 (m, 4 H), 7.81 (dt, *J*=8.1, 1.9, 1.8 Hz, 1 H), 7.87 - 7.91 (m, 2 H), 8.32 (t, *J*=1.1 Hz, 1 H), 8.41 (dd, *J*=4.9, 1.6 Hz, 1 H), 8.63 - 8.65 (m, 1 H), 13.40 (br. s., 1 H). HRMS (ESI) m/z 366.0868 [$(M+H)^+$ Calculado para $C_{22}H_{14}N_3O_3$: 366.0879].

Ejemplo 45

1-(4-ciano-3-metil-benzoil)-2-piridin-3-il-1H-indol-5-carbonitrilo



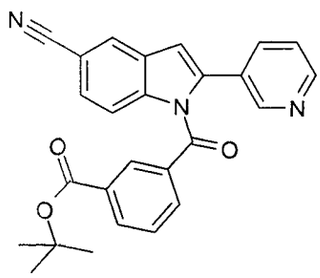
El ácido 4-ciano-3-metil-benzoico se sintetiza basándose en el método descrito en la Patente Europea Número EP1512687A1. A una solución de 2-piridin-3-il-1H-indol-5-carbonitrilo (20 miligramos, 0.09 milimoles), 4-dimetil-amino-piridina (22 miligramos, 0.01 milimoles), y ácido 4-ciano-3-metil-benzoico (29 miligramos, 0.18 milimoles) a 0°C en dicloro-metano (2 mililitros), se le agrega DCC (38 miligramos, 0.18 milimoles). Después de agitar durante 10 minutos, la reacción se calienta a temperatura ambiente. Se forma un

precipitado, y la agitación se continúa durante 16 horas. La mezcla se filtra, y el filtrado se diluye con dicloro-metano (10 mililitros), se lava con agua y una solución saturada de cloruro de sodio. Los extractos orgánicos combinados se secan sobre sulfato de sodio, se filtran, y se concentran. El residuo resultante se purifica mediante cromatografía por evaporación instantánea en gel de sílice (acetato de etilo-heptano, de 0:1 a 1:1), para proporcionar el 1-(4-ciano-3-metil-benzoil)-2-piridin-3-il-1H-indol-5-carbonitrilo.

^{1}H RMN (400 MHz, $CDCl_3$) δ ppm 2.47 (s, 3 H), 6.91 (s, 1 H), 7.14 (dd, *J*=8.0, 4.9 Hz, 1 H), 7.43 - 7.48 (m, 2 H), 7.49 - 7.54 (m, 2 H), 7.61 (dd, *J*=8.7, 1.6 Hz, 1 H), 7.93 (d, *J*=8.6 Hz, 1 H), 8.03 (d, *J*=1.0\ Hz, 1 H), 8.44 (dd, *J*=4.8, 1.5 Hz, 1 H), 8.55 (d, *J*=1.8 Hz, 1 H). HRMS (ESI) m/z 363.1245 [$(M+H)^+$: Calculado para $C_{23}H_{15}N_4O$: 363.1246].

Ejemplo 46

Terbutil-éster del ácido 3-(5-ciano-2-piridin-3-il-indol-1-carbonil)-benzoico



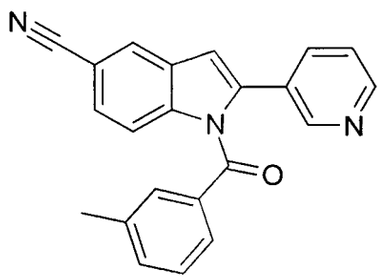
El mono-terbutil-éster de ácido isoftálico se procesa de acuerdo con el método descrito en el Ejemplo 45, para dar el terbutil-éster del ácido 3-(5-ciano-2-piridin-3-il-indol-1-carbonil)-benzoico.

219

^{1}H RMN (400 MHz, $CDCl_3$) δ ppm 1.58 (s, 9 H), 6.91 (s, 1 H), 7.10 (dd, *J*=7.6, 5.1 Hz, 1 H), 7.40 (t, *J*=7.8 Hz, 1 H), 7.52 - 7.59 (m, 2 H), 7.81 (dt, *J*=7.9, 1.5, 1.3 Hz, 1 H), 7.85 (d, *J*=8.7 Hz, 1 H), 8.02 - 8.06 (m, 2 H), 8.09 (t, *J*=1.6 Hz, 1 H), 8.40 (d, *J*=3.4 Hz, 1 H), 8.58 (d, *J*=1.8 Hz, 1 H). HRMS (ESI) m/z 424.1662 [$(M+H)^+$: Calculado para $C_{26}H_{22}N_3O_3$: 424.1661].

Ejemplo 47

1-(3-metil-benzoil)-2-piridin-3-il-1H-indol-5-carbonitrilo

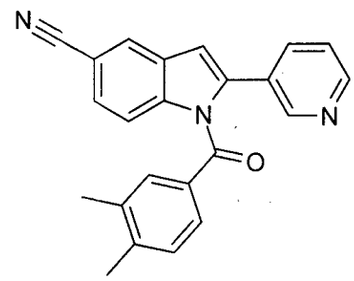


El ácido 3-metil-benzoico se procesa de acuerdo con el método descrito en el Ejemplo 45, para dar el 1-(3-metil-benzoil)-2-piridin-3-il-1H-indol-5-carbonitrilo.

^{1}H RMN (400 MHz, $CDCl_3$) δ ppm 2.29 (s, 3 H), 6.89 (s, 1 H), 7.14 (dd, *J*=8.0, 4.9 Hz, 1 H), 7.19 - 7.24 (m, 1 H), 7.27 - 7.31 (m, 1 H), 7.39 - 7.44 (m, 2 H), 7.50 - 7.57 (m, 2 H), 7.71 (d, *J*=8.6 Hz, 1 H), 8.01 (d, *J*=1.0 Hz, 1 H), 8.42 (dd, *J*=4.8, 1.5 Hz, 1 H), 8.62 (d, *J*=1.8 Hz, 1 H). HRMS (ESI) m/z 338.1289 [$(M+H)^+$: Calculado para $C_{22}H_{16}N_3O$: 338.1293]

Ejemplo 48

1-(3,4-dimetil-benzoil)-2-piridin-3-il-1H-indol-5-carbonitrilo

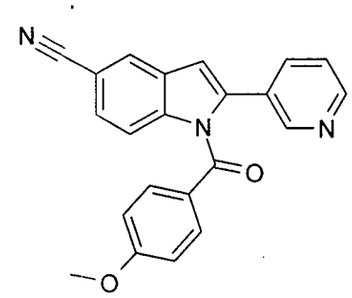


El ácido 3,4-dimetil-benzoico se procesa de acuerdo con el método descrito en el Ejemplo 45, para dar el 1-(3,4-dimetil-benzoil)-2-piridin-3-il-1H-indol-5-carbonitrilo.

^{1}H RMN (400 MHz, $CDCl_3$) δ ppm 2.21 (s, 3 H), 2.26 (s, 3 H), 6.89 (s, 1 H), 7.10 (d, *J*=7.8 Hz, 1 H), 7.15 (dd, *J*=7.5, 5.2 Hz, 1 H), 7.37 - 7.43 (m, 2 H), 7.49 (dd, *J*=8.6, 1.5 Hz, 1 H), 7.57 (dt, *J*=8.3, 2.0, 1.6 Hz, 1 H), 7.61 (d, *J*=8.8 Hz, 1 H), 8.01 (d, *J*=2.0 Hz, 1 H), 8.44 (dd, *J*=4.8, 1.5 Hz, 1 H), 8.64 (d, *J*=2.3 Hz, 1 H). HRMS (ESI) m/z 352.1458 [$(M+H)^+$: Calculado para $C_{23}H_{18}N_3O$: 352.1450].

Ejemplo 49

1-(4-metoxi-benzoil)-2-piridin-3-il-1H-indol-5-carbonitrilo

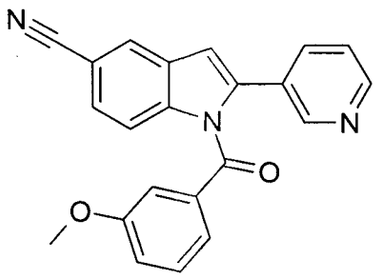


El ácido 4-metoxi-benzoico se procesa de acuerdo con el método descrito en el Ejemplo 45, para dar el 1-(4-metoxi-benzoil)-2-piridin-3-il-1H-indol-5-carbonitrilo.

^{1}H RMN (400 MHz, $CDCl_3$) δ ppm 3.83 (s, 3 H), 6.81 - 6.85 (m, 2 H), 6.90 (s, 1 H), 7.18 (dd, *J*=7.8, 3.0 Hz, 1 H), 7.49 (dd, *J*=8.6, 1.5 Hz, 1 H), 7.58 - 7.62 (m, 2 H), 7.62 - 7.66 (m, 2 H), 8.01 (d, *J*=1.5 Hz, 1 H), 8.46 (dd, *J*=4.8, 1.5 Hz, 1 H), 8.66 (d, *J*=3.0 Hz, 1 H). HRMS (ESI) m/z 354.1225 [$(M+H)^+$: Calculado para $C_{22}H_{16}N_3O_2$: 354.1243].

Ejemplo 50

1-(3-metoxi-benzoil)-2-piridin-3-il-1H-indol-5-carbonitrilo

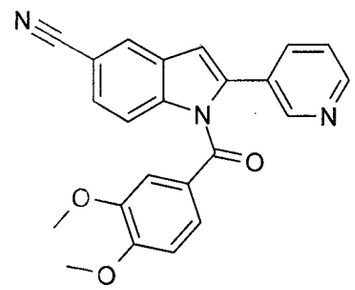


El ácido 3-metoxi-benzoico se procesa de acuerdo con el método descrito en el Ejemplo 45, para dar el 1-(3-metoxi-benzoil)-2-piridin-3-il-1H-indol-5-carbonitrilo.

^{1}H RMN (400 MHz, $CDCl_3$) δ ppm 3.78 (s, 3 H), 6.89 (s, 1 H), 7.02 (ddd, *J*=8.2, 2.6, 1.1 Hz, 1 H), 7.13 - 7.18 (m, 3 H), 7.23 (d, *J*=8.1 Hz, 1 H), 7.52 (dd, *J*=8.6, 1.5 Hz, 1 H), 7.57 (dt, *J*=8.0, 1.9 Hz, 1 H), 7.69 (d, *J*=8.8 Hz, 1 H), 8.01 (d, *J*=1.0 Hz, 1 H), 8.45 (dd, *J*=4.8, 1.5 Hz, 1 H), 8.64 (d, *J*=2.3 Hz, 1 H). HRMS (ESI) m/z 354.1231 [$(M+H)^+$: Calculado para $C_{22}H_{16}N_3O_2$: 354.1243].

Ejemplo 51

1-(3,4-dimetoxi-benzoil)-2-piridin-3-il-1H-indol-5-carbonitrilo

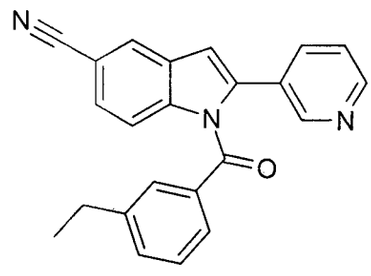


El ácido 3,4-dimetoxi-benzoico se procesa de acuerdo con el método descrito en el Ejemplo 45, para dar el 1-(3,4-dimetoxi-benzoil)-2-piridin-3-il-1H-indol-5-carbonitrilo.

^{1}H RMN (400 MHz, $CDCl_3$) δ ppm 3.87 (s, 3 H), 3.90 (s, 3 H), 6.75 (d, *J*=8.6 Hz, 1 H), 6.92 (s, 1 H), 7.19 (dd, *J*=7.8, 4.3 Hz, 1 H), 7.22 (dd, *J*=8.5, 2.2 Hz, 1 H), 7.29 (d, *J*=2.0 Hz, 1 H), 7.50 (dd, *J*=8.7, 1.6 Hz, 1 H), 7.58 - 7.63 (m, 2 H), 8.02 (d, *J*=1.0 Hz, 1 H), 8.47 (dd, *J*=4.8, 1.5 Hz, 1 H), 8.68 (dd, *J*=2.3, 0.8 Hz, 1 H). HRMS (ESI) m/z 384.1349 [$(M+H)^+$: Calculado para $C_{23}H_{18}N_3O_3$: 384.1348].

Ejemplo 52

1-(3-etil-benzoil)-2-piridin-3-il-1H-indol-5-carbonitrilo

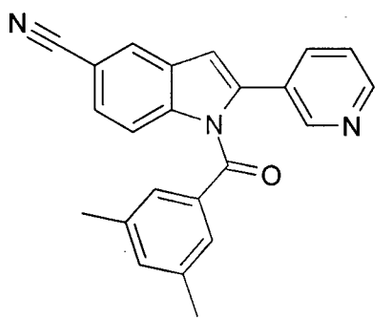


El ácido 3-etil-benzoico se procesa de acuerdo con el método descrito en el Ejemplo 45, para dar el 1-(3-etil-benzoil)-2-piridin-3-il-1H-indol-5-carbonitrilo.

^{1}H RMN (400 MHz, $CDCl_3$) δ ppm 1.16 (t, *J*=7.6 Hz, 3 H), 2.58 (q, *J*=7.6 Hz, 2 H), 6.89 (s, 1 H), 7.12 (dd, *J*=8.0, 4.9 Hz, 1 H), 7.22 - 7.25 (m, 1 H), 7.29 - 7.33 (m, 1 H), 7.40 (s, 1 H), 7.43 - 7.47 (m, 1 H), 7.51 - 7.57 (m, 2 H), 7.73 (d, *J*=8.8 Hz, 1 H), 8.02 (d, *J*=1.0 Hz, 1 H), 8.42 (dd, *J*=4.8, 1.5 Hz, 1 H), 8.63 (d, *J*=1.8 Hz, 1 H). HRMS (ESI) m/z 352.1443 [$(M+H)^+$: Calculado para $C_{23}H_{18}N_3O$: 352.1450].

Ejemplo 53

1-(3,5-dimetil-benzoil)-2-piridin-3-il-1H-indol-5-carbonitrilo



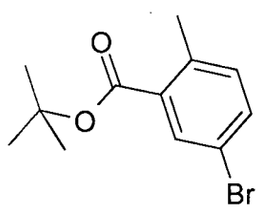
A una solución de 2-piridin-3-il-1H-indol-5-carbonitrilo (Ejemplo 8, 200 miligramos, 0.913 milimoles) a 0°C en tetrahidrofurano (6 mililitros), se le agrega hidruro de sodio al 60 por ciento (72 miligramos, 1.826 milimoles), y la mezcla se agita durante 10 minutos a 0°C. La mezcla de reacción entonces se calienta a temperatura ambiente, y se agita durante 30 minutos. Se agrega por goteo cloruro de 3,5-dimetil-benzoílo (460 miligramos, 2.740 milimoles) en tetrahidrofurano (2 mililitros), a 0°C, y la reacción se agita a temperatura ambiente durante 1 hora. La reacción se apaga

mediante la adición de bicarbonato de sodio saturado. El tetrahidrofurano se remueve al vacío, y el residuo resultante se purifica mediante cromatografía por evaporación instantánea en gel de sílice (acetato de etilo-heptano, de 0:1 a 1:1). El producto resultante se purifica además mediante HPLC utilizando una X-Bridge RP18 y un gradiente de acetonitrilo - hidróxido de amonio al 0.1 por ciento, para proporcionar el 1-(3,5-dimetil-benzoil)-2-piridin-3-il-1H-indol-5-carbonitrilo.

^{1}H RMN (400 MHz, $CDCl_3$) δ ppm 2.25 (s, 6 H), 6.88 (s, 1 H), 7.10 (s, 1 H), 7.14 (dd, *J*=7.6, 5.3 Hz, 1 H), 7.22 (s, 2 H), 7.50 - 7.56 (m, 2 H), 7.70 (d, *J*=8.8 Hz, 1 H), 8.01 (s, 1 H), 8.43 (dd, *J*=4.8, 1.5 Hz, 1 H), 8.62 (s, 1 H). HRMS (ESI) m/z 352.1452 [$(M+H)^+$: Calculado para $C_{23}H_{18}N_3O$: 352.1450].

Ejemplo 54

(a) terbutil-éster del ácido 5-bromo-2-metil-benzoico

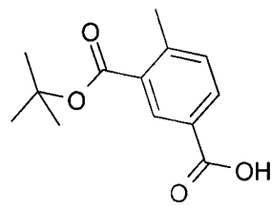


A una suspensión de sulfato de magnesio anhidro (4.5 gramos, 37.28 milimoles) en dicloro-metano (37 mililitros), se le agrega H_2SO_4 concentrado (516 microlitros, 9.302 milimoles), y la mezcla se agita vigorosamente durante 15 minutos. Se agrega ácido 5-bromo-2-metil-benzoico (2 gramos, 9.302 milimoles), seguido por terbutanol (4.39 mililitros, 46.51 milimoles). El matraz se tapa herméticamente y

se agita a temperatura ambiente durante 24 horas. Después de agregar bicarbonato de sodio saturado, la solución resultante se extrae con acetato de etilo. La capa orgánica se lava con una solución saturada de cloruro de sodio, se seca sobre sulfato de sodio, se filtra, y se concentra. El residuo resultante se purifica mediante cromatografía por evaporación instantánea en gel de sílice (acetato de etilo-heptano, de 0:1 a 3:7), para proporcionar el terbutil-éster del ácido 5-bromo-2-metil-benzoico.

^{1}H RMN (400 MHz, DMSO-d_6) δ ppm 1.59 (s, 9 H), 2.51 (s, 3 H), 7.08 (d, J=8.1 Hz, 1 H), 7.46 (dd, J=8.3, 2.3 Hz, 1 H), 7.92 (d, J=2.3 Hz, 1 H)

(b) 3-terbutil-éster del ácido 4-metil-isoftálico

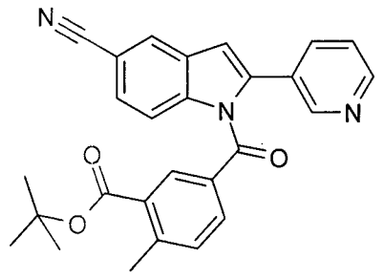


El n-butil-litio (1.6M en hexano,1.29 mililitros, 1.975 milimoles), se agrega lentamente al terbutil-éster del ácido 5-bromo-2-metil-benzoico (511 miligramos, 1.884 milimoles) en tetrahidrofurano (18 mililitros) a –78°C bajo N_2. La mezcla de reacción se agita a –78°C durante 30 minutos. Se burbujea gas de dióxido de carbono a través de la solución hasta que el color de la solución cambia a naranja. Después de agitar a –78°C durante 10 minutos, la mezcla de reacción se calienta a temperatura ambiente. La reacción se apaga con cloruro de amonio saturado, se extrae con acetato de etilo, se

seca sobre sulfato de sodio, se filtra, y se concentra. El residuo resultante se purifica mediante cromatografía por evaporación instantánea en gel de sílice (acetato de etilo-heptano, de 0:1 a 1:1), para proporcionar el 3-terbutil-éster del ácido 4-metil-isoftálico.

^{1}H RMN (400 MHz, $CDCl_3$) δ ppm 1.62 (s, 9 H), 2.65 (s, 3 H), 7.33 (d, *J*=7.83 Hz, 1 H), 8.07 (dd, *J*=7.96, 1.89 Hz, 1 H), 8.52 (d, *J*=2.02 Hz, 1 H).

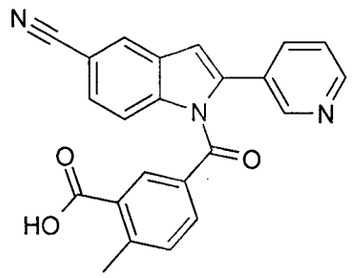
(c) Terbutil-éster del ácido 5-(5-ciano-2-piridin-3-il-indol-1-carbonil)-2-metil-benzoico



El 3-terbutil-éster del ácido 4-metil-isoftálico se procesa de acuerdo con el método descrito en el Ejemplo 45, para dar el terbutil-éster del ácido 5-(5-ciano-2-piridin-3-il-indol-1-carbonil)-2-metil-benzoico.

^{1}H RMN (400 MHz, $CDCl_3$) δ ppm 1.57 (s, 9 H), 2.55 (s, 3 H), 6.91 (s, 1 H), 7.13 (dd, *J*=7.83, 4.29 Hz, 1 H), 7.20 (d, *J*=8.08 Hz, 1 H), 7.53 - 7.58 (m, 2 H), 7.66 (dd, *J*=7.96, 2.15 Hz, 1 H), 7.76 (d, *J*=8.59 Hz, 1 H), 7.98 (d, *J*=2.02 Hz, 1 H), 8.02 (d, *J*=1.01 Hz, 1 H), 8.43 (dd, *J*=4.80, 1.52 Hz, 1 H), 8.61 (d, *J*=2.27 Hz, 1 H).

(d) Ácido 5-(5-ciano-2-piridin-3-il-indol-1-carbonil)-2-metil-benzoico

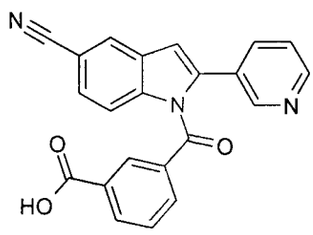


El terbutil-éster del ácido 5-(5-ciano-2-piridin-3-il-indol-1-carbonil)-2-metil-benzoico se disuelve en ácido trifluoro-acético (3 mililitros), y se agita a temperatura ambiente durante 1 hora. Después de remover el solvente, el residuo se purifica mediante HPLC con una X-Bridge de Fenilo, utilizando acetonitrilo - ácido trifluoro-acético al 0.1 por ciento como un eluyente, para proporcionar el ácido 5-(5-ciano-2-piridin-3-il-indol-1-carbonil)-2-metil-benzoico.

^{1}H RMN (400 MHz, DMSO-d_6) δ ppm (sal de TFA) 2.59 (s, 3 H), 7.32 (s, 1 H), 7.39 - 7.44 (m, 2 H), 7.71 - 7.75 (m, 1 H), 7.76 - 7.79 (m, 1 H), 7.81 (dd, *J*=7.8, 2.0 Hz, 1 H), 7.92 (dt, *J*=8.0, 1.8 Hz, 1 H), 8.11 (d, *J*=2.0 Hz, 1 H), 8.38 (d, *J*=1.5 Hz, 1 H), 8.52 (dd, *J*=5.0, 1.5 Hz, 1 H), 8.74 (d, *J*=2.0 Hz, 1 H). HRMS (ESI) m/z 382.1202 [$(M+H)^+$ Calculado para $C_{23}H_{16}N_3O_3$: 382.1192].

Ejemplo 55

Ácido 3-(5-ciano-2-piridin-3-il-indol-1-carbonil)-benzoico

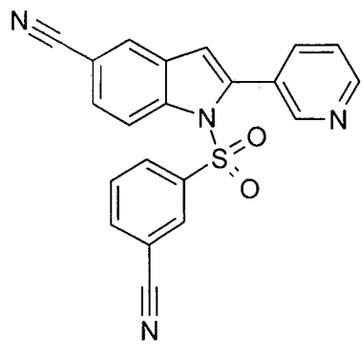


El terbutil-éster del ácido 3-(5-ciano-2-piridin-3-il-indol-1-carbonil)-benzoico (Ejemplo 46) se procesa de acuerdo con el método descrito en el Ejemplo 54d, para dar el ácido 5-(5-ciano-2-piridin-3-il-indol-1-carbonil)-2-metil-benzoico.

^{1}H RMN (400 MHz, DMSO-d_6) δ ppm (sal de TFA) 7.16 - 7.21 (m, 2 H), 7.43 (t, J=7.8 Hz, 1 H), 7.67 (dd, J=8.7, 1.64 Hz, 1 H), 7.71 - 7.75 (m, 2 H), 7.82 (dt, J=8.0, 1.5, 1.3 Hz, 1 H), 7.97 (dt, J=7.8, 1.4 Hz, 1 H), 8.00 (t, J=1.5 Hz, 1 H), 8.25 (d, J=1.0 Hz, 1 H), 8.32 (dd, J=4.8, 1.5 Hz, 1 H), 8.55 (d, J=1.6 Hz, 1 H). HRMS (ESI) m/z 368.1040 [(M+H)$^+$ Calculado para $C_{22}H_{14}N_3O_3$: 368.1035].

Ejemplo 56

1-(3-ciano-bencen-sulfonil)-2-piridin-3-il-1H-indol-5-carbonitrilo



A una solución de 2-piridin-3-il-1H-indol-5-carbonitrilo (Ejemplo 8, 300 miligramos, 1.37 milimoles) a 0°C en N,N-dimetil-formamida (12 mililitros), se le agrega hidruro de sodio al 60 por ciento (82 miligramos, 2.06 milimoles), y la mezcla se agita durante 10 minutos a 0°C. La mezcla de reacción entonces se calienta a temperatura ambiente, y se agita durante 30 minutos. Se agrega por goteo cloruro de 3-ciano-bencen-sulfonilo (552 miligramos, 2.74 milimoles) en N,N-

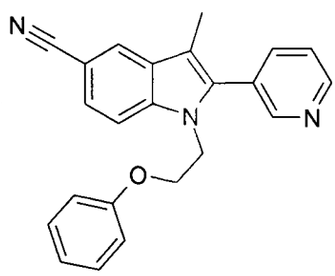
dimetil-formamida (2 mililitros), a 0°C, y la reacción se agita a temperatura ambiente durante 1 hora. La reacción se apaga mediante la adición de agua (1 mililitro). La mezcla resultante se purifica mediante HPLC X-Bridge RP18, utilizando acetonitrilo - hidróxido de amonio al 0.1 por ciento como un eluyente, para proporcionar el 1-(3-ciano-bencen-sulfonil)2-piridin-3-il-1H-indol-5-carbonitrilo.

^{1}H RMN (400 MHz, $CDCl_3$) δ ppm 7.11 (s, 1 H), 7.54 (dd, *J*=7.8, 4.8 Hz, 1 H), 7.66 (dd, *J*=8.1, 2.0 Hz, 1 H), 7.72 (t, *J*=7.7 Hz, 1 H), 7.86 (dd, *J*=8.7, 1.6 Hz, 1 H), 7.94 (t, *J*=1.5 Hz, 1 H), 7.98 (dt, *J*=8.2, 2.0, 1.8 Hz, 1 H), 8.16 (dd, *J*=7.6, 1.3 Hz, 1 H), 8.19 (d, *J*=1.0 Hz, 1 H), 8.34 (d, *J*=8.6 Hz, 1 H), 8.67 (d, *J*=2.8 Hz, 1 H), 8.71 (dd, *J*=4.9, 1.6 Hz, 1 H).

HRMS (ESI) m/z 385.0763 [$(M+H)^+$ Calculado para $C_{21}H_{13}N_4O_2S$: 385.0759].

Ejemplo 57

3-metil-1-(2-fenoxi-etil)-2-piridin-3-il-1H-indol-5-carbonitrilo



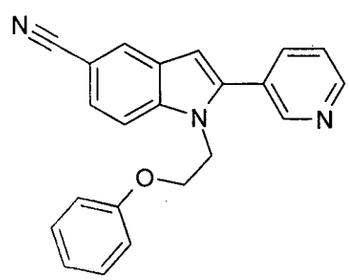
A una solución de 3-metil-2-piridin-3-il-1H-indol-5-carbonitrilo (Ejemplo 6, 47 miligramos, 0.20 milimoles) en tetrahidrofurano (5 mililitros) a temperatura ambiente, se le agrega KHMDS (0.5 M en

tolueno, 0.60 mililitros, 0.30 milimoles), seguido por (2-bromo-etoxi)-benceno (90 miligramos, 0.45 milimoles). La mezcla se agita bajo N_2 durante 2 días, y se agrega cloruro de amonio acuoso (1 mililitro) para apagar la reacción. Los volátiles se remueven al vacío, y el residuo se purifica mediante cromatografía por evaporación instantánea en gel de sílice (acetato de etilo-heptano, de 1:4 a 1:0), para dar el 3-metil-1-(2-fenoxi-etil)-2-piridin-3-il-1H-indol-5-carbonitrilo.

^{1}H RMN (400 MHz, $CDCl_3$) δ ppm 2.25 (s, 3 H), 4.10 (t, *J*=5.2 Hz, 2 H), 4.46 (t, *J*=5.3 Hz, 2 H), 6.66 (d, *J*=7.8 Hz, 2 H), 6.93 (t, *J*=7.3 Hz, 1 H), 7.17 - 7.25 (m, 2 H), 7.51 - 7.57 (m, 2 H), 7.59 - 7.65 (m, 1 H), 7.95 (d, *J*=8.6 Hz, 1 H), 7.98 (s, 1 H), 8.74 - 8.79 (m, 2 H). HRMS (ESI) m/z 354.1618 [$(M+H)^+$ Calculado para $C_{23}H_{20}N_3O$: 354.1606].

Ejemplo 58

1-(2-fenoxi-etil)-2-piridin-3-il-1H-indol-5-carbonitrilo

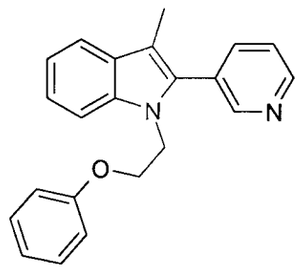


El (2-bromo-etoxi)-benceno, y 2-piridin-3-il-1H-indol-5-carbonitrilo (Ejemplo 8) se procesan de acuerdo con el método descrito en el Ejemplo 57, para dar el 1-(2-fenoxi-etil)-2-piridin-3-il-1H-indol-5-carbonitrilo.

^{1}H RMN (400 MHz, MeOD) δ ppm 4.19 (t, *J*=5.2 Hz, 2 H), 4.67 (t, *J*=5.1 Hz, 2 H), 6.63 (d, *J*=7.8 Hz, 2 H), 6.77 (s, 1 H), 6.84 (t, *J*=7.5 Hz, 1 H), 7.10 - 7.17 (m, 2 H), 7.53 (dd, *J*=8.6, 1.8 Hz, 1 H), 7.55 - 7.60 (m, 1 H), 7.77 (d, *J*=8.6 Hz, 1 H), 8.05 (s, 1 H), 8.08 - 8.13 (m, 1 H), 8.63 (dd, *J*=4.9, 1.6 Hz, 1 H), 8.79 (d, *J*=1.5 Hz, 1 H). HRMS (ESI) m/z 340.1453 [$(M+H)^+$ Calculado para $C_{22}H_{18}N_3O$: 340.1450].

Ejemplo 59

3-metil-1-(2-fenoxi-etil)-2-piridin-3-il-1H-indol



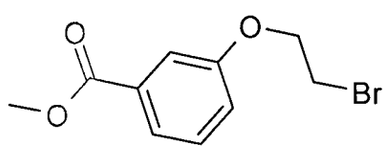
Un matraz se carga con clorhidrato de 3-metil-2-piridin-3-il-1H-indol (Ejemplo 1, 0.100 gramos, 0.408 milimoles), y dimetil-formamida (2 mililitros). La solución se enfría a 0°C, y se agrega NaH al 60 por ciento en aceite mineral (0.036 gramos, 0.898 milimoles). La mezcla se agita a temperatura ambiente durante 20 minutos, seguido por la adición de (2-bromo-etoxi)-benceno (0.205 mililitros, 1.021 milimoles). La mezcla se agita a temperatura ambiente durante 5 horas, después de lo cual, se concentra al vacío. El residuo se purifica mediante HPLC en fase inversa con una columna XBridge Shield RP18 y un gradiente de ácido trifluoro-acético acuoso al 0.1 por ciento en acetonitrilo, para proporcionar el

3-metil-1-(2-fenoxi-etil)-2-piridin-3-il-1H-indol como una sal de trifluoro-acetato color amarillo.

^{1}H RMN (400 MHz, MeOD) δ ppm (sal de TFA) 2.29 (s, 3 H), 4.18 (t, *J*=5.2 Hz, 2 H), 4.55 (t, *J*=5.1 Hz, 2 H), 6.64 (d, *J*=7.8 Hz, 2 H), 6.87 (t, *J*=7.5 Hz, 1 H), 7.11 - 7.22 (m, 3 H), 7.33 (ddd, *J*=7.6, 1.1 Hz, 1 H), 7.58 (d, *J*=8.3 Hz, 1 H), 7.64 (d, *J*=7.8 Hz, 1 H), 7.96 (dd, *J*=8.0, 5.4 Hz, 1 H), 8.44 (dt, *J*=8.0, 1.9, 1.8 Hz, 1 H), 8.77 (dd, *J*=5.6, 1.3 Hz, 1 H), 8.89 (d, *J*=1.8 Hz, 1 H). HRMS (ESI) m/z 329.1646 [$(M+H)^+$ Calculado para $C_{22}H_{21}N_2O$: 329.1654].

Ejemplo 60

(a) Metil-éster del ácido 3-(2-bromo-etoxi)-benzoico

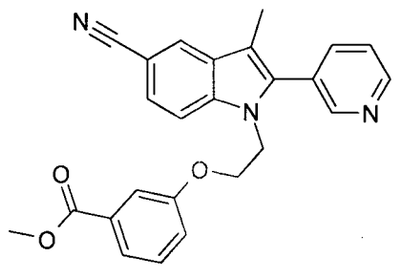


Un matraz se carga con metil-éster del ácido 3-hidroxi-benzoico (2.54 gramos, 16.0 milimoles), y acetona (50 mililitros). Se agregan 1,2-dibromo-etano (5.69 mililitros, 66.0 milimoles), y carbonato de potasio (2.76 gramos, 19.0 milimoles), y la mezcla se pone a reflujo durante 24 horas. La mezcla de reacción se enfría entonces a temperatura ambiente. Los sólidos se filtran y el filtrado se concentra al vacío. El residuo se purifica mediante cromatografía por evaporación instantánea en gel de sílice (heptano-acetato de etilo, 3:1), para proporcionar el metil-éster del ácido 3-(2-bromo-etoxi)-benzoico como un aceite incoloro.

^{1}H RMN (400 MHz, $CDCl_3$) δ ppm 3.66 (t, *J*=6.2 Hz, 2 H), 3.93

(s, 3 H), 4.35 (t, *J*=6.2 Hz, 2 H), 7.14 (m, 1 H) 7.37 (m, 1 H) 7.57 (m, 1 H) 7.68 (m, 1 H).

(b) Metil-éster del ácido 3-[2-(5-ciano-3-metil-2-piridin-3-il-indol-1-il)-etoxi]-benzoico

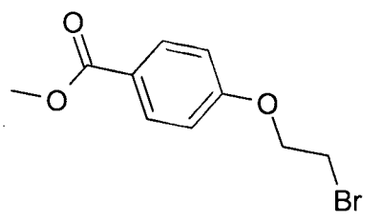


El metil-éster del ácido 3-(2-bromo-etoxi)-benzoico y 5-ciano-3-metil-2-piridin-3-il-indol-1-ilo (Ejemplo 6) se procesan de acuerdo con el método descrito en el Ejemplo 59, para dar el metil-éster del ácido 3-[2-(5-ciano-3-metil-2-piridin-3-il-indol-1-il)-etoxi]-benzoico.

^{1}H RMN (400 MHz, MeOD) δ ppm 2.26 (s, 3 H), 3.90 (s, 3 H), 4.22 (t, *J*=4.9 Hz, 2 H), 4.60 (t, *J*=5.1 Hz, 2 H), 6.91 (dd, *J*=7.8, 2.3 Hz, 1 H), 7.21 - 7.24 (m, 1 H), 7.28 (t, *J*=8.0 Hz, 1 H), 7.52 - 7.59 (m, 2 H), 7.65 (dd, *J*=7.8, 5.1 Hz, 1 H), 7.76 (d, *J*=8.6 Hz, 1 H), 7.98 - 8.09 (m, 2 H), 8.56 - 8.77 (m, 2 H). HRMS (ESI) m/z 412.1664 [$(M+H)^+$ Calculado para $C_{25}H_{22}N_3O_3$: 412.1661].

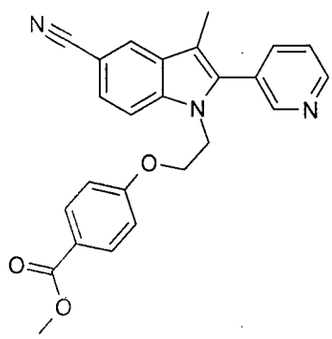
Ejemplo 61

(a) Metil-éster del ácido 4-(2-bromo-etoxi)-benzoico



El metil-éster del ácido 4-hidroxi-benzoico se procesa de acuerdo con el método descrito en el Ejemplo 60a, para dar el metil-éster del ácido 4-(2-bromo-etoxi)-benzoico.

(b) Metil-éster del ácido 4-[2-(5-ciano-3-metil-2-piridin-3-il-indol-1-il)-etoxi]-benzoico

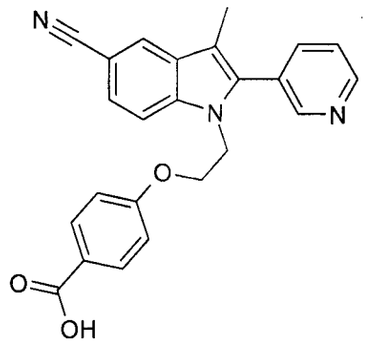


El metil-éster del ácido 4-(2-bromo-etoxi)-benzoico y 5-ciano-3-metil-2-piridin-3-il-indol-1-ilo (Ejemplo 6) se procesan de acuerdo con el método descrito en el Ejemplo 59, para dar el metil-éster del ácido 4-[2-(5-ciano-3-metil-2-piridin-3-il-indol-1-il)-etoxi]-benzoico.

^{1}H RMN (400 MHz, MeOD) δ ppm 2.28 (s, 3 H), 3.87 (s, 3 H), 4.24 (t, *J*=5.1 Hz, 2 H), 4.61 (t, *J*=5.1 Hz, 2 H), 6.73 - 6.79 (m, 2 H), 7.58 (dd, *J*=8.5, 1.6 Hz, 1 H), 7.66 (ddd, *J*=7.9, 5.0, 0.8 Hz, 1 H), 7.77 (dd, *J*=8.6, 0.5 Hz, 1 H), 7.85 - 7.88 (m, 1 H), 7.88 - 7.90 (m, 1 H), 8.03 (dt, *J*=8.1, 1.9, 1.8 Hz, 1 H), 8.07 (dd, *J*=1.5, 0.6 Hz, 1 H), 8.52 - 8.84 (m, 2 H). HRMS (ESI) m/z 412.1660 [(M+H)$^+$ Calculado para $C_{25}H_{22}N_3O_3$: 412.1661].

Ejemplo 62

Ácido 4-[2-(5-ciano-3-metil-2-piridin-3-il-indol-1-il)-etoxi]-benzoico

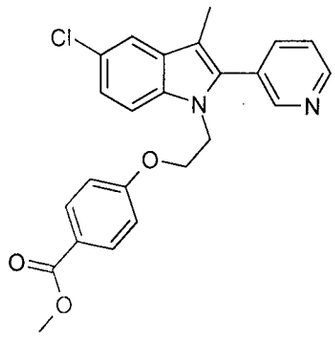


Un matraz se carga con metil-éster del ácido 4-[2-(5-ciano-3-metil-2-piridin-3-il-indol-1-il)-etoxi]-benzoico (Ejemplo 61, 0.150 gramos, 0.36 milimoles) en metanol (5 mililitros). Se agrega hidróxido de litio acuoso (1 M, 0.912 mililitros, 0.912 milimoles), y la mezcla se pone a reflujo durante la noche. La mezcla de reacción se acidifica entonces a un pH de 1 utilizando una solución acuosa de HCl 1 M, y el metanol se remueve al vacío. La solución resultante se extrae con acetato de etilo. La capa orgánica se seca sobre sulfato de sodio, se filtra, y se concentra. El residuo resultante se purifica mediante cromatografía por evaporación instantánea en gel de sílice (dicloro-metano : metanol, 9:1), para proporcionar el ácido 4-[2-(5-ciano-3-metil-2-piridin-3-il-indol-1-il)-etoxi]-benzoico como un sólido blanco.

^{1}H RMN (400 MHz, MeOD) δ ppm 2.27 (s, 3 H), 4.22 (t, *J*=5.1 Hz, 2 H), 4.60 (t, *J*=5.2 Hz, 2 H), 6.72 (d, *J*=8.8 Hz, 2 H), 7.57 (dd, *J*=8.6, 1.5 Hz, 1 H), 7.62 - 7.72 (m, 1 H), 7.76 (d, *J*=8.6 Hz, 1 H), 7.86 (d, *J*=8.6 Hz, 2 H), 8.02 (d, *J*=7.8 Hz, 1 H), 8.07 (s, 1 H), 8.72 (br. s., 2 H). HRMS (ESI) m/z 398.1487 [$(M+H)^+$ Calculado para $C_{24}H_{20}N_3O_3$: 398.1505].

Ejemplo 63

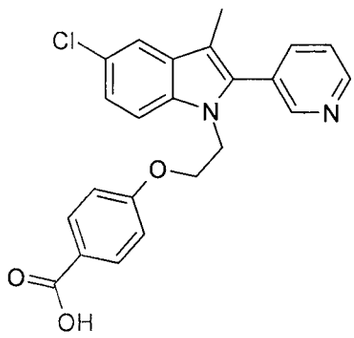
(a) Metil-éster del ácido 4-[2-(5-cloro-3-metil-2-piridin-3-il-indol-1-il)-etoxi]-benzoico



El metil-éster del ácido 4-(2-bromo-etoxi)-benzoico (Ejemplo 61a), y 5-cloro-3-metil-2-piridin-3-il-indol-1-ilo (Ejemplo 2) se procesan de acuerdo con el método descrito en el Ejemplo 59, para dar el metil-éster del ácido 4-[2-(5-cloro-3-metil-2-piridin-3-il-indol-1-il)-etoxi]-benzoico.

MS (ESI) m/z 421.01.

(b) Ácido 4-[2-(5-cloro-3-metil-2-piridin-3-il-indol-1-il)-etoxi]-benzoico



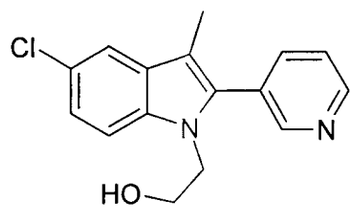
El metil-éster del ácido 4-[2-(5-cloro-3-metil-2-piridin-3-il-indol-1-il)-etoxi]-benzoico se procesa de acuerdo con el método descrito

en el Ejemplo 62, para dar el ácido 4-[2-(5-cloro-3-metil-2-piridin-3-il-indol-1-il)-etoxi]-benzoico.

^{1}H RMN (400 MHz, MeOD) δ ppm 2.22 (s, 3 H), 4.21 (t, *J*=5.1 Hz, 2 H), 4.54 (t, *J*=5.1 Hz, 2 H), 6.73 (d, *J*=8.8 Hz, 2 H), 7.25 (dd, *J*=8.7, 2.1 Hz, 1 H), 7.56 (d, *J*=8.6 Hz, 1 H), 7.59 (d, *J*=2.0 Hz, 1 H), 7.61 - 7.67 (m, 1 H), 7.87 (d, *J*=8.8 Hz, 2 H), 7.99 (d, *J*=7.8 Hz, 1 H), 8.68 (br. s., 2 H); HRMS (ESI) m/z 407.1157 [(M+H)$^+$ Calculado para $C_{23}H_{20}ClN_2O_3$: 407.1162].

Ejemplo 64

2-(5-cloro-3-metil-2-piridin-3-il-indol-1-il)-etanol



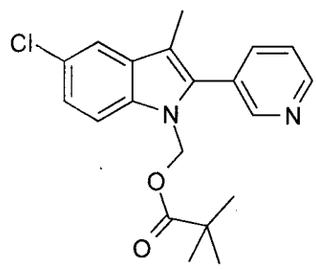
Un matraz se carga con clorhidrato de 5-cloro-3-metil-2-piridin-3-il-1H-indol (Ejemplo 2, 1.0 gramos, 3.58 milimoles), y tetrahidrofurano (20 mililitros), y se enfría a 0°C. Se agrega KHMDS (0.5 M en tolueno, 17.9 mililitros, 8.95 milimoles), y la mezcla se agita a temperatura ambiente durante 30 minutos, seguido por la adición de (2-cloro-etoxi)-trimetil-silano (1.06 mililitros, 8.95 milimoles). La mezcla de reacción se agita durante 48 horas a 60°C. Después de enfriar a temperatura ambiente, se agrega HCl 1M acuoso (30 mililitros), y la mezcla se agita a temperatura ambiente durante 30 minutos, luego se lava con agua, y se extrae con acetato de etilo dos veces. La capa orgánica se seca sobre sulfato de sodio,

y se concentra al vacío. El residuo se purifica mediante cromatografía por evaporación instantánea en gel de sílice (heptano-acetato de etilo, 1:4), para proporcionar el 2-(5-cloro-3-metil-2-piridin-3-il-indol-1-il)-etanol como un sólido.

^{1}H RMN (400 MHz, MeOD) δ ppm 2.22 (s, 3 H), 3.69 (t, *J*=5.9 Hz, 2 H), 4.18 (t, *J*=5.8 Hz, 2 H), 7.21 (dd, *J*=8.6, 2.0 Hz, 1 H), 7.47 (d, *J*=8.6 Hz, 1 H), 7.57 (d, *J*=1.8 Hz, 1 H), 7.61 - 7.67 (m, 1 H), 8.01 (dt, *J*=7.9, 2.0 Hz, 1 H), 8.61 - 8.71 (m, 2 H). HRMS (ESI) m/z 287.0953 [(M+H)$^+$ Calculado para $C_{16}H_{16}ClN_2O$: 287.0951].

Ejemplo 65

5-cloro-3-metil-2-piridin-3-il-indol-1-il-metil-éster del ácido 2,2-dimetil-propiónico



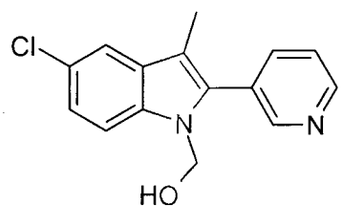
Un matraz se carga con clorhidrato de 5-cloro-3-metil-2-piridin-3-il-1H-indol (Ejemplo 2, 1.0 gramos, 3.58 milimoles), y tetrahidrofurano (20 mililitros), y se enfría a 0°C. Se agrega KHMDS (0.5 M en tolueno, 17.9 mililitros, 8.95 milimoles), y la mezcla se agita a temperatura ambiente durante 30 minutos, seguido por la adición de cloro-metil-éster del ácido 2,2-dimetil-propiónico (2.58 mililitros, 8.95 milimoles). La mezcla de reacción se agita a temperatura ambiente durante 3.5 horas, luego se lava con agua, y

se extrae con acetato de etilo dos veces. La capa orgánica se seca sobre sulfato de sodio, y se concentra al vacío. El residuo se purifica mediante cromatografía por evaporación instantánea en gel de sílice (heptano-acetato de etilo, 1:1), para proporcionar un aceite, el cual se absorbe en dietil-éter. Se agregan unas cuantas gotas de HCl concentrado. La evaporación del solvente y la liofilización dan el 5-cloro-3-metil-2-piridin-3-il-indol-1-il-metil-éster del ácido 2,2-dimetil-propiónico como un sólido.

^{1}H RMN (400 MHz, MeOD) δ ppm (sal de HCl) 1.12 (s, 9 H), 2.27 (s, 3 H), 6.06 (s, 2 H), 7.30 (dd, *J*=8.6, 2.0 Hz, 1 H), 7.60 (s, 1 H), 7.63 (d, *J*=2.3 Hz, 1 H), 7.74 (dd, *J*=7.8, 5.1 Hz, 1 H), 8.01 - 8.16 (m, 1 H), 8.64 - 8.79 (m, 2 H). HRMS (ESI) m/z 357.1121 [$(M+H)^+$ Calculado para $C_{20}H_{22}ClN_2O_2$: 357.1127].

Ejemplo 66

2-(5-cloro-3-metil-2-piridin-3-il-indol-1-il)-metanol



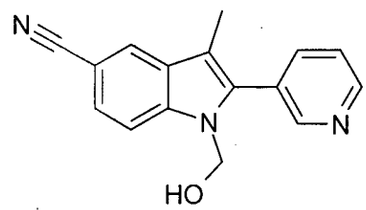
Un matraz se carga con 5-cloro-3-metil-2-piridin-3-il-indol-1-il-metil-éster del ácido 2,2-dimetil-propiónico (Ejemplo 65, 0.607 gramos, 1.684 milimoles), y dicloro-metano (10 mililitros), y se enfría a −78°C. Se agrega DIBAL-H (1M en hexano, 4.21 mililitros, 4.21 milimoles), y la mezcla se agita a −78°C durante 1 hora. La reacción se apaga con metanol (1 mililitro), y luego se lava con tartrato de

sodio y potasio acuoso saturado, y se extrae con acetato de etilo. La capa orgánica se seca sobre sulfato de sodio, y se concentra al vacío, para dar un residuo, el cual se purifica mediante cromatografía por evaporación instantánea en gel de sílice (heptano-acetato de etilo, 3:7), para proporcionar el (5-cloro-3-metil-2-piridin-3-il-indol-1-il)-metanol como un sólido color blanco.

^{1}H RMN (400 MHz, MeOD) δ ppm 2.27 (s, 3 H), 5.46 (s, 2 H), 7.25 (dd, *J*=8.6, 2.0 Hz, 1 H), 7.55 (s, 1 H), 7.58 (s, 1 H), 7.59 (d, *J*=2.0 Hz, 1 H), 7.62 - 7.67 (m, 1 H), 8.08 (dt, *J*=8.1, 2.0, 1.8 Hz, 1 H), 8.66 (dd, *J*=4.9, 1.6 Hz, 1 H), 8.75 (d, *J*=1.3 Hz, 1 H). HRMS (ESI) m/z 273.0807 [(M+H)$^+$ Calculado para $C_{15}H_{14}ClN_2O$: 273.0795].

Ejemplo 67

2-(5-ciano-3-metil-2-piridin-3-il-indol-1-il)-metanol



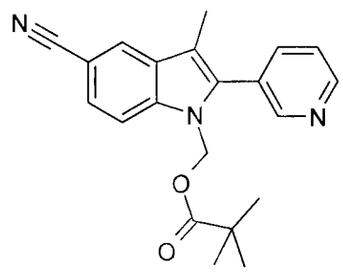
Una mezcla de 5-ciano-3-metil-2-piridin-3-il-indol (Ejemplo 6, 0.200 gramos, 0.587 milimoles) en formaldehído (4.0 mililitros) se pone a reflujo durante 5 horas. La reacción se enfría a temperatura ambiente, se diluye con acetato de etilo, y se lava con agua. La capa orgánica se seca sobre sulfato de sodio, y se concentra al vacío, para dar un residuo, el cual se purifica mediante cromatografía por evaporación instantánea en gel de sílice (dicloro-metano : acetonitrilo, 7:3), y se purifica adicionalmente mediante HPLC en

fase inversa con una columna XBridge Shield RP18 y un gradiente de ácido trifluoro-acético acuoso al 0.1 por ciento en acetonitrilo, para proporcionar el 2-(5-ciano-3-metil-2-piridin-3-il-indol-1-il)-metanol como la sal de trifluoro-acetato.

^{1}H RMN (400 MHz, MeOD) δ ppm (sal de TFA) 2.37 (s, 3 H), 5.54 (s, 2 H), 7.61 (dd, *J*=8.6, 1.5 Hz, 1 H), 7.78 (d, *J*=8.6 Hz, 1 H), 8.01 (dd, *J*=7.3, 5.3 Hz, 1 H), 8.12 (d, *J*=1.0 Hz, 1 H), 8.54 (dt, *J*=7.9, 1.9 Hz, 1 H), 8.85 (dd, *J*=5.4, 1.4 Hz, 1 H), 9.01 (d, *J*=1.5 Hz, 1 H). HRMS (ESI) m/z 264.1134 [(M+H)$^+$ Calculado para $C_{16}H_{14}N_3O$: 264.1137].

Ejemplo 68

5-ciano-3-metil-2-piridin-3-il-indol-1-il-metil-éster del ácido 2,2-dimetil-propiónico



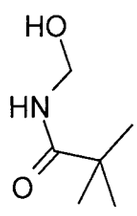
Un matraz se carga con 3-metil-2-piridin-3-il-1H-indol-5-carbonitrilo (Ejemplo 6, 0.200 gramos, 0.856 milimoles), y dimetil-formamida (10 mililitros). La mezcla se enfría a 0°C, y se agrega NaH al 60 por ciento en aceite mineral (0.086 gramos, 2.14 milimoles). La mezcla se agita a temperatura ambiente durante 20 minutos, seguido por la adición de cloro-metil-éster del ácido 2,2-dimetil-propiónico (0.310 mililitros, 2.14 milimoles). Después de

agitar a temperatura ambiente durante 1.5 horas, la mezcla se diluye con acetato de etilo, y se lava con agua. La capa orgánica se seca sobre sulfato de sodio, y se concentra al vacío. El residuo se purifica mediante HPLC en fase inversa con una columna XBridge Shield RP18 y un gradiente de NH_4OH acuoso al 0.1 por ciento en acetonitrilo, para proporcionar el producto de 5-ciano-3-metil-2-piridin-3-il-indol-1-il-metil-éster del ácido 2,2-dimetil-propiónico como un sólido blanco.

^{1}H RMN (400 MHz, MeOD) δ ppm 1.12 (s, 9 H), 2.31 (s, 3 H), 6.10 (s, 2 H), 7.62 (dd, *J*=8.5, 1.6 Hz, 1 H), 7.68 (ddd, *J*=7.9, 5.0, 0.8 Hz, 1 H), 7.81 (d, *J*=8.6 Hz, 1 H), 8.04 (dt, *J*=8.1, 2.0, 1.8 Hz, 1 H), 8.09 (d, *J*=1.0 Hz, 1 H), 8.66 - 8.76 (m, 2 H). HRMS (ESI) m/z 348.1700 [$(M+H)^+$ Calculado para $C_{21}H_{22}N_3O_2$: 348.1712].

Ejemplo 69

(a) *N*-hidroxi-metil-2,2-dimetil-propionamida

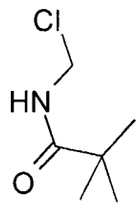


Un matraz se carga con 2,2-dimetil-propionamida (1.00 gramos, 9.98 milimoles), p-formaldehído (0.736 gramos, 9.98 milimoles), y carbonato de potasio (0.054 gramos, 3.95 milimoles). La mezcla de reacción se agita a 75°C durante 16 horas, después de lo cual, se enfría a temperatura ambiente, y se diluye con acetona. La filtración y la concentración del filtrado dan un residuo, el cual se purifica

mediante cromatografía por evaporación instantánea en gel de sílice (heptano-acetato de etilo, 4:1), para proporcionar la *N*-hidroxi-metil-2,2-dimetil-propionamida como un sólido blanco.

^{1}H RMN (400 MHz, $CDCl_3$) δ ppm 1.25 (s, 9 H), 4.73 (d, *J*=7.1 Hz, 2 H).

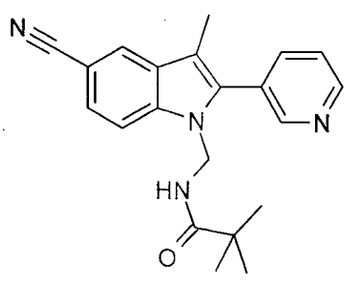
(b) *N*-cloro-metil-2,2-dimetil-propionamida



Un matraz se carga con *N*-hidroxi-metil-2,2-dimetil-propionamida (0.500 gramos, 3.81 milimoles), y dicloro-metano (4 mililitros). Se agrega cloruro de oxalilo (0.8 mililitros, 9.52 milimoles), y la mezcla de reacción se agita a temperatura ambiente durante 2 horas. La concentración al vacío da la *N*-cloro-metil-2,2-dimetil-propionamida como un sólido blanco.

^{1}H RMN (400 MHz, $CDCl_3$) δ ppm 1.23 (s, 9 H), 5.31 (s, 2 H).

(c) *N*-(5-ciano-3-metil-2-piridin-3-il-indol-1-il-metil)-2,2-dimetil-propionamida



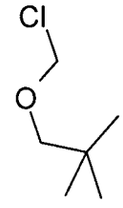
La *N*-cloro-metil-2,2-dimetil-propionamida y 3-metil-2-piridin-3-

il-1H-indol-5-carbonitrilo (Ejemplo 6) se procesan de acuerdo con el método descrito en el Ejemplo 68, para dar el *N*-(5-ciano-3-metil-2-piridin-3-il-indol-1-il-metil)-2,2-dimetil-propionamida.

^{1}H RMN (400 MHz, MeOD) δ ppm 1.06 (s, 9 H), 2.27 (s, 3 H), 5.54 (s, 2 H), 7.55 (dd, *J*=8.6, 1.8 Hz, 1 H), 7.66 (ddd, *J*=7.9, 5.0, 1.0 Hz, 1 H), 7.81 (d, *J*=8.6 Hz, 1 H), 8.01 - 8.09 (m, 2 H), 8.65 - 8.73 (m, 2 H). HRMS (ESI) m/z 347.1863 [$(M+H)^+$ Calculado para $C_{21}H_{23}N_4O$: 347.1872].

Ejemplo 70

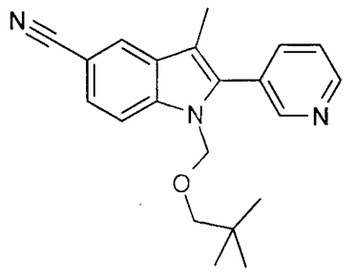
(a) 1-cloro-metoxi-2,2-dimetil-propano



Un matraz de 2 cuellos se carga con formaldehído (1.1 gramos, 36.8 milimoles), 2,2-dimetil-propan-1-ol (2.5 gramos, 28.3 milimoles), y tolueno (50 mililitros). La mezcla de reacción se enfría a –20°C y se burbujea gas de HCl durante 30 minutos. Se agrega sulfato de sodio (5.9 gramos) a la mezcla de reacción, la cual entonces se agita a –10°C durante la noche, se calienta a 0°C, y se agita durante otras 5 horas. Los sólidos se filtran, y el filtrado se concentra al vacío, para proporcionar el 1-cloro-metoxi-2,2-dimetil-propano como un aceite incoloro.

^{1}H RMN (400 MHz, $CDCl_3$) δ ppm 0.95 (s, 9 H), 3.36 (s, 2 H), 5.54 (s, 2 H).

(b) 1-(2,2-dimetil-propoxi-metil)-3-metil-2-piridin-3-il-1H-indol-5-carbonitrilo

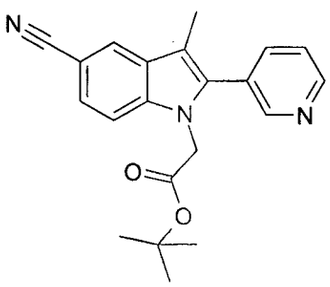


El 3-metil-2-piridin-3-il-1H-indol-5-carbonitrilo (Ejemplo 6), y 1-cloro-metoxi-2,2-dimetil-propano se procesan de acuerdo con el método descrito en el Ejemplo 68, para dar el 1-(2,2-dimetil-propoxi-metil)-3-metil-2-piridin-3-il-1H-indol-5-carbonitrilo.

^{1}H RMN (400 MHz, MeOD) δ ppm 0.84 (s, 9 H), 2.33 (s, 3 H), 3.04 (s, 2 H), 5.48 (s, 2 H), 7.59 (dd, *J*=8.6, 1.5 Hz, 1 H), 7.66 (ddd, *J*=8.0, 4.9, 1.0 Hz, 1 H), 7.77 (dd, *J*=8.6, 0.5 Hz, 1 H), 8.07 (dt, *J*=7.8, 1.9 Hz, 1 H), 8.09 (dd, *J*=1.5, 0.8 Hz, 1 H), 8.70 (dd, *J*=4.9, 1.6 Hz, 1 H), 8.75 (dd, *J*=2.3, 0.8 Hz, 1 H). HRMS (ESI) m/z 334.1914 [(M+H)$^+$ Calculado para $C_{21}H_{24}N_3O$: 334.1919].

Ejemplo 71

Terbutil-éster del ácido (5-ciano-3-metil-2-piridin-3-il-indol-1-il)-acético

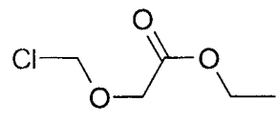


El 3-metil-2-piridin-3-il-1H-indol-5-carbonitrilo (Ejemplo 6), y bromo-acetato de terbutilo se procesan de acuerdo con el método descrito en el Ejemplo 68, para dar el terbutil-éster del ácido (5-ciano-3-metil-2-piridin-3-il-indol-1-il)-acético.

^{1}H RMN (400 MHz, MeOD) δ ppm 1.38 (s, 9 H), 2.31 (s, 3 H), 4.83 (s, 2 H), 7.56 (d, *J*=1.3 Hz, 2 H), 7.66 (ddd, *J*=7.8, 4.9, 0.9 Hz, 1 H), 7.95 (dt, *J*=7.8, 1.9 Hz, 1 H), 8.09 (s, 1 H), 8.63 (d, *J*=1.3 Hz, 1 H), 8.71 (dd, *J*=4.9, 1.6 Hz, 1 H). HRMS (ESI) m/z 348.1719 [$(M+H)^+$ Calculado para $C_{21}H_{22}N_3O_2$: 348.1712].

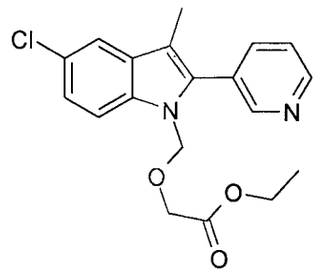
Ejemplo 72

(a) Etil-éster del ácido cloro-metoxi-acético



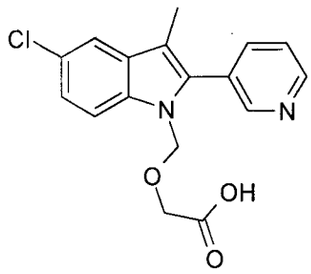
El etil-éster del ácido cloro-metoxi-acético se prepara de acuerdo con el método descrito in *Heterocycles* 2005, *65*, 1967. Un matraz de 2 cuellos se carga con formaldehído (0.747 gramos, 24.9 moles), etil-éster del ácido hidroxi-acético (2.0 gramos, 19.2 milimoles), y tolueno (50 mililitros). La mezcla de reacción se enfría a –20°C, y se burbujea gas de HCl a través de la misma durante 30 minutos. Se agrega sulfato de sodio (4 gramos) a la mezcla de reacción, la cual entonces se agita a –10°C durante la noche, se calienta a 0°C, y se agita durante otras 5 horas. Los sólidos se filtran, y el filtrado se concentra al vacío, para proporcionar el etil-éster del ácido cloro-metoxi-acético como un aceite incoloro.

(b) Etil-éster del ácido (5-cloro-3-metil-2-piridin-3-il-indol-1-il-metoxi)-acético



Un matraz se carga con clorhidrato de 5-cloro-3-metil-2-piridin-3-il-1H-indol (Ejemplo 2) (0.930 gramos, 3.33 milimoles) en tetrahidrofurano (20 mililitros), y se enfría a 0°C. Se agrega KHMDS (0.5 M en tolueno, 16.65 mililitros, 8.32 milimoles), y la mezcla se agita a temperatura ambiente durante 30 minutos, seguido por la adición de etil-éster del ácido cloro-metoxi-acético (1.27 gramos, 8.32 milimoles). La mezcla de reacción se agita durante 3 horas, luego se lava con agua, y se extrae con acetato de etilo. La capa orgánica se seca sobre sulfato de sodio, y se concentra al vacío, para dar un residuo, el cual se purifica mediante cromatografía por evaporación instantánea en gel de sílice (dicloro-metano : metanol, 19:1), para proporcionar el etil-éster del ácido (5-cloro-3-metil-2-piridinil-indol-1-il-metoxi)-acético como un sólido. MS (ESI) *m/z* 359.2 $(M+H)^+$.

(c) Ácido (5-cloro-3-metil-2-piridin-3-il-indol-1-il-metoxi)-acético

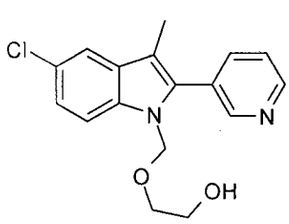


Un matraz se carga con etil-éster del ácido (5-cloro-3-metil-2-piridinil-indol-1-il-metoxi)-acético (0.622 gramos, 1.737 milimoles) en metanol (10 mililitros). Se agrega hidróxido de litio acuoso (1M, 4.34 mililitros, 4.34 milimoles), y la mezcla se agita a temperatura ambiente durante 1.5 horas. La mezcla de reacción se acidifica a un pH de 1 utilizando HCl acuoso 1M. El precipitado se filtra y se recristaliza en metanol, para proporcionar el ácido (5-cloro-3-metil-2-fenil-indol-1-il-metoxi)-acético como un sólido blanco.

^{1}H RMN (400 MHz, MeOD) δ ppm 2.27 (s, 3 H), 4.02 (s, 2 H), 5.54 (s, 2 H), 7.27 (dd, *J*=8.8, 2.0 Hz, 1 H), 7.59 - 7.68 (m, 3 H), 8.10 (ddd, *J*=8.0, 1.9, 1.8 Hz, 1 H), 8.67 (dd, *J*=4.9, 1.6 Hz, 1 H), 8.74 (d, *J*=1.5 Hz, 1 H). HRMS (ESI) m/z 331.0849 [(M+H)$^+$ Calculado para $C_{17}H_{16}ClN_2O_3$: 331.0849].

Ejemplo 73

2-(5-cloro-3-metil-2-piridin-3-il-indol-1-il-metoxi)-etanol



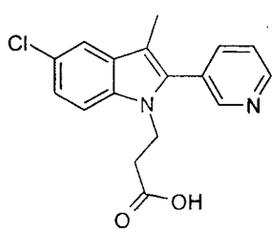
Un matraz se carga con etil-éster del ácido (5-cloro-3-metil-2-

piridin-3-il-indol-1-il-metoxi)-acético (Ejemplo 72b, 1.00 gramos, 2.79 milimoles), y tetrahidrofurano (10 mililitros). La mezcla de reacción se enfría a 0°C, y se agrega hidruro de litio y aluminio (1M en tetrahidrofurano, 6.98 mililitros, 6.98 milimoles). Después de agitar durante 1 hora a temperatura ambiente, la mezcla se apaga con agua (0.3 mililitros), seguida por NaOH acuoso al 16 por ciento (0.3 mililitros). Se agrega agua (1 mililitro), y la agitación se continúa durante 10 minutos. Los sólidos se filtran, y el filtrado se concentra al vacío. El residuo se purifica mediante cromatografía por evaporación instantánea en gel de sílice (dicloro-metano : acetonitrilo, 3:1), seguida por una purificación sobre una columna Chiralcel® IA (heptano-EtOH, 9:1), para proporcionar el 2-(5-cloro-3-metil-2-piridin-3-il-indol-1-il-metoxi)-etanol como un sólido blanco.

^{1}H RMN (400 MHz, MeOD) δ ppm 2.27 (s, 3 H), 3.42 - 3.49 (m, 2 H), 3.60 (t, *J*=4.8 Hz, 2 H), 5.47 (s, 2 H), 7.27 (dd, *J*=8.7, 1.9 Hz, 1 H), 7.57 - 7.62 (m, 2 H), 7.64 (dd, *J*=8.0, 4.9 Hz, 1 H), 8.10 (dt, *J*=7.8, 1.9 Hz, 1 H), 8.66 (dd, *J*=4.9, 1.6 Hz, 1 H), 8.74 (d, *J*=1.3 Hz, 1 H). HRMS (ESI) m/z 317.1056 [$(M+H)^+$ Calculado para $C_{17}H_{17}ClN_2O_2$: 317.1507].

Ejemplo 74

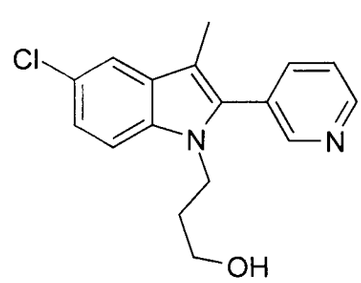
(a) ácido 3-(5-cloro-3-metil-2-piridin-3-il-indol-1-il)-propiónico



Un matraz se carga con clorhidrato de 5-cloro-3-metil-2-piridin-3-il-1H-indol (Ejemplo 2, 0.700 gramos, 2.50 milimoles) en N,N-dimetil-formamida (7 mililitros), y se enfría a 0°C. Se agrega terbutóxido de potasio (0.740 miligramos, 6.26 milimoles), y la mezcla se agita a temperatura ambiente durante 30 minutos, entonces se baja de regreso al baño de hielo. Se agrega metil-éster del ácido acrílico (0.680 mililitros, 7.52 milimoles), y la mezcla de reacción se agita durante 1.5 horas. La mezcla de reacción se acidifica a un pH de 1 utilizando HCl acuoso 1M, y se extrae con acetato de etilo. La capa orgánica se seca sobre sulfato de sodio, y se concentra al vacío, para dar un residuo, el cual se purifica mediante cromatografía por evaporación instantánea en gel de sílice (dicloro-metano : metanol, 9:1), para proporcionar el ácido 3-(5-cloro-3-metil-2-piridinil-indol-1-il)-propiónico como un sólido blanco.

MS (ESI) *m/z* 315.18 $(M+H)^+$

(b) 3-(5-cloro-3-metil-2-piridin-3-il-indol-1-il)-propan-1-ol



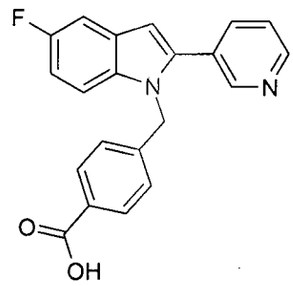
Un matraz se carga con ácido 3-(5-cloro-3-metil-2-piridinil-indol-1-il)-propiónico (0.344 gramos, 1.09 milimoles), y tetrahidrofurano (10 mililitros). La mezcla de reacción se enfría a 0°C, y se agrega LAH (1M en tetrahidrofurano, 2.73 mililitros, 2.73

milimoles). Después de agitar a temperatura ambiente durante 30 minutos, la mezcla se enfría a 0°C, se apaga con $NaHCO_3$ acuoso, y se extrae con acetato de etilo. La capa orgánica se seca sobre sulfato de sodio, y se concentra al vacío, para dar un residuo, el cual se purifica mediante cromatografía por evaporación instantánea en gel de sílice (dicloro-metano : metanol, 19:1), para proporcionar el 3-(5-cloro-3-metil-2-piridinil-indol-1-il)-propan-1-ol como un sólido blanco.

^{1}H RMN (400 MHz, MeOD) δ ppm 1.71 - 1.82 (m, 2 H), 2.23 (s, 3 H), 3.38 (t, *J*=6.1 Hz, 2 H), 4.18 - 4.24 (m, 2 H), 7.21 (dd, *J*=8.8, 2.0 Hz, 1 H), 7.49 (d, *J*=8.6 Hz, 1 H), 7.57 (d, *J*=1.8 Hz, 1 H), 7.65 (ddd, *J*=7.9, 5.0, 1.0 Hz, 1 H), 7.98 (ddd, *J*=8.1, 2.0, 1.8 Hz, 1 H), 8.65 (dd, *J*=2.3, 0.8 Hz, 1 H), 8.67 (dd, *J*=5.1, 1.8 Hz, 1 H). HRMS (ESI) m/z 301.1108 [$(M+H)^+$ Calculado para $C_{17}H_{18}ClN_2O$: 301.1108].

Ejemplo 75

Ácido 4-(5-fluoro-2-piridin-3-il-indol-1-il-metil)-benzoico



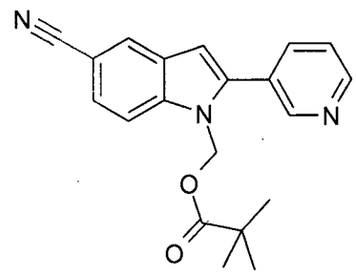
Un matraz se carga con NaH (0.284 gramos, 7.093 milimoles), y sulfóxido de dimetilo (1.5 mililitros). Se agrega 5-fluoro-2-piridin-3-il-indol (Ejemplo 7, 0.112 gramos, 0.507 milimoles) en sulfóxido de dimetilo (0.5 mililitros). El matraz y las jeringas se enjuagan con

sulfóxido de dimetilo (0.5 mililitros, 2 veces). Después de 10 minutos, se agrega 4-(bromo-metil)-benzoato de etilo puro (0.192 gramos, 0.760 milimoles). Después de 10 minutos, se agrega agua. El precipitado resultante se filtra a través de un embudo sinterizado, y se lava con agua y dicloro-metano, para dar el ácido 4-(5-fluoro-2-piridin-3-il-indol-1-il-metil)-benzoico como un sólido grisáceo.

^{1}H RMN (400 MHz, MeOD) δ ppm (sal de sodio) 5.49 (s, 2 H), 6.77 (s, 1 H), 6.92 (d, *J*=8.1 Hz, 2 H), 6.95 - 7.00 (m, 1 H), 7.31 - 7.37 (m, 2 H), 7.49 (dd, *J*=7.7, 5.2 Hz, 1 H), 7.85 (d, *J*=8.1 Hz, 2 H), 7.87 - 7.92 (m, 1 H), 8.56 (dd, *J*=4.9, 1.5 Hz, 1 H), 8.68 (d, *J*=1.5 Hz, 1 H). HRMS (ESI) m/z 347.1212 [$(M+H)^+$ Calculado para $C_{21}H_{16}FN_2O_2$: 347.1196].

Ejemplo 76

5-ciano-2-piridin-3-il-indol-1-il-metil-éster del ácido 2,2-dimetil-propiónico



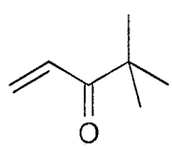
A una solución de 2-piridin-3-il-1H-indol-5-carbonitrilo (Ejemplo 8, 210 miligramos, 1.37 milimoles) en tetrahidrofurano (20 mililitros) a temperatura ambiente, se le agrega KHMDS 0.5 M en tolueno (4.1 mililitros, 2.05 milimoles). Después de 30 minutos, se agrega pivalato de cloro-metilo (510 miligramos, 3.08 milimoles). La mezcla se agita

bajo N_2 durante 1 hora. Se agrega bicarbonato de sodio acuoso saturado (0.5 mililitros) para apagar la reacción. Se agrega gel de sílice a la mezcla, y los solventes se remueven al vacío. El residuo se purifica mediante cromatografía por evaporación instantánea en gel de sílice (acetato de etilo-heptano, de 0:1 a 1:0). La purificación adicional mediante HPLC utilizando una XBridge RP18 con un gradiente de hidróxido de amonio acuoso al 0.1 por ciento en acetonitrilo, da el 5-ciano-2-piridin-3-il-indol-1-il-metil-éster del ácido 2,2-dimetil-propiónico como un sólido blanco.

^{1}H RMN (400 MHz, $CDCl_3$) δ ppm 1.20 (s, 9 H), 6.08 (s, 2 H), 6.77 (s, 1 H), 7.49 (ddd, *J*=7.8, 4.8, 0.8 Hz, 1 H), 7.56 (dd, *J*=8.6, 1.8 Hz, 1 H), 7.68 (d, *J*=8.6 Hz, 1 H), 7.94 (ddd, *J*=7.9, 2.0 Hz, 1 H), 8.01 (dd, *J*=1.5, 0.5 Hz, 1 H), 8.75 (dd, *J*=4.8, 1.8 Hz, 1 H), 8.87 (d, *J*=1.5 Hz, 1 H). HRMS (ESI) m/z 334.1566 [$(M+H)^+$ Calculado para $C_{20}H_{20}N_3O_2$: 334.1556].

Ejemplo 77

(a) 4,4-dimetil-pent-1-en-3-ona

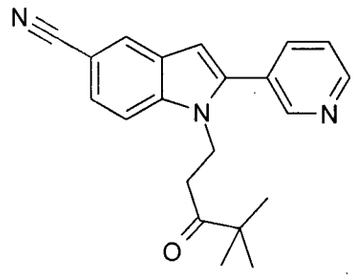


Este procedimiento se adapta a partir de *Tetrahedron Lett.* 1978, *32*, 2955. Un matraz se carga con 3,3-dimetil-butan-2-ona (1.00 gramos, 9.98 milimoles), *p*-formaldehído (1.34 gramos, 44.9 milimoles), trifluoro-acetato de *N*-metil-anilinio (3.31 gramos, 14.9 milimoles), y tetrahidrofurano (10 mililitros). La mezcla de reacción

se pone a reflujo durante 16 horas, seguido por la adición de cantidades adicionales de *p*-formaldehído (0.674 gramos, 22.45 milimoles), y trifluoro-acetato de *N*-metil-anilinio (1.64 gramos, 7.48 milimoles). Después de otras 5.5 horas a reflujo, la mezcla se enfría a temperatura ambiente, y se agrega pentano (20 mililitros). Se recolecta un aceite color café en el fondo del matraz. se remueve el sobrenadante, y se agrega pentano (25 mililitros). Después de la decantación, se remueve el sobrenadante. Los sobrenadantes se combinan y se concentran al vacío, para proporcionar la 4,4-dimetil-pent-1-en-3-ona como un aceite incoloro.

^{1}H RMN (400 MHz, $CDCl_3$) δ ppm 1.18 (s, 9 H), 5.68 (dd, *J*=10.4, 2.0 Hz, 1 H), 6.36 (dd, *J*=16.9, 2.0 Hz, 1 H), 6.83 (dd, *J*=16.9, 10.4 Hz, 1 H).

(b) 1-(4,4-dimetil-3-oxo-pentil)-2-piridin-3-il-1H-indol-5-carbonitrilo



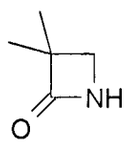
A una solución de 2-piridin-3-il-1H-indol-5-carbonitrilo (Ejemplo 8, 0.225 gramos, 1.026 milimoles) en sulfóxido de dimetilo (5 mililitros), se le agrega terbutóxido de potasio (0.182 gramos, 1.53 milimoles), y la mezcla se agita a temperatura ambiente durante 0.5 horas. Se agrega 4,4-dimetil-pent-1-en-3-ona (0.345 gramos, 3.078 milimoles), y la mezcla se agita a 50°C durante la noche. La dilución

con acetato de etilo da una solución, la cual se lava con agua dos veces, se seca sobre sulfato de sodio, y se concentra al vacío. El residuo se purifica mediante XBridge Shield RP18 con un gradiente de acetonitrilo en NH_4OH al 0.1 por ciento, para dar un aceite. La adición de dietil-éter y unas cuantas gotas de HCl concentrado, seguida por liofilización, proporciona el 1-(4,4-dimetil-3-oxo-pentil)-2-piridin-3-il-1H-indol-5-carbonitrilo como un sólido color amarillo claro.

^{1}H RMN (400 MHz, MeOD) δ ppm (sal de HCl) 0.90 (s, 9 H), 2.94 (t, *J*=6.4 Hz, 2 H), 4.61 (t, *J*=6.6 Hz, 2 H), 6.88 (s, 1 H), 7.59 (dd, *J*=8.7, 1.6 Hz, 1 H), 7.77 (d, *J*=8.6 Hz, 1 H), 7.93 (dd, *J*=8.0, 5.4 Hz, 1 H), 8.10 (d, *J*=1.0 Hz, 1 H), 8.44 (dt, *J*=7.9, 1.7 Hz, 1 H), 8.82 (dd, *J*=5.3, 1.3 Hz, 1 H), 8.96 (d, *J*=1.8 Hz, 1 H). HRMS (ESI) m/z 332.1762 [$(M+H)^+$ Calculado para $C_{21}H_{22}N_3O$: 332.1763].

Ejemplo 78

(a) 3,3-dimetil-azetidin-2-ona

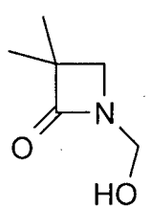


Un recipiente de vidrio Parr de 250 mililitros se carga con Rh/Al_2O_3 (2.33 gramos, 1.13 milimoles), y 2,2-dimetil-ciano-acetato de etilo (2.0 gramos) disuelto en etanol (90 mililitros). El matraz se evacua y se rellena con hidrógeno (50 psi (3.5 kg/cm^2)), y la mezcla se agita bajo 50 psi (3.5 kg/cm^2) de hidrógeno. Después de 48 horas, la mezcla se filtra y se concentra al vacío (50 Torr, 35°C, 30

minutos), para dar una mezcla cruda, la cual se disuelve en éter anhidro (60 mililitros) bajo nitrógeno, y se enfría a 0°C. Se agrega por goteo LHMDS (1.0M en tetrahidrofurano, 10 mililitros, 10 milimoles), y se remueve el baño de enfriamiento. Después de 2 horas, la mezcla se enfría a 0°C, y se apaga con bisulfato de sodio acuoso 1M, y se diluye con éter. La fase orgánica se lava con bisulfato de sodio acuoso 1M y salmuera. El pH de la fase acuosa combinada se ajusta a 14 con hidróxido de sodio acuoso 4M, y la fase acuosa se extrae repetidamente con dicloro-metano. La fase de dicloro-metano se seca sobre sulfato de magnesio, se filtra, y se concentra al vacío, para dar un residuo, el cual se purifica mediante cromatografía por evaporación instantánea en gel de sílice (acetato de etilo), para dar la 3,3-dimetil-azetidin-2-ona como un aceite incoloro.

^{1}H RMN (400 MHz, $CDCl_3$) δ ppm 1.34 (s, 6 H), 3.13 (s, 2 H).

(b) 1-hidroxi-metil-3,3-dimetil-azetidin-2-ona

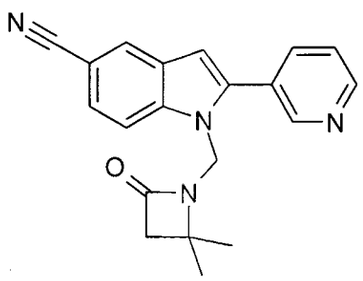


Un matraz se carga con 3,3-dimetil-azetidin-2-ona (0.159 gramos, 1.524 milimoles), formaldehído acuoso (al 37 por ciento en peso., 0.124 gramos, 1.524 milimoles), y carbonato de potasio triturado (0.009 gramos, 0.061 milimoles). El matraz se baja a un baño de aceite previamente calentado (75°C). Después de 15

minutos, el matraz se remueve del baño de aceite, y se deja reposar a temperatura ambiente. Después de 2 horas, la mezcla se absorbe en acetona, se seca sobre sulfato de magnesio, y se filtra a través de un tapón de gel de sílice. La concentración al vacío (30°C, 40 Torr) da la 1-hidroxi-metil-3,3-dimetil-azetidin-2-ona, la cual se utiliza en el siguiente paso sin mayor purificación.

^{1}H RMN (400 MHz, $CDCl_3$) δ ppm 1.32 (s, 6 H), 3.23 (s, 2 H), 4.69 (d, *J*=7.5 Hz, 2 H).

(c) 1-(3,3-dimetil-2-oxo-azetidin-1-il-metil)-2-piridin-3-il-1H-indol-5-carbonitrilo



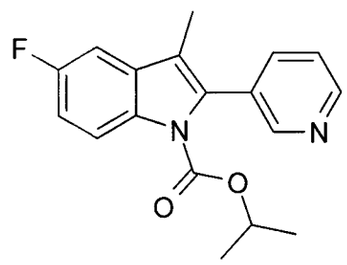
Un matraz se carga con 1-hidroxi-metil-3,3-dimetil-azetidin-2-ona (0.179 gramos, 1.317 milimoles), y dicloro-metano (5 mililitros), y se agrega cloruro de tionilo (0.63 gramos, 5.27 milimoles). La mezcla se agita a temperatura ambiente durante la noche y se concentra al vacío, para proporcionar un aceite, el cual se vuelve a disolver en N,N-dimetil-formamida (0.8 mililitros). El 2-piridin-3-il-1H-indol-5-carbonitrilo (Ejemplo 8, 0.213 gramos, 0.922 milimoles) se disuelve en N,N-dimetil-formamida (5 mililitros), se enfría a 0°C, y se agrega en porciones NaH (0.053 gramos, 1.317 milimoles). Después de 30 minutos, se agrega la solución de cloruro. Después de 1 hora,

se agrega NaH (0.027 gramos, 0.67 milimoles), y la mezcla se agita durante la noche. La mezcla se apaga con unas cuantas gotas de agua, y se diluye con metanol y sulfóxido de dimetilo. La mezcla se purifica en una XBridge C18 eluyendo con un gradiente de 9:1 a 1:9 de agua-acetonitrilo, para dar el 1-(3,3-dimetil-2-oxo-azetidin-1-il-metil)-2-piridin-3-il-1H-indol-5-carbonitrilo.

^{1}H RMN (400 MHz, $CDCl_3$) δ ppm 1.18 (s, 6 H), 2.82 (s, 2 H), 5.47 (s, 2 H), 6.71 (s, 1 H), 7.47 - 7.51 (m, 1 H), 7.56 (dd, *J*=8.6, 1.5 Hz, 1 H), 7.73 (d, *J*=8.6 Hz, 1 H), 7.80 - 7.83 (m, 1 H), 8.01 (d, *J*=1.5 Hz, 1 H), 8.75 - 8.76 (m, 2 H). HRMS (ESI) m/z 331.1558 [$(M+H)^+$ Calculado para $C_{20}H_{19}N_4O$: 331.1559].

Ejemplo 79

Isopropil-éster del ácido 5-fluoro-3-metil-2-piridin-3-il-indol-1-carboxílico



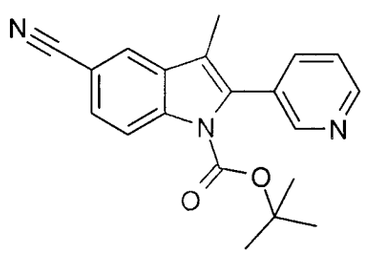
El 5-fluoro-3-metil-2-piridin-3-il-indol (Ejemplo 3, 0.246 gramos, 1.044 milimoles) se disuelve en N,N-dimetil-formamida (9 mililitros). Se agrega NaH (60 por ciento, 0.054 gramos, 1.357 milimoles), y la mezcla se agita durante 1 hora, después de lo cual, se agrega cloroformato de isopropilo (1.0M en tolueno, 2.1 mililitros, 2.1 milimoles). La mezcla se agita durante la noche, se apaga con

bicarbonato de sodio acuoso saturado, y se extrae con acetato de etilo. La fase orgánica se seca sobre $MgSO_4$ y se concentra al vacío, para dar un residuo, el cual se purifica mediante cromatografía por evaporación instantánea en gel de sílice (acetato de etilo-heptano, de 1:4 a 2:3), para dar el isopropil-éster del ácido 5-fluoro-3-metil-2-piridin-3-il-indol-1-carboxílico como un sólido amarillo pálido.

^{1}H RMN (400 MHz, MeOD) δ ppm 1.07 (d, *J*=6.3 Hz, 6 H), 2.12 (s, 3 H), 4.93 - 5.04 (m, 1 H), 7.09 - 7.17 (m, 1 H), 7.30 (dd, *J*=8.8, 2.3 Hz, 1 H), 7.54 - 7.59 (m, 1 H), 7.84 - 7.89 (m, 1 H), 8.23 (dd, *J*=9.1, 4.5 Hz, 1 H), 8.53 - 8.56 (m, 1 H), 8.61 (dd, *J*=4.5, 1.6 Hz, 1 H). HRMS (ESI) m/z 313.1353 [$(M+H)^+$ Calculado para $C_{18}H_{18}FN_2O_2$: 313.1352].

Ejemplo 80

Terbutil-éster del ácido 5-ciano-3-metil-2-piridin-3-il-indol-1-carboxílico



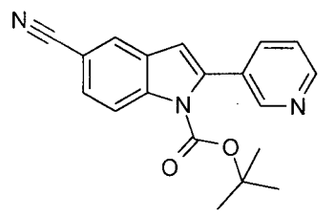
A una solución de 3-metil-2-piridin-3-il-1H-indol-5-carbonitrilo (Ejemplo 6, 96 miligramos, 0.40 milimoles) en N,N-dimetil-formamida (2 mililitros) a temperatura ambiente, se le agregan trietil-amina (30 miligramos, 0.30 milimoles), carbonato de diterbutilo (65 miligramos, 0.30 milimoles), y 4-(*N*,*N*-dimetil-amino)-piridina (2 miligramos, 0.020

milimoles). La mezcla se agita bajo N_2. La mezcla se purifica mediante XBridge RP18 con un gradiente de acetonitrilo en hidróxido de amonio acuoso al 0.1 por ciento, para dar el terbutil-éster del ácido 5-ciano-3-metil-2-piridin-3-il-indol-1-carboxílico como un sólido blanco.

^{1}H RMN (400 MHz, $CDCl_3$) δ ppm 1.30 (s, 9 H), 2.16 (s, 3 H), 7.47 - 7.55 (m, 1 H), 7.65 (dd, *J*=8.7, 1.6 Hz, 1 H), 7.76 (d, *J*=7.3 Hz, 1 H), 7.90 (d, *J*=1.0 Hz, 1 H), 8.35 (d, *J*=8.6 Hz, 1 H), 8.63 (d, *J*=1.8 Hz, 1 H), 8.69 (dd, *J*=5.1, 1.5 Hz, 1 H). HRMS (ESI) m/z 334.1566 [$(M+H)^+$ Calculado para $C_{20}H_{20}N_3O_2$: 334.1556].

Ejemplo 81

Terbutil-éster del ácido 5-ciano-2-piridin-3-il-indol-1-carboxílico



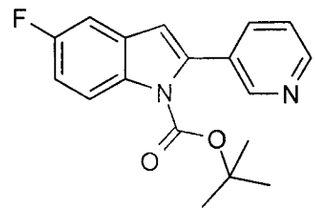
Una mezcla del ácido 1-Boc-5-ciano-indol-2-borónico (339 miligramos, 1.19 milimoles), 3-bromo-piridina (150 miligramos, 93 microlitros, 0.95 milimoles), carbonato de sodio acuoso (2M, 0.95 mililitros, 1.9 milimoles), y DME (4 mililitros), se desgasifica con nitrógeno, y se agrega PS-Pd(PPh_3) (285 miligramos, 0.11 milimoles/gramo, 0.028 milimoles). La mezcla resultante entonces se calienta en el reactor de microondas a 120°C durante 20 minutos, y a 130°C durante 25 minutos (tres veces). La mezcla de reacción se filtra a través de un embudo sinterizado, y se lava con dicloro-

metano (50 mililitros). El filtrado se seca sobre Na_2SO_4, se filtra, y se concentra. El residuo se purifica mediante HPLC en fase inversa (del 5 al 80 por ciento de acetonitrilo - amoníaco acuoso al 0.1 por ciento), para dar el terbutil-éster del ácido 5-ciano-2-piridin-3-il-indol-1-carboxílico como un sólido.

^{1}H RMN (400.3 MHz, $CDCl_3$) δ ppm 1.34 (s, 9H), 6.67 (s, 1H), 7.39 (dd, J = 4.9, 7.8 Hz, 1 H), 7.61 (dd, J= 1.6, 8.7 Hz, 1 H), 7.74 (m, 1 H), 7.92 (s, 1 H), 8.35 (d, J = 8.7 Hz, 1H), 8.65 (dd, J = 1.6 Hz, 4.9 Hz, 1 H), 8.69 (d, J = 2.2 Hz, 1 H). MS (ESI) *m/z* 320 $(M+H)^+$.

Ejemplo 82

Terbutil-éster del ácido 5-fluoro-2-piridin-3-il-indol-1-carboxílico



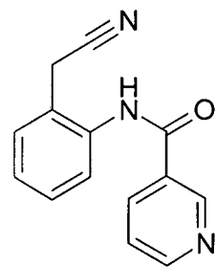
A una solución de 5-fluoro-2-piridin-3-il-indol (Ejemplo 3, 0.100 gramos, 0.452 milimoles) en N,N-dimetil-formamida (1 mililitro), se le agregan trietil-amina (0.083 gramos, 0.814 milimoles), DMAP (0.006 gramos, 0.045 milimoles), y carbonato de diterbutilo (0.120 gramos, 0.543 milimoles). Después de 15 horas, la mezcla se diluye con acetato de etilo, y se lava con agua. La fase orgánica se seca sobre $MgSO_4$, se filtra, y el filtrado se concentra al vacío, para dar un residuo, el cual se purifica mediante cromatografía en gel de sílice (heptano-acetato de etilo, de 9:1 a 4:1), para dar el terbutil-éster del ácido 5-fluoro-2-piridin-3-il-indol-1-carboxílico como un aceite color

amarillo. La trituración con éter y heptano, seguida por reposo durante varios días, proporcionan un sólido.

^{1}H RMN (400 MHz, $CDCl_3$) δ ppm 1.35 (s, 9 H), 6.58 (s, 1 H), 7.07 - 7.12 (m, 1 H), 7.23 (dd, *J*=8.6, 2.5 Hz, 1 H), 7.36 (dd, *J*=7.8, 5.1 Hz, 1 H), 7.72 - 7.75 (m, 1 H), 8.21 (dd, *J*=9.1, 4.9 Hz, 1 H), 8.62 (dd, *J*=4.9, 1.5 Hz, 1 H), 8.69 (d, *J*=1.5 Hz, 1 H). MS (ESI) *m/z* 313 $(M+H)^+$.

Ejemplo 83

(a) N-(2-ciano-metil-fenil)-nicotinamida

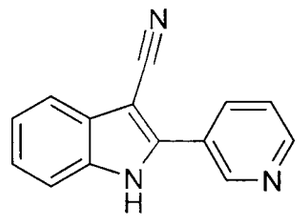


El 2-amino-fenil-acetonitrilo (5.0 gramos, 37.1 milimoles), y cloruro de nicotinoílo (7.5 gramos, 40.8 milimoles) se absorben en dicloro-metano seco (200 mililitros), y se agrega di-isopropil-etil-amina (12.1 gramos, 92.7 milimoles), mientras se enfría la mezcla con un baño de agua fría. La mezcla se agita durante la noche, después de lo cual, se lava dos veces con bicarbonato de sodio acuoso saturado. La capa acuosa combinada se retro-extrae con acetato de etilo. La fase orgánica combinada se seca sobre $MgSO_4$ y se concentra al vacío, para dar un residuo, el cual se purifica mediante cromatografía por evaporación instantánea en gel de sílice

(dicloro-metano : metanol, de 1:0 a 19:1), para dar la N-(2-ciano-metil-fenil)-nicotinamida como un sólido grisáceo.

^{1}H RMN (400 MHz, DMSO-d_6) δ ppm 4.02 (s, 2 H), 7.32 - 7.37 (m, 1 H), 7.39 - 7.44 (m, 2 H), 7.50 (d, *J*=7.1 Hz, 1 H), 7.59 (dd, *J*=8.1, 4.8 Hz, 1 H), 8.30 - 8.33 (m, 1 H), 8.78 (dd, *J*=4.8, 1.5 Hz, 1 H), 9.14 (d, *J*=1.8 Hz, 1 H), 10.36 (s, 1 H).

(b) 2-piridin-3-il-1H-indol-3-carbonitrilo

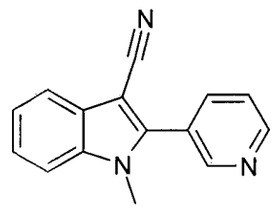


La *N*-(2-ciano-metil-fenil)-nicotinamida (0.095 gramos, 0.384 milimoles) se disuelve en N,N-dimetil-formamida (3 mililitros). Se agrega NaH (60 por ciento, 0.015 gramos, 0.384 milimoles), y la mezcla se calienta a 130°C. Después de 18 horas, la mezcla se enfría, se diluye con acetato de etilo, y se lava con hidróxido de sodio acuoso 1M. Los lavados combinados se retro-extraen con acetato de etilo. La fase orgánica combinada se seca sobre sulfato de magnesio, se filtra, y se concentra al vacío. El residuo se purifica mediante cromatografía por evaporación instantánea en gel de sílice (dicloro-metano : metanol, de 99:1 a 19:1), para dar el 2-piridin-3-il-1H-indol-3-carbonitrilo como un sólido color café.

^{1}H RMN (400 MHz, MeOD) δ ppm 7.29 - 7.32 (m, 1 H), 7.34 - 7.39 (m, 1 H), 7.57 (d, *J*=8.0 Hz, 1 H), 7.66 (dd, *J*=8.0, 4.9 Hz, 1 H), 7.70 (d, *J*=7.8 Hz, 1 H), 8.39 - 8.44 (m, 1 H), 8.68 (dd, *J*=4.8, 1.5 Hz,

1 H), 9.15 (d, *J*=1.5 Hz, 1 H).

(c) 1-metil-2-piridin-3-il-1H-indol-3-carbonitrilo

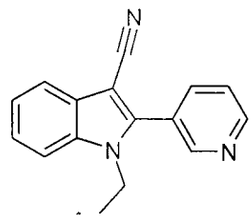


Al 2-piridin-3-il-1H-indol-3-carbonitrilo (1.0 gramos, 4.56 milimoles) en N,N-dimetil-formamida (17mL), se le agrega hidruro de sodio al 60 por ciento en aceite mineral (547 miligramos, 13.68 milimoles), y la suspensión se agita durante 30 minutos. Entonces se agrega yodo-metano (971 miligramos, 6.84 milimoles) a la mezcla de reacción, y se agita a temperatura ambiente durante 1 hora. Se agrega $NaHCO_3$ acuoso (3 mililitros), y la mezcla se concentra al vacío. El residuo se purifica mediante cromatografía por evaporación instantánea en gel de sílice (gradiente de dicloro-metano : metanol), para dar el 1-metil-2-piridin-3-il-1H-indol-3-carbonitrilo como un sólido blanco.

^{1}H RMN (400 MHz, MeOD) δ ppm 3.83 (s, 3 H), 7.35 (t, *J*=7.5 Hz, 1 H), 7.40 - 7.46 (m, 1 H), 7.64 (d, *J*=8.3 Hz, 1 H), 7.67 - 7.74 (m, 2 H), 8.16 (dt, *J*=8.0, 2.0, 1.9 Hz, 1 H), 8.76 (dd, *J*=5.1, 1.5 Hz, 1 H), 8.86 (d, *J*=1.5 Hz, 1 H). HRMS (ESI) m/z 234.1029 [$(M+H)^+$ Calculado para $C_{15}H_{12}N_3$: 234.1031].

Ejemplo 84

1-etil-2-piridin-3-il-1H-indol-3-carbonitrilo

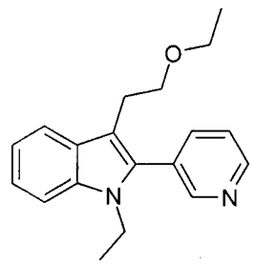


A una solución de *N*-(2-ciano-metil-fenil)-nicotinamida (Ejemplo 83a, 400 miligramos, 1.69 milimoles) en N,N-dimetil-formamida (17 mililitros), se le agrega Cs_2CO_3 (1.1 gramos, 3.37 milimoles). La reacción se calienta a 80°C, en cuyo tiempo se agrega una solución de yodo-etano (0.14 mililitros, 1.75 milimoles) en N,N-dimetil-formamida (5 mililitros), durante 75 minutos. La temperatura se aumenta entonces hasta 100°C. Después de agitar durante 2 horas adicionales, la reacción se enfría a temperatura ambiente, y se apaga con NH_4Cl acuoso saturado, y se diluye con acetato de etilo y agua. Las capas se separan, y la capa acuosa se extrae con acetato de etilo. Los extractos orgánicos combinados se secan sobre sulfato de sodio, se filtran, y se concentran. El residuo resultante se purifica mediante cromatografía por evaporación instantánea en gel de sílice (acetato de etilo-heptano, de 3:10 a 1:0), para proporcionar el 1-etil-2-piridin-3-il-1H-indol-3-carbonitrilo.

^{1}H RMN (400 MHz, $CDCl_3$) δ ppm 1.40 (t, *J*=7.2 Hz, 3 H), 4.22 (q, *J*=7.2 Hz, 2 H), 7.32 - 7.45 (m, 2 H), 7.47 - 7.51 (m, 1 H), 7.54 (dd, *J*=7.8, 5.6 Hz, 1 H), 7.82 (d, *J*=7.8 Hz, 1 H), 7.91 - 7.98 (m, 1 H), 8.78 - 8.85 (m, 2 H). HRMS (ESI) m/z 248.1190 [$(M+H)^+$ Calculado para $C_{16}H_{14}N_3$: 248.1188].

Ejemplo 85

3-(2-etoxi-etil)-1-etil-2-piridin-3-il-1H-indol



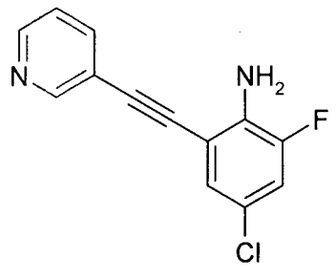
A una solución de 1-etil-2-piridin-3-il-1H-indol-3-carbonitrilo (Ejemplo 84, 590 miligramos, 2.4 milimoles) en tolueno (20 mililitros) a –60°C, se le agrega una solución 1 M de DIBAL-H (3.6 mililitros, 3.6 milimoles). La reacción se agita durante 1 hora, y se mantiene debajo de -40°C. La reacción entonces se apaga con agua (1 mililitro), y se lleva hasta la temperatura ambiente. Entonces se agrega sulfato de sodio anhidro (aproximadamente 2 gramos) a la mezcla de reacción. La mezcla de reacción se filtra a través de un tapón de Celite. Se agrega ácido sulfúrico (2M, aproximadamente 5 mililitros), y, después de la conversión completa hasta el aldehído deseado, la mezcla de reacción se lleva hasta un pH de 8 con la adición de Na_2CO_3, y se extrae con acetato de etilo. El extracto orgánico se lava con salmuera, se seca sobre Na_2SO_4, se filtra, y se concentra. El 1-etil-2-piridin-3-il-1H-indol-3-carbaldehído resultante se utiliza sin mayor purificación. A una solución de cloruro de etoxi-metil-trifenil-fosfonio (0.32 gramos, 0.9 milimoles) en tetrahidrofurano (3 mililitros), se le agrega terbutóxido de potasio (1

M en tetrahidrofurano, 0.93 mililitros, 0.93 milimoles). La solución roja resultante se deja agitándose durante 15 minutos, en cuyo tiempo se agrega una solución de 1-etil-2-piridin-3-il-1H-indol-3-carbaldehído (75 miligramos, 0.3 milimoles) en tetrahidrofurano (3 mililitros). La reacción se agita durante 1 hora, se apaga con NH_4Cl acuoso saturado, se diluye con agua, y se extrae con acetato de etilo. El extracto orgánico se seca sobre Na_2SO_4, se filtra, y se concentra. La mezcla E/Z resultante de 3-(2-etoxi-vinil)-1-etil-2-piridin-3-il-1H-indol se disuelve entonces en metanol (5 mililitros), y se agrega Pd/C al 10 por ciento (32 miligramos, 0.03 milimoles). La mezcla de reacción se agita bajo una atmósfera de gas de H_2 (globo) durante 2 horas. La reacción entonces se filtra a través de un tapón de Celite y se concentra a sequedad. El residuo resultante se purifica mediante cromatografía por evaporación instantánea en gel de sílice (acetato de etilo-heptano, de 0:1 a 2:5), para proporcionar el 3-(2-etoxi-etil)-1-etil-2-piridin-3-il-1H-indol.

^{1}H RMN (400 MHz, $CDCl_3$) δ ppm 1.17 (t, *J*=7.0 Hz, 3 H), 1.23 (t, *J*=7.2 Hz, 3 H), 2.94 (t, *J*=7.3 Hz, 2 H), 3.43 (q, *J*=7.1 Hz, 2 H), 3.61 (t, *J*=7.3 Hz, 2 H), 4.05 (q, *J*=7.3 Hz, 2 H), 7.19 (t, *J*=7.4 Hz, 1 H), 7.30 (t, *J*=7.1 Hz, 1 H), 7.40 (d, *J*=8.3 Hz, 1 H), 7.53 (dd, *J*=7.6, 5.1 Hz, 1 H), 7.69 (d, *J*=7.8 Hz, 1 H), 7.92 (d, *J*=7.8 Hz, 1 H), 8.72 (dd, *J*=4.9, 1.6 Hz, 1 H), 8.77 (d, *J*=1.5 Hz, 1 H). HRMS (ESI) m/z 295.1805 [$(M+H)^+$ Calculado para $C_{19}H_{23}N_2O$: 295.1810].

Ejemplo 86

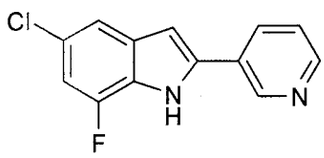
(a) 4-cloro-2-fluoro-6-piridin-3-il-etinil-fenil-amina



A una mezcla de 3-etinil-piridina (1.13 gramos, 11 milimoles), y 2-fluoro-4-cloro-6-yodo-anilina (2.71 gramos, 10 milimoles) en trietil-amina (100 mililitros), se le agrega $PdCl_2(PPh_3)_2$ (175 miligramos, 0.25 milimoles), y CuI (95 miligramos, 0.50 milimoles), y la mezcla se pone a reflujo durante 1 hora. El solvente se remueve al vacío, y el residuo se purifica mediante cromatografía por evaporación instantánea en gel de sílice (dicloro-metano : metanol, de 1:0 a 24:1), para dar la 4-cloro-2-fluoro-6-piridin-3-il-etinil-fenil-amina.

MS (ESI) *m/z* 247 $(M+H)^+$.

(b) 5-cloro-7-fluoro-2-piridin-3-il-1H-indol



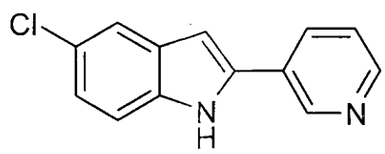
A una solución de 4-cloro-2-fluoro-6-piridin-3-il-etinil-fenil-amina (3.1 gramos, 12.57 milimoles) en NMP (40 mililitros), se le agrega terbutóxido de potasio (2.1 gramos, 18.85 milimoles), y la mezcla se agita durante la noche. Se agrega agua (1 mililitro) para apagar la reacción, y la mezcla se vierte en agua (100 mililitros). La mezcla se extrae con dietil-éter cinco veces. La fase orgánica combinada se concentra parcialmente, dando como resultado la

precipitación del producto, el cual se filtra a través de un embudo de vidrio sinterizado, y se lava con dicloro-metano, para proporcionar el 5-cloro-7-fluoro-2-piridin-3-il-1H-indol como un sólido blanco.

^{1}H RMN (400 MHz, DMSO-d_6) δ ppm 7.10 - 7.15 (m, 2 H), 7.47 - 7.53 (m, 2 H), 8.31 (dt, *J*=8.2, 1.9, 1.8 Hz, 1 H), 8.55 (d, *J*=4.3 Hz, 1 H), 9.16 (s, 1 H), 12.23 (s, 1 H).

Ejemplo 87

5-cloro-2-piridin-3-il-1H-indol

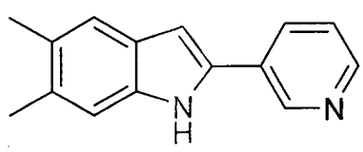


La 3-etinil-piridina y 4-cloro-6-yodo-anilina se procesan de acuerdo con el método descrito en el Ejemplo 86, para dar el 5-cloro-2-piridin-3-il-1H-indol.

^{1}H RMN (400 MHz, MeOD) δ ppm 6.96 (s, 1 H), 7.14 (dd, *J*=8.6, 2.0 Hz, 1 H), 7.41 (d, *J*=8.8 Hz, 1 H), 7.54 (dd, *J*=8.0, 4.9 Hz, 1 H), 7.59 (d, *J*=2.0 Hz, 1 H), 8.25 (dt, *J*=8.0, 1.9 Hz, 1 H), 8.50 (d, *J*=4.5 Hz, 1 H), 9.02 (s, 1 H). HRMS (ESI) m/z 229.0522 [$(M+H)^+$ Calculado para $C_{13}H_{10}ClN_2$: 229.0533].

Ejemplo 88

5,6-dimetil-2-piridin-3-il-1H-indol



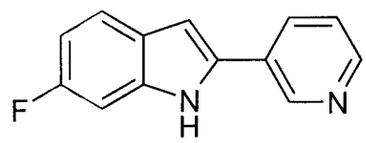
La 3-etinil-piridina y 3,4-dimetil-6-yodo-anilina se procesan de

acuerdo con el método descrito en el Ejemplo 86, para dar el 5,6-dimetil-2-piridin-3-il-1H-indol.

MS (ESI) *m/z* 223.13 $(M+H)^+$.

Ejemplo 89

6-fluoro-2-piridin-3-il-1H-indol

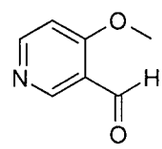


La 3-etinil-piridina y 3-fluoro-6-yodo-anilina se procesan de acuerdo con el método descrito en el Ejemplo 86, para dar el 6-fluoro-2-piridin-3-il-1H-indol.

MS (ESI) m/z 213.0 $(M+H)^+$.

Ejemplo 90

(a) 4-metoxi-piridin-3-carbaldehído

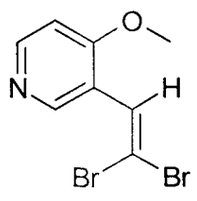


Un matraz se carga con terbutil-litio 1.7M en pentano (47.1 mililitros, 80.1 milimoles), y tetrahidrofurano (20 mililitros), y se enfría a –78°C. Se agrega por goteo 2-bromo-mesitileno (6.0 mililitros, 39 milimoles). La mezcla se agita durante 1 hora, y se agrega por goteo 4-metoxi-piridina (3.0 mililitros, 30 milimoles). La mezcla se calienta a –23°C, y se agita durante 3 horas. La mezcla se enfría nuevamente hasta –78°C, y se agrega dimetil-formamida (3.5 mililitros, 45 milimoles). Después de 1 hora, se agrega salmuera (50

mililitros) a la mezcla a –78°C, y se calienta a temperatura ambiente. La mezcla se extrae con éter, y la capa orgánica combinada se seca sobre Na_2SO_4. La concentración seguida por cromatografía en gel de sílice eluyendo con un gradiente del 0 al 6 por ciento de metanol/dicloro-metano da el 4-metoxi-piridin-3-carbaldehído.

^{1}H RMN (400 MHz, $CDCl_3$) δ ppm 4.01 (s, 3 H), 6.94 (d, *J*=5.8 Hz, 1 H), 8.65 (d, *J*=5.8 Hz, 1 H), 8.90 (s, 1 H), 10.46 (s, 1 H).

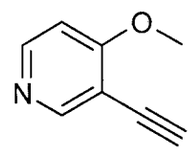
(b) 3-(2,2-dibromo-vinil)-4-metoxi-piridina



Un matraz se carga con trifenil-fosfina (21.4 gramos, 81.6 milimoles), tetrabromuro de carbono (13.5 gramos, 40.8 milimoles), y dicloro-metano (300 mililitros). Se agrega 4-metoxi-piridin-3-carbaldehído (2.8 gramos, 20.4 milimoles) en dicloro-metano (300 mililitros) a 0°C. La mezcla se agita a 0°C durante 1 hora. La mezcla se extrae con cloruro de amonio acuoso saturado, y la fase acuosa se neutraliza con $NaHCO_3$ y se extrae con dicloro-metano. La fase orgánica se seca sobre Na_2SO_4, se concentra, y se purifica mediante cromatografía en gel de sílice eluyendo con un gradiente del 0 al 10 por ciento de metanol/dicloro-metano, para dar la 3-(2,2-dibromo-vinil)-4-metoxi-piridina.

^{1}H RMN (400 MHz, $CDCl_3$) δ ppm 3.90 (s, 3 H), 6.81 (d, *J*=5.8 Hz, 1 H), 7.48 (s, 1 H), 8.48 (d, *J*=5.8 Hz, 1 H), 8.76 (s, 1 H).

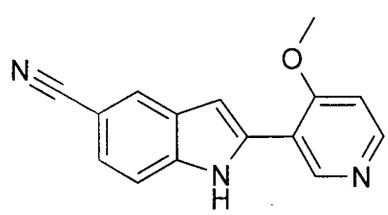
(c) 4-metoxi-3-etinil-piridina



Un matraz se carga con 3-(2,2-dibromo-vinil)-4-metoxi-piridina (3.7 gramos, 12.63 milimoles), y tetrahidrofurano (100 mililitros), y se agrega por goteo nBuLi 1.6 M en pentano (17.4 mililitros, 27.79 milimoles), a -78°C. La mezcla se agita a –78°C durante 1 hora antes de la adición de NH_4Cl acuoso saturado (0.5 mililitros). La mezcla se calienta a temperatura ambiente, y se vierte en agua (100 mililitros). La mezcla se extrae con acetato de etilo, y la fase orgánica combinada se seca sobre Na_2SO_4. La concentración seguida por la cromatografía por evaporación instantánea en gel de sílice eluyendo con un gradiente del 0 al 5 por ciento de metanol/dicloro-metano da la 4-metoxi-3-etinil-piridina.

^{1}H RMN (400 MHz, $CDCl_3$) δ ppm 3.39 (s, 1 H), 3.96 (s, 3 H), 6.82 (d, *J*=5.8 Hz, 1 H), 8.46 (d, *J*=5.8 Hz, 1 H), 8.58 (s, 1 H).

(d) 2-(4-metoxi-piridin-3-il)-1H-indol-5-carbonitrilo



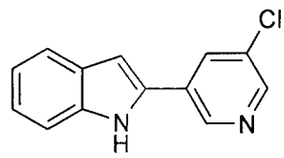
La 4-metoxi-3-etinil-piridina y 4-ciano-6-yodo-anilina se procesan de acuerdo con el método descrito en el Ejemplo 86, para dar el 2-(4-metoxi-piridin-3-il)-1H-indol-5-carbonitrilo. El 2-(4-metoxi-

piridin-3-il)-1H-indol-5-carbonitrilo se purifica mediante HPLC utilizando una XBridge Shield RP18 con un gradiente de acetonitrilo en NH_4OH al 0.1 por ciento.

^1H RMN (400 MHz, DMSO-d_6) δ ppm 4.04 (s, 3 H), 7.14 (d, J=1.3 Hz, 1 H), 7.25 (d, J=5.8 Hz, 1 H), 7.47 (dd, J=8.5, 1.6 Hz, 1 H), 7.61 (d, J=8.3 Hz, 1 H), 8.11 (s, 1 H), 8.47 (d, J=5.8 Hz, 1 H), 8.91 (s, 1 H), 11.91 (br. s., 1 H). HRMS (ESI) m/z 250.0968 [$(M+H)^+$ calculado para $C_{15}H_{12}N_3O$: 250.0980].

Ejemplo 91

2-(5-cloro-piridin-3-il)-1H-indol



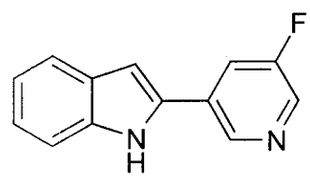
Un matraz se carga con ácido N-Boc-indol-2-borónico (0.407 gramos, 1.55 milimoles), 3-cloro-5-bromo-piridina (0.200 gramos, 1.03 milimoles), s-Phos (0.021 gramos, 0.05 milimoles), fosfato de potasio (0.441 gramos, 2.07 milimoles), y tolueno (5 mililitros). El matraz se evacua y se rellena con N_2 tres veces, y se agrega $Pd_2(dba)_3$ (0.019 gramos, 0.02 milimoles). El matraz se evacua y se rellena con N_2 tres veces. La mezcla se pone a reflujo durante 1 hora, entonces se enfría a temperatura ambiente, y se filtra a través de Celite. El filtrado se concentra al vacío, para proporcionar terbutil-éster del ácido 2-(5-cloro-piridin-3-il)-indol-1-carboxílico como un aceite. El residuo se disuelve en dicloro-metano (5 mililitros), y se agrega ácido trifluoro-acético (2 mililitros). La mezcla

de reacción se agita a temperatura ambiente durante 4 horas, seguido por apagado con una solución saturada de bicarbonato de sodio. La extracción con dicloro-metano, el secado de la capa orgánica sobre sulfato de sodio, y la concentración al vacío, dan un residuo, el cual se purifica mediante cromatografía por evaporación instantánea en gel de sílice (heptano-acetato de etilo, 3:2), para proporcionar el 2-(5-cloro-piridin-3-il)-1H-indol.

^{1}H RMN (400 MHz, MeOD) δ ppm 7.06 (s, 1 H), 7.08 (d, *J*=7.8 Hz, 1 H), 7.20 (t, *J*=7.7 Hz, 1 H), 7.45 (d, *J*=8.3 Hz, 1 H), 7.61 (d, *J*=7.8 Hz, 1 H), 8.30 (t, *J*=2.1 Hz, 1 H), 8.47 (d, *J*=2.3 Hz, 1 H), 8.96 (d, *J*=1.8 Hz, 2 H). HRMS (ESI) m/z 229.0542 [(M+H)$^+$ calculado para $C_{13}H_{10}ClN_2$: 229.0533].

Ejemplo 92

2-(5-fluoro-piridin-3-il)-1H-indol

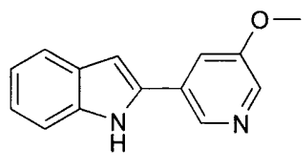


La 3-fluoro-5-bromo-piridina se procesa de acuerdo con el procedimiento descrito en el Ejemplo 91, para dar el 2-(5-fluoro-piridin-3-il)-1H-indol.

HRMS (ESI) m/z 213.0834 [(M+H)$^+$ Calculado para $C_{13}H_{10}N_2F$: 213.0828].

Ejemplo 93

5-metoxi-2-piridin-3-il-1H-indol

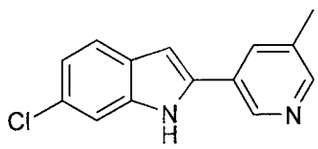


La 3-bromo-piridina y ácido N-Boc-5-metoxi-indol-2-borónico se procesan de acuerdo con el procedimiento descrito en el Ejemplo 91, para dar el 5-metoxi-2-piridin-3-il-1H-indol.

HRMS (ESI) m/z 225.1026 [$(M+H)^+$ Calculado para $C_{14}H_{13}N_2O$: 225.1028]

Ejemplo 94

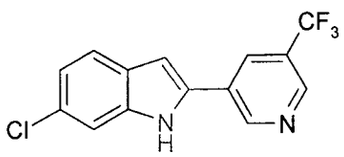
6-cloro-2-(5-metil-piridin-3-il)-1H-indol



La 3-metil-5-bromo-piridina y ácido N-Boc-6-cloro-indol-2-borónico se procesan de acuerdo con el procedimiento descrito en el Ejemplo 91, para dar el 6-cloro-2-(5-metil-piridin-3-il)-1H-indol. (ESI) *m/z* 243.0 $(M+H)^+$.

Ejemplo 95

6-cloro-2-(5-trifluoro-metil-piridin-3-il)-1H-indol



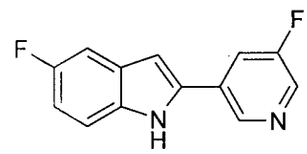
La 3-trifluoro-metil-5-bromo-piridina y ácido N-Boc-6-cloro-indol-2-borónico se procesan de acuerdo con el procedimiento descrito en el Ejemplo 91, para dar el 6-cloro-2-(5-trifluoro-metil-

piridin-3-il)-1H-indol.

(ESI) *m/z* 297.0 $(M+H)^+$.

Ejemplo 96

5-fluoro-2-(5-fluoro-piridin-3-il)-1H-indol

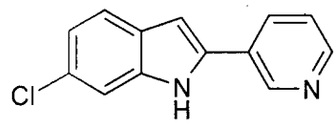


La 3-fluoro-5-bromo-piridina y ácido N-Boc-5-fluoro-indol-2-borónico se procesan de acuerdo con el procedimiento descrito en el Ejemplo 91, para dar el 5-fluoro-2-(5-fluoro-piridin-3-il)-1H-indol.

(ESI) *m/z* 231.04 $(M+H)^+$.

Ejemplo 97

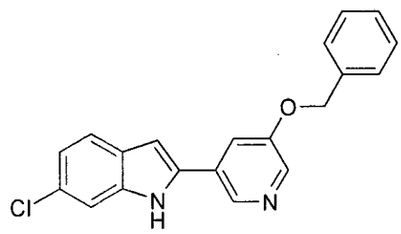
6-cloro-2-piridin-3-il-1H-indol



La 3-bromo-piridina y ácido N-Boc-6-cloro-indol-2-borónico se procesan de acuerdo con el procedimiento descrito en el Ejemplo 91, para dar el 6-cloro-2-piridin-3-il-1H-indol. (ESI) *m/z* 229.0 $(M+H)^+$.

Ejemplo 98

2-(5-benciloxi-piridin-3-il)-6-cloro-1H-indol

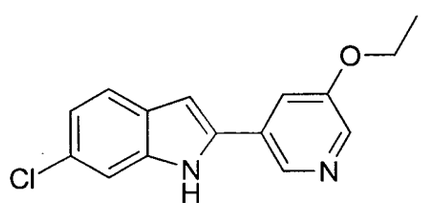


Un matraz se carga con ácido 6-cloro-1-Boc-indol-2-borónico (0.839 gramos, 2.83 milimoles), 1-benciloxi-3-bromo-piridina (0.500 gramos, 1.89 milimoles), fosfato de potasio (1.2 gramos, 5.67 milimoles), y dimetil-formamida (5 mililitros). El matraz se evacua y se rellena con nitrógeno tres veces, y se agrega $Pd(PPh_3)_4$ (0.164 gramos, 0.141 milimoles). El matraz se evacua y se rellena con nitrógeno tres veces de nuevo, y se calienta a 80°C durante 3.5 horas. La mezcla entonces se diluye con acetato de etilo, y se lava con agua tres veces. La capa orgánica se seca sobre sulfato de sodio, y se concentra al vacío. El residuo se vuelve a disolver en dicloro-metano (1 mililitro), y se agrega ácido trifluoro-acético (2 mililitros). Después de 1 hora, se agrega NaOH acuoso 4M, y, en seguida de la extracción con dicloro-metano, la capa orgánica se seca sobre sulfato de sodio, y se concentra al vacío. El residuo se purifica mediante cromatografía por evaporación instantánea en gel de sílice (heptano - acetato de etilo, 1:1), para proporcionar el 2-(3-benciloxi-fenil)-6-cloro-1H-indol como un sólido amarillo.

MS (ESI) *m/z* 335.07 $(M+H)^+$.

Ejemplo 99

2-(5-etoxi-piridin-3-il)-6-cloro-1H-indol



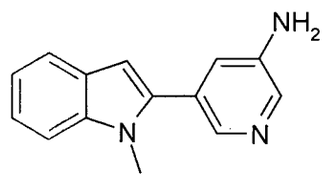
La 1-etoxi-3-bromo-piridina se procesa de acuerdo con el

método descrito en el Ejemplo 98, para dar el 2-(5-etoxi-piridin-3-il)-6-cloro-1H-indol.

MS (ESI) *m/z* 273.27 $(M+H)^+$

Ejemplo 100

2-(5-amino-piridin-3-il)-1-metil-1H-indol



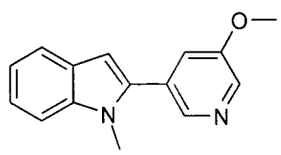
Un matraz se carga con 3-amino-5-bromo-piridina (0.173 gramos, 0.950 milimoles), ácido N-metil-indol-borónico (0.262 gramos, 1.425 milimoles), s-Phos (0.030 gramos, 0.071 milimoles), fosfato de potasio finamente triturado (0.407 gramos, 1.900 milimoles), y tolueno (4 mililitros). Después de desgasificar durante 30 minutos, se agrega Pd_2dba_3 (0.018 gramos, 0.019 milimoles), el matraz se inunda con nitrógeno, y la mezcla se calienta a 85°C. Después de 3 horas, la mezcla se deja enfriar a temperatura ambiente, se diluye con acetato de etilo, y se filtra a través de un tapón de gel de sílice (elución con acetato de etilo). El residuo se purifica mediante cromatografía por evaporación instantánea en gel de sílice (heptano-acetato de etilo, de 3:7 a 0:1), para dar el 2-(5-amino-piridin-3-il)-1-metil-1H-indol como un polvo grisáceo.

^{1}H RMN (400 MHz, DMSO-d_6) δ ppm 3.74 (s, 3 H), 5.49 (s, 2 H), 6.56 (s, 1 H), 7.05 - 7.09 (m, 1 H), 7.09 - 7.10 (m, 1 H), 7.17 - 7.21 (m, 1 H), 7.49 (d, *J*=7.6 Hz, 1 H), 7.57 (d, *J*=7.6 Hz, 1 H), 7.94

(d, *J*=2.0 Hz, 1 H), 7.99 (d, *J*=2.5 Hz, 1 H). MS (ESI) *m/z* 224 $(M+H)^+$.

Ejemplo 101

2-(5-metoxi-piridin-3-il)-1-metil-1H-indol

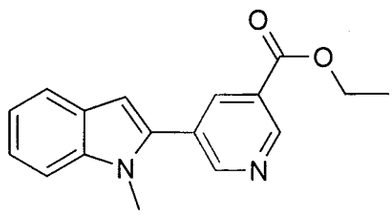


La 5-metoxi-3-bromo-piridina se procesa de acuerdo con el método descrito en el Ejemplo 100, para dar el 2-(5-metoxi-piridin-3-il)-1-metil-1H-indol.

^{1}H RMN (400 MHz, MeOD) δ ppm 3.82 (s, 3 H), 4.00 (s, 3 H), 6.69 (d, *J*=0.8 Hz, 1 H), 7.08 - 7.16 (m, 1 H), 7.23 - 7.30 (m, 1 H), 7.47 (dd, *J*=8.3, 0.8 Hz, 1 H), 7.58 - 7.66 (m, 2 H), 8.32 (d, *J*=2.8 Hz, 1 H), 8.37 (d, *J*=1.6 Hz, 1 H). HRMS (ESI) m/z 239.1175 [$(M+H)^+$ Calculado para $C_{15}H_{15}N_2O$: 239.1184].

Ejemplo 102

etil-éster del ácido 5-(1-metil-1H-indol-2-il)-nicotínico



etil-éster del ácido 5-bromo-nicotínico se procesa de acuerdo con el método descrito en el Ejemplo 100, para dar el etil-éster del ácido 5-(1-metil-1H-indol-2-il)-nicotínico.

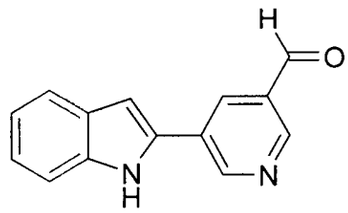
^{1}H RMN (400 MHz, MeOD) δ ppm 1.47 (t, *J*=7.1 Hz, 3 H), 3.83 (s, 3 H), 4.50 (q, *J*=7.1 Hz, 2 H), 6.76 (s, 1 H), 7.14 (t, *J*=7.5 Hz, 1

H), 7.29 (t, *J*=7.6 Hz, 1 H), 7.50 (d, *J*=8.3 Hz, 1 H), 7.64 (d, *J*=8.1 Hz, 1 H), 8.56 (t, *J*=2.0 Hz, 1 H), 9.00 (d, *J*=2.0 Hz, 1 H), 9.17 (d, *J*=2.0 Hz, 1 H).

HRMS (ESI) m/z 281.1297 [$(M+H)^+$ Calculado para $C_{17}H_{17}N_2O_2$: 281.1290].

Ejemplo 103

5-(1H-Indol-2-il)-piridin-3-carbaldehído



Un matraz se carga con 3-bromo-piridin-5-carboxaldehído (4.12 gramos, 21.48 milimoles), ácido N-Boc-indol-borónico (8.59 gramos, 32.23 milimoles), s-Phos (0.68 gramos, 1.61 milimoles), fosfato de potasio finamente triturado (9.21 gramos, 42.97 milimoles), y tolueno (70 mililitros). Después de desgasificar durante 1 hora, se agrega Pd_2dba_3 (0.40 gramos, 0.43 milimoles), el matraz se inunda con nitrógeno, y la mezcla se calienta a 85°C. Después de 30 minutos, la mezcla se deja enfriar a temperatura ambiente, se diluye con acetato de etilo, y se filtra a través de un tapón de gel de sílice. Se agrega gel de sílice (50 gramos) al filtrado, y la mezcla se concentra al vacío. El residuo se calienta a 60°C con agitación suave bajo un vacío de la bomba de aceite durante la noche. La mezcla se carga entonces sobre una columna de cromatografía por evaporación instantánea en gel de sílice y se eluye (heptano-acetato de etilo, de

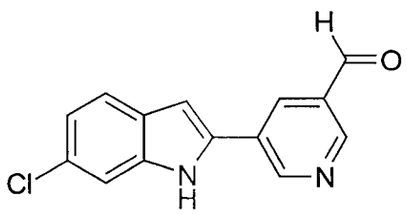
250

4:1 a 2:3), para dar el 5-(1H-indol-2-il)-piridin-3-carbaldehído.

^{1}H RMN (400 MHz, DMSO-d_6) δ ppm 7.02 - 7.08 (m, 1 H), 7.14 - 7.19 (m, 1 H), 7.20 (d, *J*=1.5 Hz, 1 H), 7.45 (d, *J*=8.1 Hz, 1 H), 7.59 (d, *J*=8.1 Hz, 1 H), 8.66 (t, *J*=2.1 Hz, 1 H), 9.00 (d, *J*=1.8 Hz, 1 H), 9.39 (d, *J*=2.3 Hz, 1 H), 10.18 (s, 1 H), 11.86 (br. s., 1 H). MS (ESI) *m/z* 223.02 $(M+H)^+$.

Ejemplo 104

5-(6-cloro-1H-indol-2-il)-piridin-3-carbaldehído

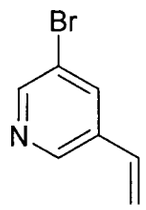


Un matraz se carga con ácido *N*-(*terbutoxi*-carbonil)-6-cloro-1H-indol-2-il-borónico (8.3 gramos, 28.1 milimoles), 5-bromo-nicotinaldehído (4.35 gramos, 23.4 milimoles), K_3PO_4 (9.94 gramos, 46.8 milimoles), s-Phos (0.480 gramos, 1.170 milimoles), y $Pd_2(dba)_3$ (0.429 gramos, 0.468 milimoles), y el matraz se inunda con N_2. Se agrega tolueno (250 mililitros), y la mezcla se calienta a 85°C durante 1.5 horas. La mezcla se enfría a temperatura ambiente. Se agrega acetato de etilo (250 mililitros), y la mezcla se filtra a través de un cojín de gel de sílice, el cual se lava con EtOAc. Se agrega gel de sílice al filtrado combinado, el cual se concentra al vacío. El residuo se coloca bajo un alto vacío a 63°C durante la noche, y después de la elución con acetato de etilo, se obtiene el 5-(6-cloro-1H-indol-2-il)-piridin-3-carbaldehído.

MS (ESI) *m/z* 257.0 y 258.9 $(M+H)^+$.

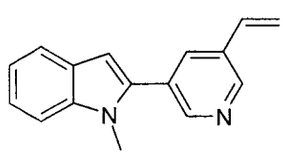
Ejemplo 105

(a) 3-bromo-5-vinil-piridina



A una solución de bromuro de metil-trifenil-fosfina (3.16 gramos, 8.87 milimoles) en tetrahidrofurano (20 mililitros), se le agrega por goteo hexametil-disilazano de sodio (solución 1M en tetrahidrofurano, 9.67 mililitros, 9.67 milimoles). La mezcla de reacción se agita a temperatura ambiente durante 30 minutos, después de lo cual, se agrega 5-bromo-piridin-3-carbaldehído (1.5 gramos, 8.06 milimoles). La mezcla de reacción se deja agitándose a temperatura ambiente durante 1 hora. La mezcla se concentra y el residuo se purifica mediante cromatografía por evaporación instantánea en gel de sílice (heptano-acetato de etilo, 7:3), para proporcionar la 3-bromo-5-vinil-piridina como un aceite incoloro. MS (ESI) *m/z* 185.91 $(M+H)^+$.

(b) 1-metil-2-(5-vinil-piridin-3-il)-1H-indol



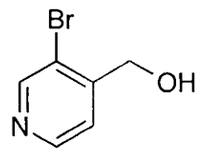
La 3-bromo-5-vinil-piridina se procesa de acuerdo con el método descrito en el Ejemplo 100, para dar el 1-metil-2-(5-vinil-

piridin-3-il)-1H-indol.

MS (ESI) *m/z* 235.40 $(M+H)^+$.

Ejemplo 106

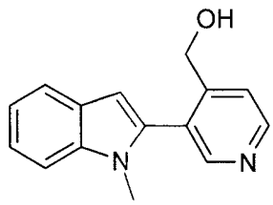
(a) (3-bromo-piridin-4-il)-metanol



A una solución de 3-bromo-piridin-4-carbaldehído (0.500 gramos, 2.68 milimoles) en metanol (5 mililitros) a 0°C, se le agrega borohidruro de sodio (0.122 gramos, 3.22 milimoles). La mezcla se agita a temperatura ambiente durante 1 hora, seguido por la remoción del solvente al vacío. El residuo se vuelve a disolver en dicloro-metano, y se lava con agua dos veces. La capa orgánica se seca sobre sulfato de sodio, y se concentra al vacío, para proporcionar el (3-bromo-piridin-4-il)-metanol como un aceite color amarillo.

MS (ESI) *m/z* 189.9 $(M+H)^+$

(b) [3-(1-metil-1H-indol-2-il)-piridin-4-il]-metanol



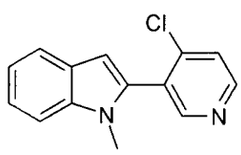
Un reactor de microondas se carga con ácido 1-metil-indol-2-borónico (1.18 gramos, 6.78 milimoles), (3-bromo-piridin-4-il)-metanol (0.850 gramos, 4.52 milimoles), fosfato de potasio (1.91

gramos, 9.04 milimoles), y dimetil-formamida (10 mililitros). El reactor se evacua y se rellena con nitrógeno tres veces, y se agrega $Pd(PPh_3)_4$ (0.261 gramos, 0.226 milimoles). El reactor se evacua y se rellena con nitrógeno tres veces nuevamente. La mezcla se calienta a 120°C durante 1 hora bajo irradiación con microondas, entonces se diluye con acetato de etilo, y se lava con agua tres veces. La capa orgánica se seca sobre sulfato de sodio, y se concentra al vacío, para dar un residuo, el cual se purifica mediante cromatografía por evaporación instantánea en gel de sílice (dicloro-metano : metanol, 19:1), para proporcionar el [3-(1-metil-1H-indol-2-il)-piridin-4-il]-metanol como un sólido blanco.

^{1}H RMN (400 MHz, MeOD) δ ppm 3.58 (s, 3 H), 4.57 (s, 2 H), 6.54 (s, 1 H), 7.14 (t, *J*=7.5 Hz, 1 H), 7.27 (ddd, *J*=7.6, 1.1 Hz, 1 H), 7.46 (d, *J*=8.3 Hz, 1 H), 7.62 (d, *J*=7.8 Hz, 1 H), 7.81 (d, *J*=5.1 Hz, 1 H), 8.49 (s, 1 H), 8.67 (d, *J*=5.1 Hz, 1 H). HRMS (ESI) m/z 239.1177 [$(M+H)^+$ Calculado para $C_{15}H_{15}N_2O$: 239.1184].

Ejemplo 107

2-(4-cloro-piridin-3-il)-1-metil-1H-indol



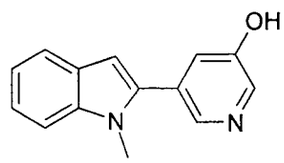
La 3-bromo-4-cloro-piridina se procesa de acuerdo con el método descrito en el Ejemplo 106b, para dar el 2-(4-cloro-piridin-3-il)-1-metil-1H-indol.

^{1}H RMN (400 MHz, MeOD) δ ppm 3.64 (s, 3 H), 6.61 (s, 1 H),

7.14 (t, *J*=7.5 Hz, 1 H), 7.28 (t, *J*=7.6 Hz, 1 H), 7.47 (d, *J*=8.3 Hz, 1 H), 7.64 (d, *J*=7.8 Hz, 1 H), 7.73 (d, *J*=5.3 Hz, 1 H), 8.62 (d, *J*=5.6 Hz, 1 H), 8.66 (s, 1 H). HRMS (ESI) m/z 243.0686 [$(M+H)^+$ Calculado para $C_{14}H_{12}ClN_2$: 243.0689].

Ejemplo 108

2-(5-hidroxi-piridin-3-il)-1-metil-1H-indol

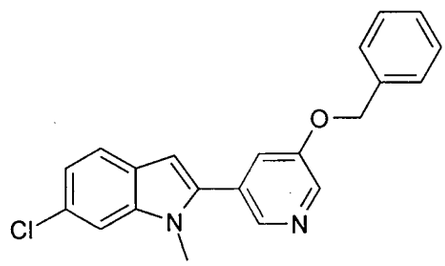


La 3-bromo-5-hidroxi-piridina se procesa de acuerdo con el método descrito en el Ejemplo 106b, para dar el 2-(5-hidroxi-piridin-3-il)-1-metil-1H-indol.

HRMS (ESI) m/z 225.1028 [$(M+H)^+$ Calculado para $C_{14}H_{13}N_2O$: 225.1028].

Ejemplo 109

2-(5-benciloxi-piridin-3-il)-6-cloro-1-metil-1H-indol



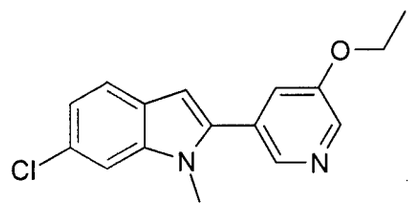
Un matraz se carga con 2-(5-benciloxi-piridin-3-il)-6-cloro-1H-indol (Ejemplo 98, 0.435 gramos, 1.29 milimoles), carbonato de dimetilo (0.328 mililitros, 3.89 milimoles), carbonato de potasio (0.098 gramos, 0.714 milimoles), y dimetil-formamida (3 mililitros).

La mezcla de reacción se agita a 150°C durante la noche. Se enfría entonces a temperatura ambiente, se diluye con acetato de etilo, y se lava con agua. La capa orgánica se seca sobre sulfato de sodio, y se concentra al vacío, para dar un residuo, el cual se purifica mediante cromatografía por evaporación instantánea (heptano-acetato de etilo, 1:1), para proporcionar el 2-(5-benciloxi-piridin-3-il)-6-cloro-1-metil-1H-indol como un sólido.

^{1}H RMN (400 MHz, MeOD) δ ppm 3.70 (s, 3 H), 5.31 (s, 2 H), 6.67 (d, *J*=0.8 Hz, 1 H), 7.10 (dd, *J*=8.3, 1.8 Hz, 1 H), 7.35 - 7.40 (m, 1 H), 7.41 - 7.47 (m, 2 H), 7.49 - 7.55 (m, 3 H), 7.57 (d, *J*=8.3 Hz, 1 H), 7.64 (dd, *J*=2.5, 1.8 Hz, 1 H), 8.35 (d, *J*=1.8 Hz, 1 H), 8.39 (d, *J*=2.8 Hz, 1 H); HRMS (ESI) m/z 349.1108 [$(M+H)^+$ Calculado para $C_{21}H_{18}ClN_2O$: 349.1108].

Ejemplo 110

2-(5-etoxi-piridin-3-il)-6-cloro-1-metil-1H-indol

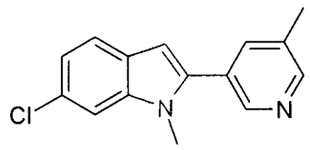


El 2-(5-etoxi-piridin-3-il)-6-cloro-1H-indol (Ejemplo 99) se procesa de acuerdo con el método descrito en el Ejemplo 109, para dar el 2-(5-etoxi-piridin-3-il)-6-cloro-1-metil-1H-indol.

MS (ESI) *m/z* 287.07 $(M+H)^+$.

Ejemplo 111

6-cloro-2-(5-metil-piridin-3-il)-1-metil-1H-indol

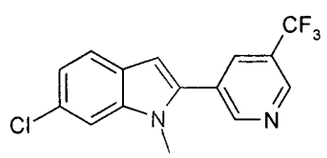


El 6-cloro-2-(5-metil-piridin-3-il)-1H-indol (Ejemplo 94) se procesa de acuerdo con el método descrito en el Ejemplo 109, para dar el 6-cloro-2-(5-metil-piridin-3-il)-1-metil-1H-indol.

MS (ESI) *m/z* 257.1 $(M+H)^+$.

Ejemplo 112

6-cloro-2-(5-trifluoro-metil-piridin-3-il)-1-metil-1H-indol

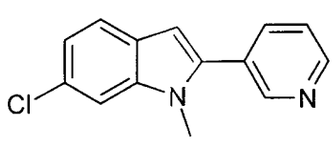


El 6-cloro-2-(5-trifluoro-metil-piridin-3-il)-1H-indol (Ejemplo 95) se procesa de acuerdo con el método descrito en el Ejemplo 109, para dar el 6-cloro-2-(5-trifluoro-metil-piridin-3-il)-1-metil-1H-indol.

MS (ESI) *m/z* 311.0 $(M+H)^+$.

Ejemplo 113

6-cloro-2-piridin-3-il-1-metil-1H-indol

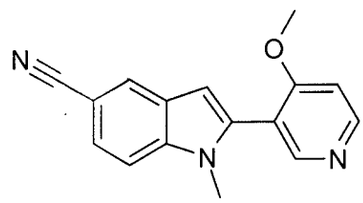


El 6-cloro-2-piridin-3-il-1H-indol (Ejemplo 97) se procesa de acuerdo con el método descrito en el Ejemplo 109, para dar el 6-cloro-2-piridin-3-il-1-metil-1H-indol.

MS (ESI) *m/z* 243.02 $(M+H)^+$.

Ejemplo 114

2-(4-metoxi-piridin-3-il)-1-metil-1H-indol-5-carbonitrilo

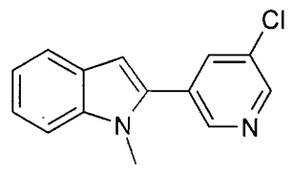


A una solución de 2-(4-metoxi-piridin-3-il)-1H-indol-5-carbonitrilo (Ejemplo 90, 178 miligramos, 0.649 milimoles) en N,N-dimetil-formamida (4 mililitros), se le agrega hidruro de sodio al 60 por ciento en aceite mineral (78 miligramos, 1.95 milimoles), y la suspensión se agita durante 30 minutos. Entonces se agrega yodo-metano (138 miligramos, 0.97 milimoles) a la mezcla de reacción, la cual se agita a temperatura ambiente durante 1 hora. Se agrega $NaHCO_3$ acuoso (3 mililitros) para apagar la reacción, y la mezcla se filtra y se purifica mediante HPLC utilizando una XBridge C18 con un gradiente de acetonitrilo en NH_4OH al 0.1 por ciento, para proporcionar el 2-(4-metoxi-piridin-3-il)-1-metil-1H-indol-5-carbonitrilo como un sólido blanco.

^{1}H RMN (400 MHz, DMSO-d_6) δ ppm 3.59 (s, 3 H), 3.89 (s, 3 H), 6.67 (s, 1 H), 7.27 (d, J=5.8 Hz, 1 H), 7.54 (dd, J=8.6, 1.5 Hz, 1 H), 7.70 (d, J=8.6 Hz, 1 H), 8.11 (d, J=1.1 Hz, 1 H), 8.42 (s, 1 H), 8.60 (d, J=5.8 Hz, 1 H). HRMS (ESI) m/z 264.1138 [$(M+H)^+$ calculado para $C_{16}H_{14}N_3O$: 264.1137].

Ejemplo 115

2-(5-cloro-piridin-3-il)-1-metil-1H-indol

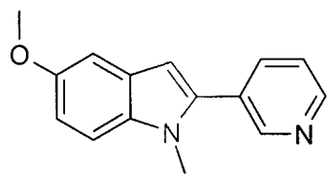


2-(5-cloro-piridin-3-il)-1H-indol (Ejemplo 91) se procesa de acuerdo con el método descrito en el Ejemplo 114, para dar el 2-(5-cloro-piridin-3-il)-1-metil-1H-indol.

^{1}H RMN (400 MHz, MeOD) δ ppm 3.83 (s, 3 H), 6.74 (s, 1 H), 7.14 (t, *J*=7.5 Hz, 1 H), 7.25 - 7.33 (m, 1 H), 7.49 (d, *J*=8.3 Hz, 1 H), 7.64 (dd, *J*=7.8, 0.6 Hz, 1 H), 8.14 (t, *J*=2.7 Hz, 1 H), 8.63 (dd, *J*=2.2, 0.9 Hz, 1 H), 8.74 (d, *J*=1.3 Hz, 1 H). HRMS (ESI) m/z 243.0686 [(M+H)$^+$ Calculado para $C_{14}H_{12}ClN_2$: 243.0689].

Ejemplo 116

5-metoxi-1-metil-2-piridin-3-il-1H-indol

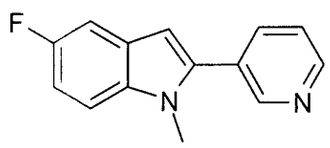


El 5-metoxi-2-piridin-3-il-1H-indol (Ejemplo 93) se procesa de acuerdo con el procedimiento descrito en el Ejemplo 114, para dar el 5-metoxi-1-metil-2-piridin-3-il-1H-indol.

^{1}H RMN (400 MHz, MeOD) δ ppm 3.78 (s, 3 H), 3.87 (s, 3 H), 6.61 (d, *J*=0.8 Hz, 1 H), 6.93 (dd, *J*=8.9, 2.5 Hz, 1 H), 7.14 (d, *J*=2.4 Hz, 1 H), 7.37 (d, *J*=9.0 Hz, 1 H), 7.60 (ddd, *J*=8.0, 4.9, 0.9 Hz, 1 H), 8.06 (dt, *J*=7.9, 2.2, 1.6 Hz, 1 H). HRMS (ESI) m/z 239.1181 [(M+H)$^+$ Calculado para $C_{15}H_{15}N_2O$: 239.1184].

Ejemplo 117

2-(5-fluoro-piridin-3-il)-1-metil-1H-indol

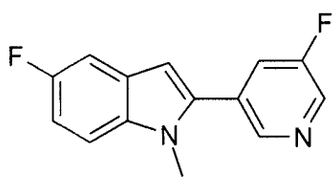


El 2-(5-fluoro-piridin-3-il)-1H-indol (Ejemplo 92) se procesa de acuerdo con el procedimiento descrito en el Ejemplo 114, para dar el 2-(5-fluoro-piridin-3-il)-1-metil-1H-indol.

^{1}H RMN (400 MHz, MeOD) δ ppm 3.83 (s, 3 H), 6.74 (s, 1 H), 7.10 - 7.17 (m, 1 H), 7.26 - 7.32 (m, 1 H), 7.48 (d, *J*=8.3 Hz, 1 H), 7.63 (d, *J*=7.8 Hz, 1 H), 7.91 (ddd, *J*=9.6, 2.8, 1.8 Hz, 1 H), 8.54 (d, *J*=2.5 Hz, 1 H), 8.67 (t, *J*=1.5 Hz, 1 H). HRMS (ESI) m/z 227.0989 [$(M+H)^+$ Calculado para $C_{14}H_{12}FN_2$: 227.0985].

Ejemplo 118

5-fluoro-2-(5-fluoro-piridin-3-il)-1-metil-1H-indol

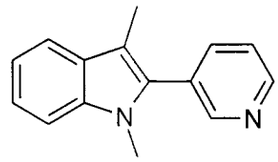


El 5-fluoro-2-(5-fluoro-piridin-3-il)-1H-indol (Ejemplo 96) se procesa de acuerdo con el procedimiento descrito en el Ejemplo 114, para dar el 5-fluoro-2-(5-fluoro-piridin-3-il)-1-metil-1H-indol.

(ESI) *m/z* 245.34 $(M+H)^+$.

Ejemplo 119

1,3-dimetil-2-(piridin-3-il)-1H-indol

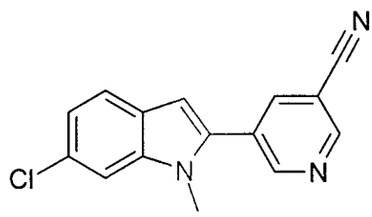


El clorhidrato de 3-metil-2-(piridin-3-il)-1H-indol (Ejemplo 1) se procesa de acuerdo con el procedimiento descrito en el Ejemplo 114, para dar el 1,3-dimetil-2-(piridin-3-il)-1H-indol.

^{1}H RMN (400 MHz, DMSO-d_6) δ ppm 2.23 (s, 3 H), 3.62 (s, 3 H), 7.06 - 7.12 (m, 1 H), 7.22 (td, *J*=7.6, 1.1 Hz, 1 H), 7.48 (d, *J*=8.3 Hz, 1 H), 7.55 - 7.61 (m, 2 H), 7.93 (dt, *J*=7.9, 2.0 Hz, 1 H), 8.66 (dd, *J*=4.8, 1.5 Hz, 1 H), 8.69 (dd, *J*=2.3, 0.8 Hz, 1 H). HRMS: (ESI) m/z 223.1236 [(M+H)+ Calculado para $C_{15}H_{15}N_2$: 223.1230].

Ejemplo 120

5-(6-cloro-1-metil-1H-indol-2-il)-nicotinonitrilo



La 3-bromo-5-ciano-piridina y ácido *N*-Boc-6-cloro-indol-borónico se procesan de acuerdo con el procedimiento descrito en el Ejemplo 103, para dar el 5-(6-cloro-1H-indol-2-il)-nicotinonitrilo, el cual se procesa de acuerdo con el procedimiento descrito en el Ejemplo 114, para dar el 5-(6-cloro-1-metil-1H-indol-2-il)-nicotinonitrilo.

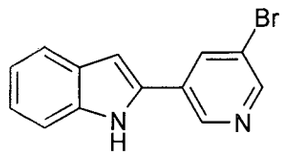
^{1}H RMN (400 MHz, MeOD) δ ppm 3.81 (s, 3 H), 6.81 (s, 1 H),

7.14 (dd, *J*=8.6, 1.8 Hz, 1 H), 7.56 (s, 1 H), 7.61 (d, *J*=8.3 Hz, 1 H), 8.46 (t, *J*=2.1 Hz, 1 H), 8.98 (d, *J*=2.0 Hz, 1 H), 9.06 (d, *J*=2.0 Hz, 1 H).

HRMS (ESI) m/z 268.0636 [$(M+H)^+$ Calculado para $C_{15}H_{10}ClN_3$ 268.0636].

Ejemplo 121

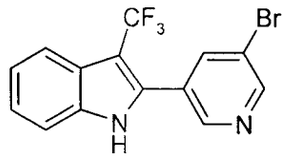
(a) 2-(5-bromo-piridin-3-il)-1H-indol



Un matraz que contiene ácido 1-(terbutoxi-carbonil)-1H-indol-2-il-borónico (2 gramos, 7.66 milimoles), 3-bromo-5-yodo-piridina (1.45 gramos, 5.11 milimoles), K_2CO_3 2M en agua (5.11 mililitros,10.21 milimoles), y PS-$Pd(PPh_3)_4$ (2.84 gramos, 0.255 milimoles) inundado con N_2, y se agrega dioxano (50 mililitros). La mezcla se agita a 60°C durante 3 horas, después de lo cual, se agrega otra porción de 3-bromo-5-yodo-piridina (300 miligramos, 1.06 milimoles). La mezcla se agita a 60°C durante la noche. La mezcla se enfría a temperatura ambiente, y se agrega gel de sílice (20 gramos). La suspensión se concentra al vacío, y el residuo se coloca bajo un alto vacío a 60°C durante el fin de semana. La mezcla se purifica mediante cromatografía en sílice eluyendo con un gradiente de 1:9 a 7:3 de EtOAc-heptano, para dar el 2-(5-bromo-piridin-3-il)-1H-indol.

MS (ESI) *m/z* 273.0, 275.1 $(M+H)^+$.

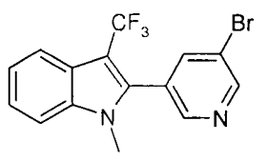
(b) 2-(5-bromo-piridin-3-il)-3-(trifluoro-metil)-1H-indol



Un matraz se carga con 2-(5-bromo-piridin-3-il)-1H-indol (1.2 gramos, 4.39 milimoles), acetonitrilo (100 mililitros), carbonato de potasio (1.2 gramos, 8.79 milimoles), y trifluoro-metan-sulfonato de 5-(trifluoro-metil)-5H-dibenzo-[b,d]-tiofenilo (2.65 gramos, 6.59 milimoles). El matraz se baja hasta un baño de aceite previamente calentado a 70°C, y la mezcla se agita bajo N_2 durante la noche. La mezcla se enfría a temperatura ambiente, y se agrega gel de sílice (10 gramos). La suspensión se concentra al vacío, y el residuo se purifica mediante cromatografía en sílice eluyendo con un gradiente del 0 a 30 por ciento de EtOAc-heptano para dar el 2-(5-bromo-piridin-3-il)-3-(trifluoro-metil)-1H-indol.

^{1}H RMN (400 MHz, DMSO-d_6) δ ppm 7.25 (t, J=7.6 Hz, 1 H), 7.33 (t, J=7.1 Hz, 1 H), 7.55 (d, J=8.1 Hz, 1 H), 7.69 (d, J=7.8 Hz, 1 H), 8.33 (t, J=2.0 Hz, 1 H), 8.79 (d, J=1.8 Hz, 1 H), 8.86 (d, J=2.0 Hz, 1 H).

(c) 2-(5-bromo-piridin-3-il)-1-metil-3-(trifluoro-metil)-1H-indol

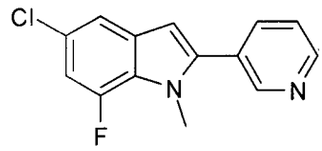


El 2-(5-bromo-piridin-3-il)-3-(trifluoro-metil)-1H-indol se procesa de acuerdo con el método descrito en el Ejemplo 114, para dar el 2-(5-bromo-piridin-3-il)-1-metil-3-(trifluoro-metil)-1H-indol.

^{1}H RMN (400 MHz, DMSO-d_6) δ ppm 3.62 (s, 3 H), 7.30 (t, J=8.0 Hz, 1 H), 7.37 - 7.44 (m, 1 H), 7.71 (d, J=8.8 Hz, 2 H), 8.36 (t, J=2.0 Hz, 1 H), 8.72 (d, J=1.8 Hz, 1 H), 8.92 (d, J=2.3 Hz, 1 H). HRMS: (ESI) m/z 355.0052 [(M+H)+ Calculado para $C_{15}H_{11}BrF_3N_2$: 355.0052].

Ejemplo 122

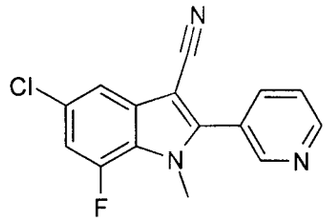
(a) 5-cloro-7-fluoro-1-metil-2-piridin-3-il-1H-indol



A una solución de 5-cloro-7-fluoro-2-piridin-3-il-1H-indol (Ejemplo 86, 276 miligramos, 1.12 milimoles) en N,N-dimetil-formamida (4 mililitros), se le agrega hidruro de sodio al 60 por ciento en aceite mineral (120 miligramos, 3.0 milimoles), y la suspensión se agita durante 30 minutos. Entonces se agrega yodo-metano (213 miligramos, 1.5 milimoles) a la mezcla de reacción, y se agita a temperatura ambiente durante 1 hora. Se agrega agua (2 mililitros) para apagar la reacción. La mezcla se filtra y se purifica mediante HPLC utilizando XBridge C18 con un gradiente de acetonitrilo en NH_4OH al 0.1 por ciento, para proporcionar el 5-cloro-7-fluoro-1-metil-2-piridin-3-il-1H-indol.

MS (ESI) *m/z* 261 $(M+H)^+$.

(b) 5-cloro-7-fluoro-1-metil-2-piridin-3-il-1H-indol-3-carbonitrilo

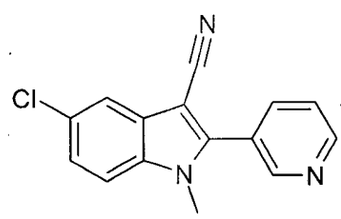


A una solución de 5-cloro-7-fluoro-1-metil-2-piridin-3-il-1H-indol (130 miligramos, 0.50 milimoles) en dicloro-metano (10 mililitros) a temperatura ambiente, se le agrega isocianato de cloro-sulfonilo (282 miligramos, 2.0 milimoles), y la mezcla se agita durante 11 horas, después de lo cual, se agrega dimetil-formamida anhidra (1 mililitro). Después de 1 hora, la mezcla se concentra y el residuo se purifica mediante HPLC utilizando una XBridge C18 con un gradiente de acetonitrilo en NH_4OH al 0.1 por ciento, para proporcionar el 5-cloro-7-fluoro-1-metil-2-piridin-3-il-1H-indol-3-carbonitrilo como un sólido blanco.

^{1}H RMN (400 MHz, DMSO-d_6) δ ppm 3.89 (d, J=1.8 Hz, 3 H), 7.46 (dd, J=12.4, 1.8 Hz, 1 H), 7.62 (d, J=1.8 Hz, 1 H), 7.71 (dd, J=7.5, 4.4 Hz, 1 H), 8.16 (dt, J=8.1, 2.0, 1.8 Hz, 1 H), 8.83 (dd, J=4.9, 1.6 Hz, 1 H), 8.89 (d, J=1.5 Hz, 1 H). HRMS (ESI) m/z 286.0558 [$(M+H)^+$ Calculado para $C_{15}H_{10}ClFN_3$: 286.0547].

Ejemplo 123

2-(5-cloro-piridin-3-il)-1-metil-1H-indol-3-carbonitrilo

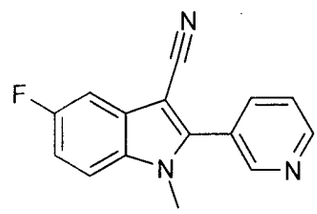


El 2-(5-cloro-piridin-3-il)-1H-indol (Ejemplo 91) se procesa de acuerdo con el método descrito en el Ejemplo 122, para dar el 2-(5-cloro-piridin-3-il)-1-metil-1H-indol-3-carbonitrilo.

^{1}H RMN (400 MHz, MeOD) δ ppm 3.87 (s, 3 H), 7.40 (t, *J*=7.6 Hz, 1 H), 7.48 (ddd, *J*=7.7, 1.3 Hz, 1 H), 7.68 (d, *J*=8.3 Hz, 1 H), 7.75 (d, *J*=8.1 Hz, 1 H), 8.28 (t, *J*=2.1 Hz, 1 H), 8.70 - 8.90 (m, 2 H). HRMS (ESI) m/z 268.0650 [(M+H)$^+$ Calculado para $C_{15}H_{11}ClN_3$: 268.0641].

Ejemplo 124

2-(5-fluoro-piridin-3-il)-1-metil-1H-indol-3-carbonitrilo



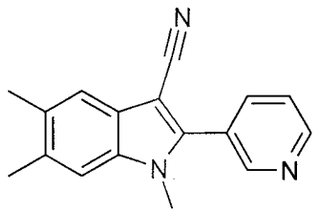
El 2-(5-fluoro-piridin-3-il)-1H-indol (Ejemplo 92) se procesa de acuerdo con el método descrito en el Ejemplo 122, para dar el 2-(5-fluoro-piridin-3-il)-1-metil-1H-indol-3-carbonitrilo.

^{1}H RMN (400 MHz, MeOD) δ ppm 3.88 (s, 3 H), 7.40 (t, *J*=7.6 Hz, 1 H), 7.48 (ddd, *J*=7.8, 1.1 Hz, 1 H), 7.69 (d, *J*=8.3 Hz, 1 H), 7.76 (d, *J*=8.1 Hz, 1 H), 8.06 (dt, *J*=9.0, 2.2 Hz, 1 H), 8.74 (d, *J*=2.5 Hz, 1 H), 8.77 (s, 1 H).

HRMS (ESI) m/z 252.0939 [(M+H)$^+$ Calculado para $C_{15}H_{11}FN_3$: 252.0937].

Ejemplo 125

1,5,6-trimetil-2-piridin-3-il-1H-indol-3-carbonitrilo

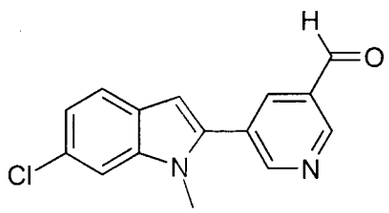


El 5,6-dimetil-2-piridin-3-il-1H-indol (Ejemplo 88) se procesa de acuerdo con el método descrito en el Ejemplo 122, para dar el 1,5,6-trimetil-2-piridin-3-il-1H-indol-3-carbonitrilo.

^{1}H RMN (400 MHz, DMSO-d_6) δ ppm 2.38 (s, 3 H), 2.40 (s, 3 H), 3.75 (s, 3 H), 7.47 (s, 1 H), 7.54 (s, 1 H), 7.67 (dd, *J*=7.8, 4.8 Hz, 1 H), 8.14 (dt, *J*=8.1, 2.0, 1.8 Hz, 1 H), 8.78 (dd, *J*=4.8, 1.8 Hz, 1 H), 8.88 (d, *J*=1.5 Hz, 1 H). HRMS (ESI) m/z 262.1352 [(M+H)$^+$ Calculado para $C_{17}H_{16}N_3$: 262.1344].

Ejemplo 126

a) 6-cloro-2-(5-formil-piridin-3-il)-1-metil-1H-indol

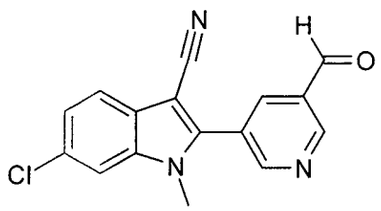


Un matraz se carga con 5-(6-cloro-1H-indol-2-il)-piridin-3-carbaldehído (Ejemplo 104, 7.8 gramos, 28.9 milimoles), MeI (5.33 gramos, 37.5 milimoles), y dimetil-formamida (300 mililitros), y se agrega NaH al 60 por ciento en aceite mineral (1.386 gramos, 34.6 milimoles) a 0°C. La mezcla se agita durante 2 horas. Se agrega agua (100 mililitros). La mezcla se extrae con EtOAc dos veces, y la fase orgánica combinada se lava con agua (200 mililitros, 2 veces), y

salmuera (200 mililitros), se seca sobre Na_2SO_4, se filtra, y se concentra al vacío. El residuo se purifica mediante cromatografía en gel de sílice con un gradiente del 0 al 2 por ciento de metanol : dicloro-metano, para dar el 6-cloro-2-(5-formil-piridin-3-il)-1-metil-1H-indol.

MS (ESI) *m/z* 271.0, 272.9 $(M+H)^+$.

b) 6-cloro-2-(5-formil-piridin-3-il)-1-metil-1H-indol-3-carbonitrilo

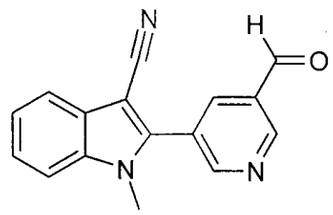


Un matraz se carga con 6-cloro-2-(5-formil-piridin-3-il)-1-metil-1H-indol (10 gramos, 36.9 milimoles), y acetonitrilo (1 litro), y se agrega isocianato de cloro-sulfonilo (15.68 gramos, 111 milimoles) a 0°C. La mezcla se agita durante 10 minutos. Se agrega dimetil-formamida (18.9 gramos, 259 milimoles) a 0°C. La mezcla se agita durante 1.5 horas. Se agregan $NaHCO_3$ saturado (20 mililitros), y trietil-amina (51.5 mililitros, 369 milimoles) a la mezcla de reacción, la cual se agita durante 10 minutos. La mezcla se concentra al vacío, para dar un residuo, el cual se purifica mediante cromatografía por evaporación instantánea en gel de sílice eluyendo con un gradiente del 0 al 5 por ciento de metanol : dicloro-metano, para dar el 6-cloro-2-(5-formil-piridin-3-il)-1-metil-1H-indol-3-carbonitrilo.

MS (ESI) *m/z* 296.0, 297.8 $(M+H)^+$.

Ejemplo 127

2-(5-formil-piridin-3-il)-1-metil-1H-indol-3-carbonitrilo

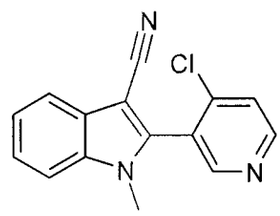


El 5-(1H-indol-2-il)-piridin-3-carbaldehído (Ejemplo 103) se procesa de acuerdo con el método descrito en el Ejemplo 122, utilizando acetonitrilo en lugar de dicloro-metano, para dar el 2-(5-formil-piridin-3-il)-1-metil-1H-indol-3-carbonitrilo.

MS (ESI) *m/z* 262.02 $(M+H)^+$.

Ejemplo 128

2-(4-cloro-piridin-3-il)-1-metil-1H-indol-3-carbonitrilo



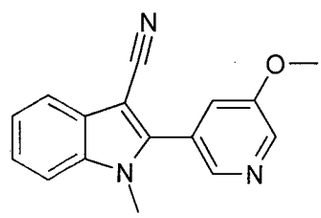
Un matraz se carga con 2-(4-cloro-piridin-3-il)-1-metil-1H-indol (Ejemplo 107, 0.110 gramos, 0.418 milimoles), y dicloro-metano (5 mililitros). Se agrega isocianato de cloro-sulfonilo (0.091 mililitros, 1.04 milimoles), y la reacción se agita durante 2 minutos, después de lo cual, se agrega dimetil-formamida (1 mililitro). Después de otros 20 minutos, la reacción se concentra al vacío, y el residuo se purifica mediante HPLC en fase inversa con una columna XBridge Shield RP18 y un gradiente de NH_4OH acuoso al 0.1 por ciento en

acetonitrilo, para proporcionar el 2-(4-cloro-piridin-3-il)-1H-indol-3-carbonitrilo como un sólido.

^{1}H RMN (400 MHz, MeOD) δ ppm 3.74 (s, 3 H), 7.41 (t, *J*=7.6 Hz, 1 H), 7.49 (t, *J*=7.7 Hz, 1 H), 7.69 (d, *J*=8.3 Hz, 1 H), 7.77 (d, *J*=8.1 Hz, 1 H), 7.84 (d, *J*=5.3 Hz, 1 H), 8.61 - 8.86 (m, 2 H). HRMS (ESI) m/z 268.0635 [$(M+H)^+$ Calculado para $C_{15}H_{11}ClN_3$: 268.0641].

Ejemplo 129

2-(5-metoxi-piridin-3-il)-1-metil-1H-indol-3-carbonitrilo

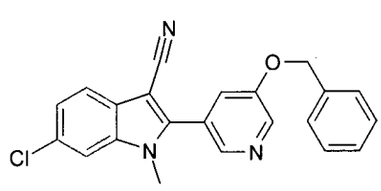


El 2-(5-metoxi-piridin-3-il)-1-metil-1H-indol (Ejemplo 101) se procesa de acuerdo con el método descrito en el Ejemplo 128, para dar el 2-(5-metoxi-piridin-3-il)-1-metil-1H-indol-3-carbonitrilo.

^{1}H RMN (400 MHz, MeOD) δ ppm 3.87 (s, 3 H), 4.02 (s, 3 H), 7.36 - 7.42 (m, 1 H), 7.47 (td, *J*=7.8, 1.1 Hz, 1 H), 7.67 (d, *J*=8.3 Hz, 1 H), 7.72 - 7.77 (m, 2 H), 8.45 (d, *J*=1.8 Hz, 1 H), 8.49 (d, *J*=2.8 Hz, 1 H). HRMS (ESI) m/z 264.1130 [$(M+H)^+$ Calculado para $C_{16}H_{14}N_3O$: 264.1137].

Ejemplo 130

2-(5-benciloxi-piridin-3-il)-6-cloro-1-metil-1H-indol-3-carbonitrilo

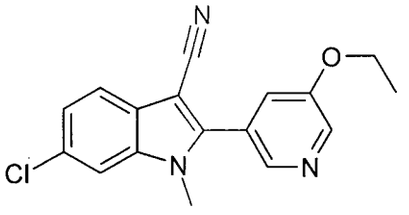


El 2-(5-benciloxi-piridin-3-il)-6-cloro-1-metil-1H-indol (Ejemplo 109) se procesa de acuerdo con el método descrito en el Ejemplo 128, para dar el 2-(5-benciloxi-piridin-3-il)-6-cloro-1-metil-1H-indol-3-carbonitrilo.

^{1}H RMN (400 MHz, MeOD) δ ppm 3.75 (s, 3 H), 5.33 (s, 2 H), 7.37 (dd, *J*=8.3, 1.8 Hz, 2 H), 7.44 (t, *J*=7.3 Hz, 2 H), 7.54 (d, *J*=7.1 Hz, 2 H), 7.71 (d, *J*=8.3 Hz, 1 H), 7.75 (d, *J*=1.5 Hz, 1 H), 7.78 (dd, *J*=2.8, 1.8 Hz, 1 H), 8.45 (d, *J*=1.8 Hz, 1 H), 8.56 (d, *J*=2.8 Hz, 1 H). HRMS (ESI) m/z 374.1070 [(M+H)$^+$ Calculado para $C_{22}H_{17}ClN_3O$: 374.1060].

Ejemplo 131

2-(5-etoxi-piridin-3-il)-6-cloro-1-metil-1H-indol-3-carbonitrilo



El 2-(5-etoxi-piridin-3-il)-6-cloro-1-metil-1H-indol (Ejemplo 110) se procesa de acuerdo con el método descrito en el Ejemplo 128, para dar el 2-(5-etoxi-piridin-3-il)-6-cloro-1-metil-1H-indol-3-carbonitrilo.

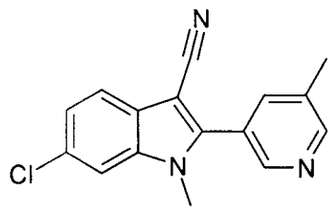
^{1}H RMN (400 MHz, MeOD) δ ppm 1.51 (t, *J*=7.1 Hz, 3 H), 3.84 (s, 3 H), 4.27 (q, *J*=6.9 Hz, 2 H), 7.37 (dd, *J*=8.6, 1.8 Hz, 1 H), 7.66 - 7.74 (m, 2 H), 7.76 (d, *J*=1.5 Hz, 1 H), 8.43 (d, *J*=1.5 Hz, 1 H), 8.47 (d, *J*=2.8 Hz, 1 H).

HRMS (ESI) m/z 312.0893 [(M+H)$^+$ Calculado para

$C_{17}H_{15}ClN_3O$: 312.0904].

Ejemplo 132

6-cloro-2-(5-metil-piridin-3-il)-1-metil-1H-indol-3- carbonitrilo

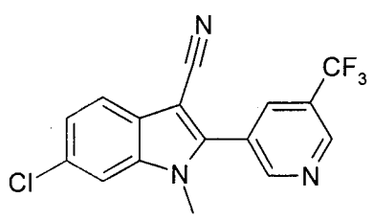


El 6-cloro-2-(5-metil-piridin-3-il)-1-metil-1H-indol (Ejemplo 111) se procesa de acuerdo con el método descrito en el Ejemplo 128, para dar el 6-cloro-2-(5-metil-piridin-3-il)-1-metil-1H-indol-3-carbonitrilo.

^{1}H RMN (400 MHz, DMSO-d_6) δ ppm 2.44 (s, 3 H), 3.78 (s, 3 H), 7.36 (dd, J=8.3, 1.8 Hz, 1 H), 7.71 (d, J=8.3 Hz, 1 H), 7.95 (d, J=1.5 Hz, 1 H), 7.97 (s, 1 H), 8.65 (d, J=1.5 Hz, 1 H), 8.68 (d, J=2.0 Hz, 1 H). HRMS (ESI) m/z 282.0803 [$(M+H)^+$ Calculado para $C_{16}H_{13}ClN_3$: 282.0798].

Ejemplo 133

6-cloro-2-(5-trifluoro-metil-piridin-3-il)-1-metil-1H-indol-3- carbonitrilo



El 6-cloro-2-(5-trifluoro-metil-piridin-3-il)-1-metil-1H-indol (Ejemplo 112) se procesa de acuerdo con el método descrito en el Ejemplo 128, para dar el 6-cloro-2-(5-trifluoro-metil-piridin-3-il)-1-

261

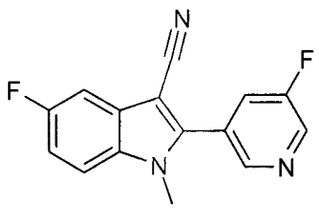
metil-1H-indol-3- carbonitrilo.

^{1}H RMN (400 MHz, DMSO-d_6) δ ppm 3.82 (s, 3 H), 7.39 (dd, *J*=8.5, 1.9 Hz, 1 H), 7.76 (d, *J*=8.3 Hz, 1 H), 8.00 (d, *J*=1.8 Hz, 1 H), 8.65 (s, 1 H), 9.22 (d, *J*=2.0 Hz, 1 H), 9.23 (d, *J*=1.3 Hz, 1 H).

HRMS (ESI) m/z 377.0790 [$(M+H+CH_3CN)^+$ Calculado para $C_{18}H_{13}ClF_3N_4$: 377.0781].

Ejemplo 134

5-fluoro-2-(5-fluoro-piridin-3-il)-1-metil-1H-indol-3-carbonitrilo

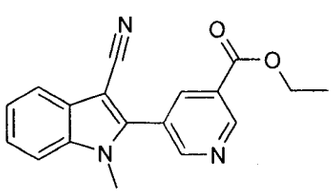


El 5-fluoro-2-(5-fluoro-piridin-3-il)-1-metil-1H-indol (Ejemplo 118) se procesa de acuerdo con el método descrito en el Ejemplo 128, para dar el 5-fluoro-2-(5-fluoro-piridin-3-il)-1-metil-1H-indol-3-carbonitrilo.

^{1}H RMN (400 MHz, MeOD) δ ppm 3.87 (s, 3 H), 7.26 (td, *J*=9.2, 2.4 Hz, 1 H), 7.44 (dd, *J*=8.7, 2.4 Hz, 1 H), 7.70 (dd, *J*=9.1, 4.3 Hz, 1 H), 8.06 (dt, *J*=9.0, 2.4, 2.3 Hz, 1 H), 8.72 - 8.79 (m, 2 H). HRMS (ESI) m/z 270.0831 [$(M+H)^+$ Calculado para $C_{15}H_{10}F_2N_3$: 270.0843].

Ejemplo 135

Etil-éster del ácido 5-(3-ciano-1-metil-1H-indol-2-il)-nicotínico

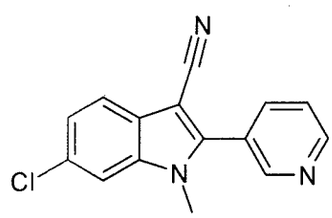


El producto del Ejemplo 102 se procesa de acuerdo con el método descrito en el Ejemplo 128, para dar el etil-éster del ácido 5-(3-ciano-1-metil-1H-indol-2-il)-nicotínico.

^{1}H RMN (400 MHz, MeOD) δ ppm 1.47 (t, *J*=7.1 Hz, 3 H), 3.88 (s, 3 H), 4.51 (q, *J*=7.2 Hz, 2 H), 7.40 (t, *J*=7.6 Hz, 1 H), 7.49 (td, *J*=7.7, 1.3 Hz, 1 H), 7.69 (d, *J*=8.3 Hz, 1 H), 7.76 (d, *J*=7.8 Hz, 1 H), 8.69 (t, *J*=2.0 Hz, 1 H), 9.09 (d, *J*=2.0 Hz, 1 H), 9.34 (d, *J*=2.0 Hz, 1 H). HRMS (ESI) m/z 306.1246 [(M+H)$^+$ Calculado para $C_{18}H_{16}N_3O_2$: 306.1243].

Ejemplo 136

6-cloro-2-piridin-3-il-1-metil-1H-indol-3-carbonitrilo

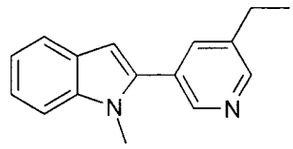


El producto del Ejemplo 113 se procesa de acuerdo con el método descrito en el Ejemplo 128, para dar el 6-cloro-2-piridin-3-il-1-metil-1H-indol-3-carbonitrilo.

^{1}H RMN (400 MHz, DMSO-d_6) δ ppm 3.79 (s, 3 H), 7.37 (dd, *J*=8.5, 1.9 Hz, 1 H), 7.69 (dd, *J*=7.5, 4.4 Hz, 1 H), 7.73 (d, *J*=8.6 Hz, 1 H), 7.98 (d, *J*=1.5 Hz, 1 H), 8.17 (dt, *J*=8.1, 2.0, 1.8 Hz, 1 H), 8.82 (dd, *J*=4.9, 1.6 Hz, 1 H), 8.90 (d, *J*=1.5 Hz, 1 H). HRMS (ESI) m/z 268.0653 [(M+H)$^+$ Calculado para $C_{15}H_{11}ClN_3$: 268.0642].

Ejemplo 137

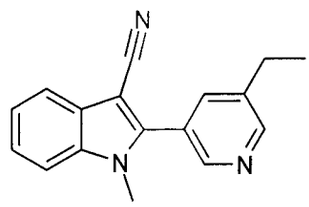
(a) 1-metil-2-(5-etil-piridin-3-il)-1H-indol



A una solución de 1-metil-2-(5-vinil-piridin-3-il)-1H-indol (Ejemplo 105, 0.473 gramos, 2.02 milimoles) en metanol (10 mililitros), se le agrega paladio sobre carbón (0.215 gramos, 0.202 milimoles). La mezcla de reacción se agita a 55°C bajo H_2 durante 16 horas. Se enfría entonces a temperatura ambiente, y se filtra a través de Celite. La capa de Celite se lava con metanol completamente, y el filtrado combinado se concentra al vacío. El residuo se purifica mediante cromatografía por evaporación instantánea en gel de sílice (heptano - acetato de etilo, 3:1), para proporcionar el 1-metil-2-(5-etil-piridin-3-il)-1H-indol como un aceite color amarillo.

MS (ESI) *m/z* 237.24 $(M+H)^+$.

(b) 2-(5-etil-piridin-3-il)-1-metil-1H-indol-3-carbonitrilo



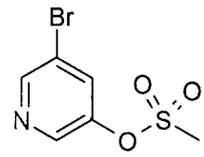
El 1-metil-2-(5-etil-piridin-3-il)-1H-indol se procesa de acuerdo con el método descrito en el Ejemplo 128, para dar el 2-(5-etil-piridin-3-il)-1-metil-1H-indol-3-carbonitrilo.

^{1}H RMN (400 MHz, MeOD) δ ppm 1.40 (t, *J*=7.6 Hz, 3 H), 2.89 (q, *J*=7.7 Hz, 2 H), 3.87 (s, 3 H), 7.35 - 7.43 (m, 1 H), 7.43 - 7.50 (m,

1 H), 7.67 (d, *J*=8.3 Hz, 1 H), 7.75 (dd, *J*=7.9, 0.8 Hz, 1 H), 8.06 (t, *J*=2.1 Hz, 1 H), 8.66 (d, *J*=1.9 Hz, 1 H), 8.70 (d, *J*=2.0 Hz, 1 H). HRMS (ESI) m/z 262.1351 [$(M+H)^+$ Calculado para $C_{17}H_{16}N_3$: 262.1344].

Ejemplo 138

(a) 5-bromo-piridin-3-il-éster del ácido metan-sulfónico



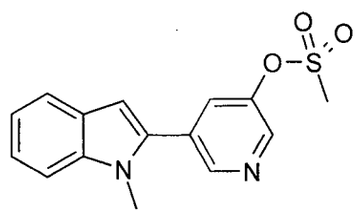
Un matraz se carga con 5-bromo-piridin-3-ol (0.200 gramos, 1.126 milimoles), carbonato de potasio (0.212 gramos, 1.487 milimoles), y acetona (3 mililitros). Entonces se agrega por goteo cloruro de metan-sulfonilo (0.143 gramos, 1.239 milimoles). Después de 2 horas, se agrega otra porción de cloruro de metan-sulfonilo (0.071 gramos, 0.61 milimoles). Después de agitar durante la noche, la suspensión se concentra, se diluye con acetato de etilo, y se filtra a través de un cojín de gel de sílice. El filtrado se concentra al vacío, para dar un residuo, el cual se purifica mediante cromatografía por evaporación instantánea en gel de sílice (heptano-acetato de etilo, de 4:1 a 7:3), para dar una mezcla de producto y material de partida. Las fracciones se combinan, se lavan tres veces con bicarbonato de sodio acuoso saturado, y se secan sobre $MgSO_4$. La concentración al vacío da el 5-bromo-piridin-3-il-éster del ácido metan-sulfónico como un aceite.

^{1}H RMN (400 MHz, $CDCl_3$) δ ppm 3.25 (s, 3 H), 7.86 (m, 1 H),

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8.52 (d, *J*=2.3 Hz, 1 H), 8.67 (d, *J*=1.8 Hz, 1 H).

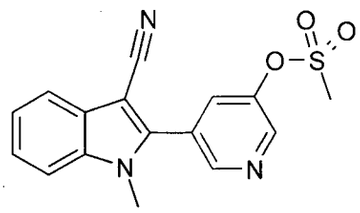
(b) 5-(1-metil-1H-indol-2-il)-piridin-3-il-éster del ácido metan-sulfónico



El 5-bromo-piridin-3-il-éster del ácido metan-sulfónico se procesa de acuerdo con el método descrito en el Ejemplo 100, para dar el el 5-(1-metil-1H-indol-2-il)-piridin-3-il-éster del ácido metan-sulfónico.

(ESI) *m/z* 303.1 $(M+H)^+$.

(c) 5-(3-ciano-1-metil-1H-indol-2-il)-piridin-3-il-éster del ácido metan-sulfónico



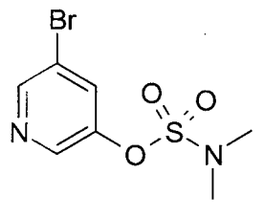
El 5-(1-metil-1H-indol-2-il)-piridin-3-il-éster del ácido metan-sulfónico se procesa de acuerdo con el método descrito en el Ejemplo 128, para dar el 5-(3-ciano-1-metil-1H-indol-2-il)-piridin-3-il-éster del ácido metan-sulfónico.

^{1}H RMN (400 MHz, DMSO-d_6) δ ppm 3.57 (s, 3 H), 3.84 (s, 3 H), 7.35 - 7.40 (m, 1 H), 7.43 - 7.48 (m, 1 H), 7.74 (d, *J*=7.8 Hz, 1 H), 7.79 (d, *J*=8.3 Hz, 1 H), 8.30 (t, *J*=2.5 Hz, 1 H), 8.85 (d, *J*=2.5 Hz, 1

H), 8.94 (d, *J*=1.8 Hz, 1 H). HRMS (ESI) m/z 328.0771 [(M+H)$^+$ Calculado para $C_{16}H_{14}N_3O_3S$: 328.0756].

Ejemplo 139

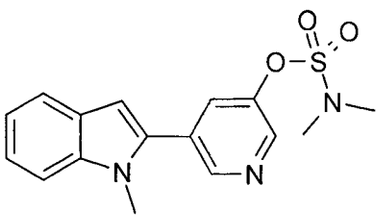
(a) 5-bromo-piridin-3-il-éster del ácido dimetil-sulfámico



Un matraz se carga con 5-bromo-piridin-3-ol (0.200 gramos, 1.126 milimoles), fosfato de potasio (0.631 gramos, 2.884 milimoles), y acetona (5 mililitros), y se enfría a 0°C. Entonces se agrega por goteo cloruro de dimetil-sulfamoílo (0.261 gramos, 1.802 milimoles), y se remueve el baño de enfriamiento. Después de 2 horas, la mezcla se diluye con acetona, se filtra, y el filtrado se concentra al vacío. El residuo se disuelve en tetrahidrofurano (30 mililitros), y se agrega tris-amina soportada por polímero (3.85 milimoles/gramo, 0.7 gramos, 2.7 milimoles). Después de 1 hora, la mezcla se filtra. La concentración al vacío da un residuo, el cual se purifica mediante cromatografía por evaporación instantánea en gel de sílice (heptano-acetato de etilo, de 9:1 a 4:1), para dar el 5-bromo-piridin-3-il-éster del ácido dimetil-sulfámico como un sólido.

^{1}H RMN (400 MHz, $CDCl_3$) δ ppm 3.05 (s, 3 H), 7.86 (m, 1 H), 8.50 (d, *J*=2.3 Hz, 1 H), 8.62 (d, *J*=1.9 Hz, 1 H).

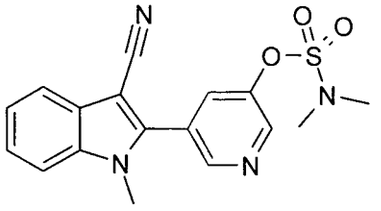
(b) 5-(1-metil-1H-indol-2-il)-piridin-3-il-éster del ácido dimetil-sulfámico



El 5-bromo-piridin-3-il-éster del ácido dimetil-sulfámico se procesa de acuerdo con el método descrito en el Ejemplo 100, para dar el 5-(1-metil-1H-indol-2-il)-piridin-3-il-éster del ácido dimetil-sulfámico.

MS (ESI) *m/z* 332.1 $(M+H)^+$.

(c) 5-(3-ciano-1-metil-1H-indol-2-il)-piridin-3-il-éster del ácido dimetil-sulfámico



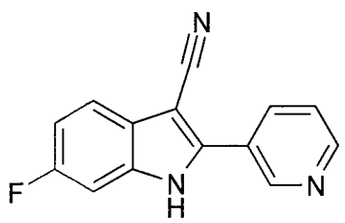
El 5-(1-metil-1H-indol-2-il)-piridin-3-il-éster del ácido dimetil-sulfámico se procesa de acuerdo con el método descrito en el Ejemplo 128, para dar el 5-(3-ciano-1-metil-1H-indol-2-il)-piridin-3-il-éster del ácido dimetil-sulfámico.

^{1}H RMN (400 MHz, DMSO-d_6) δ ppm 2.99 (s, 6 H), 3.82 (s, 3 H), 7.35 - 7.40 (m, 1 H), 7.43 - 7.48 (m, 1 H), 7.74 (d, *J*=7.8 Hz, 1 H), 7.79 (d, *J*=8.3 Hz, 1 H), 8.24 (dd, *J*=2.5, 1.8 Hz, 1 H), 8.85 (d, *J*=2.5 Hz, 1 H), 8.91 (d, *J*=1.8 Hz, 1 H).

HRMS (ESI) m/z 357.1018 [$(M+H)^+$ Calculado para $C_{17}H_{17}N_4O_3S$: 357.1021].

Ejemplo 140

6-fluoro-2-piridin-3-il-1H-indol-3-carbonitrilo

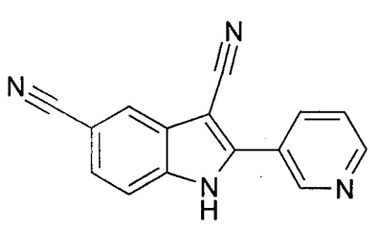


A una solución de 6-fluoro-2-piridin-3-il-1H-indol (Ejemplo 89, 212 miligramos, 1.0 milimoles) en dicloro-metano (90 mililitros) a temperatura ambiente, se le agrega isocianato de cloro-sulfonilo (0.71 gramos, 5 milimoles), y la mezcla se agita durante la noche. Se agrega dimetil-formamida anhidra (1 mililitro). Después de 1 hora, el solvente se remueve al vacío, y el residuo se purifica mediante HPLC utilizando una XBridge C18 con un gradiente de acetonitrilo en NH_4OH al 0.1 por ciento, para dar el 6-fluoro-2-piridin-3-il-1H-indol-3-carbonitrilo como un sólido blanco.

^{1}H RMN (400 MHz, DMSO-d_6) d ppm 7.12 - 7.21 (m, 1 H), 7.39 (dd, *J*=9.5, 2.4 Hz, 1 H), 7.64 - 7.74 (m, 2 H), 8.27 - 8.35 (m, 1 H), 8.73 (dd, *J*=4.9, 1.6 Hz, 1 H), 9.14 (d, *J*=1.8 Hz, 1 H), 12.89 (s, 1 H). MS (ESI) m/z 238.0 $(M+H)^+$.

Ejemplo 141

2-piridin-3-il-1H-indol-3,5-dicarbonitrilo

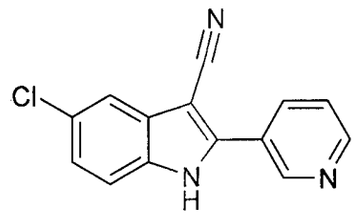


El 2-piridin-3-il-1H-indol-5-carbonitrilo (Ejemplo 8) se procesa de acuerdo con el método descrito en el Ejemplo 140, utilizando acetonitrilo en lugar de dicloro-metano, para dar el 2-piridin-3-il-1H-indol-3,5-dicarbonitrilo.

^{1}H RMN (400 MHz, MeOD) δ ppm 7.68 (dd, *J*=8.6 Hz, 1 H), 7.72 (dd, *J*=8.1, 4.8 Hz, 1 H), 7.75 (d, *J*=8.3 Hz, 1 H), 8.17 (s, 1 H), 8.47 (dt, *J*=8.1, 1.9 Hz, 1 H), 8.76 (dd, *J*=4.8, 1.5 Hz, 1 H), 9.19 (d, *J*=1.5 Hz, 1 H). HRMS (ESI) m/z 245.0823 [(M+H)$^+$ calculado para $C_{15}H_9N_4$: 245.0827].

Ejemplo 142

5-cloro-2-piridin-3-il-1H-indol-3-carbonitrilo

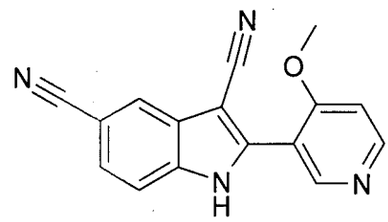


El 5-cloro-2-piridin-3-il-1H-indol (Ejemplo 87) se procesa de acuerdo con el método descrito en el Ejemplo 140, utilizando acetonitrilo en lugar de dicloro-metano, para dar el 5-cloro-2-piridin-3-il-1H-indol-3-carbonitrilo.

^{1}H RMN (400 MHz, MeOD) δ ppm 7.36 (dd, *J*=8.6, 2.0 Hz, 1 H), 7.57 (d, *J*=8.6 Hz, 1 H), 7.65 - 7.77 (m, 2 H), 8.43 (dt, *J*=8.1, 2.0 Hz, 1 H), 8.72 (d, *J*=4.8 Hz, 1 H), 9.16 (s, 1 H). HRMS (ESI) m/z 254.0495 [(M+H)$^+$ calculado para $C_{14}H_9ClN_3$: 254.0485].

Ejemplo 143

2-(4-metoxi-piridin-3-il)-1H-indol-3,5-dicarbonitrilo

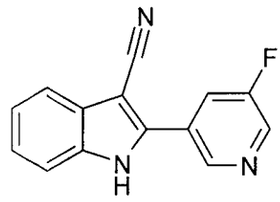


El 2-(4-metoxi-piridin-3-il)-1H-indol-5-carbonitrilo (Ejemplo 128) se procesa de acuerdo con el método descrito en el Ejemplo 140, utilizando acetonitrilo en lugar de dicloro-metano, para dar el 2-(4-metoxi-piridin-3-il)-1H-indol-3,5-dicarbonitrilo.

MS (ESI) m/z 275.08 $(M+H)^+$.

Ejemplo 144

2-(5-fluoro-piridin-3-il)-1H-indol-3-carbonitrilo

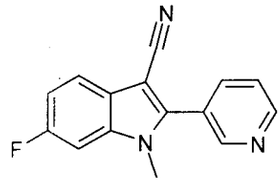


El 2-(5-fluoro-piridin-3-il)-1H-indol (Ejemplo 92) se procesa de acuerdo con el método descrito en el Ejemplo 140, utilizando una mezcla de dicloro-metano y acetonitrilo en lugar de dicloro-metano, para dar el 2-(5-fluoro-piridin-3-il)-1H-indol-3-carbonitrilo.

MS (ESI) m/z 238.0 $(M+H)^+$.

Ejemplo 145

6-fluoro-1-metil-2-piridin-3-il-1H-indol-3-carbonitrilo

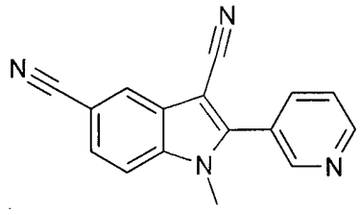


Un matraz se carga con 6-fluoro-2-piridin-3-il-1H-indol-3-carbonitrilo (Ejemplo 140, 50 miligramos, 0.21 milimoles), y dimetil-formamida (2 mililitros), y se agrega hidruro de sodio al 60 por ciento (25 miligramos, 0.63 milimoles). La mezcla se agita a temperatura ambiente durante 30 minutos antes de la adición de yodo-metano (45 miligramos, 0.315 milimoles). Después de 1 hora, se agrega una solución acuosa saturada de $NaHCO_3$ (3 mililitros) para apagar la reacción, y la mezcla se filtra y se purifica en una XBridge C18 eluyendo con un gradiente de 9:1 a 1:9 de agua-acetonitrilo, para dar el 6-fluoro-1-metil-2-piridin-3-il-1H-indol-3-carbonitrilo.

^{1}H RMN (400 MHz, DMSO-d_6) δ ppm 3.77 (s, 3 H), 7.19 - 7.26 (m, 1 H), 7.66 - 7.76 (m, 3 H), 8.14 - 8.19 (m, 1 H), 8.80 (dd, *J*=4.9, 1.6 Hz, 1 H), 8.89 (dd, *J*=2.3, 0.8 Hz, 1 H). HRMS (ESI) m/z 293.1210 [$(M+H+CH_3CN)^+$ calculado para $C_{17}H_{14}FN_4$: 293.1203].

Ejemplo 146

1-metil-2-piridin-3-il-1H-indol-3,5-dicarbonitrilo



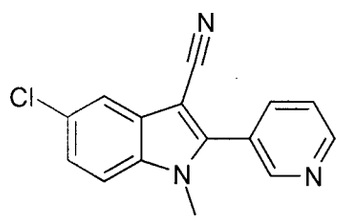
El 2-piridin-3-il-1H-indol-3,5-dicarbonitrilo (Ejemplo 141) se procesa de acuerdo con el método descrito en el Ejemplo 145, para dar el 1-metil-2-piridin-3-il-1H-indol-3,5-dicarbonitrilo.

^{1}H RMN (400 MHz, MeOD) δ ppm 3.90 (s, 3 H), 7.65 - 7.79 (m, 2 H), 7.87 (d, *J*=8.6 Hz, 1 H), 8.20 (s, 1 H), 8.22 (dt, *J*=8.0, 1.9, 1.8

Hz, 1 H), 8.83 (dd, *J*=4.9, 1.6 Hz, 1 H), 8.92 (d, *J*=2.0 Hz, 1 H). HRMS (ESI) m/z 259.0979 [(M+H) $^+$ calculado para $C_{16}H_{11}N_4$: 259.0984].

Ejemplo 147

5-cloro-1-metil-2-piridin-3-il-1H-indol-3-carbonitrilo

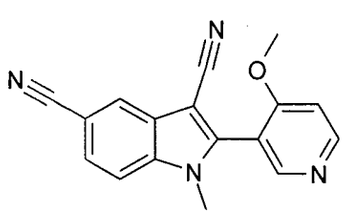


El 5-cloro-2-piridin-3-il-1H-indol-3-carbonitrilo (Ejemplo 142) se procesa de acuerdo con el método descrito en el Ejemplo 145, para dar el 5-cloro-1-metil-2-piridin-3-il-1H-indol-3-carbonitrilo.

^{1}H RMN (400 MHz, MeOD) δ ppm 3.86 (s, 3 H), 7.44 (dd, *J*=8.8, 2.0 Hz, 1 H), 7.68 (d, *J*=8.8 Hz, 1 H), 7.71 - 7.81 (m, 2 H), 8.20 (dt, *J*=8.0, 1.9 Hz, 1 H), 8.81 (dd, *J*=4.9, 1.6 Hz, 1 H), 8.89 (d, *J*=1.5 Hz, 1 H). HRMS (ESI) m/z 268.0646 [(M+H) $^+$ calculado para $C_{15}H_{11}ClN_3$: 268.0641].

Ejemplo 148

1-metil-2-(4-metoxi-piridin-3-il)-1H-indol-3,5-dicarbonitrilo



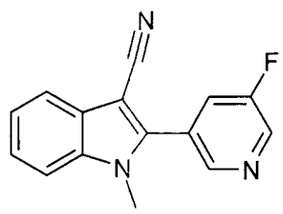
El 2-(4-metoxi-piridin-3-il)-1H-indol-3,5-dicarbonitrilo (Ejemplo 143) se procesa de acuerdo con el método descrito en el Ejemplo

145, para dar el 1-metil-2-(4-metoxi-piridin-3-il)-1H-indol-3,5-dicarbonitrilo.

^{1}H RMN (400 MHz, DMSO-d_6) δ ppm 3.69 (s, 3 H), 3.94 (s, 3 H), 7.38 (d, *J*=5.8 Hz, 1 H), 7.79 (dd, *J*=8.6, 1.5 Hz, 1 H), 7.95 (dd, *J*=8.7, 0.6 Hz, 1 H), 8.27 (dd, *J*=1.5, 0.6 Hz, 1 H), 8.57 (s, 1 H), 8.72 (d, *J*=5.8 Hz, 1 H). HRMS (ESI) m/z 289.1096 [(M+H)$^+$ calculado para $C_{17}H_{13}N_4O$: 289.1089].

Ejemplo 149

1-metil-2-(5-fluoro-piridin-3-il)-1H-indol-3-carbonitrilo

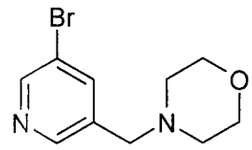


El 2-(5-fluoro-piridin-3-il)-1H-indol-3-carbonitrilo (Ejemplo 144) se procesa de acuerdo con el método descrito en el Ejemplo 145, para dar el 1-metil-2-(5-fluoro-piridin-3-il)-1H-indol-3-carbonitrilo.

^{1}H RMN (400 MHz, DMSO-d_6) δ ppm 3.80 (s, 3 H), 7.30 (td, *J*=9.3, 2.5 Hz, 1 H), 7.52 (dd, *J*=9.0, 2.4 Hz, 1 H), 7.69 (dd, *J*=8.0, 4.9 Hz, 1 H), 7.82 (dd, *J*=9.1, 4.3 Hz, 1 H), 8.17 (dt, *J*=8.1, 2.0, 1.8 Hz, 1 H), 8.81 (dd, *J*=4.8, 1.5 Hz, 1 H), 8.90 (d, *J*=1.5 Hz, 1 H). HRMS (ESI) m/z 252.0948 [(M+H)$^+$ calculado para $C_{15}H_{11}FN_3$: 252.0937].

Ejemplo 150

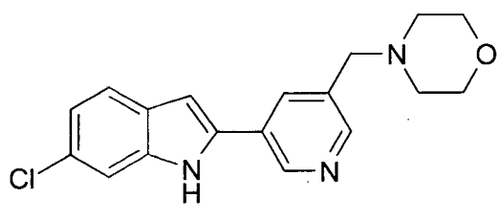
(a) 1-(5-bromo-piridin-3-il-metil)-morfolina



A una solución de 3-bromo-5-carboxaldehído-piridina (0.400 gramos, 2.086 milimoles) en dicloro-etano (10 mililitros) a 0°C, se le agrega morfolina (0.275 gramos, 3.129 milimoles), seguida por $Na(OAc)_3BH$ (0.931 gramos, 4.172 milimoles). Después de 2 horas, se remueve el baño de enfriamiento. Después de agitar durante la noche, la mezcla se diluye con dicloro-metano (0.2 litros), y se lava dos veces con agua y salmuera. La fase acuosa combinada se extrae (dos veces) con dicloro-metano. La fase orgánica combinada se seca sobre $MgSO_4$, se filtra, y se concentra, para dar un residuo, el cual se purifica mediante cromatografía por evaporación instantánea en gel de sílice (dicloro-metano : metanol, de 99:1 a 49:1) para dar la 1-(5-bromo-piridin-3-il-metil)-morfolina como un aceite incoloro.

MS (ESI) *m/z* 257 y 259 $(M+H)^+$.

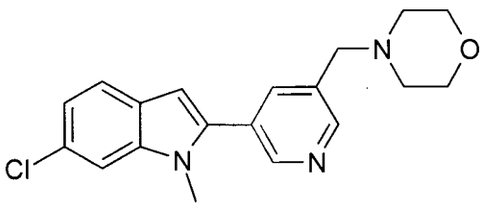
(b) 6-cloro-2-(5-morfolin-4-il-metil-piridin-3-il)-1H-indol



La 1-(5-bromo-piridin-3-il-metil)-morfolina y ácido 6-cloro-1-Boc-indol-2-borónico se procesan de acuerdo con el método descrito en el Ejemplo 91, para dar el 6-cloro-2-(5-morfolin-4-il-metil-piridin-3-il)-1H-indol.

MS (ESI) *m/z* 328.2 $(M+H)^+$.

(c) 6-cloro-1-metil-2-(5-morfolin-4-il-metil-piridin-3-il)-1H-indol

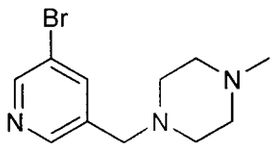


El 6-cloro-2-(5-morfolin-4-il-metil-piridin-3-il)-1H-indol se procesa de acuerdo con el método descrito en el Ejemplo 109, para proporcionar el 6-cloro-1-metil-2-(5-morfolin-4-il-metil-piridin-3-il)-1H-indol.

^{1}H RMN (400 MHz, MeOD) δ ppm 2.52 - 2.60 (m, 4 H), 3.70 (s, 2 H), 3.72 - 3.77 (m, 4 H), 3.79 (s, 3 H), 6.70 (s, 1 H), 7.11 (dd, *J*=8.3, 1.8 Hz, 1 H), 7.53 (s, 1 H), 7.59 (d, *J*=8.6 Hz, 1 H), 8.06 (t, *J*=2.0 Hz, 1 H), 8.60 (d, *J*=1.8 Hz, 1 H), 8.69 (d, *J*=2.0 Hz, 1 H). HRMS (ESI) m/z 342.1369 [$(M+H)^+$ Calculado para $C_{19}H_{21}ClN_3O$: 342.1373].

Ejemplo 151

(a) 1-(5-bromo-piridin-3-il-metil)-4-metil-piperazina

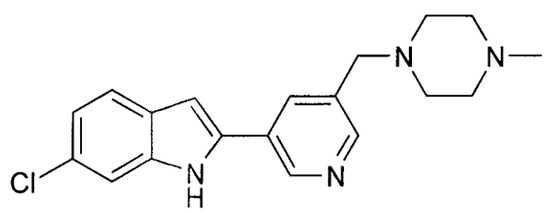


A una solución de 3-bromo-5-carboxaldehído-piridina (0.400 gramos, 2.086 milimoles) en dicloro-etano (10 mililitros) a 0°C, se le agrega 1-metil-piperazina (0.317 gramos, 3.129 milimoles), seguida por $Na(OAc)_3BH$ (0.931 gramos, 4.172 milimoles). Después de 2

horas, se remueve el baño de enfriamiento. Después de agitar durante la noche, la mezcla se diluye con dicloro-metano (0.2 litros), y se lava con bicarbonato de sodio acuoso saturado. La fase orgánica se seca sobre $MgSO_4$, se filtra, y se concentra, para dar la 1-(5-bromo-piridin-3-il-metil)-4-metil-piperazina como un sólido amarillo.

(ESI) *m/z* 270 y 272 $(M+H)^+$.

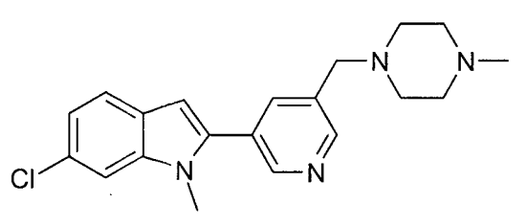
(b) 6-cloro-2-[5-(4-metil-piperazin-1-il-metil)-piridin-3-il]-1H-indol



La 1-(5-bromo-piridin-3-il-metil)-4-metil-piperazina y ácido 6-cloro-1-Boc-indol-2-borónico se procesan de acuerdo con el método descrito en el Ejemplo 91, para dar el 6-cloro-2-[5-(4-metil-piperazin-1-il-metil)-piridin-3-il]-1H-indol.

(ESI) *m/z* 341.1 $(M+H)^+$.

(c) 6-cloro-1-metil-2-[5-(4-metil-piperazin-1-il-metil)-piridin-3-il]-1H-indol



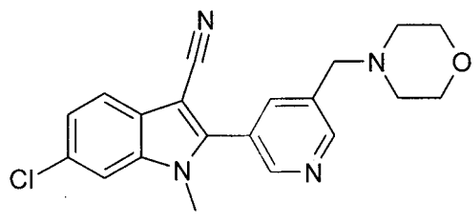
El 6-cloro-1-metil-2-[5-(4-metil-piperazin-1-il-metil)-piridin-3-il]-1H-indol se procesa de acuerdo con el método descrito en el Ejemplo

109, para proporcionar el 6-cloro-1-metil-2-[5-(4-metil-piperazin-1-il-metil)-piridin-3-il]-1H-indol.

^{1}H RMN (400 MHz, MeOD) δ ppm 2.33 (s, 3 H), 2.60 (br. s., 8 H), 3.73 (s, 2 H), 3.79 (s, 3 H), 6.70 (s, 1 H), 7.11 (dd, *J*=8.5, 1.9 Hz, 1 H), 7.53 (d, *J*=1.8 Hz, 1 H), 7.59 (d, *J*=8.3 Hz, 1 H), 8.05 (t, *J*=2.0 Hz, 1 H), 8.59 (d, *J*=2.0 Hz, 1 H), 8.69 (d, *J*=2.0 Hz, 1 H). HRMS (ESI) m/z 355.1688 [$(M+H)^+$ Calculado para $C_{20}H_{24}ClN_4$: 355.1689].

Ejemplo 152

6-cloro-1-metil-2-(5-morfolin-4-il-metil-piridin-3-il)-1H-indol-3-carbonitrilo



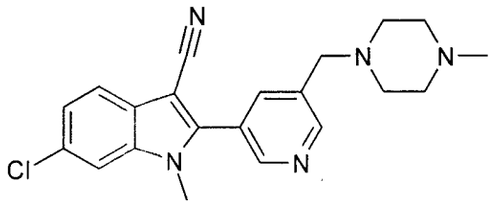
El 6-cloro-1-metil-2-(5-morfolin-4-il-metil-piridin-3-il)-1H-indol (Ejemplo 150) se procesa de acuerdo con el método descrito en el Ejemplo 128, para dar el 6-cloro-1-metil-2-(5-morfolin-4-il-metil-piridin-3-il)-1H-indol-3-carbonitrilo.

^{1}H RMN (400 MHz, MeOD) δ ppm 2.51 - 2.66 (m, 4 H), 3.69 - 3.79 (m, 6 H), 3.85 (s, 3 H), 7.38 (dd, *J*=8.3, 1.8 Hz, 1 H), 7.72 (d, *J*=8.3 Hz, 1 H), 7.77 (d, *J*=1.5 Hz, 1 H), 8.20 (t, *J*=2.0 Hz, 1 H), 8.77 (dd, *J*=13.3, 2.1 Hz, 2 H). HRMS (ESI) m/z 367.1321 [$(M+H)^+$ Calculado para $C_{20}H_{20}ClN_4O$: 367.1326].

Ejemplo 153

6-cloro-1-metil-2-[5-(4-metil-piperazin-1-il-metil)-piridin-3-il]-1H-

indol-3-carbonitrilo

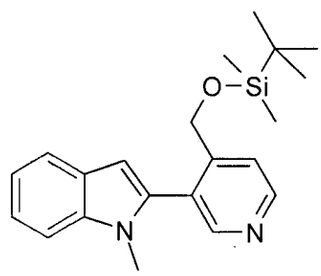


El 6-cloro-1-metil-2-[5-(4-metil-piperazin-1-il-metil)-piridin-3-il]-1H-indol (Ejemplo 151) se procesa de acuerdo con el método descrito en el Ejemplo 128, para dar el 6-cloro-1-metil-2-[5-(4-metil-piperazin-1-il-metil)-piridin-3-il]-1H-indol-3-carbonitrilo.

^{1}H RMN (400 MHz, MeOD) δ ppm 2.34 (s, 3 H), 2.61 (br. s., 8 H), 3.77 (s, 2 H), 3.85 (s, 3 H), 7.38 (dd, *J*=8.6, 1.8 Hz, 1 H), 7.72 (d, *J*=8.6 Hz, 1 H), 7.77 (d, *J*=1.5 Hz, 1 H), 8.18 (t, *J*=2.0 Hz, 1 H), 8.75 (d, *J*=2.0 Hz, 1 H), 8.79 (d, *J*=2.3 Hz, 1 H). HRMS (ESI) m/z 380.1624 [$(M+H)^+$ Calculado para $C_{21}H_{23}ClN_5$: 380.1642].

Ejemplo 154

(a) 2-[4-(terbutil-dimetil-silaniloxi-metil)-piridin-3-il]-1-metil-1H-indol

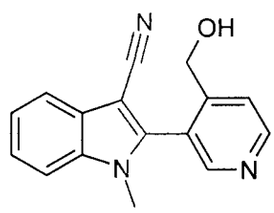


Un matraz se carga con [3-(1-metil-1H-indol-2-il)-piridin-4-il]-metanol (Ejemplo 106, 0.270 gramos, 1.13 milimoles), cloruro de terbutil-dimetil-sililo (0.187 gramos, 1.24 milimoles), imidazol (0.231

gramos, 3.39 milimoles), DMAP (0.025 gramos, 0.193 milimoles), y dimetil-formamida (3 mililitros). La reacción se agita a temperatura ambiente durante 3 horas, se agrega agua, y la mezcla se extrae con acetato de etilo. La capa orgánica combinada se seca sobre sulfato de sodio, y se concentra al vacío, para proporcionar el 2-[4-(terbutil-dimetil-silaniloxi-metil)-piridin-3-il]-1-metil-1H-indol como un aceite, el cual se utiliza en el siguiente paso sin mayor purificación.

MS (ESI) *m/z* 353.31 $(M+H)^+$

(b) 2-(4-hidroxi-metil-piridin-3-il)-1-metil-1H-indol-3-carbonitrilo



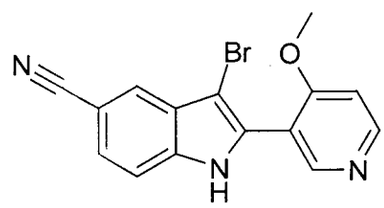
A una solución de 2-[4-(terbutil-dimetil-silaniloxi-metil)-piridin-3-il]-1-metil-1H-indol (0.263 gramos, 0.747 milimoles) en dicloro-metano (5 mililitros), se le agrega isocianato de cloro-sulfonilo (0.162 mililitros, 1.867 milimoles). Después de 5 minutos, se agrega N,N-dimetil-formamida (1 mililitro). Después de otros 30 minutos, la reacción se concentra al vacío para proporcionar el 2-[4-(terbutil-dimetil-silaniloxi-metil)-piridin-3-il]-1-metil-1H-indol-3-carbonitrilo como un sólido amarillo claro, el cual se vuelve a disolver en dicloro-metano (3 mililitros). Se agrega HCl 4M en1,4-dioxano (1 mililitro), y la mezcla se agita a temperatura ambiente durante 30 minutos. La purificación mediante HPLC en fase inversa con una columna XBridge Shield RP18 y un gradiente de NH_4OH acuoso al 0.1 por

ciento en acetonitrilo, proporciona el 2-(4-hidroxi-metil-piridin-3-il)-1-metil-1H-indol-3-carbonitrilo como un sólido.

^{1}H RMN (400 MHz, MeOD) δ ppm 3.67 (s, 3 H), 4.44 - 4.67 (m, 2 H), 7.39 (t, *J*=7.6 Hz, 1 H), 7.47 (t, *J*=8.3 Hz, 1 H), 7.66 (d, *J*=8.3 Hz, 1 H), 7.74 (d, *J*=7.8 Hz, 1 H), 7.87 (d, *J*=5.3 Hz, 1 H), 8.60 (s, 1 H), 8.80 (d, *J*=5.3 Hz, 1 H). HRMS (ESI) m/z 264.1142 [$(M+H)^+$ Calculado para $C_{16}H_{14}N_3O$: 264.11379].

Ejemplo 155

3-bromo-2-(4-hidroxi-piridin-3-il)-1H-indol-5-carbonitrilo



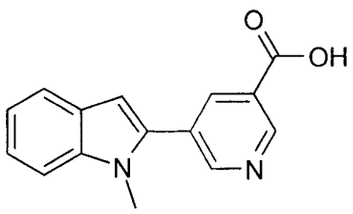
Un matraz se carga con 2-(4-metoxi-piridin-3-il)-1H-indol-5-carbonitrilo (Ejemplo 90, 190 miligramos, 0.80 milimoles), y dicloro-etano (8 mililitros), y se agrega BBr_3 1.0 M en dicloro-metano (4.8 mililitros, 4.8 milimoles). La mezcla se agita a temperatura ambiente durante la noche. La mezcla de reacción se vierte en $NaHCO_3$ acuoso saturado, y se extrae con dicloro-metano. La fase acuosa se concentra, se acidifica con HCl 1M en agua, y se concentra al vacío. El residuo se purifica con una XBridge C18 eluyendo con un gradiente de 1:9 a 9:1 de acetonitrilo-agua, para dar el 3-bromo-2-(4-hidroxi-piridin-3-il)-1H-indol-5-carbonitrilo.

^{1}H RMN (400 MHz, DMSO-d_6) δ ppm 6.40 (d, *J*=7.1 Hz, 1 H), 7.48 (dd, *J*=8.5, 1.6 Hz, 1 H), 7.71 (d, *J*=8.6 Hz, 1 H), 7.81 (dd,

J=7.1, 1.3 Hz, 1 H), 7.86 (d, *J*=1.0 Hz, 1 H), 8.67 (d, *J*=1.3 Hz, 1 H). HRMS (ESI) m/z 313.9932 [(M+H) $^+$ calculado para $C_{14}H_9BrN_3O$: 313.9929].

Ejemplo 156

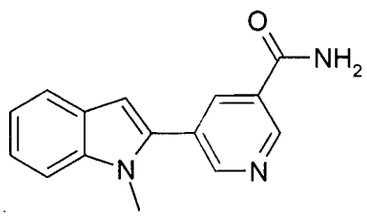
(a) Ácido 5-(1-metil-1H-indol-2-il)-nicotínico



A una solución de etil-éster del ácido 5-(1-metil-1H-indol-2-il)-nicotínico (Ejemplo 102, 0.156 gramos, 0.55 milimoles), y metanol (5 mililitros), se le agrega LiOH acuoso 1M (1.4 mililitros, 1.39 milimoles). La reacción se agita a temperatura ambiente durante 2.5 horas. La purificación mediante HPLC en fase inversa con una columna XBridge Shield RP18 y un gradiente de NH_4OH acuoso al 0.1 por ciento en acetonitrilo, da el ácido 5-(1-metil-1H-indol-2-il)-nicotínico.

MS (ESI) *m/z* 253.34 $(M+H)^+$.

(b) 5-(1-metil-1H-indol-2-il)-nicotinamida



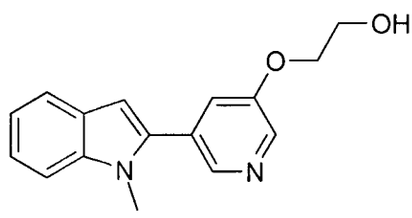
Un matraz se carga con ácido 5-(1-metil-1H-indol-2-il)-nicotínico (0.037 gramos, 0.146 milimoles), HOBT (0.024 gramos,

0.175 milimoles), EDCI (0.034 gramos, 0.175 milimoles), di-isopropil-etil-amina (0.076 mililitros, 0.439 milimoles), y dimetil-formamida (3 mililitros). Se agrega cloruro de amonio (0.012 gramos, 0.219 milimoles), y la reacción se agita a temperatura ambiente durante la noche. La purificación mediante HPLC en fase inversa con una columna XBridge Shield RP18 y un gradiente de NH_4OH acuoso al 0.1 por ciento en acetonitrilo, da la 5-(1-metil-1H-indol-2-il)-nicotinamida.

^{1}H RMN (400 MHz, MeOD) δ ppm 3.85 (s, 3 H), 6.77 (d, *J*=0.6 Hz, 1 H), 7.08 - 7.19 (m, 1 H), 7.29 (ddd, *J*=8.2, 7.1, 1.1 Hz, 1 H), 7.50 (dd, *J*=8.3, 0.7 Hz, 1 H), 7.65 (d, *J*=8.0 Hz, 1 H), 8.49 (t, *J*=2.1 Hz, 1 H), 8.95 (d, *J*=2.1 Hz, 1 H), 9.09 (d, *J*=2.1 Hz, 1 H). HRMS (ESI) m/z 252.1145 [$(M+H)^+$ Calculado para $C_{15}H_{14}N_3O$: 252.1137].

Ejemplo 157

2-[5-(1-metil-1H-indol-2-il)-piridin-3-iloxi]-etanol



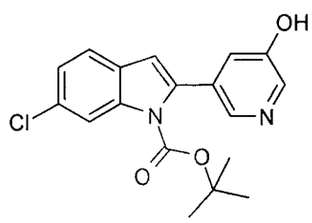
A una solución de 5-(1-metil-1H-indol-2-il)-piridin-3-ol (Ejemplo 108, 0.300 gramos, 1.33 milimoles), carbonato de potasio (0.462 gramos, 3.34 milimoles), y dimetil-formamida (3 mililitros), se le agrega (2-cloro-etoxi)-trimetil-silano (0.324 mililitros, 2.00 milimoles), y la reacción se agita a 70°C durante la noche y a 100°C durante otras 24 horas. Se enfría entonces a temperatura ambiente, se diluye

con acetato de etilo, y se lava con agua. La capa orgánica se seca sobre sulfato de sodio, y se concentra al vacío, para proporcionar un residuo, el cual se purifica mediante HPLC en fase inversa con una columna XBridge Shield RP18 y un gradiente de NH_4OH acuoso al 0.1 por ciento en acetonitrilo. El aceite resultante se disuelve en dietil-éter, y se agregan unas cuantas gotas de HCl concentrado. La liofilización da el 2-[5-(1-metil-1H-indol-2-il)-piridin-3-iloxi]-etanol como la sal de HCl.

^{1}H RMN (400 MHz, MeOD) δ ppm (sal de HCl) 3.78 (s, 3 H), 3.93 (t, *J*=4.8 Hz, 2 H), 4.22 (t, *J*=4.5 Hz, 2 H), 6.65 (s, 1 H), 7.09 (t, *J*=7.5 Hz, 1 H), 7.23 (ddd, *J*=7.6, 1.1 Hz, 1 H), 7.44 (d, *J*=8.1 Hz, 1 H), 7.58 (d, *J*=7.8 Hz, 1 H), 7.62 (dd, *J*=2.8, 1.8 Hz, 1 H), 8.31 (d, *J*=2.8 Hz, 1 H), 8.34 (d, *J*=1.5 Hz, 1 H). HRMS (ESI) m/z 269.1302 [$(M+H)^+$ Calculado para $C_{16}H_{17}N_2O_2$: 269.1290].

Ejemplo 158

(a) Terbutil-éster del ácido 6-cloro-2-(5-hidroxi-piridin-3-il)-indol-1-carboxílico

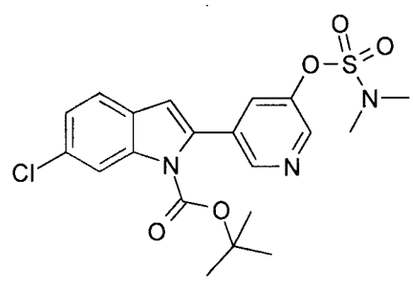


Un matraz para microondas se carga con ácido 6-cloro-1-Boc-indol-2-borónico (1.91 gramos, 6.46 milimoles), 3-hidroxi-5-bromo-piridina (0.750 gramos, 4.31 milimoles), fosfato de potasio (1.83 gramos, 8.62 milimoles), y dimetil-formamida (15 mililitros). El

matraz se evacua y se rellena con nitrógeno tres veces, y se agrega $Pd(PPh_3)_4$ (0.250 gramos, 0.215 milimoles). El matraz se evacua y se rellena con nitrógeno tres veces de nuevo, y se calienta a 110°C bajo irradiación con microondas durante 45 minutos. Se agrega $Pd(PPh_3)_4$ (0.100 gramos, 0.086 milimoles), y el frasco se calienta nuevamente hasta 110°C bajo irradiación con microondas durante 45 minutos. La mezcla entonces se diluye con acetato de etilo, y se lava con agua tres veces. La capa orgánica se seca sobre sulfato de sodio, y se concentra al vacío. El residuo se purifica mediante cromatografía por evaporación instantánea en gel de sílice (dicloro-metano : metanol, 19:1), para proporcionar el terbutil-éster del ácido 6-cloro-2-(5-hidroxi-piridin-3-il)-indol-1-carboxílico como un sólido.

MS (ESI) *m/z* 345.06 $(M+H)^+$

(b) Terbutil-éster del ácido 6-cloro-2-(5-dietil-sulfamoiloxi-piridin-3-il)-indol-1-carboxílico

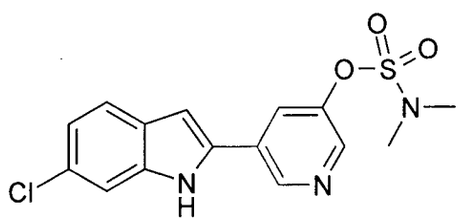


Un matraz se carga con el terbutil-éster del ácido 6-cloro-2-(5-hidroxi-piridin-3-il)-indol-1-carboxílico (0.200 gramos, 0.581 milimoles), y acetona (5 mililitros). Se agregan cloruro de dietil-amino-sulfamoílo (0.150 gramos, 0.872 milimoles), y fosfato de potasio (0.308 gramos, 1.45 milimoles), y la reacción se agita a temperatura

ambiente durante la noche. La mezcla entonces se concentra al vacío. El residuo se disuelve en dicloro-metano, y se lava con agua. La capa orgánica se seca sobre sulfato de sodio, y se concentra, para proporcionar el terbutil-éster del ácido 6-cloro-2-(5-dietil-sulfamoiloxi-piridin-3-il)-indol-1-carboxílico como un aceite, el cual se utiliza sin mayor purificación.

MS (ESI) *m/z* 480.1 $(M+H)^+$.

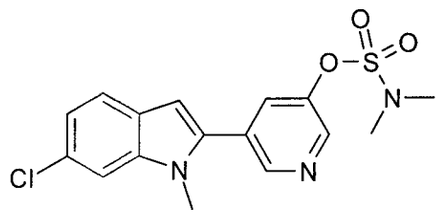
(c) 5-(6-cloro-1H-indol-2-il)-piridin-3-il-éster del ácido dietil-sulfámico



El terbutil-éster del ácido 6-cloro-2-(5-dietil-sulfamoiloxi-piridin-3-il)-indol-1-carboxílico se vuelve a disolver en dicloro-metano (2 mililitros), y se agrega ácido trifluoro-acético (2 mililitros). Después de 1 hora, se agrega bicarbonato de sodio acuoso saturado y, en seguida de la extracción con dicloro-metano, la capa orgánica se seca sobre sulfato de sodio, y se concentra para dar el 5-(6-cloro-1H-indol-2-il)-piridin-3-il-éster del ácido dietil-sulfámico, el cual se utiliza en el siguiente paso sin mayor purificación.

MS (ESI) *m/z* 378.1 $(M+H)^+$

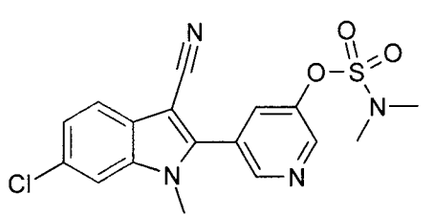
(d) 5-(6-cloro-1-metil-1H-indol-2-il)-piridin-3-il-éster del ácido dietil-sulfámico



Un matraz se carga con 5-(6-cloro-1H-indol-2-il)-piridin-3-il-éster del ácido dietil-sulfámico (0.175 gramos, 0.560 milimoles), y dimetil-formamida (5 mililitros). Se agregan carbonato de dimetilo (0.116 mililitros, 1.38 milimoles), y carbonato de potasio (0.035 gramos, 0.253 milimoles), y la reacción se agita a 150°C durante la noche. La mezcla de reacción se enfría a temperatura ambiente, se diluye con acetato de etilo, y se lava con agua. La capa orgánica se seca sobre sulfato de sodio, y se concentra al vacío. El residuo se purifica mediante cromatografía por evaporación instantánea (heptano-acetato de etilo, 3:1), para proporcionar el 5-(6-cloro-1-metil-1H-indol-2-il)-piridin-3-il-éster del ácido dietil-sulfámico como un sólido amarillo.

MS (ESI) *m/z* 394.04 $(M+H)^+$

(e) 5-(6-cloro-3-ciano-1-metil-1H-indol-2-il)-piridin-3-il-éster del ácido dietil-sulfámico



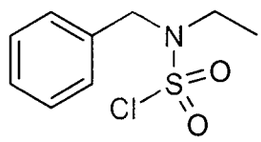
El 5-(6-cloro-1-metil-1H-indol-2-il)-piridin-3-il-éster del ácido

dietil-sulfámico se procesa de acuerdo con el método descrito en el Ejemplo 128, para dar el 5-(6-cloro-3-ciano-1-metil-1H-indol-2-il)-piridin-3-il-éster del ácido dietil-sulfámico.

^{1}H RMN (400 MHz, MeOD) δ ppm 1.28 (t, *J*=7.2 Hz, 6 H), 3.51 (q, *J*=7.1 Hz, 4 H), 3.85 (s, 3 H), 7.39 (dd, *J*=8.5, 1.9 Hz, 1 H), 7.74 (d, *J*=8.6 Hz, 1 H), 7.78 (d, *J*=1.8 Hz, 1 H), 8.15 (t, *J*=2.0 Hz, 1 H), 8.77 (d, *J*=2.5 Hz, 1 H), 8.84 (d, *J*=1.8 Hz, 1 H). HRMS (ESI) m/z 419.0966 [$(M+H)^+$ Calculado para $C_{19}H_{20}ClN_4O_3S$: 419.0945].

Ejemplo 159

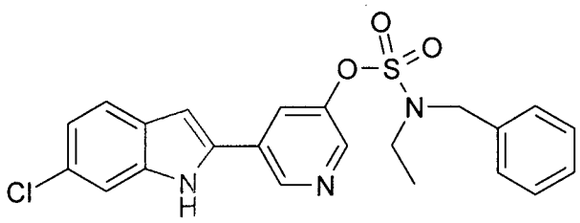
(a) Cloruro de *N*-etil-*N*-bencil-amino-sulfamoílo



A una solución de cloruro de sulfurilo (1.19 mililitros, 14.8 milimoles) en dicloro-metano (10 mililitros), se le agrega *N*-etil-*N*-bencil-amina (2.0 gramos, 14.7 milimoles) a –10°C. Se remueve el baño de enfriamiento después de 30 minutos, y la mezcla se agita durante la noche. La mezcla se lava con agua y, en seguida de la retro-extracción con dicloro-metano, la capa orgánica combinada se seca sobre sulfato de sodio, y se concentra al vacío, para dar el cloruro de N-etil-*N*-bencil-amino-sulfamoílo.

^{1}H RMN (400 MHz, $CDCl_3$) δ ppm 1.19 (t, *J*=7.2 Hz, 3 H), 3.40 (q, *J*=7.3 Hz, 2 H), 4.50 (br. s., 2 H), 7.32 - 7.48 (m, 5 H).

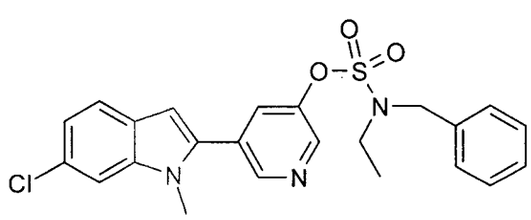
(b) 5-(6-cloro-1H-indol-2-il)-piridin-3-il-éster del ácido bencil-etil-sulfámico



El cloruro de *N*-etil-*N*-bencil-amino-sulfamoílo y terbutil-éster del ácido 6-cloro-2-(5-hidroxi-piridin-3-il)-indol-1-carboxílico (Ejemplo 158a) se procesan de acuerdo con el método descrito en el Ejemplo 158b, para dar el terbutil-éster del ácido 2-[5-(bencil-etil-sulfamoiloxi)-piridin-3-il]-6-cloro-indol-1-carboxílico. El producto crudo se carga sobre gel de sílice, y se calienta a 50°C durante la noche al vacío. La elución con heptano-etanol, 1:1, proporciona el 5-(6-cloro-1H-indol-2-il)-piridin-3-il-éster del ácido bencil-etil-sulfámico.

MS (ESI) *m/z* 442.1 $(M+H)^+$.

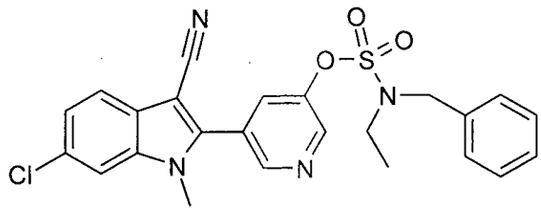
(c) 5-(6-cloro-1-metil-1H-indol-2-il)-piridin-3-il-éster del ácido bencil-etil-sulfámico



El 5-(6-cloro-1H-indol-2-il)-piridin-3-il-éster del ácido bencil-etil-sulfámico se procesa de acuerdo con el método descrito en el Ejemplo 114, para dar el 5-(6-cloro-1-metil-1H-indol-2-il)-piridin-3-il-éster del ácido bencil-etil-sulfámico.

MS (ESI) *m/z* 456.0 $(M+H)^+$

(d) 5-(6-cloro-3-ciano-1-metil-1H-indol-2-il)-piridin-3-il-éster del ácido bencil-etil-sulfámico

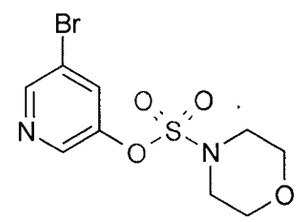


El 5-(6-cloro-1-metil-1H-indol-2-il)-piridin-3-il-éster del ácido bencil-etil-sulfámico se procesa de acuerdo con el método descrito en el Ejemplo 128, para dar el 5-(6-cloro-3-ciano-1-metil-1H-indol-2-il)-piridin-3-il-éster del ácido bencil-etil-sulfámico.

^{1}H RMN (400 MHz, MeOD) δ ppm 1.15 (t, *J*=7.2 Hz, 3 H), 3.43 (q, *J*=7.1 Hz, 2 H), 3.82 (s, 3 H), 4.61 (s, 2 H), 7.27 - 7.47 (m, 6 H), 7.73 (d, *J*=8.6 Hz, 1 H), 7.77 (d, *J*=1.5 Hz, 1 H), 8.06 (t, *J*=2.5 Hz, 1 H), 8.72 (d, *J*=2.5 Hz, 1 H), 8.83 (d, *J*=1.8 Hz, 1 H). HRMS (ESI) m/z 481.1085 [(M+H)$^+$ Calculado para $C_{24}H_{22}ClN_4O_3S$: 481.1101].

Ejemplo 160

(a) 5-bromo-piridin-3-il-éster del ácido morfolin-4-sulfónico

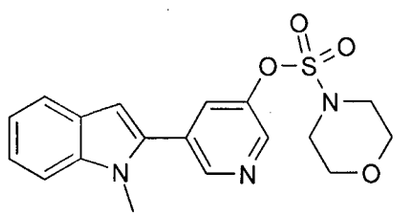


Un matraz se carga con 5-bromo-piridin-3-ol (0.310 gramos, 1.78 milimoles), fosfato de potasio (0.982 gramos, 4.63 milimoles), y acetona (10 mililitros), y se agrega por goteo cloruro de morfolin-4-sulfonilo (0.529 gramos, 2.85 milimoles) a 0°C. La mezcla se agita a

temperatura ambiente durante la noche. Se agrega $NaHCO_3$ saturado en agua (1 mililitro), y la mezcla se concentra al vacío. El residuo se purifica sobre cromatografía en gel de sílice eluyendo con un gradiente de 9:1 a 4:1 de heptano-acetato de etilo, para dar el 5-bromo-piridin-3-il-éster del ácido morfolin-4-sulfónico.

MS (ESI) *m/z* 322.9 y 324.9 $(M+H)^+$.

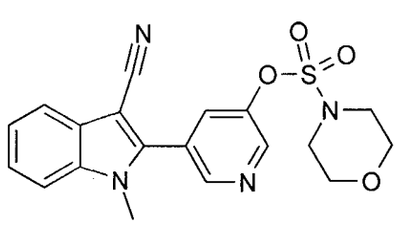
(b) 5-(1-metil-1H-indol-2-il)-piridin-3-il-éster del ácido morfolin-4-sulfónico



El 5-bromo-piridin-3-il-éster del ácido morfolin-4-sulfónico y ácido N-metil-indol-borónico se procesan de acuerdo con el método descrito en el Ejemplo 100, para dar el 5-(1-metil-1H-indol-2-il)-piridin-3-il-éster del ácido morfolin-4-sulfónico.

MS (ESI) *m/z* 374.1 $(M+H)^+$

(c) 5-(3-ciano-1-metil-1H-indol-2-il)-piridin-3-il-éster del ácido morfolin-4-sulfónico



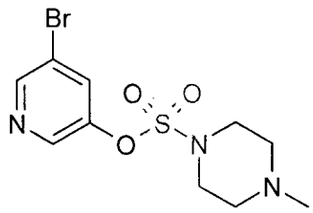
El 5-(1-metil-1H-indol-2-il)-piridin-3-il-éster del ácido morfolin-4-sulfónico se procesa de acuerdo con el método descrito en el

Ejemplo 128. para dar el 5-(3-ciano-1-metil-1H-indol-2-il)-piridin-3-il-éster del ácido morfolin-4-sulfónico.

^{1}H RMN (400 MHz, DMSO-d_6) δ ppm 3.38 - 3.43 (m, 4 H), 3.66 - 3.70 (m, 4 H), 3.81 (s, 3 H), 7.34 - 7.39 (m, 1 H), 7.42 - 7.48 (m, 1 H), 7.73 (d, *J*=7.8 Hz, 1 H), 7.78 (d, *J*=8.3 Hz, 1 H), 8.26 (dd, *J*=2.5, 2.0 Hz, 1 H), 8.86 (d, *J*=2.5 Hz, 1 H), 8.90 (d, *J*=1.8 Hz, 1 H). HRMS (ESI) m/z 399.1124 [(M+H)$^+$ Calculado para $C_{19}H_{19}N_4O_4S$: 399.1127].

Ejemplo 161

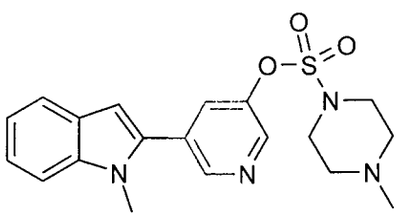
(a) 5-bromo-piridin-3-il-éster del ácido 4-metil-piperazin-1-sulfónico

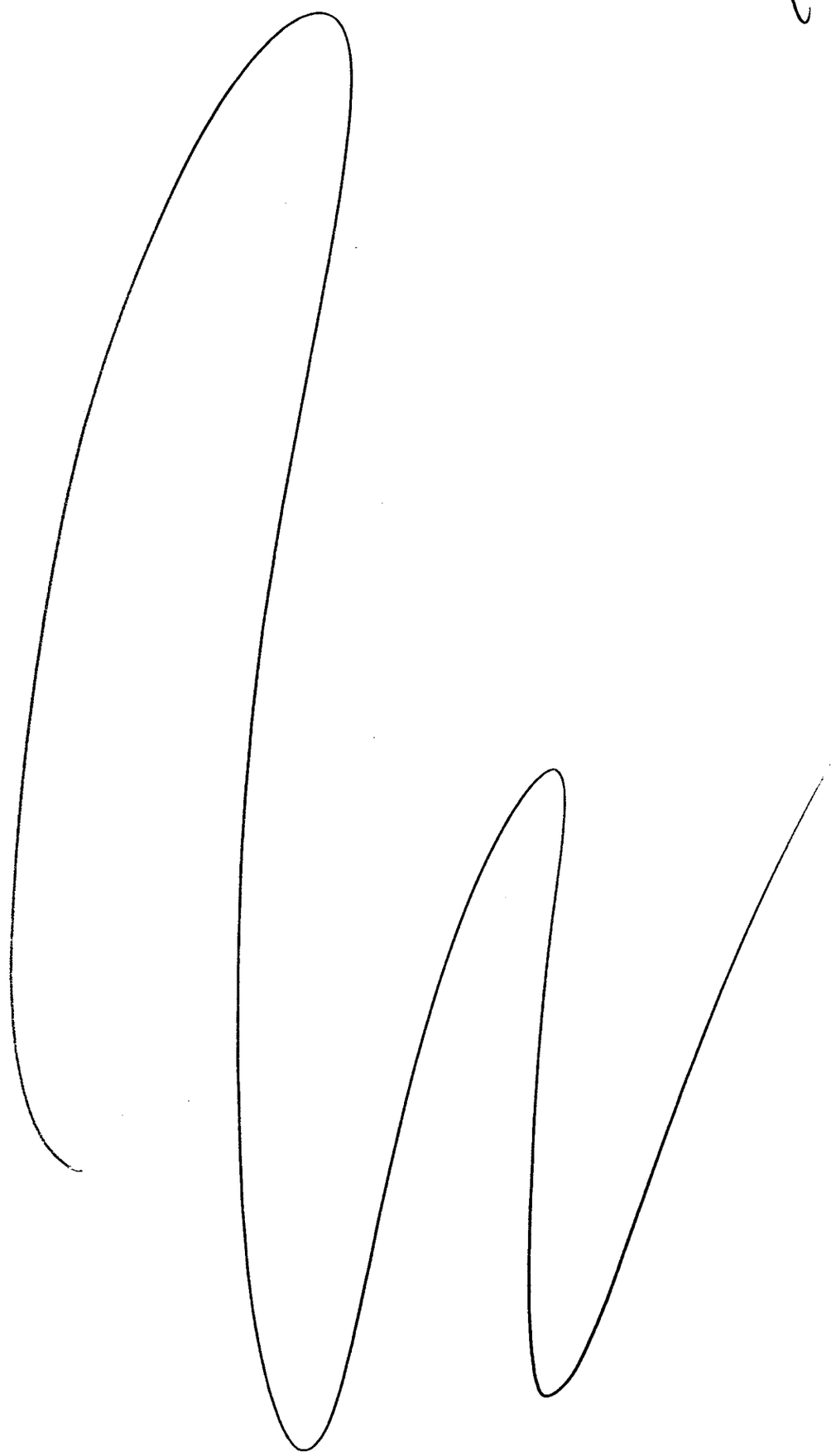


El cloruro de 4-metil-piperazin-1-sulfonilo se procesa de acuerdo con el método descrito en el Ejemplo 160a, para dar el 5-bromo-piridin-3-il-éster del ácido 4-metil-piperazin-1-sulfónico.

MS (ESI) *m/z* 335.9 y 337.9 (M+H)$^+$.

(b) 5-(1-metil-1H-indol-2-il)-piridin-3-il-éster del ácido 4-metil-piperazin-1-sulfónico



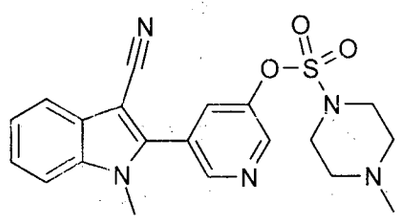




El 5-bromo-piridin-3-il-éster del ácido 4-metil-piperazin-1-sulfónico y ácido N-metil-indol-borónico se procesan de acuerdo con el método descrito en el Ejemplo 100, para dar el 5-(1-metil-1H-indol-2-il)-piridin-3-il-éster del ácido 4-metil-piperazin-1-sulfónico.

MS (ESI) *m/z* 387.1 $(M+H)^+$.

(c) 5-(3-ciano-1-metil-1H-indol-2-il)-piridin-3-il-éster del ácido 4-metil-piperazin-1-sulfónico

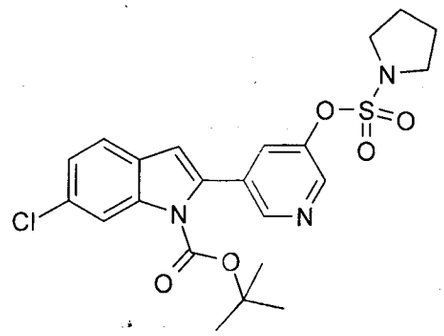


El 5-(1-metil-1H-indol-2-il)-piridin-3-il-éster del ácido 4-metil-piperazin-1-sulfónico se procesa de acuerdo con el método descrito en el Ejemplo 128, para dar el 5-(3-ciano-1-metil-1H-indol-2-il)-piridin-3-il-éster del ácido 4-metil-piperazin-1-sulfónico.

^{1}H RMN (400 MHz, DMSO-d_6) δ ppm 2.21 (s, 3 H), 2.38 - 2.43 (m, 4 H), 3.38 - 3.43 (m, 4 H), 3.81 (s, 3 H), 7.34 - 7.39 (m, 1 H), 7.42 - 7.48 (m, 1 H), 7.73 (d, *J*=7.8 Hz, 1 H), 7.78 (d, *J*=8.3 Hz, 1 H), 8.24 (dd, *J*=2.5, 1.8 Hz, 1 H), 8.84 (d, *J*=2.5 Hz, 1 H), 8.90 (d, *J*=1.8 Hz, 1 H). HRMS (ESI) m/z 412.1443 [$(M+H)^+$ Calculado para $C_{20}H_{22}N_5O_3S$: 412.1443].

Ejemplo 162

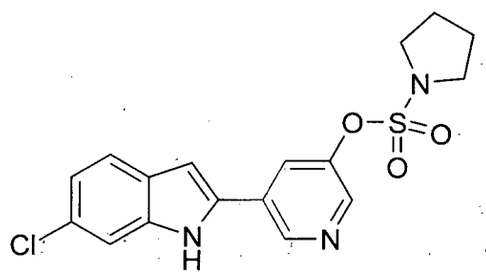
(a) Terbutil-éster del ácido 6-cloro-2-[5-(pirrolidin-1-sulfoniloxi)-piridin-3-il]-indol-1-carboxílico



El cloruro de 1-pirrolidin-sulfonilo y terbutil-éster del ácido 6-cloro-2-(5-hidroxi-piridin-3-il)-indol-1-carboxílico (Ejemplo 160a) se procesan de acuerdo con el método descrito en el Ejemplo 160b, para dar el terbutil-éster del ácido 6-cloro-2-[5-(pirrolidin-1-sulfoniloxi)-piridin-3-il]-indol-1-carboxílico, el cual se lleva al siguiente paso sin mayor purificación.

MS (ESI) *m/z* 478.1 $(M+H)^+$.

(b) 5-(6-cloro-1H-indol-2-il)-piridin-3-il-éster del ácido pirrolidin-1-sulfónico

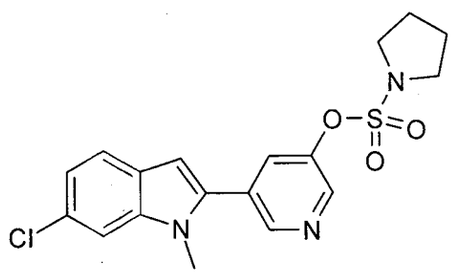


El terbutil-éster del ácido 6-cloro-2-[5-(pirrolidin-1-sulfoniloxi)-piridin-3-il]-indol-1-carboxílico se disuelve en dicloro-metano (2 mililitros), y la mezcla se enfría a 0°C. Se agrega ácido trifluoro-acético (2 mililitros), y la mezcla se agita a temperatura ambiente durante 1 hora. Entonces se agrega bicarbonato de sodio saturado, y

la mezcla se extrae con dicloro-metano. La capa orgánica se seca sobre sulfato de sodio, y se concentra al vacío, para proporcionar el 5-(6-cloro-1H-indol-2-il)-piridin-3-il-éster del ácido pirrolidin-1-sulfónico como un aceite, el cual se lleva al siguiente paso sin mayor purificación.

MS (ESI) *m/z* 376.2 $(M+H)^+$.

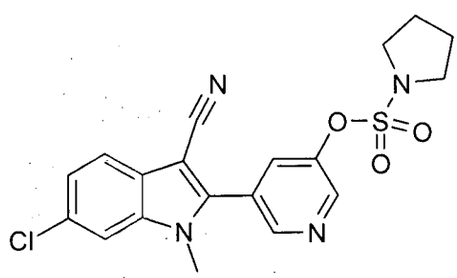
(c) 5-(6-cloro-1-metil-1H-indol-2-il)-piridin-3-il-éster del ácido pirrolidin-1-sulfónico



El 5-(6-cloro-1H-indol-2-il)-piridin-3-il-éster del ácido pirrolidin-1-sulfónico se procesa de acuerdo con el método descrito en el Ejemplo 109, para dar el 5-(6-cloro-1-metil-1H-indol-2-il)-piridin-3-il-éster del ácido pirrolidin-1-sulfónico.

MS (ESI) *m/z* 392.0 $(M+H)^+$.

(d) 5-(6-cloro-3-ciano-1-metil-1H-indol-2-il)-piridin-3-il-éster del ácido pirrolidin-1-sulfónico

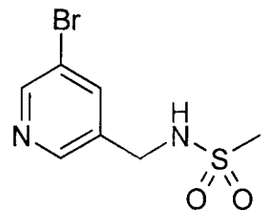


El 5-(6-cloro-1-metil-1H-indol-2-il)-piridin-3-il-éster del ácido pirrolidin-1-sulfónico se procesa de acuerdo con el método descrito en el Ejemplo 128, para dar el 5-(6-cloro-3-ciano-1-metil-1H-indol-2-il)-piridin-3-il-éster del ácido pirrolidin-1-sulfónico.

^{1}H RMN (400 MHz, MeOD) δ ppm 2.01 - 2.09 (m, 4 H), 3.53 - 3.60 (m, 4 H), 3.85 (s, 3 H), 7.39 (dd, *J*=8.3, 1.8 Hz, 1 H), 7.74 (d, *J*=8.6 Hz, 1 H), 7.79 (d, *J*=1.5 Hz, 1 H), 8.17 (dd, *J*=2.5, 1.8 Hz, 1 H), 8.81 (d, *J*=2.5 Hz, 1 H), 8.85 (d, *J*=1.8 Hz, 1 H). HRMS (ESI) *m/z* 417.0788 [(M+H)$^+$ Calculado para $C_{19}H_{19}N_4O_3SCl$: 417.0788].

Ejemplo 163

(a) *N*-(5-bromo-piridin-3-il-metil)-metan-sulfonamida

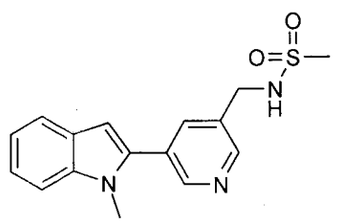


A una solución de 5-bromo-3-piridin-carboxaldehído (1.5 gramos, 7.9 milimoles), metan-sulfonamida (0.5 gramos, 5.3 milimoles), ácido acético (0.637 gramos, 10.6 milimoles), y trietil-amina (1.07 gramos, 10.6 milimoles) en dicloro-etano (50 mililitros) a temperatura ambiente, se le agrega $NaBH(OAc)_3$ (3.14 gramos, 14.84 milimoles). La mezcla de reacción se agita durante la noche. Se agrega $NaHCO_3$ acuoso (20 mililitros), y la fase orgánica se separa. La fase acuosa se extrae con dicloro-metano, y la fase orgánica combinada se seca sobre Na_2SO_4. La concentración proporciona un residuo, el cual se purifica mediante cromatografía por evaporación

instantánea en gel de sílice con un gradiente de metanol en diclorometano, para proporcionar la *N*-(5-bromo-piridin-3-il-metil)-metan-sulfonamida como un sólido.

MS (ESI) *m/z* 266.9 $(M+H)^+$.

(b) *N*-[5-(1-metil-1H-indol-2-il)-piridin-3-il-metil]-metan-sulfonamida

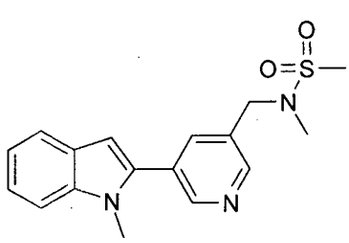


La *N*-(5-bromo-piridin-3-il-metil)-metan-sulfonamida y ácido N-metil-indol-borónico se procesan de acuerdo con el método descrito en el Ejemplo 100, para dar la *N*-[5-(1-metil-1H-indol-2-il)-piridin-3-il-metil]-metan-sulfonamida.

^{1}H.RMN (400 MHz, MeOD) δ ppm 3.03 (s, 3 H), 3.82 (s, 3 H), 4.45 (s, 2 H), 6.70 (s, 1 H), 7.13 (t, *J*=7.5 Hz, 1 H), 7.23 - 7.31 (m, 1 H), 7.48 (d, *J*=8.1 Hz, 1 H), 7.63 (d, *J*=7.8 Hz, 1 H), 8.10 (t, *J*=2.0 Hz, 1 H), 8.62 (d, *J*=2.0 Hz, 1 H), 8.72 (d, *J*=2.0 Hz, 1 H). HRMS (ESI) *m/z* 316.1108 [$(M+H)^+$ Calculado para $C_{16}H_{18}N_3O_2S$: 316.1120].

Ejemplo 164

N-metil-*N*-[5-(1-metil-1H-indol-2-il)-piridin-3-il-metil]-metan-sulfonamida

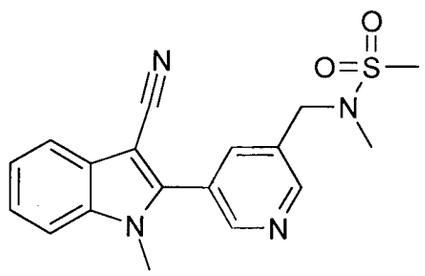


La *N*-[5-(1-metil-1H-indol-2-il)-piridin-3-il-metil]-metan-sulfonamida (Ejemplo 163) se procesa de acuerdo con el método descrito en el Ejemplo 114, para dar la *N*-metil-*N*-[5-(1-metil-1H-indol-2-il)-piridin-3-il-metil]-metan-sulfonamida.

^{1}H RMN (400 MHz, DMSO-d_6) δ ppm 2.77 (s, 3 H), 3.02 (s, 3 H), 3.78 (s, 3 H), 4.41 (s, 2 H), 6.72 (s, 1 H), 7.07 - 7.13 (m, 1 H), 7.20 - 7.25 (m, 1 H), 7.54 (d, *J*=8.3 Hz, 1 H), 7.61 (d, *J*=7.8 Hz, 1 H), 7.95 (t, *J*=2.0 Hz, 1 H), 8.60 (d, *J*=2.0 Hz, 1 H), 8.78 (d, *J*=2.0 Hz, 1 H). MS (ESI) *m/z* 330.1 $(M+H)^+$.

Ejemplo 165

N-metil-*N*-[5-(1-metil-3-ciano-1H-indol-2-il)-piridin-3-il-metil]-metan-sulfonamida



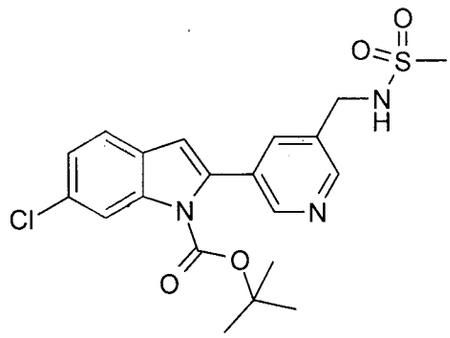
La *N*-metil-*N*-[5-(1-metil-1H-indol-2-il)-piridin-3-il-metil]-metan-sulfonamida (Ejemplo 164) se procesa de acuerdo con el método descrito en el Ejemplo 128, para dar la *N*-metil-*N*-[5-(1-metil-3-ciano-1H-indol-2-il)-piridin-3-il-metil]-metan-sulfonamida.

^{1}H RMN (400 MHz, DMSO-d_6) δ ppm 2.80 (s, 3 H), 3.03 (s, 3 H), 3.82 (s, 3 H), 4.46 (s, 2 H), 7.34 - 7.39 (m, 1 H), 7.42 - 7.47 (m, 1 H), 7.72 (d, *J*=7.8 Hz, 1 H), 7.77 (d, *J*=8.3 Hz, 1 H), 8.09 (t, *J*=2.1 Hz, 1 H), 8.77 (d, *J*=2.0 Hz, 1 H), 8.87 (d, *J*=2.3 Hz, 1 H). HRMS

(ESI) m/z 355.1229 [$(M+H)^+$ Calculado para $C_{18}H_{19}N_4O_2S$: 355.1229].

Ejemplo 166

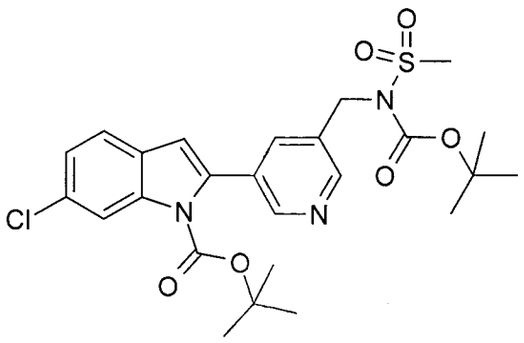
(a) Terbutil-éster del ácido 6-cloro-2-[5-(metan-sulfonil-amino-metil)-piridin-3-il]-indol-1-carboxílico



Un matraz se carga con *N*-(5-bromo-piridin-3-il-metil)-metan-sulfonamida (Ejemplo 163a, 530 miligramos, 2 milimoles), ácido N-Boc-6-cloro-indol-2-borónico (525 miligramos, 3.0 milimoles), s-Phos (41 miligramos, 0.10 milimoles), fosfato de potasio finamente triturado (849 miligramos, 4.0 milimoles), y tolueno (20 mililitros), y la mezcla se desgasifica durante 15 minutos. Se agrega Pd_2dba_3 (37 miligramos, 0.04 milimoles), y la mezcla se agita a 85°C durante 1 hora. La mezcla se enfría a temperatura ambiente, se diluye con dicloro-metano, y se agrega gel de sílice (10 gramos). La mezcla se concentra al vacío, y el residuo se purifica mediante cromatografía por evaporación instantánea en gel de sílice, eluyendo con un gradiente del 0 al 90 por ciento de acetato de etilo-heptano, para dar el terbutil-éster del ácido 6-cloro-2-[5-(metan-sulfonil-amino-metil)-piridin-3-il]-indol-1-carboxílico.

MS (ESI) *m/z* 436.1 y 437.9 $(M+H)^+$.

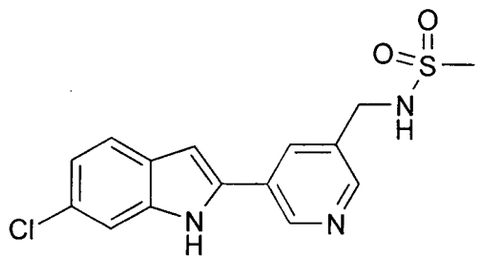
(b) Terbutil-éster del ácido 6-cloro-2-[5-(metan-sulfonil-(terbutoxi-carbonil)-amino-metil)-piridin-3-il]-indol-1-carboxílico



A una solución del terbutil-éster del ácido 6-cloro-2-[5-(metan-sulfonil-amino-metil)-piridin-3-il]-indol-1-carboxílico (530 miligramos, 1.22 milimoles) en acetonitrilo (10 mililitros), se le agregan Boc_2O (398 miligramos, 1.82 milimoles), y DMAP (15 miligramos, 0.12 milimoles). La mezcla se agita durante 1 hora. Se agrega gel de sílice (1 gramo), y la mezcla se concentra al vacío. El residuo se purifica mediante cromatografía en gel de sílice, para dar el terbutil-éster del ácido 6-cloro-2-[5-(metan-sulfonil-(terbutoxi-carbonil)-amino-metil)-piridin-3-il]-indol-1-carboxílico.

MS (ESI) *m/z* 536.2 y 538.1 $(M+H)^+$.

(c) *N*-[5-(6-cloro-1H-indol-2-il)-piridin-3-il-metil]-metan-sulfonamida

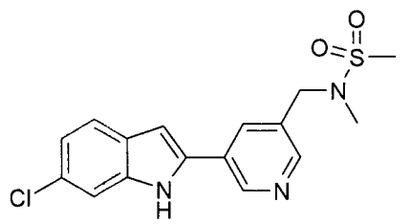


Un matraz se carga con terbutil-éster del ácido 6-cloro-2-[5-

(metan-sulfonil-(terbutoxi-carbonil)-amino-metil)-piridin-3-il]-indol-1-carboxílico (0.52 gramos, 0.97 milimoles), y ácido trifluoro-acético (5 mililitros), y la mezcla se agita a temperatura ambiente durante 1 hora. La mezcla se concentra al vacío, para dar la *N*-[5-(6-cloro-1H-indol-2-il)-piridin-3-il-metil]-metan-sulfonamida, la cual se utiliza en el siguiente paso sin mayor purificación.

MS (ESI) *m/z* 336.0 y 337.9 $(M+H)^+$.

(d) *N*-[5-(6-cloro-1H-indol-2-il)-piridin-3-il-metil]-*N*-metil-metan-sulfonamida



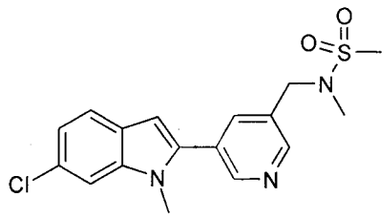
Un matraz se carga con *N*-[5-(6-cloro-1H-indol-2-il)-piridin-3-il-metil]-metan-sulfonamida (670 miligramos, 1.49 milimoles), dimetil-formamida (10 mililitros), carbonato de dimetilo (403 miligramos, 4.47 milimoles), y carbonato de potasio (319 miligramos, 2.31 milimoles), y la mezcla se agita a 150°C durante 5 horas. La mezcla se enfría a temperatura ambiente, y se purifica utilizando XBridge C18 eluyendo con un gradiente de 1:9 a 9:1 de acetonitrilo-agua, para dar la *N*-[5-(6-cloro-1H-indol-2-il)-piridin-3-il-metil]-*N*-metil-metan-sulfonamida.

^{1}H RMN (400 MHz, DMSO-d_6) δ ppm 2.74 (s, 3 H), 3.02 (s, 3 H), 4.35 (s, 2 H), 7.04 (dd, *J*=8.5, 1.9 Hz, 1 H), 7.09 (d, *J*=1.5 Hz, 1 H), 7.43 (d, *J*=1.8 Hz, 1 H), 7.59 (d, *J*=8.6 Hz, 1 H), 8.14 (t, *J*=2.1 Hz, 1 H), 8.47 (d, *J*=2.0 Hz, 1 H), 9.05 (d, *J*=2.3 Hz, 1 H), 11.92 (s, 1

H). HRMS (ESI) m/z 350.0738 [(M+H)$^+$ Calculado para $C_{16}H_{17}ClN_3O_2S$: 350.0730].

Ejemplo 167

N-[5-(6-cloro-1-metil-1H-indol-2-il)-piridin-3-il-metil]-*N*-metil-metan-sulfonamida

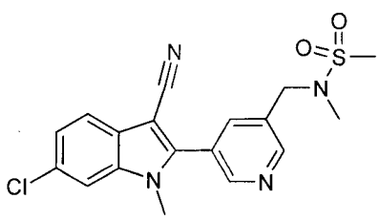


El método descrito en el Ejemplo 166d también genera la *N*-[5-(6-cloro-1-metil-1H-indol-2-il)-piridin-3-il-metil]-N-metil-metan-sulfonamida.

^{1}H RMN (400 MHz, DMSO-d_6) δ ppm 2.78 (s, 3 H), 3.02 (s, 3 H), 3.77 (s, 3 H), 4.41 (s, 2 H), 6.76 (d, *J*=0.8 Hz, 1 H), 7.11 (dd, *J*=8.5, 1.9 Hz, 1 H), 7.62 (d, *J*=8.5 Hz, 1 H), 7.70 (d, *J*=1.8 Hz, 1 H), 7.96 (t, *J*=2.2 Hz, 1 H), 8.62 (d, *J*=2.2 Hz, 1 H), 8.78 (d, *J*=2.2 Hz, 1 H). MS (ESI) *m/z* 364.1 (M+H)$^+$.

Ejemplo 168

N-[5-(6-cloro-3-ciano-1-metil-1H-indol-2-il)-piridin-3-il-metil]-*N*-metil-metan-sulfonamida



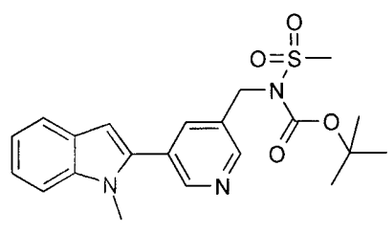
La *N*-[5-(6-cloro-1-metil-1H-indol-2-il)-piridin-3-il-metil]-*N*-metil-

metan-sulfonamida (Ejemplo 167) se procesa de acuerdo con el método descrito en el Ejemplo 128, para dar la *N*-[5-(6-cloro-3-ciano-1-metil-1H-indol-2-il)-piridin-3-il-metil]-*N*-metil-metan-sulfonamida.

^{1}H RMN (400 MHz, DMSO-d_6) δ ppm 2.78 (s, 3 H), 3.02 (s, 3 H), 3.79 (s, 3 H), 4.45 (s, 2 H), 7.37 (dd, *J*=8.5, 1.9 Hz, 1 H), 7.73 (d, *J*=8.6 Hz, 1 H), 7.97 (d, *J*=1.5 Hz, 1 H), 8.08 (t, *J*=2.0 Hz, 1 H), 8.76 (d, *J*=2.0 Hz, 1 H), 8.85 (d, *J*=2.0 Hz, 1 H). HRMS (ESI) m/z 389.0835 [(M+H)$^+$ Calculado para $C_{18}H_{18}ClN_4O_2S$: 389.0839].

Ejemplo 169

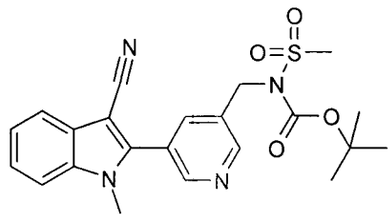
(a) 2-[5-(Metan-sulfonil-(terbutoxi-carbonil)-amino-metil)-piridin-3-il]-1-metil-indol



A una solución de *N*-[5-(1-metil-1H-indol-2-il)-piridin-3-il-metil]-metan-sulfonamida (Ejemplo 163b) (337 miligramos, 0.200 milimoles) en acetonitrilo (5 mililitros), se le agregan Boc_2O (293 miligramos, 1.34 milimoles), y DMAP (14 miligramos, 0.11 milimoles). La mezcla de reacción se agita durante 1 hora y, después de la remoción del solvente, el residuo se purifica mediante cromatografía por evaporación instantánea en gel de sílice, para proporcionar el 2-[5-(metan-sulfonil-(terbutoxi-carbonil)-amino-metil)-piridin-3-il]-1-metil-indol.

MS (ESI) *m/z* 416.2 (M+H)$^+$.

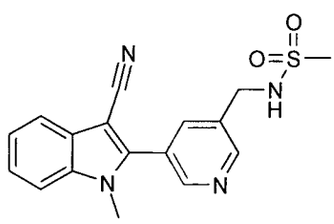
(b) 2-[5-(metan-sulfonil-(terbutoxi-carbonil)-amino-metil)-piridin-3-il]-1-metil-3-ciano-indol



A una solución de 2-[5-(metan-sulfonil-(terbutoxi-carbonil)-amino-metil)-piridin-3-il]-1-metil-indol (350 miligramos, 0.842 milimoles) en dicloro-metano (10 mililitros), se le agrega isocianato de cloro-sulfonilo (0.358 gramos, 2.53 milimoles). La mezcla se agita a temperatura ambiente durante 20 minutos, después de lo cual, se agrega dimetil-formamida anhidra (2 mililitros). Después de 1 hora, la mezcla se concentra hasta un volumen de 3 mililitros, y se filtra. La purificación mediante HPLC en fase inversa proporciona el 2-[5-(metan-sulfonil-(terbutoxi-carbonil)-amino-metil)-piridin-3-il]-1-metil-3-ciano-indol.

MS (ESI) *m/z* 441.1 $(M+H)^+$.

(c) *N*-[5-(3-ciano-1-metil-1H-indol-2-il)-piridin-3-il-metil]-metan-sulfonamida



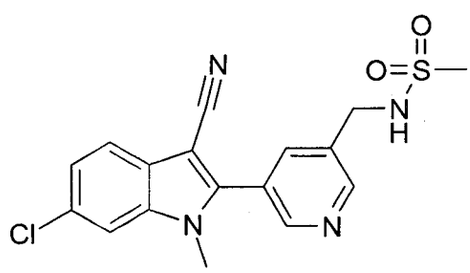
El 2-[5-(metan-sulfonil-(terbutoxi-carbonil)-amino-metil)-piridin-3-il]-1-metil-3-ciano-indol (260 miligramos, 0.59 milimoles) en ácido

trifluoro-acético (3 mililitros) a temperatura ambiente se agita durante 30 minutos. Entonces se remueve el solvente al vacío, y el residuo se purifica mediante HPLC en fase inversa. Las fracciones que contienen el producto se reservan y se concentran, y el residuo se purifica además mediante cromatografía por evaporación instantánea en gel de sílice (gradiente de metanol-dicloro-metano), para dar la *N*-[5-(3-ciano-1-metil-1H-indol-2-il)-piridin-3-il-metil]-metan-sulfonamida.

^{1}H RMN (400 MHz, DMSO-d_6) δ ppm 2.97 (s, 3 H), 3.79 (s, 3 H), 4.36 (br. s., 2 H), 7.33 - 7.39 (m, 1 H), 7.40 - 7.46 (m, 1 H), 7.69 - 7.79 (m, 3 H), 8.10 (t, *J*=2.1 Hz, 1 H), 8.77 (d, *J*=2.3 Hz, 1 H), 8.81 (d, *J*=2.3 Hz, 1 H). HRMS (ESI) *m/z* 341.1068 [(M+H)$^+$ Calculado para $C_{17}H_{17}N_4O_2S$: 341.1072].

Ejemplo 170

N-[5-(6-cloro-3-ciano-1-metil-1H-indol-2-il)-piridin-3-il-metil]-metan-sulfonamida



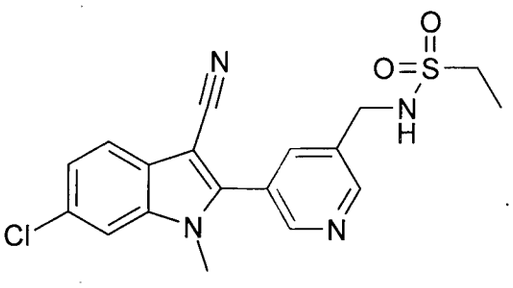
El 6-cloro-2-(5-formil-piridin-3-il)-1-metil-1H-indol-3-carbonitrilo (Ejemplo 126, 50 miligramos, 0.169 milimoles), metan-sulfonamida (24 miligramos, 0.254 milimoles), ácido acético (20 miligramos, 0.338 milimoles), y trietil-amina (34 miligramos, 0.338 milimoles) en

dicloro-etano (10 mililitros) se agitan durante 30 minutos a temperatura ambiente antes de agregar $NaBH(OAc)_3$ (100 miligramos, 0.473 milimoles). La mezcla de reacción se agita durante la noche. Se agrega $NaHCO_3$ (1 mililitro), y los solventes se remueven al vacío. El residuo se purifica utilizando una Sunfire C18 con un gradiente de acetonitrilo en ácido trifluoro-acético acuoso al 0.1 por ciento, y se purifica adicionalmente con una XBridge C18, utilizando un gradiente de acetonitrilo en NH_4OH al 0.1 por ciento, para dar la *N*-[5-(6-cloro-3-ciano-1-metil-1H-indol-2-il)-piridin-3-il-metil]-metan-sulfonamida como un sólido.

^{1}H RMN (400 MHz, DMSO-d_6) δ ppm 2.97 (s, 3 H), 3.78 (s, 3 H), 4.36 (s, 2 H), 7.37 (dd, *J*=8.6, 1.8 Hz, 1 H), 7.73 (d, *J*=8.6 Hz, 1 H), 7.75 (br. s., 1 H), 7.97 (d, *J*=1.8 Hz, 1 H), 8.10 (t, *J*=2.1 Hz, 1 H), 8.78 (d, *J*=2.0 Hz, 1 H), 8.81 (d, *J*=2.3 Hz, 1 H). HRMS (ESI) *m/z* 375.0681 [(M+H)$^+$ Calculado para $C_{17}H_{16}ClN_4O_2S$: 375.0682].

Ejemplo 171

N-[5-(6-cloro-3-ciano-1-metil-1H-indol-2-il)-piridin-3-il-metil]-etan-sulfonamida



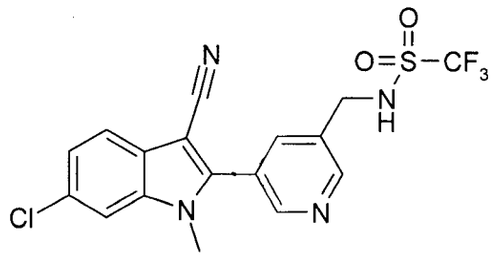
Se agregan por goteo 6-cloro-2-(5-formil-piridin-3-il)-1-metil-1H-indol-3-carbonitrilo (Ejemplo 126b, 2.0 gramos, 6.09 milimoles),

etan-sulfonamida (1.33 gramos, 12.17 milimoles), tolueno (250 mililitros), y isopropóxido de titanio(IV) (2.59 gramos, 9.13 milimoles). La mezcla se agita a 120°C durante la noche. La mezcla entonces se concentra al vacío. El residuo se absorbe en dicloro-metano (150 mililitros) y metanol (150 mililitros), y se agrega $NaBH_4$ (0.461 gramos, 12.17 milimoles) a 0°C. La mezcla se agita a 0°C durante 30 minutos. Se agrega agua (50 mililitros), y la mezcla se agita durante 5 minutos. La suspensión se filtra a través de un cojín de Celite. La capa de Celite se lava con dicloro-metano (50 mililitros, 3 veces). La fase orgánica combinada se seca sobre Na_2SO_4 y se concentra, para dar un residuo, el cual se purifica mediante cromatografía por evaporación instantánea en gel de sílice (acetato de etilo). Las fracciones resultantes que contienen el producto se concentran y se vuelven a purificar mediante cromatografía por evaporación instantánea en gel de sílice (dicloro-metano : metanol, de 1:0 a 97:3). El producto concentrado se vuelve a disolver en metanol (500 mililitros) a 60°C, y se concentra al vacío, para dar la *N*-[5-(6-cloro-3-ciano-1-metil-1H-indol-2-il)-piridin-3-il-metil]-etan-sulfonamida.

^{1}H RMN (400 MHz, DMSO-d_6) δ ppm 1.20 (t, *J*=7.3 Hz, 3 H), 3.06 (q, *J*=7.3 Hz, 2 H), 3.78 (s, 3 H), 4.34 (d, J=6.3 Hz, 2 H), 7.37 (dd, *J*=8.6, 1.8 Hz, 1 H), 7.73 (d, *J*=8.3 Hz, 1 H), 7.77 (t, *J*=6.2 Hz, 1 H), 7.97 (d, *J*=1.8 Hz, 1 H), 8.09 (t, *J*=2.1 Hz, 1 H), 8.78 (d, *J*=1.8 Hz, 1 H), 8.80 (d, *J*=1.8 Hz, 1 H). HRMS (ESI) *m/z* 389.0853 [$(M+H)^+$ Calculado para $C_{18}H_{17}ClN_4O_2S$: 389.0839].

Ejemplo 172

N-[5-(6-cloro-3-ciano-1-metil-1H-indol-2-il)-piridin-3-il-metil]-C,*C*,*C*-trifluoro-metan-sulfonamida

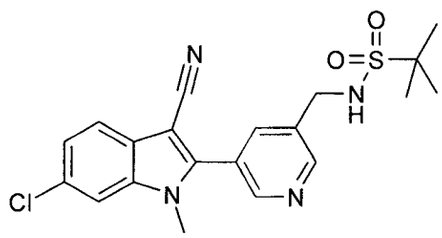


El 6-cloro-2-(5-formil-piridin-3-il)-1-metil-1H-indol-3-carbonitrilo (Ejemplo 126), y trifluoro-metan-sulfonamida, se procesan de acuerdo con el método descrito en el Ejemplo 170, para dar la *N*-[5-(6-cloro-3-ciano-1-metil-1H-indol-2-il)-piridin-3-il-metil]-*C*,*C*,*C*-trifluoro-metan-sulfonamida.

^{1}H RMN (400 MHz, DMSO-d_6) δ ppm 3.78 (s, 3 H), 4.56 (s, 2 H), 7.37 (dd, *J*=8.5, 1.9 Hz, 1 H), 7.73 (d, *J*=8.6 Hz, 1 H), 7.97 (d, *J*=1.5 Hz, 1 H), 8.09 (t, *J*=2.1 Hz, 1 H), 8.78 (d, *J*=2.3 Hz, 1 H), 8.83 (d, *J*=2.0 Hz, 1 H), 10.16 (br. s., 1 H). HRMS (ESI) *m/z* 429.0412 [$(M+H)^+$ Calculado para $C_{17}H_{13}ClF_3N_4O_2S$: 429.0400].

Ejemplo 173

[5-(6-cloro-3-ciano-1-metil-1H-indol-2-il)-piridin-3-il-metil]-amida del ácido 2-metil-propan-2-sulfónico

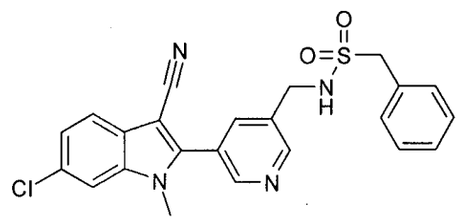


El 6-cloro-2-(5-formil-piridin-3-il)-1-metil-1H-indol-3-carbonitrilo (Ejemplo 126), y amida del ácido 2-metil-propan-2-sulfónico se procesan de acuerdo con el método descrito en el Ejemplo 170, para dar la [5-(6-cloro-3-ciano-1-metil-1H-indol-2-il)-piridin-3-il-metil]-amida del ácido 2-metil-propan-2-sulfónico.

^{1}H RMN (400 MHz, DMSO-d_6) δ ppm 1.32 (s, 9 H), 3.78 (s, 3 H), 4.43 (d, *J*=6.1 Hz, 2 H), 7.37 (dd, *J*=8.6, 1.8 Hz, 1 H), 7.65 (t, *J*=6.2 Hz, 1 H), 7.73 (d, *J*=8.3 Hz, 1 H), 7.97 (d, *J*=1.5 Hz, 1 H), 8.06 (t, *J*=2.1 Hz, 1 H), 8.77 (d, *J*=1.8 Hz, 1 H), 8.80 (d, *J*=2.0 Hz, 1 H). HRMS (ESI) *m/z* 417.1150 [(M+H)$^+$ Calculado para $C_{20}H_{21}ClN_4O_2S$: 417.1152].

Ejemplo 174

N-[5-(6-cloro-3-ciano-1-metil-1H-indol-2-il)-piridin-3-il-metil]-*C*-fenil-metan-sulfonamida



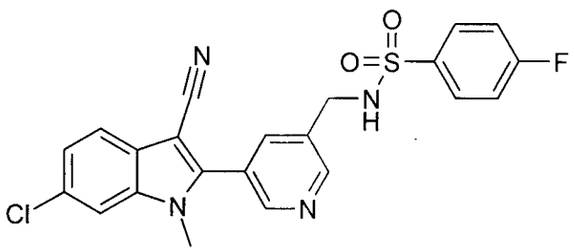
El 6-cloro-2-(5-formil-piridin-3-il)-1-metil-1H-indol-3-carbonitrilo (Ejemplo 126), y fenil-metan-sulfonamida, se procesan de acuerdo con el método descrito en el Ejemplo 170, para dar la *N*-[5-(6-cloro-3-ciano-1-metil-1H-indol-2-il)-piridin-3-il-metil]-*C*-fenil-metan-sulfonamida.

^{1}H RMN (400 MHz, DMSO-d_6) δ ppm 3.77 (s, 3 H), 4.31 (s, 2

H), 4.44 (s, 2 H), 7.30 - 7.41 (m, 6 H), 7.73 (d, *J*=8.3 Hz, 1 H), 7.83 (br. s., 1 H), 7.97 (d, *J*=1.5 Hz, 1 H), 8.03 (t, *J*=2.1 Hz, 1 H), 8.73 (d, *J*=2.0 Hz, 1 H), 8.79 (d, *J*=2.0 Hz, 1 H). HRMS (ESI) *m/z* 451.1006 [$(M+H)^+$ Calculado para $C_{23}H_{20}ClN_4O_2S$: 451.0996].

Ejemplo 175

N-[5-(6-cloro-3-ciano-1-metil-1H-indol-2-il)-piridin-3-il-metil]-4-fluoro-bencen-sulfonamida

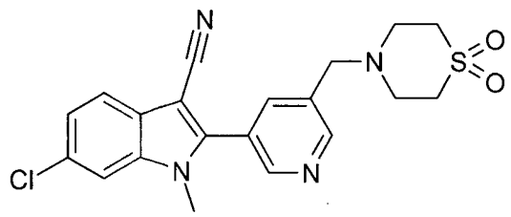


El 6-cloro-2-(5-formil-piridin-3-il)-1-metil-1H-indol-3-carbonitrilo (Ejemplo 126), y 4-fluoro-bencen-sulfonamida, se procesan de acuerdo con el método descrito en el Ejemplo 170, para dar la *N*-[5-(6-cloro-3-ciano-1-metil-1H-indol-2-il)-piridin-3-il-metil]-4-fluoro-bencen-sulfonamida.

^{1}H RMN (400 MHz, DMSO-d_6) δ ppm 3.74 (s, 3 H), 4.23 (s, 2 H), 7.33 - 7.41 (m, 3 H), 7.72 (d, *J*=8.6 Hz, 1 H), 7.82 - 7.88 (m, 2 H), 7.95 (d, *J*=1.5 Hz, 2 H), 8.44 (s, 1 H), 8.62 (d, *J*=2.0 Hz, 1 H), 8.73 (d, *J*=2.0 Hz, 1 H). HRMS (ESI) *m/z* 455.0746 [$(M+H)^+$ Calculado para $C_{22}H_{17}ClFN_4O_2S$: 455.0745].

Ejemplo 176

6-cloro-2-[5-(1,1-dioxo-1lambda*6*-tiomorfolin-4-il-metil)-piridin-3-il]-1-metil-1H-indol-3-carbonitrilo

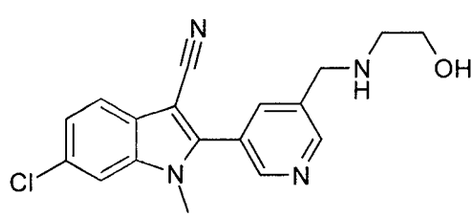


El 6-cloro-2-(5-formil-piridin-3-il)-1-metil-1H-indol-3-carbonitrilo (Ejemplo 126), y 1,1-dióxido de tiomorfolina, se procesan de acuerdo con el método descrito en el Ejemplo 170, para dar el 6-cloro-2-[5-(1,1-dioxo-1lambda*6*-tiomorfolin-4-il-metil)-piridin-3-il]-1-metil-1H-indol-3-carbonitrilo.

^{1}H RMN (400 MHz, DMSO-d_6) δ ppm 2.93 - 2.98 (m, 4 H), 3.12 - 3.18 (m, 4 H), 3.81 (s, 3 H), 3.87 (s, 2 H), 7.37 (dd, *J*=8.5, 1.9 Hz, 1 H), 7.73 (d, *J*=8.3 Hz, 1 H), 7.97 (d, *J*=1.5 Hz, 1 H), 8.13 (t, *J*=2.0 Hz, 1 H), 8.75 (d, *J*=2.0 Hz, 1 H), 8.81 (d, *J*=2.3 Hz, 1 H). HRMS (ESI) *m/z* 415.1015 [(M+H)$^+$ Calculado para $C_{20}H_{20}ClN_4O_2S$: 415.0996].

Ejemplo 177

6-cloro-2-{5-[(2-hidroxi-etil-amino)-metil]-piridin-3-il}-1-metil-1H-indol-3-carbonitrilo



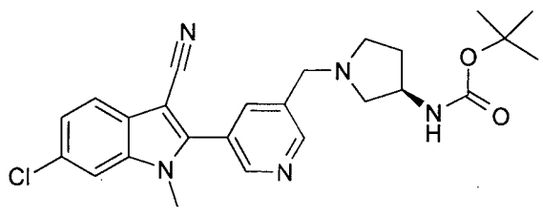
El 6-cloro-2-(5-formil-piridin-3-il)-1-metil-1H-indol-3-carbonitrilo (Ejemplo 126), y 2-amino-etanol, se procesan de acuerdo con el método descrito en el Ejemplo 170, para dar el 6-cloro-2-{5-[(2-

hidroxi-etil-amino)-metil]-piridin-3-il}-1-metil-1H-indol-3-carbonitrilo.

^{1}H RMN (400 MHz, DMSO-d_6) δ ppm 2.65 - 2.72 (m, 2 H), 3.49 - 3.55 (m, 2 H), 3.79 (s, 3 H), 3.92 - 3.98 (m, 2 H), 4.61 (br. s., 1 H), 7.37 (dd, *J*=8.3, 1.8 Hz, 1 H), 7.73 (d, *J*=8.3 Hz, 1 H), 7.97 (d, *J*=1.8 Hz, 1 H), 8.10 - 8.13 (m, 1 H), 8.75 - 8.79 (m, 2 H). HRMS (ESI) *m/z* 341.1175 [(M+H)$^+$ Calculado para $C_{19}H_{18}ClN_4O$: 341.1169].

Ejemplo 178

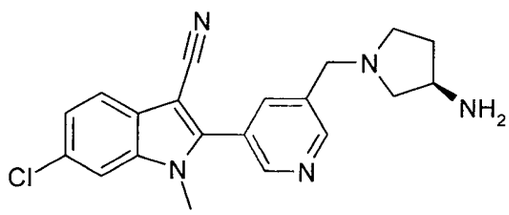
(a) {(*R*)-terbutil-éster del ácido 1-[5-(6-cloro-3-ciano-1-metil-1H-indol-2-il)-piridin-3-il-metil]-pirrolidin-3-il}-carbámico



El 6-cloro-2-(5-formil-piridin-3-il)-1-metil-1H-indol-3-carbonitrilo (Ejemplo 126), y (R)-terbutil-éster del ácido pirrolidin-3-il-carbámico se procesan de acuerdo con el método descrito en el Ejemplo 170, para dar el {(*R*)-terbutil-éster del ácido 1-[5-(6-cloro-3-ciano-1-metil-1H-indol-2-il)-piridin-3-il-metil]-pirrolidin-3-il}-carbámico.

MS (ESI) *m/z* 466.17 (M+H)$^+$.

(b) 2-[5-((*R*)-3-amino-pirrolidin-1-il-metil)-piridin-3-il]-6-cloro-1-metil-1H-indol-3-carbonitrilo

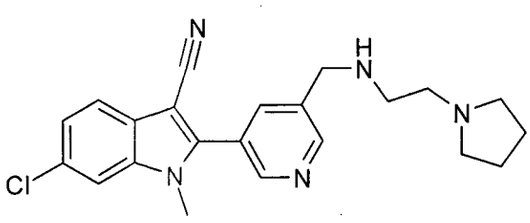


A una solución del {(*R*)-terbutil-éster del ácido 1-[5-(6-cloro-3-ciano-1-metil-1H-indol-2-il)-piridin-3-il-metil]-pirrolidin-3-il}-carbámico (140 miligramos, 0.3 milimoles) en dicloro-metano (5 mililitros), se le agrega ácido trifluoro-acético (2 mililitros), y la mezcla se agita a temperatura ambiente durante 2 horas. Los solventes se remueven entonces al vacío, y el residuo se purifica mediante XBridge C18 con un gradiente de acetonitrilo en NH_4OH al 0.1 por ciento, para dar el 2-[5-((*R*)-3-amino-pirrolidin-1-il-metil)-piridin-3-il]-6-cloro-1-metil-1H-indol-3-carbonitrilo.

^{1}H RMN (400 MHz, DMSO-d_6) δ ppm 1.33 - 1.43 (m, 1 H), 1.64 (br. s., 2 H), 1.97 - 2.08 (m, 1 H), 2.21 (dd, *J*=9.0, 4.9 Hz, 1 H), 2.59 - 2.68 (m, 1 H), 2.71 (dd, *J*=9.1, 6.6 Hz, 1 H), 3.32 - 3.39 (m, 1 H), 3.72 (q, *J*=13.6 Hz, 2 H), 3.79 (s, 3 H), 7.36 (dd, *J*=8.3, 1.8 Hz, 1 H), 7.72 (d, *J*=8.6 Hz, 1 H), 7.96 (d, *J*=1.5 Hz, 1 H), 8.05 (t, *J*=2.0 Hz, 1 H), 8.72 (d, *J*=2.0 Hz, 1 H), 8.77 (d, *J*=2.3 Hz, 1 H). HRMS (ESI) *m/z* 366.1483 [$(M+H)^+$ Calculado para $C_{20}H_{21}ClN_5$: 366.1485].

Ejemplo 179

6-cloro-1-metil-2-{5-[(2-pirrolidin-1-il-etil-amino)-metil]-piridin-3-il}-1H-indol-3-carbonitrilo



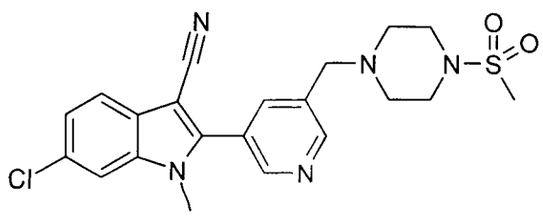
El 6-cloro-2-(5-formil-piridin-3-il)-1-metil-1H-indol-3-carbonitrilo (Ejemplo 126), y 2-pirrolidin-1-il-etil-amina, se procesan de acuerdo

con el método descrito en el Ejemplo 170, para dar el 6-cloro-1-metil-2-{5-[(2-pirrolidin-1-il-etil-amino)-metil]-piridin-3-il}-1H-indol-3-carbonitrilo. La base libre se absorbe en HCl 4M en dioxano, se concentra al vacío, se disuelve en agua, y se liofiliza para dar la sal de HCl.

^{1}H RMN (400 MHz, DMSO-d_6) δ ppm (sal de HCl) 1.83 - 1.93 (m, 2 H), 2.04 (br. s., 2 H), 3.06 (br. s., 2 H), 3.50 (br. s., 2 H), 3.54 - 3.60 (m, 2 H), 3.66 (br. s., 2 H), 3.84 (s, 3 H), 4.43 (br. s., 2 H), 7.39 (dd, *J*=8.6, 1.8 Hz, 1 H), 7.75 (d, *J*=8.3 Hz, 1 H), 8.01 (d, *J*=1.5 Hz, 1 H), 8.43 (t, *J*=2.0 Hz, 1 H), 8.94 (d, *J*=2.0 Hz, 1 H), 8.99 (d, *J*=2.0 Hz, 1 H), 9.97 (br. s., 2 H), 10.89 (br. s., 1 H). HRMS (ESI) *m/z* 394.1803 [(M+H)$^+$ Calculado para $C_{22}H_{25}ClN_5$: 394.1798].

Ejemplo 180

6-cloro-2-[5-(4-metan-sulfonil-piperazin-1-il-metil)-piridin-3-il]-1-metil-1H-indol-3-carbonitrilo



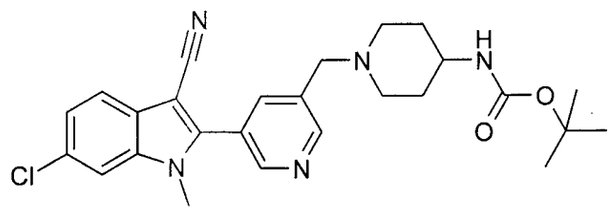
El 6-cloro-2-(5-formil-piridin-3-il)-1-metil-1H-indol-3-carbonitrilo (Ejemplo 126), y 1-metan-sulfonil-piperazina, se procesan de acuerdo con el método descrito en el Ejemplo 170, para dar el 6-cloro-2-[5-(4-metan-sulfonil-piperazin-1-il-metil)-piridin-3-il]-1-metil-1H-indol-3-carbonitrilo.

^{1}H RMN (400 MHz, DMSO-d_6) δ ppm 2.55 (t, *J*=4.5 Hz, 4 H),

3.14 (t, *J*=4.5 Hz, 4 H), 3.30 (s, 3 H), 3.72 (s, 2 H), 3.80 (s, 3 H), 7.36 (dd, *J*=8.5, 1.9 Hz, 1 H), 7.72 (d, *J*=8.3 Hz, 1 H), 7.96 (d, *J*=1.5 Hz, 1 H), 8.06 (t, *J*=2.0 Hz, 1 H), 8.73 (d, *J*=2.0 Hz, 1 H), 8.80 (d, *J*=2.0 Hz, 1 H). HRMS (ESI) *m/z* 444.1265 [(M+H)$^+$ Calculado para $C_{22}H_{25}ClN_5$: 444.1261].

Ejemplo 181

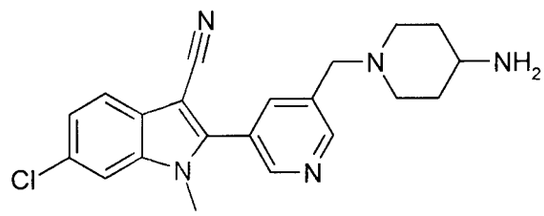
(a) Terbutil-éster del ácido {1-[5-(6-cloro-3-ciano-1-metil-1H-indol-2-il)-piridin-3-il-metil]-piperidin-4-il}-carbámico



El 6-cloro-2-(5-formil-piridin-3-il)-1-metil-1H-indol-3-carbonitrilo (Ejemplo 126), y terbutil-éster del ácido piperidin-4-il-carbámico se procesan de acuerdo con el método descrito en el Ejemplo 170, para dar el terbutil-éster del ácido {1-[5-(6-cloro-3-ciano-1-metil-1H-indol-2-il)-piridin-3-il-metil]-piperidin-4-il}-carbámico.

MS (ESI) *m/z* 480.1 (M+H)$^+$.

(b) 2-[5-(4-amino-piperidin-1-il-metil)-piridin-3-il]-6-cloro-1-metil-1H-indol-3-carbonitrilo



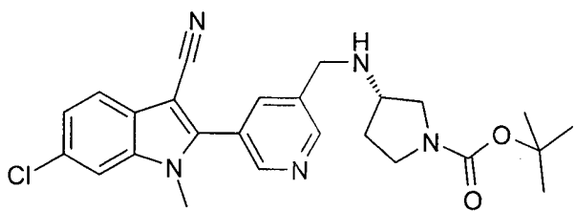
El terbutil-éster del ácido {1-[5-(6-cloro-3-ciano-1-metil-1H-

indol-2-il)-piridin-3-il-metil]-piperidin-4-il}-carbámico se procesa de acuerdo con el método descrito en el Ejemplo 178b, para dar el 2-[5-(4-amino-piperidin-1-il-metil)-piridin-3-il]-6-cloro-1-metil-1H-indol-3-carbonitrilo.

^{1}H RMN (400 MHz, DMSO-d_6) δ ppm (sal de trifluoro-acetato) 1.75 (br. s., 2 H), 2.07 (s, 3 H), 3.08 (br. s., 2 H), 3.54 (br. s., 2 H), 3.84 (s, 3 H), 4.47 (br. s., 2 H), 7.39 (dd, *J*=8.3, 1.8 Hz, 1 H), 7.75 (d, *J*=8.3 Hz, 1 H), 8.01 (d, *J*=1.5 Hz, 1 H), 8.09 (br. s., 3 H), 8.27 (s, 1 H), 8.89 (s, 1 H), 9.01 (s, 1 H), 10.11 (br. s., 1 H). HRMS (ESI) *m/z* 380.1630 [(M+H)$^+$ Calculado para $C_{21}H_{23}ClN_5$: 380.1642].

Ejemplo 182

(a) (*S*)-terbutil-éster del ácido 3-{[5-(6-cloro-3-ciano-1-metil-1H-indol-2-il)-piridin-3-il-metil]-amino}-pirrolidin-1-carboxílico

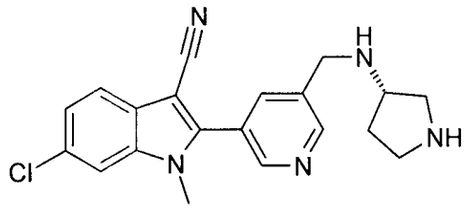


El 6-cloro-2-(5-formil-piridin-3-il)-1-metil-1H-indol-3-carbonitrilo (Ejemplo 126), y (*S*)-terbutil-éster del ácido 3-amino-pirrolidin-1-carboxílico se procesan de acuerdo con el método descrito en el Ejemplo 170, para dar el (S)-terbutil-éster del ácido 3-{[5-(6-cloro-3-ciano-1-metil-1H-indol-2-il)-piridin-3-il-metil]-amino}-pirrolidin-1-carboxílico.

MS (ESI) *m/z* 466.1 (M+H)$^+$.

(b) 6-cloro-1-metil-2-[5-((*S*)-pirrolidin-3-il-amino-metil)-piridin-3-il]-

1H-indol-3-carbonitrilo

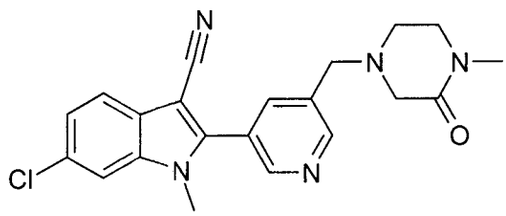


El terbutil-éster del ácido (*S*)-3-{[5-(6-cloro-3-ciano-1-metil-1H-indol-2-il)-piridin-3-il-metil]-amino}-pirrolidin-1-carboxílico se procesa de acuerdo con el método descrito en el Ejemplo 178b, para dar el 6-cloro-1-metil-2-[5-((*S*)-pirrolidin-3-il-amino-metil)-piridin-3-il]-1H-indol-3-carbonitrilo.

^{1}H RMN (400 MHz, DMSO-d_6) δ ppm 1.50 - 1.59 (m, 1 H), 1.77 - 1.88 (m, 1 H), 2.64 - 2.69 (m, 1 H), 2.72 - 2.79 (m, 1 H), 2.84 (dd, *J*=11.2, 5.9 Hz, 1 H), 2.88 - 2.96 (m, 1 H), 3.13 - 3.20 (m, 1 H), 3.31 (br. s., 2 H), 3.79 (s, 3 H), 3.82 (s, 2 H), 7.37 (dd, *J*=8.6, 1.8 Hz, 1 H), 7.72 (d, *J*=8.6 Hz, 1 H), 7.97 (d, *J*=1.5 Hz, 1 H), 8.09 (t, *J*=2.1 Hz, 1 H), 8.73 - 8.77 (m, 2 H). HRMS (ESI) *m/z* 366.1495 [(M+H)$^+$ Calculado para $C_{20}H_{21}ClN_5$: 366.1485].

Ejemplo 183

6-cloro-1-metil-2-[5-(4-metil-3-oxo-piperazin-1-il-metil)-piridin-3-il]-1H-indol-3-carbonitrilo



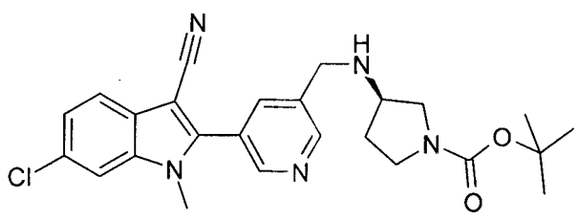
El 6-cloro-2-(5-formil-piridin-3-il)-1-metil-1H-indol-3-carbonitrilo

(Ejemplo 126), y 1-metil-piperazin-2-ona, se procesan de acuerdo con el método descrito en el Ejemplo 170, para dar el 6-cloro-1-metil-2-[5-(4-metil-3-oxo-piperazin-1-il-metil)-piridin-3-il]-1H-indol-3-carbonitrilo.

^{1}H RMN (400 MHz, DMSO-d_6) δ ppm 2.70 (br. s., 2 H), 2.82 (s, 3 H), 3.09 (s, 2 H), 3.29 (dd, *J*=11.0, 5.4 Hz, 2 H), 3.73 (s, 2 H), 3.80 (s, 3 H), 7.36 (dd, *J*=8.6, 1.8 Hz, 1 H), 7.72 (d, *J*=8.3 Hz, 1 H), 7.96 (d, *J*=1.5 Hz, 1 H), 8.09 (s, 1 H), 8.74 (d, *J*=2.0 Hz, 1 H), 8.81 (d, *J*=2.0 Hz, 1 H). HRMS (ESI) *m/z* 394.1437 [(M+H)$^+$ Calculado para $C_{21}H_{21}ClN_5O$: 394.1435].

Ejemplo 184

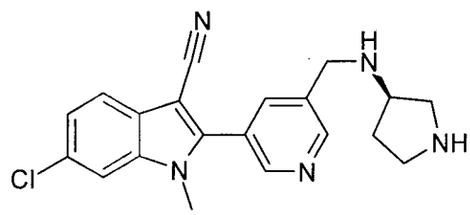
(a) (*R*)-terbutil-éster del ácido 3-{[5-(6-cloro-3-ciano-1-metil-1H-indol-2-il)-piridin-3-il-metil]-amino}-pirrolidin-1-carboxílico



El 6-cloro-2-(5-formil-piridin-3-il)-1-metil-1H-indol-3-carbonitrilo (Ejemplo 126), y terbutil-éster del ácido (R)-3-amino-pirrolidin-1-carboxílico, se procesan de acuerdo con el método descrito en el Ejemplo 170, para dar el (*R*)-terbutil-éster del ácido 3-{[5-(6-cloro-3-ciano-1-metil-1H-indol-2-il)-piridin-3-il-metil]-amino}-pirrolidin-1-carboxílico.

MS (ESI) *m/z* 466.11 (M+H)$^+$.

(b) 6-cloro-1-metil-2-[5-((*R*)-pirrolidin-3-il-amino-metil)-piridin-3-il]-1H-indol-3-carbonitrilo

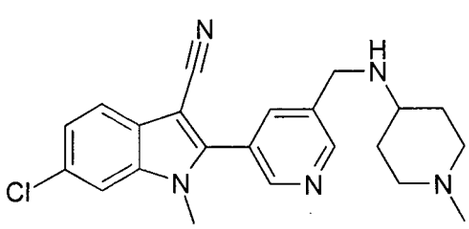


El (*R*)-terbutil-éster del ácido 3-{[5-(6-cloro-3-ciano-1-metil-1H-indol-2-il)-piridin-3-il-metil]-amino}-pirrolidin-1-carboxílico se procesa de acuerdo con el método descrito en el Ejemplo 178b, para dar el 6-cloro-1-metil-2-[5-((*R*)-pirrolidin-3-il-amino-metil)-piridin-3-il]-1H-indol-3-carbonitrilo.

^{1}H RMN (400 MHz, DMSO-d_6) δ ppm 1.52 - 1.61 (m, 1 H), 1.79 - 1.88 (m, 1 H), 2.70 (dd, *J*=11.2, 3.9 Hz, 1 H), 2.75 - 2.82 (m, 1 H), 2.86 (dd, *J*=11.1, 5.8 Hz, 1 H), 2.90 - 2.98 (m, 1 H), 3.14 - 3.21 (m, 1 H), 3.39 (br. s., 2 H), 3.79 (s, 3 H), 3.83 (s, 2 H), 7.37 (dd, *J*=8.3, 1.8 Hz, 1 H), 7.72 (d, *J*=8.6 Hz, 1 H), 7.96 (d, *J*=1.5 Hz, 1 H), 8.10 (t, *J*=2.1 Hz, 1 H), 8.74 - 8.77 (m, 2 H). HRMS (ESI) *m/z* 366.1486 [(M+H)$^+$ Calculado para $C_{20}H_{21}ClN_5$ 366.1485].

Ejemplo 185

6-cloro-1-metil-2-{5-[(1-metil-piperidin-4-il-amino)-metil]-piridin-3-il}-1H-indol-3-carbonitrilo

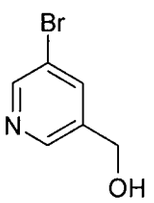


A una solución de 6-cloro-2-(5-formil-piridin-3-il)-1-metil-1H-indol-3-carbonitrilo (Ejemplo 126, 0.150 gramos, 0.482 milimoles) en tetrahidrofurano (3 mililitros), y N,N-dimetil-formamida (1 mililitro), se le agrega 4-amino-1-metil-piperidina (0.067 gramos, 0.578 milimoles), seguida por MP-$NaBH_3CN$ (2.42 milimoles/gramo, 0.498 gramos, 1.205 milimoles). Después de 16 horas, se agrega MP-$NaBH_3CN$ (2.42 milimoles/gramo, 0.200 gramos, 0.484 milimoles). Después de otras 46 horas, se agrega PL-benzaldehído (1.8 milimoles/gramo, 0.268 gramos, 0.482 milimoles), y después de otras 8 horas, la mezcla se filtra y los sólidos se lavan con tetrahidrofurano. Después de la evaporación de los solventes, el residuo se purifica mediante HPLC en fase inversa en una Sunfire C18, eluyendo con un gradiente de ácido trifluoro-acético al 0.1 por ciento-acetonitrilo acuoso, para dar el 6-cloro-1-metil-2-{5-[(1-metil-piperidin-4-il-amino)-metil]-piridin-3-il}-1H-indol-3-carbonitrilo como una goma, la cual se tritura con HCl 1M en éter, para dar la sal de HCl.

^{1}H RMN (400 MHz, DMSO-d_6) δ ppm (sal de HCl) 1.46-1.66 (m, 2 H), 1.93 - 2.04 (m, 2 H), 2.50-2.57 (m, 4 H), 2.66-2.76 (m, 2 H), 3.10-3.20 (m, 2 H), 3.80 (s, 3 H), 3.95 (br. s., 2 H), 7.37 (dd, *J*=8.6, 1.8 Hz, 1 H), 7.73 (d, *J*=8.6 Hz, 1 H), 7.98 (d, *J*=1.8 Hz, 1 H), 8.16 (s, 1 H), 8.79 (d, *J*=2.0 Hz, 1 H), 8.80 (d, *J*=2.0 Hz, 1 H). HRMS (ESI) *m/z* 394.1804 [$(M+H)^+$ Calculado para $C_{22}H_{25}ClN_5$: 394.1798].

Ejemplo 186

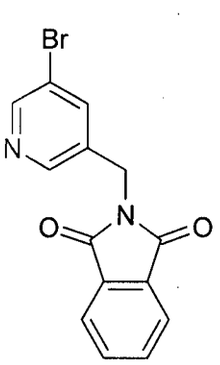
(a) 2-(5-bromo-piridin-3-il)-metanol



Un matraz se carga con 5-bromo-piridin-3-carbaldehído (5.0 gramos, 26.1 milimoles), y metanol (200 mililitros), y se enfría a 0°C. Se agrega borohidruro de sodio (2.99 gramos, 78.23 milimoles), y la reacción se agita a temperatura ambiente durante 2 horas. El solvente se remueve al vacío. El residuo se vuelve a disolver en dicloro-metano, y se lava con agua dos veces. La capa acuosa combinada se satura con cloruro de sodio, y se extrae con acetato de etilo. La capa orgánica combinada se seca sobre sulfato de sodio, y se concentra al vacío, para proporcionar el 2-(5-bromo-piridin-3-il)-metanol como un sólido.

MS (ESI) *m/z* 189.9 $(M+H)^+$

(b) 2-(5-bromo-piridin-3-il-metil)-isoindol-1,3-diona

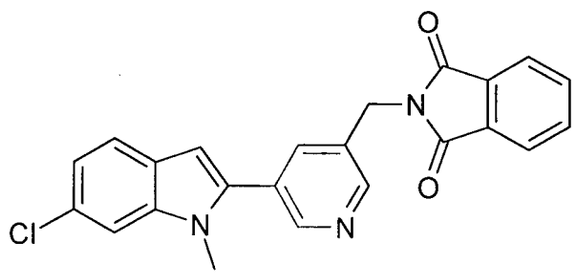


Un matraz se carga con 2-(5-bromo-piridin-3-il)-metanol (4.70

gramos, 23.75 milimoles), ftalimida (3.92 gramos, 26.12 milimoles), tributil-fosfina (11.04 mililitros, 44.527 milimoles), y tetrahidrofurano (50 mililitros). Se agrega 1,1'-(azodicarbonil)-dipiperidina (11.80 gramos, 46.31 milimoles), y la reacción se agita a temperatura ambiente durante 6 horas, se diluye con acetato de etilo, y se lava con agua tres veces. La capa orgánica se seca sobre sulfato de sodio, y se concentra al vacío, para dar un residuo, el cual se purifica mediante cromatografía por evaporación instantánea en gel de sílice (heptano-acetato de etilo, 1:1), para proporcionar la 2-(5-bromo-piridin-3-il-metil)-isoindol-1,3-diona como un sólido.

MS (ESI) *m/z* 319.1 $(M+H)^+$.

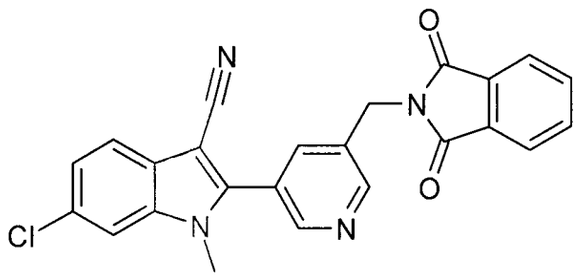
(c) 2-[5-(6-cloro-1-metil-1H-indol-2-il)-piridin-3-il-metil]-isoindol-1,3-diona



El ácido 6-cloro-1-metil-indol-2-borónico y 2-(5-bromo-piridin-3-il-metil)-isoindol-1,3-diona se procesan de acuerdo con el método descrito en el Ejemplo 100, para dar la 2-[5-(6-cloro-1-metil-1H-indol-2-il)-piridin-3-il-metil]-isoindol-1,3-diona.

MS (ESI) *m/z* 402.1 $(M+H)^+$.

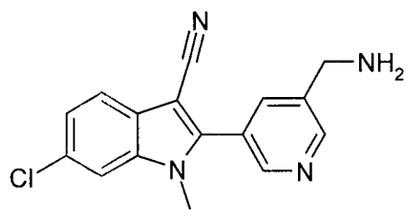
(d) 6-cloro-2-[5-(1,3-dioxo-1,3-dihidro-isoindol-2-il-metil)-piridin-3-il]-1-metil-1H-indol-3-carbonitrilo



La 2-[5-(6-cloro-1-metil-1H-indol-2-il)-piridin-3-il-metil]-isoindol-1,3-diona se procesa de acuerdo con el método descrito en el Ejemplo 128, para dar el 6-cloro-2-[5-(1,3-dioxo-1,3-dihidro-isoindol-2-il-metil)-piridin-3-il]-1-metil-1H-indol-3-carbonitrilo como un sólido.

MS (ESI) *m/z* 427.0 $(M+H)^+$.

(e) 2-(5-amino-metil-piridin-3-il)-6-cloro-1-metil-1H-indol-3-carbonitrilo

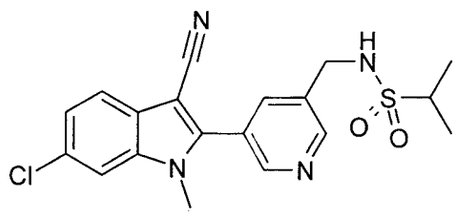


A una solución de 6-cloro-2-[5-(1,3-dioxo-1,3-dihidro-isoindol-2-il-metil)-piridin-3-il]-1-metil-1H-indol-3-carbonitrilo (8.96 gramos, 18.89 milimoles) en etanol (200 mililitros), se le agrega hidrazina (12.10 mililitros, 378 milimoles), y la mezcla de reacción se agita durante la noche. La mezcla entonces se filtra, y los sólidos se lavan con acetato de etilo. El filtrado se concentra parcialmente para remover el acetato de etilo. Se agrega HCl acuoso 1M, y la mezcla acuosa se lava con EtOAc. La capa acuosa entonces se basifica con NaOH acuoso 4M, y se extrae con dicloro-metano tres veces. Los

extractos de dicloro-metano se secan sobre Na_2SO_4 y se concentran al vacío, para proporcionar el 2-(5-amino-metil-piridin-3-il)-6-cloro-1-metil-1H-indol-3-carbonitrilo como un sólido.

MS (ESI) *m/z* 297.0 $(M+H)^+$

(f) [5-(6-cloro-3-ciano-1-metil-1H-indol-2-il)-piridin-3-il-metil]-amida del ácido propan-2-sulfónico



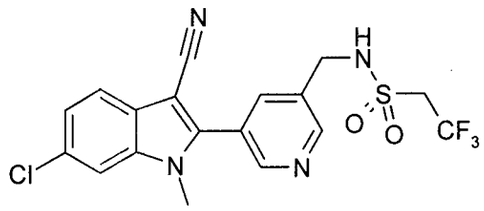
Un matraz se carga con 2-(5-amino-metil-piridin-3-il)-6-cloro-1-metil-1H-indol-3-carbonitrilo (0.075 gramos, 0.253 milimoles), y dicloro-metano (2 mililitros). Se agregan cloruro de isopropil-sulfonilo (0.031 mililitros, 0.278 milimoles), y trietil-amina (0.071 mililitros, 0.506 milimoles), y la reacción se agita a temperatura ambiente durante la noche. La mezcla de reacción se concentra al vacío. El residuo se purifica mediante HPLC en fase inversa con una columna XBridge Shield RP18 y un gradiente de NH_4OH acuoso al 0.1 por ciento en acetonitrilo, para proporcionar la [5-(6-cloro-3-ciano-1-metil-1H-indol-2-il)-piridin-3-il-metil]-amida del ácido propan-2-sulfónico como un sólido.

^{1}H RMN (400 MHz, MeOD) δ ppm 1.40 (d, *J*=6.8 Hz, 6 H), 3.25 - 3.32 (m, 1 H), 3.84 (s, 3 H), 4.50 (s, 2 H), 7.38 (dd, *J*=8.6, 1.8 Hz, 1 H), 7.72 (d, *J*=8.6 Hz, 1 H), 7.77 (d, *J*=1.5 Hz, 1 H), 8.18 (t, *J*=2.0 Hz, 1 H), 8.81 (t, *J*=1.9 Hz, 2 H). HRMS (ESI) *m/z* 403.0997 $[(M+H)^+$

Calculado para $C_{19}H_{20}ClN_4O_2S$: 403.0996].

Ejemplo 187

[5-(6-cloro-3-ciano-1-metil-1H-indol-2-il)-piridin-3-il-metil]-amida del ácido 2,2,2-trifluoro-etan-sulfónico

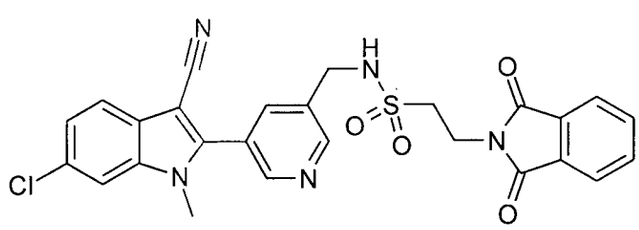


El 2-(5-amino-metil-piridin-3-il)-6-cloro-1-metil-1H-indol-3-carbonitrilo (Ejemplo 186e), y cloruro de 2,2,2-trifluoro-etan-sulfonilo, se procesan de acuerdo con el método descrito en el Ejemplo 186f, para dar la [5-(6-cloro-3-ciano-1-metil-1H-indol-2-il)-piridin-3-il-metil]-amida del ácido 2,2,2-trifluoro-etan-sulfónico.

^{1}H RMN (400 MHz, MeOD) δ ppm 3.84 (s, 3 H), 4.29 (q, *J*=9.6 Hz, 2 H), 4.54 (s, 2 H), 7.39 (dd, *J*=8.6, 1.8 Hz, 1 H), 7.73 (d, *J*=8.3 Hz, 1 H), 7.78 (d, *J*=1.8 Hz, 1 H), 8.18 (t, *J*=2.0 Hz, 1 H), 8.81 (d, *J*=2.0 Hz, 1 H), 8.83 (d, *J*=2.0 Hz, 1 H). HRMS (ESI) *m/z* 443.0557 [(M+H)$^+$ Calculado para $C_{18}H_{15}N_4O_2F_3SCl$: 443.0556].

Ejemplo 188

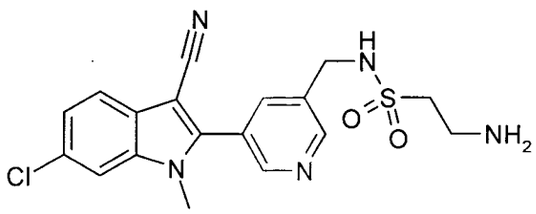
(a) [5-(6-cloro-3-ciano-1-metil-1H-indol-2-il)-piridin-3-il-metil]-amida del ácido 2-(1,3-dioxo-1,3-dihidro-isoindol-2-il)-etan-sulfónico



Un matraz se carga con 2-(5-amino-metil-piridin-3-il)-6-cloro-1-metil-1H-indol-3-carbonitrilo (Ejemplo 186e, 0.050 gramos, 0.160 milimoles), y dicloro-metano (2 mililitros). Se agregan cloruro de 2-(1,3-dioxo-1,3-dihidro-isoindol-2-il)-etan-sulfonilo (0.068 gramos, 0.239 milimoles), y trietil-amina (0.045 mililitros, 0.319 milimoles), y la reacción se agita a temperatura ambiente durante 5 minutos. La mezcla de reacción se lava con agua, y se extrae con dicloro-metano dos veces. La fase orgánica combinada se separa, se seca sobre sulfato de sodio, y se concentra al vacío, para dar un residuo, el cual se purifica mediante cromatografía por evaporación instantánea en gel de sílice (dicloro-metano : metanol, 19:1), para proporcionar la [5-(6-cloro-3-ciano-1-metil-1H-indol-2-il)-piridin-3-il-metil]-amida del ácido 2-(1,3-dioxo-1,3-dihidro-isoindol-2-il)-etan-sulfónico como un sólido blanco.

MS (ESI) *m/z* 537.3 $(M+H)^+$.

(b) [5-(6-cloro-3-ciano-1-metil-1H-indol-2-il)-piridin-3-il-metil]-amida del ácido 2-amino-etan-sulfónico



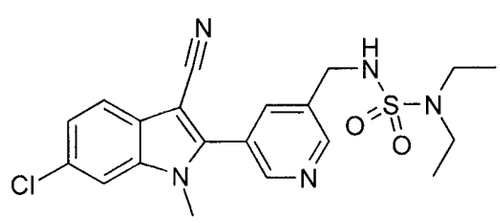
Un matraz se carga con la [5-(6-cloro-3-ciano-1-metil-1H-indol-2-il)-piridin-3-il-metil]-amida del ácido 2-(1,3-dioxo-1,3-dihidro-isoindol-2-il)-etan-sulfónico (0.065 gramos, 0.109 milimoles), y metanol (4 mililitros). Se agrega hidrazina (0.069 mililitros, 2.183

milimoles), y la reacción se agita a temperatura ambiente durante la noche. Se agrega HCl acuoso 2M, seguido por concentración al vacío. Se agrega dicloro-metano, y la mezcla se filtra a través de Celite. La capa orgánica se lava con agua una vez, y la capa acuosa se basifica utilizando NaOH acuoso 4M, y se extrae con dicloro-metano tres veces. La fracción de dicloro-metano combinada se seca sobre sulfato de sodio, y se concentra al vacío, para proporcionar un residuo, el cual se purifica mediante HPLC de fase inversa, para proporcionar la [5-(6-cloro-3-ciano-1-metil-1H-indol-2-il)-piridin-3-il-metil]-amida del ácido 2-amino-etan-sulfónico como un sólido.

^{1}H RMN (400 MHz, MeOD) δ ppm 3.12 (t, *J*=6.6 Hz, 2 H), 3.29 (t, *J*=6.6 Hz, 2 H), 3.84 (s, 3 H), 4.49 (s, 2 H), 7.38 (dd, *J*=8.6, 1.8 Hz, 1 H), 7.73 (d, *J*=8.6 Hz, 1 H), 7.78 (d, *J*=1.5 Hz, 1 H), 8.19 (t, *J*=2.1 Hz, 1 H), 8.81 (d, *J*=2.3 Hz, 1 H), 8.82 (d, *J*=2.3 Hz, 1 H). HRMS (ESI) *m/z* 404.0944 [(M+H)$^+$ Calculado para $C_{18}H_{19}ClN_5O_2S$: 404.0948].

Ejemplo 189

N,*N*-dietil-*N*'-[5-(6-cloro-3-ciano-1-metil-1H-indol-2-il)-piridin-3-il-metil]-sulfamida



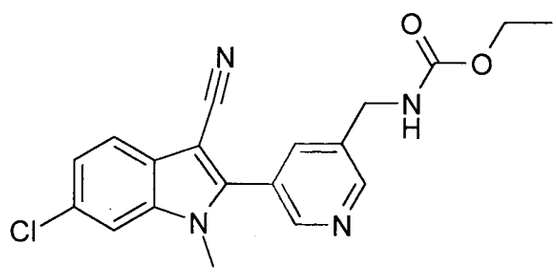
Un matraz se carga con 2-(5-amino-metil-piridin-3-il)-6-cloro-1-metil-1H-indol-3-carbonitrilo (Ejemplo 186e, 0.103 gramos, 0.349

milimoles), y dicloro-metano (2 mililitros). Se agregan cloruro de dietil-amino-sulfamoílo (0.072 gramos, 0.419 milimoles), y trietil-amina (0.100 mililitros, 0.699 milimoles), y la reacción se agita a temperatura ambiente durante la noche. La mezcla de reacción se concentra al vacío, y el residuo se purifica mediante HPLC en fase inversa con una columna XBridge Shield RP18 y un gradiente de NH_4OH acuoso al 0.1 por ciento en acetonitrilo, para proporcionar la *N*,*N*-dietil-*N*'-[5-(6-cloro-3-ciano-1-metil-1H-indol-2-il)-piridin-3-il-metil]-sulfamida como un sólido.

^{1}H RMN (400 MHz, MeOD) δ ppm 1.20 (t, *J*=7.1 Hz, 6 H), 3.30 (q, *J*=7.1 Hz, 4 H), 3.83 (s, 3 H), 4.35 (s, 2 H), 7.38 (dd, *J*=8.6, 1.8 Hz, 1 H), 7.71 (d, *J*=8.6 Hz, 1 H), 7.77 (d, *J*=1.5 Hz, 1 H), 8.17 (t, *J*=2.1 Hz, 1 H), 8.79 (dd, *J*=3.7, 2.1 Hz, 2 H). HRMS (ESI) *m/z* 432.1278 [$(M+H)^+$ Calculado para $C_{20}H_{23}ClN_5O_2S$: 432.1261].

Ejemplo 190

Etil-éster del ácido 5-(6-cloro-3-ciano-1H-indol-2-il)-piridin-3-il-metil]-carbámico



Un matraz se carga con 2-(5-amino-metil-piridin-3-il)-6-cloro-1-metil-1H-indol-3-carbonitrilo (Ejemplo 186e, 0.100 gramos, 0.349 milimoles), y dicloro-metano (4 mililitros). Se agregan cloro-formato

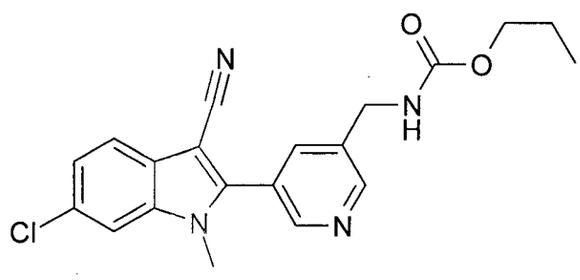
de etilo (0.055 gramos, 0.506 milimoles), y trietil-amina (0.100 mililitros, 0.675 milimoles), y la reacción se agita a temperatura ambiente durante 10 minutos. La mezcla de reacción se concentra al vacío, y el residuo se purifica mediante HPLC en fase inversa con una columna XBridge Shield RP18 y un gradiente de NH_4OH acuoso al 0.1 por ciento en acetonitrilo, para proporcionar el etil-éster del ácido 5-(6-cloro-3-ciano-1H-indol-2-il)-piridin-3-il-metil]-carbámico como un sólido.

^{1}H RMN (400 MHz, MeOD) δ ppm 1.28 (t, *J*=7.1 Hz, 3 H), 3.83 (s, 3 H), 4.15 (q, *J*=7.1 Hz, 2 H), 4.48 (s, 2 H), 7.37 (dd, *J*=8.6, 1.8 Hz, 1 H), 7.71 (d, *J*=8.6 Hz, 1 H), 7.76 (d, *J*=1.5 Hz, 1 H), 8.09 (t, *J*=1.9 Hz, 1 H), 8.73 (d, *J*=2.0 Hz, 1 H), 8.78 (d, *J*=2.0 Hz, 1 H).

HRMS (ESI) *m/z* 369.1125 [$(M+H)^+$ Calculado para $C_{19}H_{18}ClN_4O_2$: 369.1118].

Ejemplo 191

Propil-éster del ácido [5-(6-cloro-3-ciano-1H-indol-2-il)-piridin-3-il-metil]-carbámico



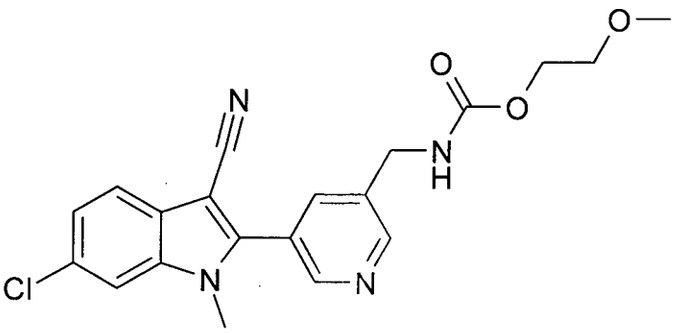
El 2-(5-amino-metil-piridin-3-il)-6-cloro-1-metil-1H-indol-3-carbonitrilo (Ejemplo 186e), y cloroformato de propilo normal, se procesan de acuerdo con el método descrito en el Ejemplo 190, para

dar el propil-éster del ácido [5-(6-cloro-3-ciano-1H-indol-2-il)-piridin-3-il-metil]-carbámico como un sólido.

^{1}H RMN (400 MHz, MeOD) δ ppm 0.98 (t, *J*=7.3 Hz, 3 H), 1.58 - 1.74 (m, 2 H), 3.83 (s, 3 H), 4.06 (t, *J*=6.6 Hz, 2 H), 4.49 (s, 2 H), 7.38 (dd, *J*=8.6, 1.77 Hz, 1 H), 7.72 (d, *J*=8.6 Hz, 1 H), 7.77 (d, *J*=1.5 Hz, 1 H), 8.09 (t, *J*=2.0 Hz, 1 H), 8.74 (d, *J*=2.0 Hz, 1 H), 8.78 (d, *J*=2.0 Hz, 1 H). HRMS (ESI) *m/z* 383.1260 [(M+H)$^+$ Calculado para $C_{20}H_{20}ClN_4O_2$: 383.1275].

Ejemplo 192

2-metoxi-etil-éster del ácido 5-(6-cloro-3-ciano-1-metil-1H-indol-2-il)-piridin-3-il-metil]-carbámico



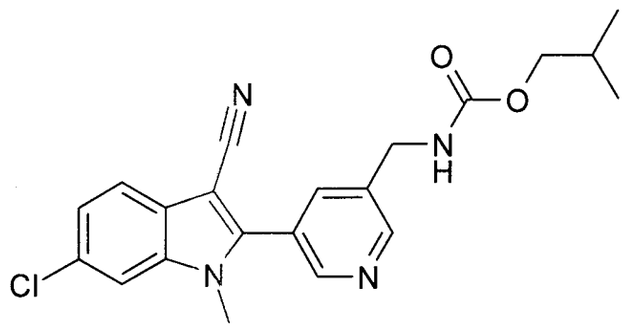
El 2-(5-amino-metil-piridin-3-il)-6-cloro-1-metil-1H-indol-3-carbonitrilo (Ejemplo 186e), y cloroformato de 3-metoxi-etilo, se procesan de acuerdo con el método descrito en el Ejemplo 190, para dar el 2-metoxi-etil-éster del ácido 5-(6-cloro-3-ciano-1-metil-1H-indol-2-il)-piridin-3-il-metil]-carbámico como un sólido.

^{1}H RMN (400 MHz, MeOD) δ ppm 3.37 (s, 3 H), 3.58 - 3.65 (m, 2 H), 3.83 (s, 3 H), 4.14 - 4.27 (m, 2 H), 4.50 (s, 2 H), 7.38 (dd, *J*=8.6, 1.8 Hz, 1 H), 7.72 (d, *J*=8.6 Hz, 1 H), 7.77 (d, *J*=1.5 Hz, 1 H),

8.10 (s, 1 H), 8.74 (d, *J*=2.0 Hz, 1 H), 8.78 (d, *J*=2.0 Hz, 1 H). HRMS (ESI) *m/z* 399.1221 [(M+H)$^+$ Calculado para $C_{20}H_{20}ClN_4O_3$: 399.1224].

Ejemplo 193

Isobutil-éster del ácido 5-(6-cloro-3-ciano-1-metil-1H-indol-2-il)-piridin-3-il-metil]-carbámico

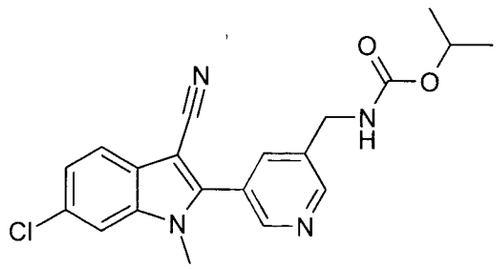


El 2-(5-amino-metil-piridin-3-il)-6-cloro-1-metil-1H-indol-3-carbonitrilo (Ejemplo 186e), y cloroformato de isobutilo, se procesan de acuerdo con el método descrito en el Ejemplo 190, para dar el isobutil-éster del ácido 5-(6-cloro-3-ciano-1-metil-1H-indol-2-il)-piridin-3-il-metil]-carbámico.

^{1}H RMN (400 MHz, MeOD) δ ppm 0.97 (d, *J*=6.6 Hz, 6 H), 1.85 - 2.01 (m, 1 H), 3.83 (s, 3 H), 3.89 (d, *J*=6.6 Hz, 2 H), 4.49 (s, 2 H), 7.38 (dd, *J*=8.6, 1.8 Hz, 1 H), 7.72 (d, *J*=8.3 Hz, 1 H), 7.77 (d, *J*=1.8 Hz, 1 H), 8.09 (t, *J*=2.1 Hz, 1 H), 8.74 (d, *J*=1.8 Hz, 1 H), 8.78 (d, *J*=2.0 Hz, 1 H). HRMS (ESI) m/z 397.1424 [(M+H)$^+$ Calculado para $C_{21}H_{22}ClN_4O_2$: 397.1431].

Ejemplo 194

Isopropil-éster del ácido 5-(6-cloro-3-ciano-1-metil-1H-indol-2-il)-piridin-3-il-metil]-carbámico

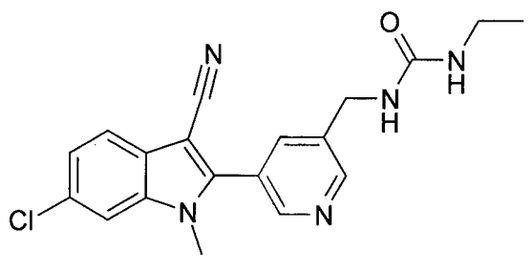


El 2-(5-amino-metil-piridin-3-il)-6-cloro-1-metil-1H-indol-3-carbonitrilo (Ejemplo 186e) y cloroformato de isopropilo, se procesan de acuerdo con el método descrito en el Ejemplo 190, para dar el isopropil-éster del ácido 5-(6-cloro-3-ciano-1-metil-1H-indol-2-il)-piridin-3-il-metil]-carbámico.

^{1}H RMN (400 MHz, MeOD) δ ppm 1.27 (d, *J*=6.3 Hz, 6 H), 3.83 (s, 3 H), 4.48 (s, 2 H), 4.88 - 4.94 (m, 1 H), 7.38 (dd, *J*=8.6, 1.8 Hz, 1 H), 7.72 (d, *J*=8.6 Hz, 1 H), 7.77 (d, *J*=1.5 Hz, 1 H), 8.09 (t, *J*=1.9 Hz, 1 H), 8.73 (d, *J*=1.8 Hz, 1 H), 8.78 (d, *J*=2.0 Hz, 1 H). HRMS (ESI) *m/z* 383.1266 [(M+H)$^+$ Calculado para $C_{20}H_{20}ClN_4O_2$: 383.1275].

Ejemplo 195

1-[5-(6-cloro-3-ciano-1-metil-1H-indol-2-il)-piridin-3-il-metil]-3-etil-urea



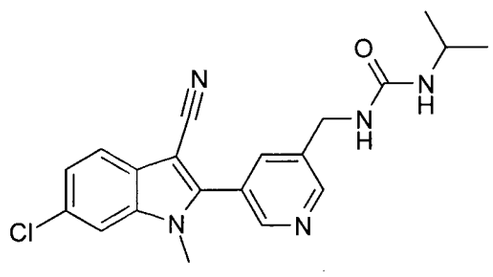
A una solución de 2-(5-amino-metil-piridin-3-il)-6-cloro-1-metil-1H-indol-3-carbonitrilo (Ejemplo 186e, 0.100 gramos, 0.337

milimoles) en dicloro-metano (3 mililitros), se le agrega isocianato de etilo (0.030 gramos, 0.422 milimoles), y la reacción se agita a temperatura ambiente durante 45 minutos. La mezcla luego se lava con agua, y se extrae con dicloro-metano dos veces. La fase orgánica se concentra al vacío, para dar un residuo, el cual se purifica mediante HPLC en fase inversa con una columna XBridge Shield RP18 y un gradiente de NH_4OH acuoso al 0.1 por ciento en acetonitrilo, para proporcionar la 1-[5-(6-cloro-3-ciano-1-metil-1H-indol-2-il)-piridin-3-il-metil]-3-etil-urea como un sólido.

^{1}H RMN (400 MHz, MeOD) δ ppm 1.14 (t, *J*=7.2 Hz, 3 H), 3.20 (q, *J*=7.3 Hz, 2 H), 3.82 (s, 3 H), 4.52 (s, 2 H), 7.38 (dd, *J*=8.3, 1.8 Hz, 1 H), 7.71 (d, *J*=8.6 Hz, 1 H), 7.76 (d, *J*=1.5 Hz, 1 H), 8.08 (t, *J*=2.1 Hz, 1 H), 8.73 (d, *J*=2.0 Hz, 1 H), 8.76 (d, *J*=2.3 Hz, 1 H). HRMS (ESI) *m/z* 368.1275 [$(M+H)^+$ Calculado para $C_{19}H_{19}ClN_5O$: 368.1278].

Ejemplo 196

1-[5-(6-cloro-3-ciano-1-metil-1H-indol-2-il)-piridin-3-il-metil]-3-isopropil-urea



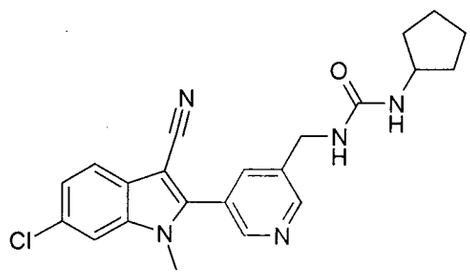
A una solución de 2-(5-amino-metil-piridin-3-il)-6-cloro-1-metil-1H-indol-3-carbonitrilo (Ejemplo 186e, 0.060 gramos, 0.192 mili-

moles) en dicloro-metano (3 mililitros), se le agrega isocianato de isopropilo (0.027 gramos, 0.240 milimoles), y la reacción se agita a temperatura ambiente durante 45 minutos. La mezcla luego se lava con agua, y se extrae con dicloro-metano dos veces. La fase orgánica se concentra al vacío, para dar un residuo, el cual se vuelve a disolver en metanol. Se presenta un precipitado después de reposar. El sólido se filtra para proporcionar la 1-[5-(6-cloro-3-ciano-1-metil-1H-indol-2-il)-piridin-3-il-metil]-3-isopropil-urea como un sólido.

^{1}H RMN (400 MHz, MeOD) δ ppm 1.17 (d, *J*=6.6 Hz, 6 H), 3.76 - 3.91 (m, 4 H), 4.52 (s, 2 H), 7.38 (dd, *J*=8.5, 1. 9 Hz, 1 H), 7.72 (d, *J*=8.3 Hz, 1 H), 7.77 (d, *J*=1.5 Hz, 1 H), 8.08 (t, *J*=2.1 Hz, 1 H), 8.73 (d, *J*=2.0 Hz, 1 H), 8.76 (d, *J*=2.0 Hz, 1 H). HRMS (ESI) *m/z* 382.1431 [(M+H)$^+$ Calculado para $C_{20}H_{21}N_5OCl$: 382.1435].

Ejemplo 197

1-[5-(6-cloro-3-ciano-1-metil-1H-indol-2-il)-piridin-3-il-metil]-3-ciclopentil-urea



El 2-(5-amino-metil-piridin-3-il)-6-cloro-1-metil-1H-indol-3-carbonitrilo (Ejemplo 186e), e isocianato de ciclopentilo, se procesan de acuerdo con el método descrito en el Ejemplo 196, para dar la 1-

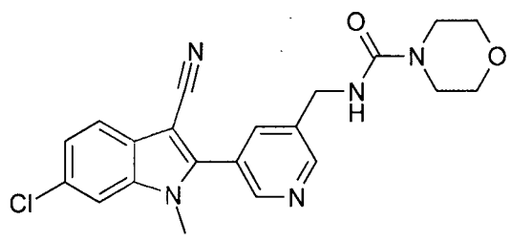
[5-(6-cloro-3-ciano-1-metil-1H-indol-2-il)-piridin-3-il-metil]-3-ciclopentil-urea como un sólido.

^{1}H RMN (400 MHz, MeOD) δ ppm 1.31 - 1.54 (m, 2 H), 1.56 - 1.68 (m, 2 H), 1.68 - 1.78 (m, 2 H), 1.86 - 2.13 (m, 2 H), 3.83 (s, 3 H), 3.94 - 4.09 (m, 1 H), 4.52 (s, 2 H), 7.38 (dd, *J*=8.3, 1.8 Hz, 1 H), 7.72 (d, *J*=8.6 Hz, 1 H), 7.77 (d, *J*=1.5 Hz, 1 H), 8.08 (t, *J*=2.0 Hz, 1 H), 8.72 (d, *J*=2.0 Hz, 1 H), 8.76 (d, *J*=2.0 Hz, 1 H).

HRMS (ESI) *m/z* 408.1591 [(M+H)$^+$ Calculado para $C_{22}H_{23}N_5OCl$: 408.1591].

Ejemplo 198

[5-(6-cloro-3-ciano-1-metil-1H-indol-2-il)-piridin-3-il-metil]-amida del ácido morfolin-4-carboxílico



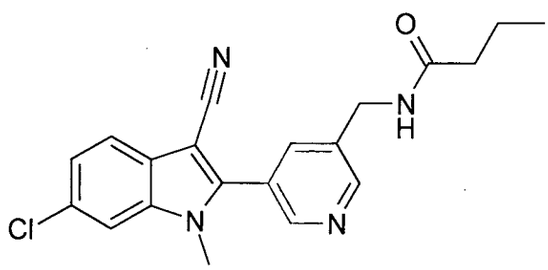
A una solución de 2-(5-amino-metil-piridin-3-il)-6-cloro-1-metil-1H-indol-3-carbonitrilo (Ejemplo 186e, 0.060 gramos, 0.202 milimoles) en dicloro-metano (2 mililitros), se le agregan cloruro de morfolin-4-carbonilo (0.026 gramos, 0.222 milimoles), y trietil-amina (0.056 mililitros, 0.405 milimoles), y la reacción se agita a temperatura ambiente durante la noche. La mezcla luego se lava con agua, y se extrae con dicloro-metano dos veces. La fase orgánica se seca sobre sulfato de sodio, y se concentra al vacío. El residuo se

purifica mediante cromatografía por evaporación instantánea en gel de sílice (dicloro-metano : metanol, 19:1), para proporcionar la [5-(6-cloro-3-ciano-1-metil-1H-indol-2-il)-piridin-3-il-metil]-amida del ácido morfolin-4-carboxílico como un sólido.

^{1}H RMN (400 MHz, MeOD) δ ppm 3.41 - 3.47 (m, 4 H), 3.66 - 3.72 (m, 4 H), 3.84 (s, 3 H), 4.55 (s, 2 H), 7.38 (dd, *J*=8.5, 1.9 Hz, 1 H), 7.72 (d, *J*=8.6 Hz, 1 H), 7.77 (d, *J*=1.8 Hz, 1 H), 8.11 (t, *J*=2.1 Hz, 1 H), 8.73 (d, *J*=2.0 Hz, 1 H), 8.76 (d, *J*=2.0 Hz, 1 H). MS (ESI) *m/z* 410.00 $(M+H)^+$.

Ejemplo 199

N-[5-(6-cloro-3-ciano-1-metil-1H-indol-2-il)-piridin-3-il-metil]-butiramida



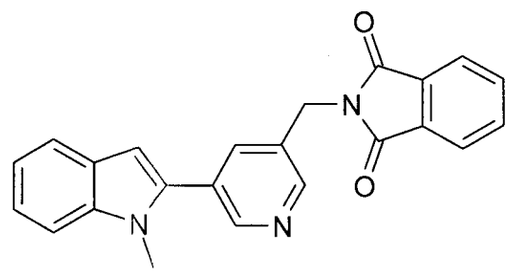
A una solución de 2-(5-amino-metil-piridin-3-il)-6-cloro-1-metil-1H-indol-3-carbonitrilo (Ejemplo 186e, 0.060 gramos, 0.202 milimoles) en dicloro-metano (2 mililitros), se le agregan cloruro de butirilo (0.024 gramos, 0.222 milimoles), y trietil-amina (0.056 mililitros, 0.405 milimoles), y la reacción se agita a temperatura ambiente durante 30 minutos. La mezcla de reacción se diluye con dicloro-metano, y se lava con agua. La capa orgánica se seca sobre

sulfato de sodio, y se concentra al vacío. El residuo se purifica mediante cromatografía por evaporación instantánea en gel de sílice (dicloro-metano : metanol, 19:1), para proporcionar la *N*-[5-(6-cloro-3-ciano-1-metil-1H-indol-2-il)-piridin-3-il-metil]-butiramida como un sólido blanco.

^{1}H RMN (400 MHz, MeOD) δ ppm 0.98 (t, *J*=7.5 Hz, 3 H), 1.65 - 1.77 (m, 2 H), 2.29 (t, *J*=7.5 Hz, 2 H), 3.82 (s, 3 H), 4.57 (s, 2 H), 7.38 (dd, *J*=8.6, 1.8 Hz, 1 H), 7.72 (d, *J*=8.6 Hz, 1 H), 7.77 (d, *J*=1.5 Hz, 1 H), 8.09 (t, *J*=2.1 Hz, 1 H), 8.73 (d, *J*=2.0 Hz, 1 H), 8.78 (d, *J*=2.0 Hz, 1 H). HRMS (ESI) *m/z* 367.1327 [(M+H)$^+$ Calculado para $C_{20}H_{20}N_4OCl$: 367.1326].

Ejemplo 200

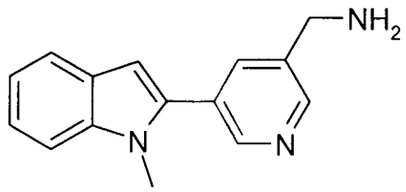
(a) 2-[5-(1-metil-1H-indol-2-il)-piridin-3-il-metil]-isoindol-1,3-diona



La 2-(5-bromo-piridin-3-il-metil)-isoindol-1,3-diona (Ejemplo 186b), y ácido 1-metil-indol-2-borónico se procesan de acuerdo con el método descrito en el Ejemplo 100, para dar la 2-[5-(1-metil-1H-indol-2-il)-piridin-3-il-metil]-isoindol-1,3-diona como un sólido.

MS (ESI) *m/z* 368.09 (M+H)$^+$.

(b) *C*-[5-(1-metil-1H-indol-2-il)-piridin-3-il]-metil-amina

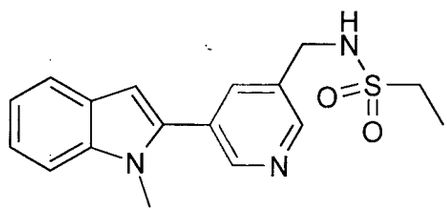


La 2-[5-(1-metil-1H-indol-2-il)-piridin-3-il-metil]-isoindol-1,3-diona se procesa de acuerdo con el método descrito en el Ejemplo 186e, para dar la C-[5-(1-metil-1H-indol-2-il)-piridin-3-il]-metil-amina como un sólido.

MS (ESI) *m/z* 238.06 $(M+H)^+$.

Ejemplo 201

N-[5-(1-metil-1H-indol-2-il)-piridin-3-il-metil]-etan-sulfonamida

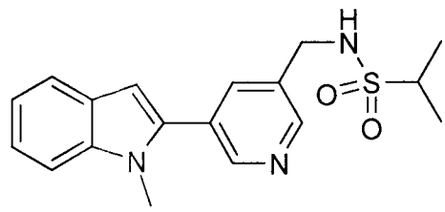


La *C*-[5-(1-metil-1H-indol-2-il)-piridin-3-il]-metil-amina (Ejemplo 200b), y cloruro de etan-sulfonilo se procesan de acuerdo con el método descrito en el Ejemplo 186f, para dar la *N*-[5-(1-metil-1H-indol-2-il)-piridin-3-il-metil]-etan-sulfonamida.

^{1}H RMN (400 MHz, MeOD) δ ppm 1.37 (t, *J*=7.3 Hz, 3 H), 3.13 (q, *J*=7.4 Hz, 2 H), 3.82 (s, 3 H), 4.43 (s, 2 H), 6.70 (s, 1 H), 7.01 - 7.18 (m, 1 H), 7.20 - 7.36 (m, 1 H), 7.48 (d, *J*=8.3 Hz, 1 H), 7.62 (d, *J*=7.8 Hz, 1 H), 8.10 (t, *J*=2.1 Hz, 1 H), 8.61 (d, *J*=2.0 Hz, 1 H), 8.71 (d, *J*=2.0 Hz, 1 H). HRMS (ESI) *m/z* 330.1288 [$(M+H)^+$ Calculado para $C_{17}H_{20}N_3O_2S$: 330.1276].

Ejemplo 202

N-[5-(1-metil-1H-indol-2-il)-piridin-3-il-metil]-isopropil-sulfonamida

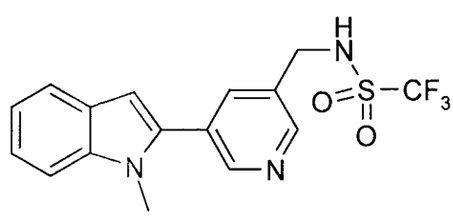


La *C*-[5-(1-metil-1H-indol-2-il)-piridin-3-il]-metil-amina (Ejemplo 200b) y cloruro de isopropil-sulfonilo se procesan de acuerdo con el método descrito en el Ejemplo 186f, para dar la *N*-[5-(1-metil-1H-indol-2-il)-piridin-3-il-metil]-isopropil-sulfonamida.

^{1}H RMN (400 MHz, MeOD) δ ppm 1.40 (d, *J*=6.82 Hz, 6 H), 3.23 - 3.32 (m, 1 H), 3.83 (s, 3 H), 4.45 (s, 2 H), 6.70 (s, 1 H), 7.09 - 7.17 (m, 1 H), 7.27 (ddd, *J*=7.6, 1.14 Hz, 1 H), 7.48 (d, *J*=8.3 Hz, 1 H), 7.63 (d, *J*=8.1 Hz, 1 H), 8.11 (t, *J*=2.1 Hz, 1 H), 8.61 (d, *J*=2.0 Hz, 1 H), 8.71 (d, *J*=2.0 Hz, 1 H). HRMS (ESI) *m/z* 344.1431 [(M+H)$^+$ Calculado para $C_{18}H_{22}N_3O_2S$: 344.1433].

Ejemplo 203

C,C,C-trifluoro-N-[5-(1-metil-1H-indol-2-il)-piridin-3-il-metil]-metan-sulfonamida



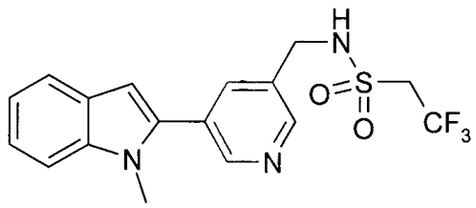
La *C*-[5-(1-metil-1H-indol-2-il)-piridin-3-il]-metil-amina (Ejemplo 200b), y cloruro de trifluoro-metan-sulfonilo se procesan de acuerdo

con el método descrito en el Ejemplo 186f, para dar la *C*,*C*,*C*-trifluoro-*N*-[5-(1-metil-1H-indol-2-il)-piridin-3-il-metil]-metan-sulfonamida.

^{1}H RMN (400 MHz, MeOD) δ ppm 3.78 (s, 3 H), 4.23 (q, *J*=9.6 Hz, 2 H), 6.66 (d, *J*=0.5 Hz, 1 H), 7.04 - 7.13 (m, 1 H), 7.23 (ddd, *J*=7.7, 1.1 Hz, 1 H), 7.44 (d, *J*=8.2 Hz, 1 H), 7.58 (d, *J*=7.8 Hz, 1 H), 8.04 (t, *J*=2.0 Hz, 1 H), 8.56 (d, *J*=2.0 Hz, 1 H), 8.68 (d, *J*=1.9 Hz, 1 H). HRMS (ESI) *m/z* 370.0835 [(M+H)$^+$ Calculado para $C_{16}H_{15}F_3N_3O_2S$: 370.0837].

Ejemplo 204

[5-(1-metil-1H-indol-2-il)-piridin-3-il-metil]-amida del ácido 2,2,2-trifluoro-etan-sulfónico



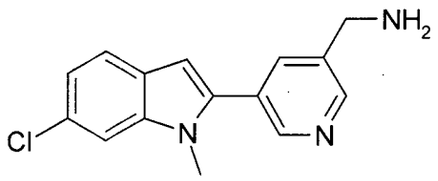
La *C*-[5-(1-metil-1H-indol-2-il)-piridin-3-il]-metil-amina (Ejemplo 200b), y cloruro de 2,2,2-trifluoro-etan-sulfonilo se procesan de acuerdo con el método descrito en el Ejemplo 186f, para dar la [5-(1-metil-1H-indol-2-il)-piridin-3-il-metil]-amida del ácido 2,2,2-trifluoro-etan-sulfónico.

^{1}H RMN (400 MHz, MeOD) δ ppm 3.78 (s, 3 H), 4.23 (q, *J*=9.6 Hz, 2 H), 4.44 (s, 2 H), 6.66 (d, *J*=0.5 Hz, 1 H), 7.06 - 7.12 (m, 1 H), 7.23 (ddd, *J*=7.7, 1.1 Hz, 1 H), 7.44 (d, *J*=8.2 Hz, 1 H), 7.58 (d, *J*=7.8 Hz, 1 H), 8.04 (t, *J*=2.0Hz, 1 H), 8.56 (d, *J*=2.0 Hz, 1 H), 8.68 (d,

J=1.9 Hz, 1 H). HRMS (ESI) *m/z* 384.0999 [(M+H)$^+$ Calculado para $C_{17}H_{17}F_3N_3O_2S$: 384.0994].

Ejemplo 205

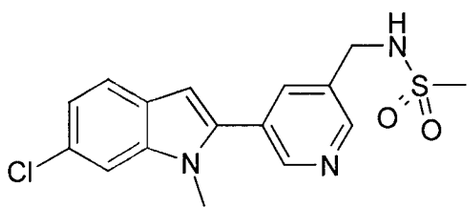
(a) *C*-[5-(6-cloro-1-metil-1H-indol-2-il)-piridin-3-il]-metil-amina



La 2-[5-(6-cloro-1-metil-1H-indol-2-il)-piridin-3-il-metil]-isoindol-1,3-diona (Ejemplo 186c) se procesa de acuerdo con el método descrito en el Ejemplo 186e, para dar la C-[5-(6-cloro-1-metil-1H-indol-2-il)-piridin-3-il]-metil-amina.

MS (ESI) *m/z* 272.01 (M+H)$^+$.

(b) *N*-[5-(6-cloro-1-metil-1H-indol-2-il)-piridin-3-il-metil]-metan-sulfonamida



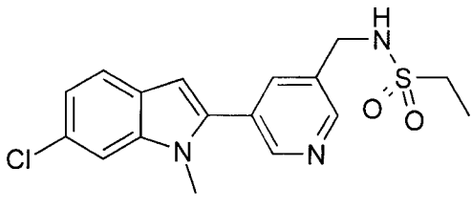
La *C*-[5-(6-cloro-1-metil-1H-indol-2-il)-piridin-3-il]-metil-amina y cloruro de metan-sulfonilo se procesan de acuerdo con el método descrito en el Ejemplo 186f, para dar la *N*-[5-(6-cloro-1-metil-1H-indol-2-il)-piridin-3-il-metil]-metan-sulfonamida.

^{1}H RMN (400 MHz, MeOD) δ ppm 3.03 (s, 3 H), 3.80 (s, 3 H), 4.45 (s, 2 H), 6.71 (s, 1 H), 7.12 (dd, *J*=8.3, 1.8 Hz, 1 H), 7.54 (s, 1

H), 7.59 (d, *J*=8.6 Hz, 1 H), 8.09 (t, *J*=2.2 Hz, 1 H), 8.63 (d, *J*=2. Hz, 1 H), 8.71 (d, *J*=2. Hz, 1 H). HRMS (ESI) *m/z* 350.0728 [$(M+H)^+$ Calculado para $C_{16}H_{17}ClN_3O_2S$: 350.0730].

Ejemplo 206

N-[5-(6-cloro-1-metil-1H-indol-2-il)-piridin-3-il-metil]-etan-sulfonamida



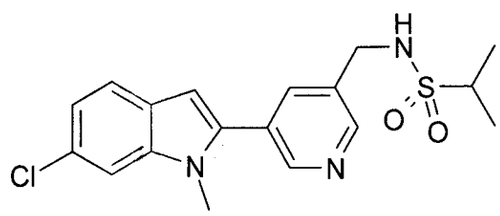
Un matraz se carga con 6-cloro-2-(5-formil-piridin-3-il)-1-metil-1H-indol (Ejemplo 126a, 1.2 gramos, 4.43 milimoles), etan-sulfonamida (0.726 gramos, 6.65 milimoles), isopropóxido de titanio(IV) (2.60 mililitros, 8.87 milimoles), y tolueno (50 mililitros). La mezcla de reacción se pone a reflujo durante la noche, y entonces se concentra a sequedad. El material crudo (1.60 gramos) se disuelve en metanol (24 mililitros) y dicloro-metano (24 mililitros), y se agrega borohidruro de sodio (0.335 gramos, 8.87 milimoles). La mezcla de reacción se agita a temperatura ambiente durante 2 horas, y entonces se concentra al vacío. El residuo se absorbe en dicloro-metano, y se lava con agua dos veces. La capa orgánica se seca sobre sulfato de sodio, se filtra, y se concentra al vacío. La purificación se logra mediante cromatografía en gel de sílice por evaporación instantánea, para dar la *N*-[5-(6-cloro-1-metil-1H-indol-2-il)-piridin-3-il-metil]-etan-sulfonamida.

^{1}H RMN (400 MHz, MeOD) δ ppm 1.38 (t, *J*=7.3 Hz, 3 H), 3.14

(q, *J*=7.3 Hz, 2 H), 3.80 (s, 3 H), 4.43 (s, 2 H), 6.72 (s, 1 H), 7.12 (dd, *J*=8.5, 1.9 Hz, 1 H), 7.54 (d, *J*=1.8 Hz, 1 H), 7.59 (d, *J*=8.6 Hz, 1 H), 8.10 (t, *J*=2.1 Hz, 1 H), 8.63 (d, *J*=2.0 Hz, 1 H), 8.71 (d, *J*=2.0 Hz, 1 H). HRMS (ESI) *m/z* 364.0869 [(M+H)$^+$ Calculado para $C_{17}H_{19}ClN_3O_2S$: 364.0887].

Ejemplo 207

N-[5-(6-cloro-1-metil-1H-indol-2-il)-piridin-3-il-metil]-isopropil-sulfonamida

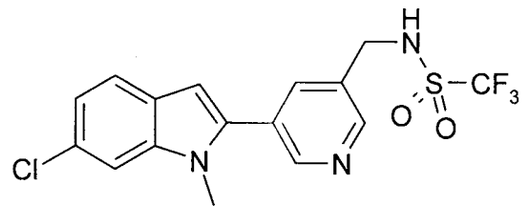


La *C*-[5-(6-cloro-1-metil-1H-indol-2-il)-piridin-3-il]-metil-amina (Ejemplo 205a) y cloruro de isopropil-sulfonilo se procesan de acuerdo con el método descrito en el Ejemplo 186f, para dar la *N*-[5-(6-cloro-1-metil-1H-indol-2-il)-piridin-3-il-metil]-isopropil-sulfonamida.

^{1}H RMN (400 MHz, MeOD) δ ppm 1.35 (d, *J*=6.8 Hz, 6 H), 3.19 - 3.27 (m, 1 H), 3.76 (s, 3 H), 4.40 (s, 2 H), 6.67 (d, *J*=0.6 Hz, 1 H), 7.07 (dd, *J*=8.4, 1.8 Hz, 1 H), 7.49 (d, *J*=1.6 Hz, 1 H), 7.55 (d, *J*=8.5 Hz, 1 H), 8.06 (t, *J*=2.0 Hz, 1 H), 8.58 (d, *J*=1.9 Hz, 1 H), 8.66 (d, *J*=2.0 Hz, 1 H). HRMS (ESI) *m/z* 378.1036 [(M+H)$^+$ Calculado para $C_{18}H_{21}ClN_3O_2S$: 378.1043].

Ejemplo 208

C,C,C-trifluoro-*N*-[5-(6-cloro-1-metil-1H-indol-2-il)-piridin-3-il-metil]-metan-sulfonamida

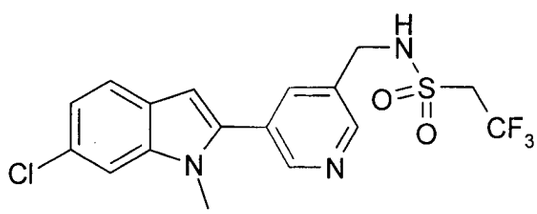


La *C*-[5-(6-cloro-1-metil-1H-indol-2-il)-piridin-3-il]-metil-amina (Ejemplo 205a), y cloruro de trifluoro-metan-sulfonilo se procesan de acuerdo con el método descrito en el Ejemplo 186f, para dar la *C,C,C*-trifluoro-N-[5-(6-cloro-1-metil-1H-indol-2-il)-piridin-3-il-metil]-metan-sulfonamida.

^{1}H RMN (400 MHz, MeOD) δ ppm 3.80 (s, 3 H), 4.59 (s, 2 H), 6.72 (s, 1 H), 7.12 (dd, *J*=8.5, 1.9 Hz, 1 H), 7.54 (s, 1 H), 7.60 (d, *J*=8.6 Hz, 1 H), 8.05 (t, *J*=2.1 Hz, 1 H), 8.63 (d, *J*=2.0 Hz, 1 H), 8.76 (d, *J*=2.0 Hz, 1 H). HRMS (ESI) *m/z* 404.0443 [(M+H)$^+$ Calculado para $C_{16}H_{14}ClF_3N_3O_2S$: 404.0447].

Ejemplo 209

[5-(6-cloro-1-metil-1H-indol-2-il)-piridin-3-il-metil]-amida del ácido 2,2,2-trifluoro-etan-sulfónico



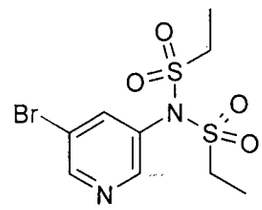
La *C*-[5-(6-cloro-1-metil-1H-indol-2-il)-piridin-3-il]-metil-amina (Ejemplo 205a), y cloruro de 2,2,2-trifluoro-etan-sulfonilo se procesan de acuerdo con el método descrito en el Ejemplo 186f, para

dar la [5-(6-cloro-1-metil-1H-indol-2-il)-piridin-3-il-metil]-amida del ácido 2,2,2-trifluoro-etan-sulfónico.

^{1}H RMN (400 MHz, MeOD) δ ppm 3.75 (d, *J*=0.6 Hz, 3 H), 4.16 - 4.28 (m, 2 H), 4.44 (s, 2 H), 6.67 (s, 1 H), 7.07 (ddd, *J*=8.4, 1.8, 0.8 Hz, 1 H), 7.50 (s, 1 H), 7.55 (d, *J*=8.3 Hz, 1 H), 8.04 (d, *J*=0.6 Hz, 1 H), 8.58 (d, *J*=1.4 Hz, 1 H), 8.68 (d, *J*=1.6 Hz, 1 H). HRMS (ESI) *m/z* 418.06107[(M+H)$^+$ Calculado para $C_{17}H_{16}N_3O_2F_3SCl$: 418.06039].

Ejemplo 210

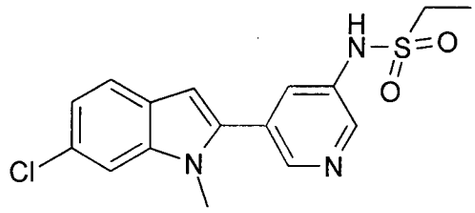
(a) (5-bromo-piridin-3-il)-amida del ácido bis-etan-sulfónico



A una solución de 3-amino-5-bromo-piridina (4.300 gramos, 23.611 milimoles) en dicloro-metano (100 mililitros), se le agrega cloruro de etan-sulfonilo (6.849 gramos, 70.834 milimoles), seguido por di-isopropil-etil-amina (16.61 mililitros, 94.445 milimoles). La mezcla se agita a temperatura ambiente durante 5 horas, después de lo cual, se diluye con acetato de etilo, y se lava con agua dos veces. La capa orgánica se seca sobre sulfato de sodio, y se concentra al vacío. El residuo se purifica mediante cromatografía por evaporación instantánea en gel de sílice (heptano-acetato de etilo, 3:2), para proporcionar la (5-bromo-piridin-3-il)-amida del ácido bis-etan-sulfónico como un sólido.

MS (ESI) *m/z* 359.0 (M+H)$^+$.

(b) 3-(6-cloro-1-metil-1H-indol-2-il)-bencil-amida del ácido etan-sulfónico



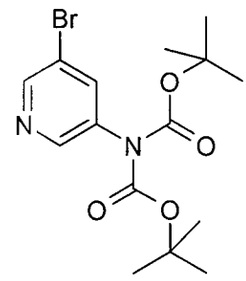
Un matraz se carga con ácido 6-cloro-1-metil-indol-2-borónico (0.165 gramos, 0.756 milimoles), (5-bromo-piridin-3-il)-amida del ácido bis-etan-sulfónico (0.200 gramos, 0.504 milimoles), fosfato de potasio (0.221 gramos, 1.008 milimoles), y dimetil-formamida (5 mililitros). El matraz se evacua y se retro-llena con N_2 tres veces, y se agrega $Pd(PPh_3)_4$ (0.029 gramos, 0.025 milimoles). La mezcla se evacua y se retro-llena con N_2 tres veces de nuevo, y se agita a 90°C durante la noche. Se enfría entonces a temperatura ambiente, se diluye con acetato de etilo, y se lava con agua tres veces. La capa orgánica se seca sobre sulfato de sodio, y se concentra al vacío. El residuo se purifica mediante cromatografía por evaporación instantánea en gel de sílice (dicloro-metano : metanol, 19:1), y se purifica adicionalmente mediante HPLC en fase inversa con una columna XBridge Shield RP18 y un gradiente de NH_4OH acuoso al 0.1 por ciento en acetonitrilo, para proporcionar la 3-(6-cloro-1-metil-1H-indol-2-il)-bencil-amida del ácido etan-sulfónico como un sólido.

^{1}H RMN (400 MHz, MeOD) δ ppm 1.40 (t, *J*=7.3 Hz, 3 H), 3.24

(q, *J*=7.3 Hz, 2 H), 3.80 (s, 3 H), 6.71 (s, 1 H), 7.12 (dd, *J*=8.3, 1.8 Hz, 1 H), 7.54 (s, 1 H), 7.59 (d, *J*=8.3 Hz, 1 H), 7.92 (t, *J*=2.1 Hz, 1 H), 8.47 (d, *J*=2.5 Hz, 1 H), 8.49 (d, *J*=1.8 Hz, 1 H). HRMS (ESI) *m/z* 350.0731 [(M+H)$^+$ Calculado para $C_{16}H_{17}ClN_3O_2S$: 350.0730].

Ejemplo 211

(a) 3-[bis-[[(1,1-dimetil-etil)-oxi]-carbonil]-amino]-5-bromo-piridina

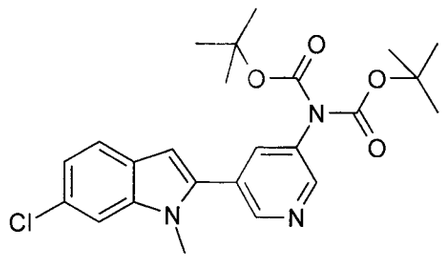


A la 5-amino-3-bromo-piridina (1.73 gramos, 10 milimoles), y Boc_2O (4.8 gramos, 22 milimoles) en acetonitrilo (100 mililitros) a temperatura ambiente, se le agrega DMAP (212 miligramos, 1 milimol), y la mezcla de reacción se calienta a 50°C, y se agita durante la noche. Se agrega Boc_2O (2.2 gramos, 10 milimoles) a la mezcla de reacción, la cual se agita a 50°C durante otras 4 horas. La mezcla de reacción se enfría entonces a temperatura ambiente. El solvente se remueve al vacío, y el residuo se purifica mediante cromatografía por evaporación instantánea en gel de sílice para proporcionar la 3-[bis-[[(1,1-dimetil-etil)-oxi]-carbonil]-amino]-5-bromo-piridina como un sólido blanco.

MS (ESI) *m/z* 374.9 (M+H)$^+$.

(b) 3-[bis-[[(1,1-dimetil-etil)-oxi]-carbonil]-amino]-5-(6-cloro-1-metil-1H-indol-2-il)-piridina

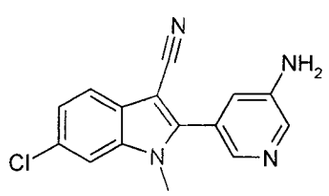
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Un matraz se carga con 3-[bis-[[(1,1-dimetil-etil)-oxi]-carbonil]-amino]-5-bromo-piridina (1.12 gramos, 3.0 milimoles), ácido N-metil-6-cloro-indol-2-borónico (754 miligramos, 3.6 milimoles), fosfato de potasio finamente triturado (1.27 gramos, 6.0 milimoles), y dimetil-formamida (20 mililitros). Después de desgasificar durante 15 minutos, se agrega $Pd(PPh_3)_4$ (173 miligramos, 0.15 milimoles). El matraz se inunda con nitrógeno y la mezcla se calienta a 90°C, y se agita durante 5 horas. La mezcla se enfría entonces a temperatura ambiente, y se vierte en agua (100 mililitros). La mezcla se extrae con EtOAc tres veces, y la fase orgánica combinada se lava con agua (10 mililitros) dos veces. La fase orgánica se seca entonces sobre Na_2SO_4 y se concentra. El residuo se purifica mediante cromatografía por evaporación instantánea en gel de sílice (acetato de etilo-heptano, de 0:1 a 1:9), para dar la 3-[bis-[[(1,1-dimetil-etil)-oxi]-carbonil]-amino]-5-(6-cloro-1-metil-1H-indol-2-il)-piridina.

MS (ESI) *m/z* 458.1 $(M+H)^+$.

(c) 2-(5-amino-piridin-3-il)-6-cloro-1-metil-1H-indol-3-carbonitrilo

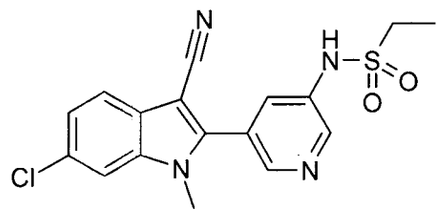


El Isocianato de cloro-sulfonilo (1.63 gramos, 11.5 milimoles) se agrega a una solución de 3-[bis-[[(1,1-dimetil-etil)-oxi]-carbonil]-amino]-5-(6-cloro-1-metil-1H-indol-2-il)-piridina (0.91 gramos, 1.99 milimoles) en acetonitrilo (200 mililitros), y la mezcla de reacción se agita durante 10 minutos. Se agrega dimetil-formamida (3 mililitros), y la mezcla de reacción se agita durante 3 horas. Se agregan 20 gramos de gel de sílice a la mezcla, y el solvente se remueve al vacío. El sólido resultante se calienta a 65°C bajo un alto vacío durante 2 horas. La mezcla se enfría a temperatura ambiente, y entonces se purifica mediante cromatografía por evaporación instantánea en gel de sílice (dicloro-metano : metanol : trietil-amina, 83:8:9), para proporcionar el 2-(5-amino-piridin-3-il)-6-cloro-1-metil-1H-indol-3-carbonitrilo.

^{1}H RMN (400 MHz, DMSO-d_6) δ ppm 3.76 (s, 3 H), 5.72 (s, 2 H), 7.15 (t, *J*=2.3 Hz, 1 H), 7.35 (dd, *J*=8.5, 1.9 Hz, 1 H), 7.69 (d, *J*=8.3 Hz, 1 H), 7.92 (d, *J*=1.8 Hz, 1 H), 7.97 (d, *J*=1.8 Hz, 1 H), 8.12 (d, *J*=2.5 Hz, 1 H). MS (ESI) *m/z* 283.0 $(M+H)^+$.

Ejemplo 212

[5-(6-cloro-3-ciano-1-metil-1H-indol-2-il)-piridin-3-il]-amida del ácido etan-sulfónico



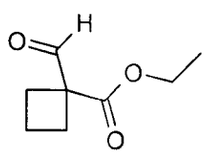
A una solución de 2-(5-amino-piridin-3-il)-6-cloro-1-metil-1H-

indol-3-carbonitrilo (Ejemplo 211, 85 miligramos, 0.3 milimoles) en dicloro-metano (15 mililitros), se le agregan trietil-amina (122 miligramos, 1.2 milimoles), y cloruro de etan-sulfonilo (77 miligramos, 0.6 milimoles), y la mezcla de reacción se agita durante la noche. El solvente se remueve, y el residuo se vuelve a disolver en metanol (15 mililitros). Se agrega NaOH acuoso 1M (1 mililitro), y la mezcla de reacción se agita durante la noche. El solvente se remueve al vacío, y el residuo se purifica mediante cromatografía por evaporación instantánea en gel de sílice (gradiente de metanol en dicloro-metano), para dar la [5-(6-cloro-3-ciano-1-metil-1H-indol-2-il)-piridin-3-il]-amida del ácido etan-sulfónico como un sólido.

^{1}H RMN (400 MHz, DMSO-d_6) δ ppm 1.25 (t, J=7.3 Hz, 3 H), 3.23 - 3.33 (m, 2 H), 3.79 (s, 3 H), 7.36 (dd, J=8.6, 1.8 Hz, 1 H), 7.72 (d, J=8.6 Hz, 1 H), 7.90 (t, J=2.3 Hz, 1 H), 7.95 (d, J=1.5 Hz, 1 H), 8.61 (d, J=2.3 Hz, 2 H), 10.43 (s, 1 H). HRMS (ESI) *m/z* 375.0692 [$(M+H)^+$ Calculado para $C_{17}H_{16}ClN_4O_2S$: 375.0682].

Ejemplo 213

(a) Etil-éster del ácido 1-formil-ciclobutan-carboxílico

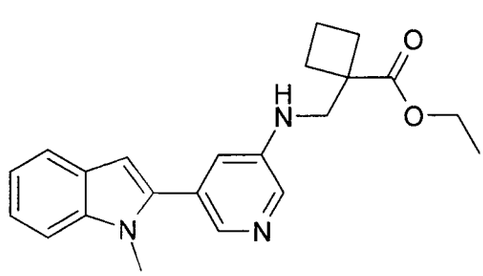


A una solución de 1,1'-ciclobutan-dicarboxilato de dietilo (9.9 gramos, 48.4 milimoles) en dicloro-metano (100 mililitros) enfriada con un baño de hielo seco/acetona, se le agrega DIBAL-H (20 por ciento en peso en tolueno, 101 mililitros, 121.1 milimoles) mediante

una cánula durante 10 minutos. La mezcla se agita durante otros 30 minutos, después de lo cual, se reemplaza el baño de acetona con un baño de agua helada, y se agrega con precaución HCl acuoso 2M (250 mililitros), con agitación vigorosa. La agitación vigorosa se continúa durante 20 minutos, después de lo cual, se obtienen dos fases transparentes. Las dos fases se separan, la fase acuosa se lava con dicloro-metano, y la fase orgánica combinada se seca sobre $MgSO_4$, se filtra, y se concentra al vacío. El residuo se purifica mediante cromatografía por evaporación instantánea en gel de sílice (heptano-acetato de etilo, de1:0 a 9:1), para dar el etil-éster del ácido 1-formil-ciclobutan-carboxílico como un aceite incoloro.

^{1}H RMN (400 MHz, $CDCl_3$) δ ppm 1.29 (t, *J*=7.1 Hz, 3 H), 1.88-2.05 (m, 2 H), 2.45-2.49 (m, 4 H), 4.24 (t, *J*=7.1 Hz, 2 H), 9.78 (s, 2 H).

(b) Etil-éster del ácido 1-{[5-(1-metil-1H-indol-2-il)-piridin-3-il-amino]-metil}-ciclobutan-carboxílico

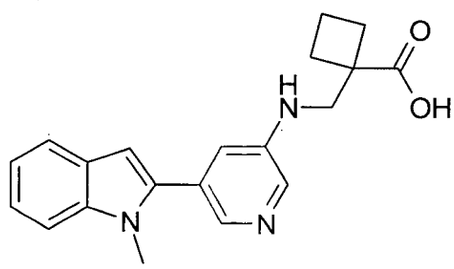


A una solución de 2-(5-amino-piridin-3-il)-1-metil-1H-indol (Ejemplo 100, 0.400 gramos, 1.756 milimoles), y etil-éster del ácido 1-formil-ciclobutan-carboxílico (0.457 gramos, 2.633 milimoles) en dicloro-metano (13 mililitros), se le agrega ácido acético (0.102

gramos, 1.756 milimoles), y la mezcla se pone a reflujo. Después de 2 horas, la mezcla se enfría con un baño de agua helada, y se agrega triacetoxi-borohidruro de sodio (1.175 gramos, 5.267 milimoles). Después de 13 horas, la mezcla se calienta a reflujo durante 1.5 horas, se enfría a temperatura ambiente, se diluye con dicloro-metano, se lava con NaOH acuoso 1M, agua y salmuera. La fase acuosa combinada se extrae una vez con dicloro-metano, y la fase orgánica combinada se seca sobre $MgSO_4$, se filtra, y se concentra al vacío. El residuo se purifica mediante cromatografía por evaporación instantánea en gel de sílice (heptano-acetato de etilo, 1:1), para dar el etil-éster del ácido 1-{[5-(1-metil-1H-indol-2-il)-piridin-3-il-amino]-metil}-ciclobutan-carboxílico como un aceite.

^{1}H RMN (400 MHz, $CDCl_3$) δ ppm 1.28 (t, *J*=7.1 Hz, 3 H), 1.99 - 2.12 (m, 4 H), 2.49 - 2.59 (m, 2 H), 3.53 (d, *J*=5.8 Hz, 2 H), 3.78 (s, 3 H), 4.12 - 4.18 (m, 1 H), 4.20 (q, *J*=7.1 Hz, 2 H), 6.61 (d, *J*=0.8 Hz, 1 H), 7.04 (dd, *J*=2.8, 1.9 Hz, 1 H), 7.15 - 7.19 (m, 1 H), 7.26 - 7.30 (m, 1 H), 7.39 (dd, *J*=8.2, 0.8 Hz, 1 H), 7.65 (d, *J*=7.7 Hz, 1 H), 8.09 (d, *J*=2.8 Hz, 1 H), 8.12 (d, *J*=1.9 Hz, 1 H).

(c) Ácido 1-{[5-(1-metil-1H-indol-2-il)-piridin-3-il-amino]-metil}-ciclobutan-carboxílico

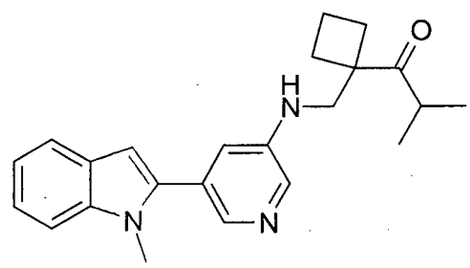


A una solución del etil-éster del ácido 1-{[5-(1-metil-1H-indol-2-il)-piridin-3-il-amino]-metil}-ciclobutan-carboxílico (0.107 gramos, 0.288 milimoles) en tetrahidrofurano (2 mililitros), y metanol (1 mililitro), se le agrega hidróxido de litio acuoso (1M, 0.58 mililitros, 0.58 milimoles), y la solución se agita durante la noche. El producto se aísla mediante HPLC en fase inversa en una XBridge C18, eluyendo con un gradiente de acetonitrilo en NH_4OH acuoso al 0.1 por ciento, para dar el ácido 1-{[5-(1-metil-1H-indol-2-il)-piridin-3-il-amino]-metil}-ciclobutan-carboxílico como un polvo blanco.

^{1}H RMN (400 MHz, DMSO-d_6) δ ppm 1.74 - 1.86 (m, 1 H), 1.87 - 1.97 (m, 3 H), 2.26 - 2.35 (m, 2 H), 3.33 (br. s., 1 H), 3.39 (s, 2 H), 3.75 (s, 3 H), 6.60 (s, 1 H), 7.05 - 7.09 (m, 1 H), 7.15 (m, 1 H), 7.17 - 7.21 (m, 1 H), 7.50 (d, *J*=8.3 Hz, 1 H), 7.57 (d, *J*=7.7 Hz, 1 H), 7.94 (d, *J*=1.8 Hz, 1 H), 8.06 (d, *J*=2.7 Hz, 1 H). MS (ESI) *m/z* 336 $(M+H)^+$.

Ejemplo 214

2-metil-1-(1-{[5-(1-metil-1H-indol-2-il)-piridin-3-il-amino]-metil}-ciclobutil)-propan-1-ona



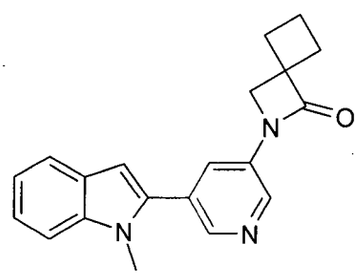
A una solución del etil-éster del ácido 1-{[5-(1-metil-1H-indol-2-il)-piridin-3-il-amino]-metil}-ciclobutan-carboxílico (Ejemplo 213b, 0.45 gramos, 1.21 milimoles) en tetrahidrofurano (150 mililitros)

enfriada con un baño de agua helada, se le agrega por goteo iPrMgCl (2.0M en tetrahidrofurano, 2.43 mililitros, 4.85 milimoles). Después de 45 minutos, la mezcla se apaga con $NaHSO_4$ acuoso 1M (5 mililitros), se lava con bicarbonato de sodio acuoso saturado y salmuera, se seca sobre $MgSO_4$, se filtra, y se concentra al vacío. El residuo se purifica mediante cromatografía por evaporación instantánea en gel de sílice (heptano-acetato de etilo, de 3:2 a 1:1), seguida por purificación mediante HPLC en fase inversa en una XBridge RP18 eluyendo con un gradiente de acetonitrilo en NH_4OH acuoso al 0.1 por ciento para dar la 2-metil-1-(1-{[5-(1-metil-1H-indol-2-il)-piridin-3-il-amino]-metil}-ciclobutil)-propan-1-ona.

^{1}H RMN (400 MHz, DMSO-d_6) δ ppm 0.95 (d, J=6.8 Hz, 6 H), 1.68 - 1.78 (m, 1 H), 1.95 - 2.03 (m, 3 H), 2.31 - 2.41 (m, 2 H), 2.97 - 3.09 (m, 1 H), 3.60 (d, J=5.7 Hz, 2 H), 3.76 (s, 3 H), 5.77 (t, J=5.7 Hz, 1 H), 6.61 (s, 1 H), 7.06 - 7.10 (m, 1 H), 7.16 - 7.25 (m, 2 H), 7.51 (d, J=8.2 Hz, 1 H), 7.58 (d, J=7.8 Hz, 1 H), 7.99 (s, 1 H), 8.12 (d, J=2.1 Hz, 1 H). MS (ESI) *m/z* 362 $(M+H)^+$.

Ejemplo 215

2-[5-(1-metil-1H-indol-2-il)-piridin-3-il]-2-aza-espiro-[3.3]-heptan-1-ona

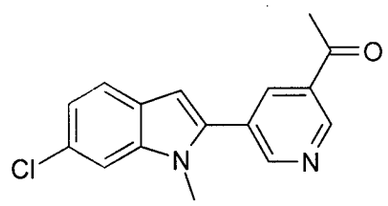


El método descrito en el Ejemplo 214 también proporciona la 2-[5-(1-metil-1H-indol-2-il)-piridin-3-il]-2-aza-espiro-[3.3]-heptan-1-ona.

^{1}H RMN (400 MHz, DMSO-d_6) δ ppm 1.88 - 2.03 (m, 2 H), 2.32 - 2.45 (m, 4 H), 3.77 (s, 3 H), 3.83 (s, 2 H), 6.71 (d, *J*=0.8 Hz, 1 H), 7.06 - 7.14 (m, 1 H), 7.19 - 7.27 (m, 1 H), 7.54 (m, 1 H), 7.61 (m, 1 H), 7.85 (dd, *J*=2.4, 1.9 Hz, 1 H), 8.54 (d, *J*=1.9 Hz, 1 H), 8.68 (d, *J*=2.4 Hz, 1 H). MS (ESI) *m/z* 318.1 $(M+H)^+$.

Ejemplo 216

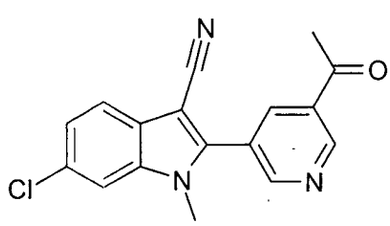
(a) 1-[5-(6-cloro-1-metil-1H-indol-2-il)-piridin-3-il]-etanona



El ácido 6-cloro-1-metil-indol-2-borónico y 5-acetil-3-bromo-piridina se procesan de acuerdo con el método descrito en el Ejemplo 100, para dar la 1-[5-(6-cloro-1-metil-1H-indol-2-il)-piridin-3-il]-etanona.

MS (ESI) *m/z* 284.98 $(M+H)^+$.

(b) 2-(5-acetil-piridin-3-il)-6-cloro-1-metil-1H-indol-3-carbonitrilo

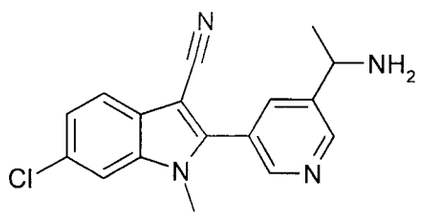


La 1-[5-(6-cloro-1-metil-1H-indol-2-il)-piridin-3-il]-etanona se procesa de acuerdo con el método descrito en el Ejemplo 128, para

dar el 2-(5-acetil-piridin-3-il)-6-cloro-1-metil-1H-indol-3-carbonitrilo.

MS (ESI) *m/z* 310.07 $(M+H)^+$.

(c) 2-[5-(1-amino-etil)-piridin-3-il]-6-cloro-1-metil-1H-indol-3-carbonitrilo

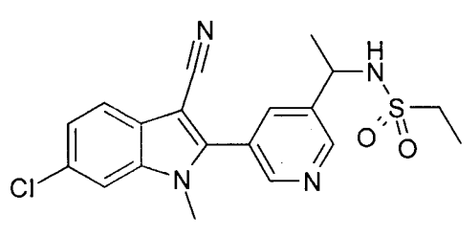


Se agrega acetato de amonio (0.567 gramos, 7.207 milimoles) a una solución de 2-(5-acetil-piridin-3-il)-6-cloro-1-metil-1H-indol-3-carbonitrilo (0.470 gramos, 1.441 milimoles) en metanol (10 mililitros), y la reacción se agita a 50°C durante 48 horas. Se agrega triacetoxi-borohidruro de sodio (2.251 gramos, 10.09 milimoles), y la reacción se agita durante 24 horas a 50°C. Se agrega triacetoxi-borohidruro de sodio adicional (2.251 gramos, 10.09 milimoles), y la reacción se agita durante otras 24 horas a 50°C. Entonces se diluye con acetato de etilo, y se lava con agua tres veces. La capa orgánica se seca sobre sulfato de sodio, y se concentra al vacío, para dar el 6-cloro-2-[5-(1-hidroxi-etil)-piridin-3-il]-1-metil-1H-indol-3-carbonitrilo y cantidades menores de 2-[5-(1-amino-etil)-piridin-3-il]-6-cloro-1-metil-1H-indol-3-carbonitrilo. La mezcla se vuelve a disolver en tetrahidrofurano (5 mililitros), y se agregan ftalimida (0.181 gramos, 1.206 milimoles), y trifenil-fosfina (0.172 gramos, 0.804 milimoles), seguidas por azodicarboxilato de di-isopropilo (0.157 mililitros, 0.804 milimoles). La reacción se agita a temperatura ambiente durante 4

horas. Entonces se diluye con acetato de etilo, y se lava con agua tres veces. La capa orgánica se seca sobre sulfato de sodio, y se concentra al vacío, para dar un residuo, el cual se purifica mediante cromatografía por evaporación instantánea en gel de sílice (heptano-acetato de etilo, 1:1), para proporcionar una mezcla de 6-cloro-2-{5-[1-(1,3-dioxo-1,3-dihidro-isoindol-2-il)-etil]-piridin-3-il}-1-metil-1H-indol-3-carbonitrilo y trifenil-fosfina. La mezcla se vuelve a disolver en etanol (5 mililitros). Se agrega hidrato de hidrazina (al 65 por ciento) (0.411 mililitros, 8.506 milimoles), y la reacción se agita a temperatura ambiente durante la noche. Se acidifica entonces con HCl acuoso 2M y se concentra al vacío. El residuo se vuelve a disolver en dicloro-metano, y se filtra a través de Celite, para remover el precipitado formado. La capa orgánica se lava con agua. La capa acuosa se separa y se basifica con NaOH acuoso 4M, y entonces se extrae con dicloro-metano tres veces. La capa orgánica se seca sobre sulfato de sodio, y se concentra al vacío, para proporcionar el 2-[5-(1-amino-etil)-piridin-3-il]-6-cloro-1-metil-1H-indol-3-carbonitrilo como un sólido.

MS (ESI) *m/z* 311.1 $(M+H)^+$

(d) {1-[5-(6-cloro-3-ciano-1-metil-1H-indol-2-il)-piridin-3-il]-etil}-amida del ácido etan-sulfónico



Un matraz se carga con 2-[5-(1-amino-etil)-piridin-3-il]-6-cloro-1-metil-1H-indol-3-carbonitrilo (0.072 gramos, 0.209 milimoles), y dicloro-metano (3 mililitros). Se agregan cloruro de etan-sulfonilo (0.060 gramos, 0.525 milimoles), y trietil-amina (0.059 mililitros, 0.417 milimoles), y la reacción se agita a temperatura ambiente durante la noche. La mezcla de reacción se concentra al vacío, para dar un residuo, el cual se purifica mediante cromatografía por evaporación instantánea en gel de sílice (heptano-acetato de etilo, 1:1), para proporcionar la {1-[5-(6-cloro-3-ciano-1-metil-1H-indol-2-il)-piridin-3-il]-etil}-amida del ácido etan-sulfónico como un sólido blanco.

^{1}H RMN (400 MHz, MeOD) δ ppm 1.32 (t, *J*=7.5 Hz, 3 H), 1.65 (d, *J*=7.1 Hz, 3 H), 2.96 - 3.15 (m, 2 H), 3.84 (s, 3 H), 4.75 - 4.86 (m, 1 H), 7.39 (dd, *J*=8.6, 1.8 Hz, 1 H), 7.73 (d, *J*=8.6 Hz, 1 H), 7.78 (d, *J*=1.5 Hz, 1 H), 8.20 (t, *J*=2.0 Hz, 1 H), 8.80 (d, *J*=2.0 Hz, 1 H), 8.83 (d, *J*=2.3 Hz, 1 H). HRMS (ESI) *m/z* 403.1005 [(M+H)$^+$ Calculado para $C_{19}H_{20}N_4O_2SCl$: 403.0996].

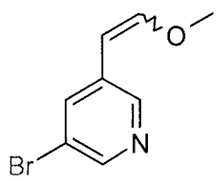
(e) (*R*) y (*S*)-{1-[5-(6-cloro-3-ciano-1-metil-1H-indol-2-il)-piridin-3-il]-etil}-amida del ácido etan-sulfónico

La {1-[5-(6-cloro-3-ciano-1-metil-1H-indol-2-il)-piridin-3-il]-etil}-amida del ácido etan-sulfónico racémica se resuelve mediante cromatografía quiral utilizando una columna Chiralpak® AS, eluyendo con una mezcla de 3:2 de heptano-etanol, para dar la (*R*) y (*S*)-{1-[5-(6-cloro-3-ciano-1-metil-1H-indol-2-il)-piridin-3-il]-etil}-amida del ácido etan-sulfónico. Los tiempos de retención son de 6.9 y 9.2

minutos a 0.8 mililitros/minuto en una columna analítica Chiralpak® AS.

Ejemplo 217

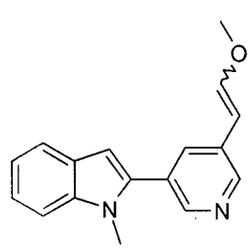
(a) 3-bromo-5-(2-metoxi-vinil)-piridina



Un matraz se carga con cloruro de metoxi-metil-trifenil-fosfina (3.04 gramos, 8.87 milimoles), y tetrahidrofurano (20 mililitros). La mezcla se enfría a –78°C, y se agrega por goteo hexametil-disilazano de sodio (solución 1M en tetrahidrofurano, 9.60 mililitros, 9.67 milimoles). La mezcla de reacción se agita a –78°C durante 30 minutos, después de lo cual, se agrega 5-bromo-piridin-3-carbaldehído (1.5 gramos, 8.06 milimoles). La mezcla se deja calentar a temperatura ambiente, y se agita durante la noche. La purificación mediante cromatografía por evaporación instantánea en gel de sílice (heptano-acetato de etilo, 4:1), proporciona una mezcla *E/Z* de 3-bromo-5-(2-metoxi-vinil)-piridina como un aceite incoloro.

MS (ESI) *m/z* 215.95 $(M+H)^+$.

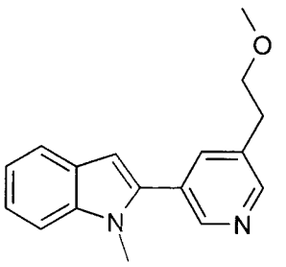
(b) 2-[5-(2-metoxi-vinil)-piridin-3-il]-1-metil-1H-indol



La 3-bromo-5-(2-metoxi-vinil)-piridina se procesa de acuerdo con el método descrito en el Ejemplo 106b, para dar una mezcla E/Z del 2-[5-(2-metoxi-vinil)-piridin-3-il]-1-metil-1H-indol como un aceite.

MS (ESI) *m/z* 265.20 $(M+H)^+$.

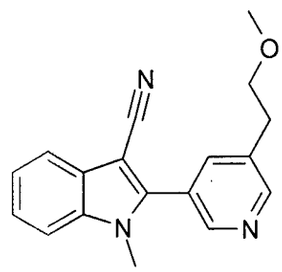
(c) 2-[5-(2-metoxi-etil)-piridin-3-il]-1-metil-1H-indol



Un matraz se carga con 2-[5-(2-metoxi-vinil)-piridin-3-il]-1-metil-1H-indol (0.550 gramos, 2.08 milimoles), y metanol (5 mililitros). Se agrega paladio sobre carbón (0.221 gramos, 0.208 milimoles), y la mezcla de reacción se agita a 50°C bajo H_2 durante 16 horas. Se enfría entonces a temperatura ambiente, y se filtra a través de Celite. La capa de Celite se lava completamente con metanol. El filtrado se concentra al vacío, para dar un residuo, el cual se purifica mediante cromatografía por evaporación instantánea en gel de sílice (heptano-acetato de etilo, 7:3), para proporcionar el 2-[5-(2-metoxi-etil)-piridin-3-il]-1-metil-1H-indol como un aceite.

MS (ESI) *m/z* 267.36 $(M+H)^+$.

(d) 2-[5-(2-metoxi-etil)-piridin-3-il]-1-metil-1H-indol-3-carbonitrilo

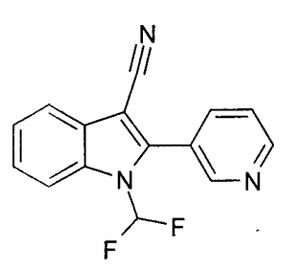


El 2-[5-(2-metoxi-etil)-piridin-3-il]-1-metil-1H-indol se procesa de acuerdo con el método descrito en el Ejemplo 128, para dar el 2-[5-(2-metoxi-etil)-piridin-3-il]-1-metil-1H-indol-3-carbonitrilo como un sólido.

^{1}H RMN (400 MHz, MeOD) δ ppm 3.09 (t, *J*=6.2 Hz, 2 H), 3.41 (s, 3 H), 3.76 (t, *J*=6.3 Hz, 2 H), 3.87 (s, 3 H), 7.36 - 7.42 (m, 1 H), 7.44 - 7.51 (m, 1 H), 7.68 (d, *J*=8.3 Hz, 1 H), 7.75 (dd, *J*=7.8, 1.1 Hz, 1 H), 8.10 (t, *J*=2.1 Hz, 1 H), 8.68 (d, *J*=2.0 Hz, 1 H), 8.74 (d, *J*=2.1 Hz, 1 H). HRMS (ESI) *m/z* 292.1458 [(M+H)$^+$ Calculado para $C_{18}H_{18}N_3O$: 292.1450].

Ejemplo 218

1-difluoro-metil-2-piridin-3-il-1H-indol-3-carbonitrilo



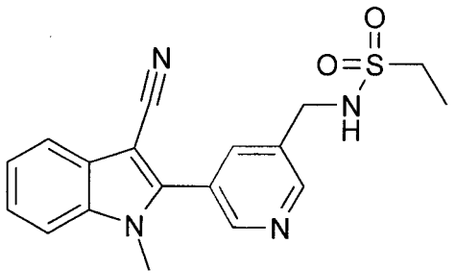
Un matraz se carga con 2-piridin-3-il-1H-indol-3-carbonitrilo

(Ejemplo 83b, 340 miligramos, 1.55 milimoles), y dimetil-formamida (10 mililitros), y se agrega NaH al 60 por ciento en aceite mineral (68 miligramos, 1.71 milimoles). La mezcla se agita a temperatura ambiente durante 20 minutos. Se burbujea $CClF_2H$ en la mezcla de reacción mientras que se eleva la temperatura de reacción a 100°C. La temperatura de reacción se eleva hasta 150°C durante 30 minutos. La mezcla se enfría a temperatura ambiente, y se agrega agua (1 mililitro). La mezcla entonces se filtra, y el filtrado se purifica en una XBridge C18 eluyendo con un gradiente de 1:9 a 9:1 de acetonitrilo-agua, para dar el 1-difluoro-metil-2-piridin-3-il-1H-indol-3-carbonitrilo.

^{1}H RMN (400 MHz, DMSO-d_6) δ ppm 7.48 - 7.53 (m, 1 H), 7.56 (td, *J*=7.7, 1.3 Hz, 1 H), 7.68 - 7.73 (m, 1 H), 7.86 (t, *J*=56.6 Hz, 1 H), 7.86 (dd, *J*=37.6, 8.1 Hz, 1 H), 7.91 (d, *J*=8.3 Hz, 1 H), 8.13 (dt, *J*=8.0, 2.0, 1.9 Hz, 1 H), 8.85 (dd, *J*=4.9, 1.6 Hz, 1 H), 8.87 (d, *J*=1.8 Hz, 1 H). HRMS (ESI) *m/z* 270.0841 [$(M+H)^+$ Calculado para $C_{15}H_{10}F_2N_3$: 270.0843].

Ejemplo 219

[5-(3-ciano-1-metil-1H-indol-2-il)-piridin-3-il-metil]-amida del ácido etan-sulfónico

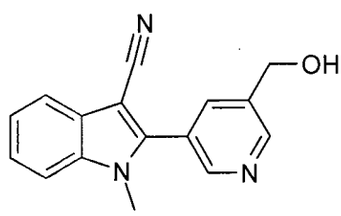


El 2-(5-formil-piridin-3-il)-1-metil-1H-indol-3-carbonitrilo (Ejemplo 127), y etan-sulfonamida, se procesan de acuerdo con el método descrito en el Ejemplo 170, para dar la [5-(3-ciano-1-metil-1H-indol-2-il)-piridin-3-il-metil]-amida del ácido etan-sulfónico.

^{1}H RMN (400 MHz, DMSO-d_6) δ ppm 1.20 (t, J=7.3 Hz, 3 H), 3.07 (q, J=7.4 Hz, 2 H), 3.79 (s, 3 H), 4.34 (d, J=6.1 Hz, 2 H), 7.34 - 7.38 (m, 1 H), 7.41 - 7.46 (m, 1 H), 7.72 (d, J=7.6 Hz, 1 H), 7.75 - 7.82 (m, 2 H), 8.09 (t, J=2.1 Hz, 1 H), 8.77 (d, J=2.0 Hz, 1 H), 8.81 (d, J=2.1 Hz, 1 H). HRMS (ESI) *m/z* 355.1247 [(M+H)$^+$ Calculado para $C_{18}H_{19}N_4O_2S$: 355.1229].

Ejemplo 220

2-(5-hidroxi-metil-piridin-3-il)-1-metil-1H-indol-3-carbonitrilo

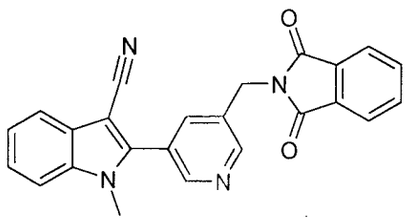


El método descrito en el Ejemplo 219 utilizando 2-(5-formil-piridin-3-il)-1-metil-1H-indol-3-carbonitrilo (Ejemplo 127) también proporciona el 2-(5-hidroxi-metil-piridin-3-il)-1-metil-1H-indol-3-carbonitrilo como un producto de la reacción.

MS (ESI) *m/z* 264.07 (M+H)$^+$.

Ejemplo 221

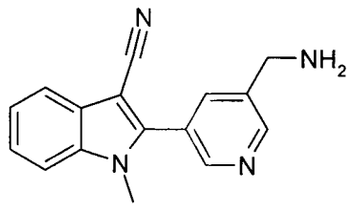
(a) 2-[5-(1,3-dioxo-1,3-dihidro-isoindol-2-il-metil)-piridin-3-il]-1-metil-1H-indol-3-carbonitrilo



A una solución de 2-(5-hidroxi-metil-piridin-3-il)-1-metil-1H-indol-3-carbonitrilo (Ejemplo 220, 190 miligramos, 0.72 milimoles) en tetrahidrofurano (5 mililitros) se le agregan en secuencia ftalimida (116 miligramos, 0.79 milimoles), 1,1'-(azodicarbonil)-dipiperidina (346 miligramos, 1.37 milimoles), y tributil-fosfina (277 miligramos, 1.37 milimoles). La mezcla se agita a temperatura ambiente durante la noche. La mezcla entonces se concentra al vacío, y el residuo se purifica mediante cromatografía por evaporación instantánea en gel de sílice (heptano-acetato de etilo, de 1:0 a 0:1), para dar el 2-[5-(1,3-dioxo-1,3-dihidro-isoindol-2-il-metil)-piridin-3-il]-1-metil-1H-indol-3-carbonitrilo.

MS (ESI) *m/z* 393.02 $(M+H)^+$.

(b) 2-(5-amino-metil-piridin-3-il)-1-metil-1H-indol-3-carbonitrilo

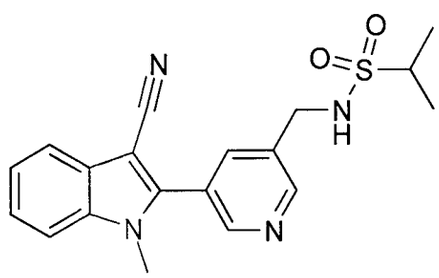


A una solución de 2-[5-(1,3-dioxo-1,3-dihidro-isoindol-2-il-metil)-piridin-3-il]-1-metil-1H-indol-3-carbonitrilo (200 miligramos, 0.51 milimoles) en etanol (15 mililitros), se le agrega hidrato de hidrazina (327 miligramos, 10.2 milimoles). La mezcla se agita a

temperatura ambiente durante la noche. La mezcla de reacción se vierte en dicloro-metano (100 mililitros), y se extrae con HCl 1M en agua. La fase acuosa combinada se basifica con NaOH 5M en agua, y se extrae con dicloro-metano. La fase orgánica combinada se seca sobre Na_2SO_4 y se concentra al vacío, para dar el 2-(5-amino-metil-piridin-3-il)-1-metil-1H-indol-3-carbonitrilo, el cual se utiliza en el siguiente paso sin mayor purificación.

MS (ESI) *m/z* 263.27 $(M+H)^+$.

(c) [5-(3-ciano-1-metil-1H-indol-2-il)-piridin-3-il-metil]-amida del ácido propan-2-sulfónico



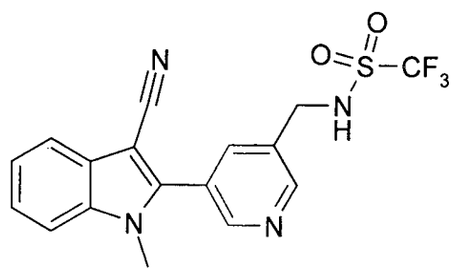
Un matraz se carga con 2-(5-amino-metil-piridin-3-il)-1-metil-1H-indol-3-carbonitrilo (130 miligramos, 0.5 milimoles), DBU (304 miligramos, 2.0 milimoles), y dicloro-etano (15 mililitros), y se agrega cloruro de isopropil-sulfonilo (142 miligramos, 1.0 milimoles). La mezcla se agita a temperatura ambiente durante 1 hora, y se concentra al vacío. El residuo se purifica mediante cromatografía por evaporación instantánea en gel de sílice (dicloro-metano : metanol, de 1:0 a 97:3), para dar la [5-(3-ciano-1-metil-1H-indol-2-il)-piridin-3-il-metil]-amida del ácido propan-2-sulfónico.

^{1}H RMN (400 MHz, DMSO-d_6) δ ppm 1.24 (d, *J*=6.8 Hz, 6 H),

3.18 - 3.26 (m, 1 H), 3.79 (s, 3 H), 4.37 (d, *J*=6.1 Hz, 2 H), 7.34 - 7.38 (m, 1 H), 7.41 - 7.46 (m, 1 H), 7.70 - 7.79 (m, 3 H), 8.08 (t, *J*=2.0 Hz, 1 H), 8.77 (d, *J*=2.3 Hz, 1 H), 8.81 (d, *J*=2.3 Hz, 1 H). HRMS (ESI) *m/z* 369.1389 [(M+H)$^+$ Calculado para $C_{19}H_{21}N_4O_2S$: 369.1385].

Ejemplo 222

Trifluoro-[5-(3-ciano-1-metil-1H-indol-2-il)-piridin-3-il-metil]-amida del ácido metan-sulfónico



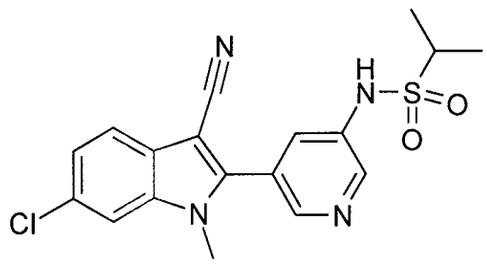
El 2-(5-formil-piridin-3-il)-1-metil-1H-indol-3-carbonitrilo (Ejemplo 127), y trifluoro-metan-sulfonamida se procesan de acuerdo con el método descrito en el Ejemplo 170, para dar el trifluoro-[5-(3-ciano-1-metil-1H-indol-2-il)-piridin-3-il-metil]-amida del ácido metan-sulfónico.

^{1}H RMN (400 MHz, DMSO-d_6) δ ppm 3.79 (s, 3 H), 4.58 (s, 2 H), 7.34 - 7.39 (m, 1 H), 7.42 - 7.47 (m, 1 H), 7.72 (d, *J*=7.7 Hz, 1 H), 7.77 (d, *J*=8.3 Hz, 1 H), 8.10 (t, *J*=2.1 Hz, 1 H), 8.78 (d, *J*=2.1 Hz, 1 H), 8.85 (d, *J*=2.1 Hz, 1 H), 10.19 (br. s., 1 H). HRMS (ESI) *m/z* 395.0779 [(M+H)$^+$ Calculado para $C_{17}H_{14}F_3N_4O_2S$: 395.0790].

Ejemplo 223

[5-(6-cloro-3-ciano-1-metil-1H-indol-2-il)-piridin-3-il]-amida del ácido

propan-2-sulfónico

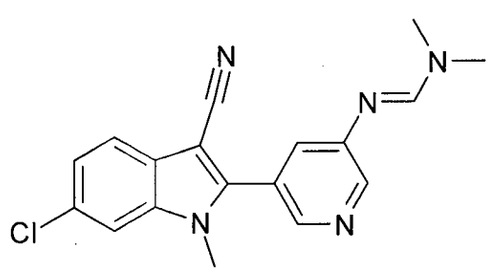


El 2-(5-amino-piridin-3-il)-6-cloro-1-metil-1H-indol-3-carbonitrilo (Ejemplo 211) se procesa de acuerdo con el método descrito en el Ejemplo 221c, para dar la [5-(6-cloro-3-ciano-1-metil-1H-indol-2-il)-piridin-3-il]-amida del ácido propan-2-sulfónico.

^{1}H RMN (400 MHz, DMSO-d_6) δ ppm 1.30 (d, J=6.8 Hz, 6 H), 3.46 (dq, J=6.8 Hz, 1 H), 3.79 (s, 3 H), 7.37 (dd, J=8.5, 1.9 Hz, 1 H), 7.73 (d, J=8.6 Hz, 1 H), 7.93 (t, J=2.1 Hz, 1 H), 7.96 (d, J=1.8 Hz, 1 H), 8.60 (d, J=1.8 Hz, 1 H), 8.63 (d, J=2.5 Hz, 1 H), 10.41 (s, 1 H). HRMS (ESI) *m/z* 389.0836 [(M+H)$^+$ Calculado para $C_{18}H_{18}ClN_4O_2S$: 389.0839].

Ejemplo 224

N'-[5-(6-cloro-3-ciano-1-metil-1H-indol-2-il)-piridin-3-il]-*N*,N-dimetil-formamidina



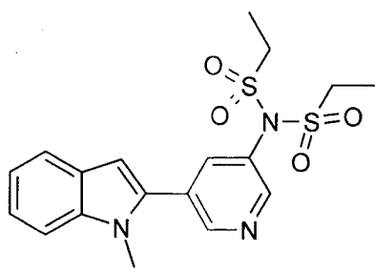
A una solución de 2-(5-amino-piridin-3-il)-6-cloro-1-metil-1H-

indol-3-carbonitrilo (Ejemplo 211, 85 miligramos, 0.3 milimoles) en N,N-dimetil-formamida (5 mililitros), se le agrega NaH al 60 por ciento en aceite mineral (48 miligramos, 1.2 milimoles), seguido por cloruro de propan-2-sulfonilo (86 miligramos, 60.6 milimoles). La mezcla se agita a temperatura ambiente durante 5 horas. La mezcla se filtra, y el filtrado se purifica en una XBridge C18 eluyendo con un gradiente de 1:9 a 9:1 de acetonitrilo-agua, para dar la *N*'-[5-(6-cloro-3-ciano-1-metil-1H-indol-2-il)-piridin-3-il]-*N*,*N*-dimetil-formamidina.

^{1}H RMN (400 MHz, DMSO-d_6) δ ppm 2.98 (s, 3 H), 3.06 (s, 3 H), 3.79 (s, 3 H), 7.35 (dd, *J*=8.3, 1.8 Hz, 1 H), 7.62 (t, *J*=2.1 Hz, 1 H), 7.70 (d, *J*=8.3 Hz, 1 H), 7.95 (d, *J*=1.8 Hz, 1 H), 7.96 (s, 1 H), 8.37 - 8.39 (m, 2 H). HRMS (ESI) *m/z* 338.1182 [(M+H)$^+$ Calculado para $C_{18}H_{17}ClN_5$: 338.1173].

Ejemplo 225

(a) [5-(1-metil-1H-indol-2-il)-piridin-3-il]-N-etan-sulfonil-amida del ácido etan-sulfónico

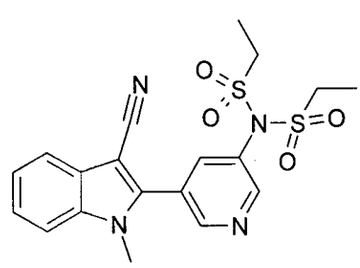


A una solución de 2-(5-amino-piridin-3-il)-1-metil-1H-indol (Ejemplo 100) (223 miligramos, 1.0 milimoles) en dicloro-metano (20 mililitros), se le agrega cloruro de etan-sulfonilo (386 miligramos, 3.0

milimoles), y di-isopropil-etil-amina (517 miligramos, 4.0 milimoles). La mezcla se agita a temperatura ambiente durante 1 hora. Se agregan $NaHCO_3$ saturado en agua (0.5 mililitros), y gel de sílice (10 gramos), y la mezcla se concentra al vacío. El residuo se purifica mediante cromatografía en gel de sílice (heptano-acetato de etilo, de 1:0 a 1:9), para dar la [5-(1-metil-1H-indol-2-il)-piridin-3-il]-N-etan-sulfonil-amida del ácido etan-sulfónico.

MS (ESI) *m/z* 408.1 $(M+H)^+$.

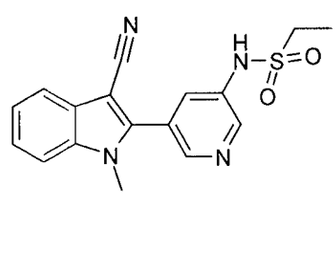
(b) [5-(3-ciano-1-metil-1H-indol-2-il)-piridin-3-il]-N-etan-sulfonil-amida del ácido etan-sulfónico



La [5-(1-metil-1H-indol-2-il)-piridin-3-il]-N-etan-sulfonil-amida del ácido etan-sulfónico se procesa de acuerdo con el método descrito en el Ejemplo 128, para dar la [5-(3-ciano-1-metil-1H-indol-2-il)-piridin-3-il]-N-etan-sulfonil-amida del ácido etan-sulfónico.

MS (ESI) *m/z* 432.96 $(M+H)^+$.

(c) [5-(3-ciano-1-metil-1H-indol-2-il)-piridin-3-il]-amida del ácido etan-sulfónico

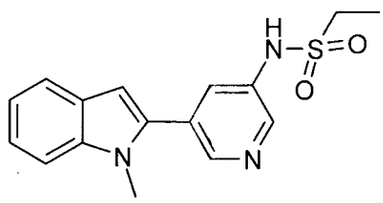


Una solución de la [5-(3-ciano-1-metil-1H-indol-2-il)-piridin-3-il]-N-etan-sulfonil-amida del ácido etan-sulfónico en N,N-dimetil-formamida (2 mililitros), metanol (10 mililitros), y NaOH 5 M en agua (1 mililitro), se agita a temperatura ambiente durante 1 hora. La mezcla se purifica en una XBridge C18 eluyendo con un gradiente de 1:9 a 9:1 de acetonitrilo-agua, para dar la [5-(3-ciano-1-metil-1H-indol-2-il)-piridin-3-il]-amida del ácido etan-sulfónico.

^{1}H RMN (400 MHz, DMSO-d_6) δ ppm 1.25 (t, J=7.3 Hz, 3 H), 3.24 - 3.32 (m, 2 H), 3.80 (s, 3 H), 7.32 - 7.38 (m, 1 H), 7.43 (td, J=7.8, 1.1 Hz, 1 H), 7.70 (d, J=7.8 Hz, 1 H), 7.75 (d, J=8.3 Hz, 1 H), 7.90 (t, J=2.3 Hz, 1 H), 8.58 - 8.62 (m, 2 H), 10.42 (s, 1 H). HRMS (ESI) m/z 341.1078 [$(M+H)^+$ Calculado para $C_{17}H_{17}N_4O_2S$: 341.1072].

Ejemplo 226

[5-(1-metil-1H-indol-2-il)-piridin-3-il]-amida del ácido etan-sulfónico



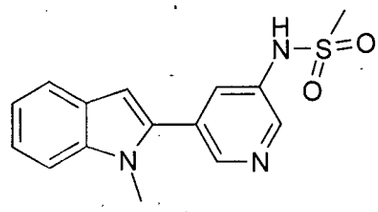
La [5-(1-metil-1H-indol-2-il)-piridin-3-il]-N-etan-sulfonil-amida del ácido etan-sulfónico (Ejemplo 225a) se procesa de acuerdo con el método descrito en el Ejemplo 225c, para dar la [5-(1-metil-1H-indol-2-il)-piridin-3-il]-amida del ácido etan-sulfónico.

^{1}H RMN (400 MHz, DMSO-d_6) δ ppm 1.26 (t, J=7.3 Hz, 3 H), 3.26 (q, J=7.3 Hz, 2 H), 3.77 (s, 3 H), 6.71 (s, 1 H), 7.08 - 7.13 (m, 1 H), 7.20 - 7.27 (m, 1 H), 7.54 (d, J=8.1 Hz, 1 H), 7.61 (d, J=7.8 Hz, 1

H), 7.79 (t, *J*=2.3 Hz, 1 H), 8.48 (d, *J*=2.5 Hz, 1 H), 8.56 (d, *J*=1.8 Hz, 1 H), 10.23 (s, 1 H). HRMS (ESI) *m/z* 316.1125 [(M+H)$^+$ Calculado para $C_{16}H_{18}N_3O_2S$: 316.1120].

Ejemplo 227

[5-(1-metil-1H-indol-2-il)-piridin-3-il]-amida del ácido metan-sulfónico

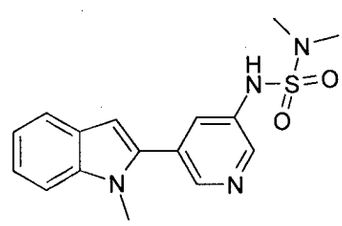


El 2-(5-amino-piridin-3-il)-1-metil-1H-indol (Ejemplo 100), y cloruro de metan-sulfonilo, se procesan de acuerdo con los métodos descritos en los Ejemplos 225a y 225c, para dar la [5-(1-metil-1H-indol-2-il)-piridin-3-il]-amida del ácido metan-sulfónico.

^{1}H RMN (400 MHz, DMSO-d_6) δ ppm 3.15 (s, 3 H), 3.77 (s, 3 H), 6.71 (s, 1 H), 7.06 - 7.13 (m, 1 H), 7.23 (ddd, *J*=8.2, 7.1, 1.1 Hz, 1 H), 7.53 (d, *J*=7.6 Hz, 1 H), 7.61 (d, *J*=7.6 Hz, 1 H), 7.79 (t, *J*=2.2 Hz, 1 H), 8.48 (d, *J*=2.3 Hz, 1 H), 8.58 (d, *J*=2.0 Hz, 1 H), 10.18 (s, 1 H). HRMS: (ESI) m/z 302.0966 [(M+H)$^+$ Calculado para $C_{15}H_{16}N_3O_2S$ 302.0958].

Ejemplo 228

5-(1-metil-1H-indol-2-il)-piridin-3-il-amida del ácido dietil-sulfámico

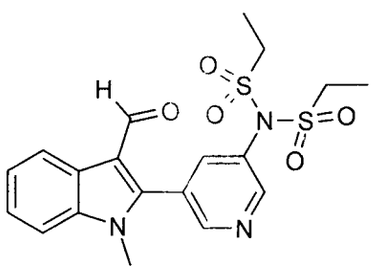


A una solución de 2-(5-amino-piridin-3-il)-1-metil-1H-indol (Ejemplo 100, 60 miligramos, 0.269 milimoles), y cloruro de dimetil-sulfamoílo (58 miligramos, 0.403 milimoles) en dicloro-metano (1 mililitro), se le agrega trietil-amina (54 miligramos, 0.537 milimoles). Después de agitar durante la noche, la mezcla se concentra y se purifica mediante cromatografía por evaporación instantánea en gel de sílice (heptano-acetato de etilo. 3:7), para dar la 5-(1-metil-1H-indol-2-il)-piridin-3-il-amida del ácido dietil-sulfámico.

^{1}H RMN (400 MHz, DMSO-d_6) δ ppm 2.77 (s, 6 H), 3.76 (s, 3 H), 6.89 (s, 1 H), 7.07 - 7.12 (m, 1 H), 7.20 - 7.25 (m, 1 H), 7.53 (d, *J*=8.3 Hz, 1 H), 7.61 (d, *J*=7.8 Hz, 1 H), 7.75 (t, *J*=2.1 Hz, 1 H), 8.46 (d, *J*=2.5 Hz, 1 H), 8.52 (d, *J*=2.0 Hz, 1 H). HRMS: (ESI) *m/z* 331.1226 [(M+H)$^+$ Calculado para $C_{16}H_{18}N_4O_2S$ 331.1223].

Ejemplo 229

(a) [5-(1-metil-3-carboxaldehído-1H-indol-2-il)-piridin-3-il]-N-etan-sulfonil-amida del ácido etan-sulfónico

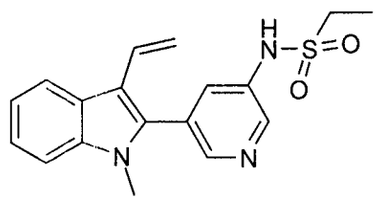


Un matraz se carga con dimetil-formamida (10 mililitros), y se enfría a 0°C. Se agrega oxicloruro de fósforo (0.297 mililitros, 3.19 milimoles), y la mezcla de reacción se agita a 0°C durante 20 minutos, seguido por la adición de una solución de la [5-(1-metil-1H-

indol-2-il)-piridin-3-il]-N-etan-sulfonil-amida del ácido etan-sulfónico (Ejemplo 225a, 1.00 gramos, 2.454 milimoles) en N,N-dimetil-formamida (10 mililitros). La mezcla de reacción se agita a temperatura ambiente durante 16 horas. La reacción se detiene, se lava con una solución saturada de $NaHCO_3$ y se extrae con acetato de etilo. La capa orgánica se separa y se lava con agua tres veces, entonces se seca sobre Na_2SO_4 y se concentra al vacío, para proporcionar la [5-(1-metil-3-carboxaldehído-1H-indol-2-il)-piridin-3-il]-N-etan-sulfonil-amida del ácido etan-sulfónico.

MS (ESI) *m/z* 436.2 $(M+H)^+$

(b) [5-(1-metil-3-vinil-1H-indol-2-il)-piridin-3-il]-amida del ácido etan-sulfónico

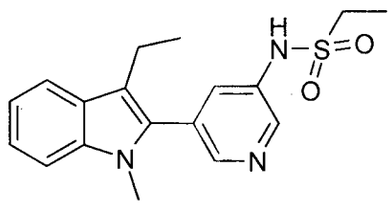


Un matraz se carga con bromuro de metil-trifenil-fosfina (0.492 gramos, 1.378 milimoles), y tetrahidrofurano (20 mililitros). La mezcla de reacción se enfria a –78°C, y se agrega NaHMDS 1M en tetrahidrofurano (1.515 mililitros, 1.515 milimoles). La reacción se agita a –78°C durante 1 hora, seguido por la adición de la [5-(1-metil-3-carboxaldehído-1H-indol-2-il)-piridin-3-il]-N-etan-sulfonil-amida del ácido etan-sulfónico (0.300 gramos, 0.689 milimoles) a -78°C. La mezcla de reacción se deja calentar a temperatura ambiente, y se agita durante la noche. La mezcla se lava con agua, y

se extrae con acetato de etilo. La capa orgánica se seca sobre sulfato de sodio, y se concentra al vacío. El producto crudo se purifica mediante cromatografía por evaporación instantánea en gel de sílice (heptano-acetato de etilo, de 1:0 a 0-1), para proporcionar el producto de [5-(1-metil-3-vinil-1H-indol-2-il)-piridin-3-il]-amida del ácido etan-sulfónico.

MS (ESI) *m/z* 342.2 $(M+H)^+$

(c) [5-(1-metil-3-etil-1H-indol-2-il)-piridin-3-il]-amida del ácido etan-sulfónico

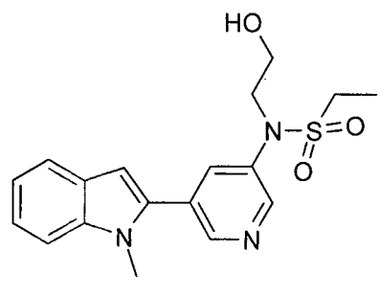


Un matraz se carga con la [5-(1-metil-3-vinil-1H-indol-2-il)-piridin-3-il]-amida del ácido etan-sulfónico (35 miligramos, 0.082 milimoles), y metanol (5 mililitros). El matraz se evacua y se inunda con N_2 tres veces. Se agrega Pd/C (4.36 miligramos), y la reacción se agita bajo H_2 durante la noche a 50°C. La reacción se filtra sobre Celite, y la capa de Celite se lava completamente con metanol. El filtrado se concentra al vacío. El producto crudo se purifica mediante cromatografía por evaporación instantánea en gel de sílice (diclorometano : metanol, 19:1), seguida por HPLC de purificación utilizando una XBridge C18 eluyendo con un gradiente del 10 al 100 por ciento de acetonitrilo-agua, para proporcionar el producto puro de la [5-(3-etil-1-metil-1H-indol-2-il)-piridin-3-il]-amida del ácido etan-sulfónico.

^{1}H RMN (400 MHz, MeOD) δ ppm 1.27 (t, *J*=7.6 Hz, 3 H), 1.40 (t, *J*=7.3 Hz, 3 H), 2.76 (q, *J*=7.6 Hz, 2 H), 3.25 (q, *J*=7.3 Hz, 2 H), 3.66 (s, 3 H), 7.09 - 7.17 (m, 1 H), 7.23 - 7.31 (m, 1 H), 7.43 (d, *J*=8.3 Hz, 1 H), 7.65 (d, *J*=7.8 Hz, 1 H), 7.83 (t, *J*=2.3 Hz, 1 H), 8.36 (d, *J*=1.8 Hz, 1 H), 8.49 (d, *J*=2.5 Hz, 1 H). HRMS: (ESI) m/z 344.1435 [(M+H)$^+$ Calculado para $C_{18}H_{21}N_3O_2S$ 344.1427].

Ejemplo 230

(2-hidroxi-etil)-[5-(1-metil-1H-indol-2-il)-piridin-3-il]-amida del ácido etan-sulfónico



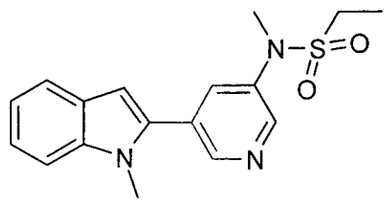
Un matraz se carga con la [5-(1-metil-1H-indol-2-il)-piridin-3-il]-amida del ácido etan-sulfónico (Ejemplo 226, 200 miligramos, 0.634 milimoles), y dimetil-formamida (3 mililitros). La reacción se enfría a 0°C, y se agrega hidruro de sodio (38.0 miligramos, 0.951 milimoles). La reacción se agita a temperatura ambiente durante 10 minutos, y entonces se agrega 2-cloro-etoxi-trimetil-silano (0.154 mililitros, 0.951 milimoles). La reacción se agita a 100°C durante 16 horas, y entonces se enfría a temperatura ambiente. Se agrega HCl 1M acuoso (1 mililitro), y la agitación se continúa durante 30 minutos. La mezcla se purifica utilizando una XBridge C18 eluyendo con un gradiente del 10 al 100 por ciento de acetonitrilo-agua, para

proporcionar la (2-hidroxi-etil)-[5-(1-metil-1H-indol-2-il)-piridin-3-il]-amida del ácido etan-sulfónico.

MS (ESI) *m/z* 360.1 $(M+H)^+$. ^1H RMN (400 MHz, MeOD) δ ppm 1.42 (t, *J*=7.3 Hz, 3 H), 3.29 (t, 2 H), 3.70 (t, *J*=5.6 Hz, 2 H), 3.84 (s, 3 H), 3.96 (t, *J*=5.6 Hz, 2 H), 6.75 (s, 1 H), 7.14 (td, *J*=7.5, 0.9 Hz, 1 H), 7.28 (td, *J*=7.7, 1.0 Hz, 1 H), 7.49 (d, *J*=8.3 Hz, 1 H), 7.64 (d, *J*=7.6 Hz, 1 H), 8.18 (t, *J*=2.1 Hz, 1 H), 8.71 (d, *J*=2.3 Hz, 1 H), 8.75 (d, *J*=1.8 Hz, 1 H). HRMS (ESI) m/z 360.1383 $[(M+H)^+$ Calculado para $C_{18}H_{12}N_3O_3S$ 360.1376].

Ejemplo 231

Metil-[5-(1-metil-1H-indol-2-il)-piridin-3-il]-amida del ácido etan-sulfónico



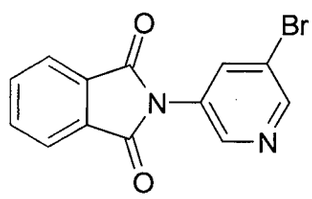
Un matraz se carga con la [5-(1-metil-1H-indol-2-il)-piridin-3-il]-amida del ácido etan-sulfónico (Ejemplo 226, 100 miligramos, 0.317 milimoles), y dimetil-formamida (4 mililitros). La reacción se enfría a 0°C, y se agrega hidruro de sodio (15.85 miligramos, 0.396 milimoles). La reacción se agita a 0°C durante 10 minutos, y entonces se agrega yoduro de metilo (56.3 miligramos, 0.396 milimoles). La reacción se agita durante 1 hora a temperatura ambiente. La reacción se apaga con agua (0.5 mililitros), y se filtra. El filtrado se purifica utilizando una XBridge C18, eluyendo con un

gradiente del 10 al 100 por ciento de acetonitrilo-agua, para proporcionar la metil-[5-(1-metil-1H-indol-2-il)-piridin-3-il]-amida del ácido etan-sulfónico.

^{1}H RMN (400 MHz, MeOD) δ ppm 1.39 (t, *J*=7.5 Hz, 3 H), 3.28 (q, *J*=7.5 Hz, 2 H), 3.49 (s, 3 H), 3.84 (s, 3 H), 6.74 (s, 1 H), 7.14 (t, *J*=7.6 Hz, 1 H), 7.28 (ddd, *J*=7.6, 1.1 Hz, 1 H), 7.49 (d, *J*=8.3 Hz, 1 H), 7.63 (d, *J*=7.8 Hz, 1 H), 8.13 (t, *J*=2.1 Hz, 1 H), 8.70 (d, *J*=2.0 Hz, 1 H), 8.70 (d, *J*=2.5 Hz, 1 H). HRMS (ESI) m/z 330.1281 [(M+H)$^+$ Calculado para $C_{17}H_{19}N_3O_2S$ 330.1270].

Ejemplo 232

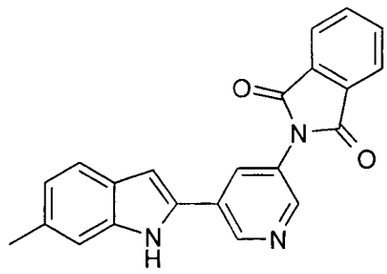
(a) 2-(5-bromo-piridin-3-il)-isoindol-1,3-diona



Un matraz se carga con 3-amino-5-bromo-piridina (1.00 gramos, 5.78 milimoles), anhídrido ftálico (0.856 gramos, 5.78 milimoles), y ácido acético (20 mililitros). La reacción se pone a reflujo durante la noche. La reacción se enfría entonces a temperatura ambiente, y se concentra al vacío. El producto crudo se disuelve en acetato de etilo, y se lava con agua una vez. La capa orgánica se seca sobre sulfato de sodio, y se concentra al vacío, para proporcionar la 2-(5-bromo-piridin-3-il)-isoindol-1,3-diona.

MS (ESI) *m/z* 305.1 (M+H)$^+$

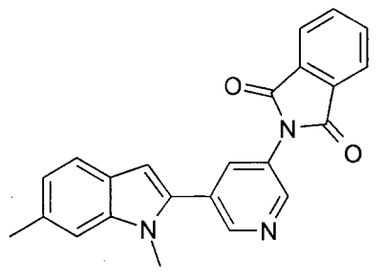
(b) 2-[5-(6-metil-1H-indol-2-il)-piridin-3-il]-isoindol-1,3-diona



La 2-(5-bromo-piridin-3-il)-isoindol-1,3-diona y el ácido *N*-Boc-6-metil-indol-borónico se procesan de acuerdo con el procedimiento descrito en el Ejemplo 103, para dar la 2-[5-(6-metil-1H-indol-2-il)-piridin-3-il]-isoindol-1,3-diona.

MS (ESI) *m/z* 354.1 $(M+H)^+$

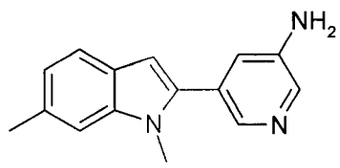
(c) 2-[5-(1,6-dimetil-1H-indol-2-il)-piridin-3-il]-isoindol-1,3-diona



La 2-[5-(6-metil-1H-indol-2-il)-piridin-3-il]-isoindol-1,3-diona se procesa de acuerdo con el procedimiento descrito en el Ejemplo 114, para dar la 2-[5-(1,6-dimetil-1H-indol-2-il)-piridin-3-il]-isoindol-1,3-diona.

MS (ESI) *m/z* 368.3 $(M+H)^+$

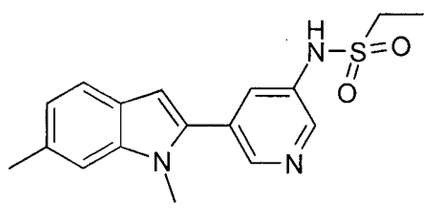
(d) 5-(1,6-dimetil-1H-indol-2-il)-piridin-3-il-amina



Un matraz se carga con 2-[5-(1,6-dimetil-1H-indol-2-il)-piridin-3-il]-isoindol-1,3-diona (1.10 gramos, 2.096 milimoles), y EtOH (30 mililitros). Se agrega hidrazina (1.316 mililitros, 41.9 milimoles), y la mezcla de reacción se pone a reflujo durante 1 hora. La mezcla de reacción se enfría a temperatura ambiente, se filtra, y el precipitado se lava completamente con acetato de etilo. El filtrado se concentra al vacío. El producto crudo se absorbe en una solución de HCl 1M, y entonces se extrae con EtOAc. La capa acuosa se separa, se basifica a un pH de 14 utilizando NaOH acuoso 4M, y se extrae con dicloro-metano tres veces. La capa orgánica se seca sobre Na_2SO_4 y se concentra al vacío, para proporcionar la 5-(1,6-dimetil-1H-indol-2-il)-piridin-3-il-amina.

MS (ESI) *m/z* 238.4 $(M+H)^+$

(e) [5-(1,6-dimetil-1H-indol-2-il)-piridin-3-il]-amida del ácido etan-sulfónico



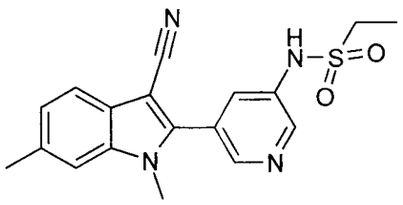
La 5-(1,6-dimetil-1H-indol-2-il)-piridin-3-il-amina se procesa de acuerdo con los procedimientos descritos en los Ejemplos 225a y 225c, para dar la [5-(1,6-dimetil-1H-indol-2-il)-piridin-3-il]-amida del ácido etan-sulfónico.

^{1}H RMN (400 MHz, MeOD) δ ppm 1.40 (t, *J*=7.3 Hz, 3 H), 2.53 (s, 3 H), 3.26 (q, *J*=7.3 Hz, 2 H), 3.79 (s, 3 H), 6.65 (s, 1 H), 6.98 (d,

J=8.1 Hz, 1 H), 7.28 (s, 1 H), 7.50 (d, *J*=8.1 Hz, 1 H), 7.93 (t, *J*=2.3 Hz, 1 H), 8.46 (d, *J*=2.3 Hz, 1 H), 8.53 (d, *J*=1.8 Hz, 1 H). HRMS (ESI) m/z 330.1285 [(M+H)$^+$ Calculado para $C_{17}H_{19}N_3O_2S$ 330.1270].

Ejemplo 233

[5-(1,6-dimetil-3-ciano-1H-indol-2-il)-piridin-3-il]-amida del ácido etan-sulfónico

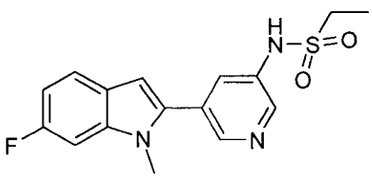


La 5-(1,6-dimetil-1H-indol-2-il)-piridin-3-il-amina (Ejemplo 232d) se procesa de acuerdo con los procedimientos descritos en los Ejemplos 225a, 128 y 225c, para dar la [5-(1,6-dimetil-3-ciano-1H-indol-2-il)-piridin-3-il]-amida del ácido etan-sulfónico.

^{1}H RMN (400 MHz, MeOD) δ ppm 1.39 (t, *J*=7.3 Hz, 3 H), 2.57 (s, 3 H), 3.22 (q, *J*=7.3 Hz, 2 H), 3.84 (s, 3 H), 7.22 (d, *J*=8.1 Hz, 1 H), 7.46 (s, 1 H), 7.60 (d, *J*=8.1 Hz, 1 H), 7.92 - 7.94 (m, 1 H), 8.39 (d, *J*=1.8 Hz, 1 H), 8.50 (d, *J*=2.5 Hz, 1 H). HRMS: (ESI) m/z 355.1230 [(M+H)$^+$ Calculado para $C_{18}H_{18}N_4O_2S$ 355.1223].

Ejemplo 234

[5-(1-metil-6-fluoro-1H-indol-2-il)-piridin-3-il]-amida del ácido etan-sulfónico

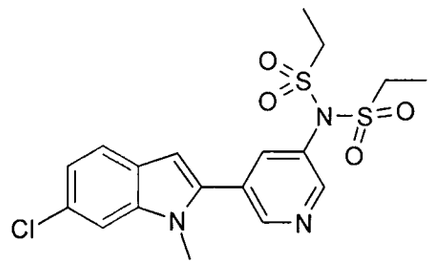


El ácido 6-fluoro-1-metil-indol-borónico y 3-bromo-5-amino-piridina se procesan de acuerdo con los procedimientos descritos en los Ejemplos 100, 225a y 225c, para dar la [5-(1-metil-6-fluoro-1H-indol-2-il)-piridin-3-il]-amida del ácido etan-sulfónico.

^{1}H RMN (400 MHz, DMSO-d_6) δ ppm 1.24 (t, J=7.3 Hz, 3 H), 3.17 - 3.28 (m, 5 H), 6.53 (d, J=3.0 Hz, 1 H), 7.01 (dd, J=10.2, 8.7 Hz, 1 H), 7.29 (d, J=3.3 Hz, 1 H), 7.60 - 7.68 (m, 2 H), 8.41 (d, J=1.8 Hz, 1 H), 8.53 (d, J=2.5 Hz, 1 H), 10.23 (s, 1 H). HRMS (ESI) m/z 334.1029 [(M+H)$^+$ Calculado para $C_{16}H_{16}FN_3O_2S$ 334.1020].

Ejemplo 235

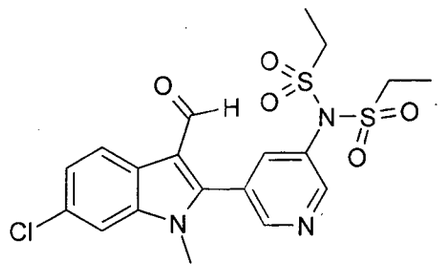
(a) [5-(1-metil-6-cloro-1H-indol-2-il)-piridin-3-il)-amida del ácido bis-etan-sulfónico



La (5-bromo-piridin-3-il)-amida del ácido bis-etan-sulfónico (Ejemplo 210a), y ácido 6-cloro-1-metil-indol-2-borónico se procesan de acuerdo con el procedimiento descrito en el Ejemplo 100, para dar la [5-(1-metil-6-cloro-1H-indol-2-il)-piridin-3-il)-amida del ácido bis-etan-sulfónico.

MS (ESI) *m/z* 442.1 (M+H)$^+$

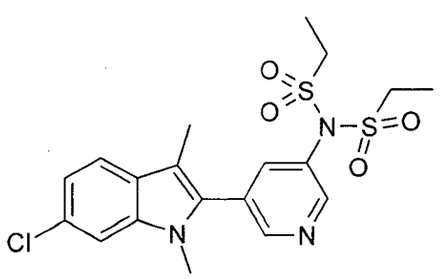
(b) [5-(1-metil-3-carboxaldehído-6-cloro-1H-indol-2-il)-piridin-3-il)-amida del ácido bis-etan-sulfónico



Un matraz se carga con dimetil-formamida (10 mililitros), y se enfría a 0°C. Se agrega oxicloruro de fósforo (0.205 mililitros, 2.178 milimoles), y la mezcla de reacción se agita durante 20 minutos. Se agrega la [5-(1-metil-6-cloro-1H-indol-2-il)-piridin-3-il)-amida del ácido bis-etan-sulfónico (0.875 gramos, 1.980 milimoles), y la mezcla de reacción se deja agitándose a temperatura ambiente durante la noche. La reacción se lava con $NaHCO_3$ acuoso saturado, y se extrae con acetato de etilo. La capa orgánica se separa y se lava con agua tres veces, entonces se seca sobre Na_2SO_4 y se concentra al vacío, para proporcionar la [5-(1-metil-3-carboxaldehído-6-cloro-1H-indol-2-il)-piridin-3-il)-amida del ácido bis-etan-sulfónico.

MS (ESI) *m/z* 469.9 $(M+H)^+$.

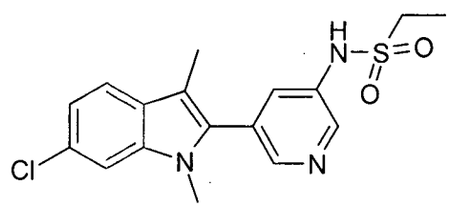
(c) [5-(1,3-dimetil-6-cloro-1H-indol-2-il)-piridin-3-il)-amida del ácido bis-etan-sulfónico



Un matraz se carga con la [5-(1-metil-3-carboxaldehído-6-cloro-1H-indol-2-il)-piridin-3-il)-amida del ácido bis-etan-sulfónico (0.225 gramos, 0.479 milimoles), yoduro de zinc (0.2320 gramos, 0.718 milimoles), $NaCN(BH)_3$ (0.228 gramos, 3.591 milimoles), y dicloro-etano (5 mililitros). La reacción se pone a reflujo durante 1.5 horas. La mezcla de reacción se enfría a temperatura ambiente, y se filtra sobre Celite. La capa de Celite se lava con dicloro-metano. El filtrado se lava con una solución reguladora que contiene 1:1 de hidróxido de amonio saturado y una solución saturada de cloruro de amonio. La capa orgánica se seca sobre sulfato de sodio, y se concentra al vacío, para dar la [5-(1,3-dimetil-6-cloro-1H-indol-2-il)-piridin-3-il)-amida del ácido bis-etan-sulfónico.

MS (ESI) *m/z* 455.9 $(M+H)^+$

(d) [5-(1,3-dimetil-6-cloro-1H-indol-2-il)-piridin-3-il)-amida del ácido etan-sulfónico



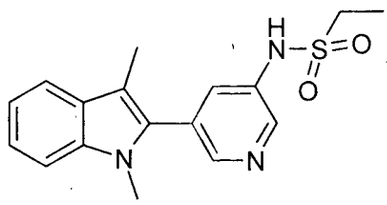
La [5-(1,3-dimetil-6-cloro-1H-indol-2-il)-piridin-3-il)-amida del ácido bis-etan-sulfónico se procesa de acuerdo con el procedimiento descrito en el Ejemplo 225c, para dar la [5-(1,3-dimetil-6-cloro-1H-indol-2-il)-piridin-3-il)-amida del ácido etan-sulfónico.

^1H RMN (400 MHz, MeOD) δ ppm 1.41 (t, *J*=7.33 Hz, 3 H), 2.31 (s, 3 H), 3.26 (q, *J*=7.33 Hz, 2 H), 3.67 (s, 3 H), 7.12 (dd, *J*=8.46,

1.89 Hz, 1 H), 7.49 (d, *J*=1.77 Hz, 1 H), 7.57 (d, *J*=8.34 Hz, 1 H), 7.81 - 7.86 (m, 1 H), 8.41 (d, *J*=1.77 Hz, 1 H), 8.51 (d, *J*=2.27 Hz, 1 H). HRMS (ESI) m/z 364.0894 [$(M+H)^+$ Calculado para $C_{17}H_{18}N_3O_2SCl$ 364.0881].

Ejemplo 236

[5-(1,3-dimetil-1H-indol-2-il)-piridin-3-il)-amida del ácido etan-sulfónico

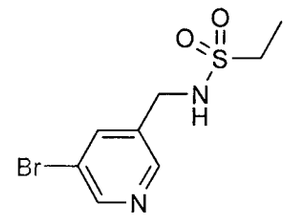


La [5-(1-metil-1H-indol-2-il)-piridin-3-il]-N-etan-sulfonil-amida del ácido etan-sulfónico (Ejemplo 225a) se procesa de acuerdo con los procedimientos descritos en los Ejemplos 235b, 235c y 225c para dar la [5-(1,3-dimetil-1H-indol-2-il)-piridin-3-il)-amida del ácido etan-sulfónico.

^{1}H RMN (400 MHz, MeOD) δ ppm 1.41 (t, *J*=7.5 Hz, 3 H), 2.33 (s, 3 H), 3.27 (q, *J*=7.3 Hz, 2 H), 3.69 (s, 3 H), 7.14 (t, *J*=7.5 Hz, 1 H), 7.24 - 7.31 (m, 1 H), 7.43 (d, *J*=8.3 Hz, 1 H), 7.61 (d, *J*=8.1 Hz, 1 H), 7.84 (t, *J*=2.1 Hz, 1 H), 8.42 (d, *J*=1.8 Hz, 1 H), 8.50 (d, *J*=2.5 Hz, 1 H). HRMS: (ESI) m/z 330.1276 [$(M+H)^+$ Calculado para $C_{17}H_{19}N_3O_2S$ 330.1270].

Ejemplo 237

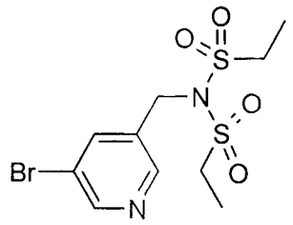
(a) *N*-((5-bromo-piridin-3-il)-metil)-etan-sulfonamida



Un matraz se carga con 5-bromo-nicotin-aldehído (1.15 gramos, 6.18 milimoles), etan-sulfonamida (1.35 gramos, 12.37 milimoles), y tolueno (120 mililitros), y se agregan por goteo isopropóxido de titanio (2.64 gramos, 9.27 milimoles). La mezcla se agita a 120°C durante la noche. La mezcla se concentra al vacío. El residuo se absorbe en dicloro-metano (100 mililitros) y metanol (100 mililitros), y se agrega $NaBH_4$ (0.468 gramos, 12.37 milimoles) a 0°C. La mezcla se agita a 0°C durante 30 minutos. Entonces se agrega agua (50 mililitros), y la mezcla se agita durante 5 minutos. La suspensión se filtra a través de un cojín de Celite. La capa de Celite se lava con dicloro-metano (50 mililitros, 3 veces). El filtrado se concentra al vacío. La fase acuosa resultante se extrae con dicloro-metano (500 mililitros), y la fase orgánica se seca sobre Na_2SO_4, se agrega gel de sílice (20 gramos), y se concentra al vacío. El residuo se purifica mediante cromatografía en sílice eluyendo con un gradiente del 0 al 7 por ciento de MeOH-DCM, para dar la *N*-((5-bromo-piridin-3-il)-metil)-etan-sulfonamida.

MS (ESI) *m/z* 278.9, 280.8, $(M+H)^+$.

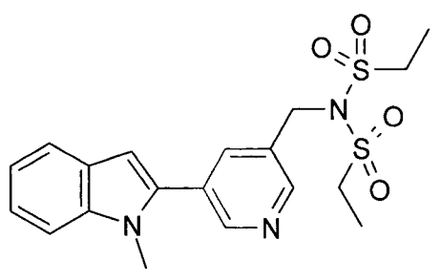
(b) *N*-((5-bromo-piridin-3-il)-metil)-l-(etil-sulfonil)-etan-sulfonamida



A una solución de *N*-((5-bromo-piridin-3-il)-metil)-etan-sulfonamida (1.8 gramos, 5.55 milimoles), y trietil-amina (1.683 gramos, 16.64 milimoles) en dicloro-metano (20 mililitros) a 0°C, se le agrega cloruro de etan-sulfonilo (1.426 gramos, 11.09 milimoles), y la mezcla se agita a 0°C durante 1 hora. Se agrega gel de sílice (10 gramos), y la mezcla se concentra al vacío. El residuo se purifica mediante cromatografía en sílice eluyendo con del 0 al 2 por ciento de MeOH-DCM, para dar la *N*-((5-bromo-piridin-3-il)-metil)-*N*-(etil-sulfonil)-etan-sulfonamida.

^{1}H RMN (400 MHz, DMSO-d_6) δ ppm 1.14 (t, *J*=7.3 Hz, 6 H), 3.48 (q, *J*=7.3 Hz, 4 H), 4.92 (s, 2 H), 8.0 (t, *J*=2.1 Hz, 1 H), 8.59 (d, *J*=2.0 Hz, 1 H), 8.72 (d, *J*=2.3 Hz, 1 H).

(c) *N*-(etil-sulfonil)-*N*-((5-(1-metil-1H-indol-2-il)-piridin-3-il)-metil)-etan-sulfonamida

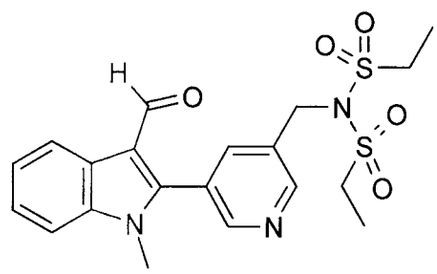


La *N*-((5-bromo-piridin-3-il)-metil)-l-(etil-sulfonil)-etan-sulfonamida y ácido *N*-metil-indol-2-borónico se procesan de acuerdo

con el procedimiento descrito en el Ejemplo 100, para dar la *N*-(etil-sulfonil)-*N*-((5-(1-metil-1H-indol-2-il)-piridin-3-il)-metil)-etan-sulfonamida.

MS (ESI) *m/z* 422.0 $(M+H)^+$.

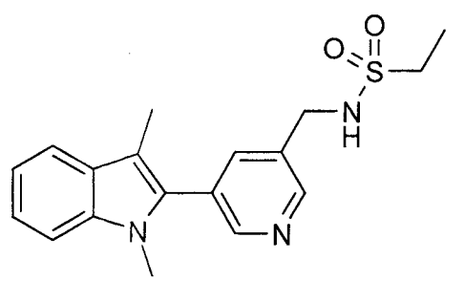
(d) *N*-(etil-sulfonil)-*N*-((5-(3-formil-1-metil-1H-indol-2-il)-piridin-3-il)-metil)-etan-sulfonamida



La *N*-(etil-sulfonil)-*N*-((5-(1-metil-1H-indol-2-il)-piridin-3-il)-metil)-etan-sulfonamida se procesa de acuerdo con el procedimiento descrito en el Ejemplo 235b, para dar la *N*-(etil-sulfonil)-*N*-((5-(3-formil-1-metil-1H-indol-2-il)-piridin-3-il)-metil)-etan-sulfonamida.

MS (ESI) *m/z* 450.0 $(M+H)^+$.

(e) *N*-((5-(1,3-dimetil-1H-indol-2-il)-piridin-3-il)-metil)-etan-sulfonamida



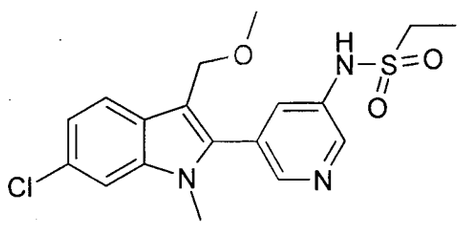
La *N*-(etil-sulfonil)-*N*-((5-(3-formil-1-metil-1H-indol-2-il)-piridin-3-il)-metil)-etan-sulfonamida se procesa de acuerdo con el

procedimiento descrito en el Ejemplo 235c, para dar la *N*-(etil-sulfonil)-*N*-((5-(1,3-dimetil-1H-indol-2-il)-piridin-3-il)-metil)-etan-sulfonamida, la cual se procesa de acuerdo con el procedimiento descrito en el Ejemplo 225c, para dar la *N*-((5-(1,3-dimetil-1H-indol-2-il)-piridin-3-il)-metil)-etan-sulfonamida.

^{1}H RMN (400 MHz, DMSO-d_6) δ ppm 1.20 (t, *J*=7.3 Hz, 3 H), 2.24 (s, 3 H), 3.04 (q, *J*=7.3 Hz, 2 H), 3.62 (s, 3 H), 4.31 (s, 2 H), 7.10 (t, *J*=7.5 Hz, 1 H), 7.22 (ddd, *J*=8.2, 7.0, 1.3 Hz, 1 H), 7.49 (d, *J*=8.1 Hz, 1 H), 7.58 (d, *J*=7.8 Hz, 1 H), 7.72 (br. s., 1 H), 7.87 (t, *J*=2.0 Hz, 1 H), 8.61 (dd, *J*=7.2, 2.2 Hz, 2 H). HRMS: (ESI) m/z 344.1442 [(M+H)+ Calculado para $C_{18}H_{22}N_3O_2S$: 344.1427].

Ejemplo 238

(a) [5-(1-metil-3-metoxi-metil-6-cloro-1H-indol-2-il)-piridin-3-il)-amida del ácido etan-sulfónico



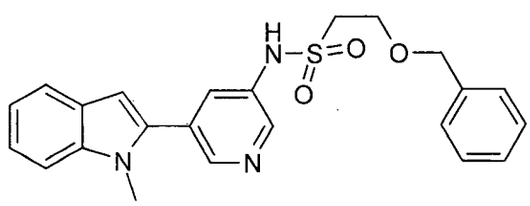
La [5-(1-metil-3-carboxaldehído-6-cloro-1H-indol-2-il)-piridin-3-il)-amida del ácido bis-etan-sulfónico (Ejemplo 235b, 0.150 gramos, 0.319 milimoles) se disuelve en metanol (5 mililitros), y se enfría a 0°C. Se agrega $NaBH_4$ (0.019 gramos, 0.798 milimoles), y la mezcla de reacción se agita a temperatura ambiente durante 2 horas. Se agrega NaOH acuoso 4M (1 mililitro), y la reacción se agita a

temperatura ambiente durante 1 hora. El metanol se remueve entonces al vacío. El producto crudo se absorbe en dicloro-metano, y se lava con agua dos veces. La capa orgánica se seca sobre Na_2SO_4 y se concentra al vacío. El producto crudo se purifica mediante cromatografía por evaporación instantánea en gel de sílice (dicloro-metano : metanol, 9:1), para proporcionar la [5-(1-metil-3-metoxi-metil-6-cloro-1H-indol-2-il)-piridin-3-il)-amida del ácido bis-etan-sulfónico.

^{1}H RMN (400 MHz, MeOD) δ ppm 1.41 (t, *J*=7.3 Hz, 3 H), 3.28 (q, *J*=7.3 Hz, 2 H), 3.39 (s, 3 H), 3.72 (s, 3 H), 4.54 (s, 2 H), 7.18 (dd, *J*=8.6, 1.8 Hz, 1 H), 7.56 (d, *J*=1.8 Hz, 1 H), 7.71 (d, *J*=8.6 Hz, 1 H), 7.93 (t, *J*=2.3 Hz, 1 H), 8.48 (d, *J*=1.8 Hz, 1 H), 8.54 (d, *J*=2.5 Hz, 1 H). HRMS: (ESI) m/z 394.0990 [$(M+H)^+$ Calculado para $C_{18}H_{20}N_3O_3SCl$ 394.0986].

Ejemplo 239

(a) 2-(benciloxi)-*N*-(5-(1-metil-1H-indol-2-il)-piridin-3-il)-etan-sulfonamida

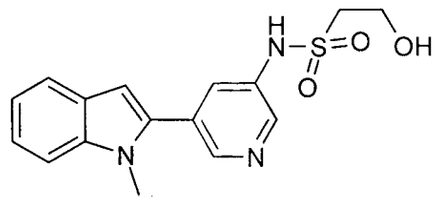


A una solución de 5-(1-metil-1H-indol-2-il)-piridin-3-amina (Ejemplo 100, 150 miligramos, 0.672 milimoles), y trietil-amina (272 miligramos, 2.69 milimoles) en dicloro-metano (6 mililitros), se le agrega por goteo cloruro de 2-cloro-etan-sulfonilo (274 miligramos,

1.68 milimoles) en dicloro-metano (2 mililitros) a 0°C. La mezcla se agita a 0°C durante 1 hora. Se agrega gel de sílice (5 gramos), y la mezcla se concentra. Después de la elución, las fracciones que contienen el producto se concentran para dar un residuo, el cual se vuelve a disolver en alcohol bencílico (20 mililitros). Se agrega NaH al 60 por ciento en aceite mineral. La mezcla se agita a 70°C durante 1 día. La mezcla entonces se filtra, y el filtrado se purifica en una XBridge C18 eluyendo con un gradiente de 1:9 a 9:1 de acetonitrilo-agua, para dar la 2-(benciloxi)-*N*-(5-(1-metil-1H-indol-2-il)-piridin-3-il)-etan-sulfonamida.

MS (ESI) *m/z* 422.1 $(M+H)^+$.

(b) 2-hidroxi-*N*-(5-(1-metil-1H-indol-2-il)-piridin-3-il)-etan-sulfonamida



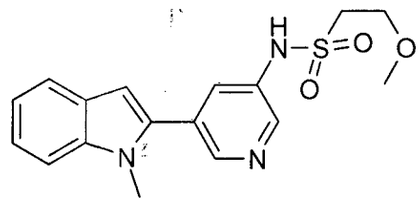
Un matraz se carga con 2-(benciloxi)-N-(5-(1-metil-1H-indol-2-il)-piridin-3-il)-etan-sulfonamida (90 miligramos, 0.214 milimoles), y metanol (5 mililitros), y el matraz se inunda con N_2. Se agrega Pd/C al 10 por ciento (22.7 miligramos, 0.021 milimoles) a la mezcla. El matraz se inunda con H_2 y se agita bajo una atmósfera de H_2 a 50°C durante la noche. La mezcla se filtra, y el filtrado se purifica mediante cromatografía en sílice eluyendo con un gradiente del 0 al 4 por ciento de metanol : dicloro-metano, para dar la 2-hidroxi-*N*-(5-

(1-metil-1H-indol-2-il)-piridin-3-il)-etan-sulfonamida.

^{1}H RMN (400 MHz, DMSO-d_6) δ ppm 3.37 (t, *J*=6.2 Hz, 2 H), 3.77 (s, 3 H), 3.80 (t, *J*=6.3 Hz, 2 H), 4.96 (br. s., 1 H), 6.70 (s, 1 H), 7.10 (t, *J*=7.1 Hz, 1 H), 7.23 (td, *J*=7.6, 1.1 Hz, 1 H), 7.53 (d, *J*=7.8 Hz, 1 H), 7.61 (d, *J*=7.8 Hz, 1 H), 7.79 (t, *J*=2.3 Hz, 1 H), 8.47 (d, *J*=2.5 Hz, 1 H), 8.55 (d, *J*=1.8 Hz, 1 H), 10.12 (br. s., 1 H). HRMS: (ESI) m/z 332.1072 [(M+H)$^+$ Calculado para $C_{16}H_{18}N_3O_3S$ 332.1063].

Ejemplo 240

2-metoxi-*N*-(5-(1-metil-1H-indol-2-il)-piridin-3-il)-etan-sulfonamida



Un matraz se carga con la 5-(1-metil-1*H*-indol-2-il)-piridin-3-amina (Ejemplo 100, 22 miligramos, 0.10 milimoles), dicloro-metano (2 mililitros), y trietil-amina (20 miligramos, 0.20 milimoles). Se agrega por goteo cloruro de 2-cloro-etan-sulfonilo (16 miligramos, 0.10 milimoles) en dicloro-metano (0.5 mililitros) a 0°C. La mezcla se agita durante el fin de semana a temperatura ambiente. El solvente se remueve al vacío, y se agregan metanol (2 mililitros), y NaOH acuoso 5 M (3 mililitros). La mezcla se agita a 60°C durante la noche, se concentra al vacío, y el residuo se extrae con dicloro-metano. La fase orgánica combinada se seca sobre Na_2SO_4 y se concentra. El residuo se purifica mediante cromatografía en gel de sílice eluyendo con un gradiente del 0 al 5 por ciento de metanol :

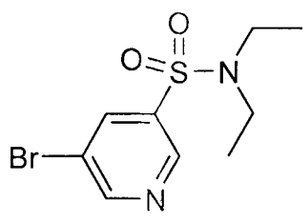
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dicloro-metano, para dar la 2-metoxi-*N*-(5-(1-metil-1H-indol-2-il)-piridin-3-il)-etan-sulfonamida.

^{1}H RMN (400 MHz, DMSO-d_6) δ ppm 3.18 (s, 3 H), 3.51 (t, *J*=5.7 Hz, 2 H), 3.70 (t, *J*=5.7 Hz, 2 H), 3.77 (s, 3 H), 6.70 (d, *J*=0.5 Hz, 1 H), 7.10 (td, *J*=7.5, 1.0 Hz, 1 H), 7.23 (ddd, *J*=8.2, 7.1, 1.1 Hz, 1 H), 7.53 (d, *J*=8.3 Hz, 1 H), 7.61 (d, *J*=7.8 Hz, 1 H), 7.78 (t, *J*=2.3 Hz, 1 H), 8.46 (d, *J*=2.5 Hz, 1 H), 8.55 (d, *J*=2.0 Hz, 1 H). HRMS: (ESI) m/z 346.1251 [(M+H)+ Calculado para $C_{17}H_{20}N_3O_3S$: 346.1225].

Ejemplo 241

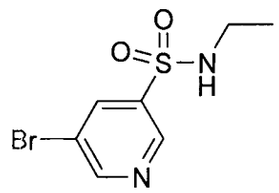
(a) 5-bromo-*N*,*N*-dietil-piridin-3-sulfonamida



A una suspensión de 5-bromo-piridin-3-sulfonamida (237 miligramos, 1 milimol), y K_2CO_3 (276 miligramos, 2 milimoles) en N,N-dimetil-formamida (1 mililitro), se le agrega yodo-etano (156 miligramos, 1 milimol) en N,N-dimetil-formamida (5 mililitros) mediante una bomba de jeringa, durante 2 horas. La mezcla se agita entonces a temperatura ambiente durante la noche. Se agrega por goteo yodo-etano (0.020 mililitros, 0.2 milimoles) en N,N-dimetil-formamida (1 mililitro). La mezcla se agita durante el fin de semana y se filtra. El filtrado se purifica mediante Xterra RP18 eluyendo con un gradiente de 1:9 a 9:1 de acetonitrilo-agua, para dar la 5-bromo-*N*,*N*-dietil-piridin-3-sulfonamida.

MS (ESI) *m/z* 293.0, 295.1 $(M+H)^+$.

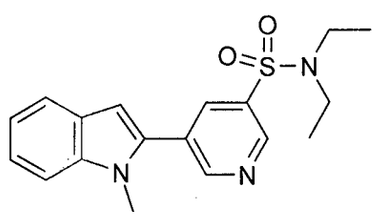
(b) *N*-etil-5-(1-metil-1H-indol-2-il)-piridin-3-sulfonamida.



El método descrito en el Ejemplo 241a también proporciona la *N*-etil-5-(1-metil-1H-indol-2-il)-piridin-3-sulfonamida como un producto de la reacción.

MS (ESI) *m/z* 265.0, 267.0 $(M+H)^+$.

(c) *N*,*N*-dietil-5-(1-metil-1H-indol-2-il)-piridin-3-sulfonamida



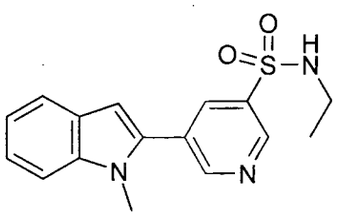
Un matraz se carga con ácido 1-metil-1H-indol-2-il-borónico (90 miligramos, 0.512 milimoles), 5-bromo-*N*,*N*-dietil-piridin-3-sulfonamida (100 miligramos, 0.341 milimoles), y $Pd(PPh_3)_4$ soportado por polímero (189 miligramos, 0.017 milimoles), y el matraz se inunda con N_2 durante 5 minutos. Se agregan 1,4-dioxano (10 mililitros), y K_2CO_3 2M en agua (0.512 mililitros, 1.023 milimoles) bajo N_2, y la mezcla se agita a 90°C bajo N_2 durante 2 horas. La mezcla se enfría entonces a temperatura ambiente, y se agrega dimetil-formamida (4 mililitros). La mezcla se concentra al vacío, y el residuo se filtra, y el filtrado se purifica mediante Xterra RP18

eluyendo con un gradiente de 1:9 a 9:1 de acetonitrilo-agua, para dar la *N*,*N*-dietil-5-(1-metil-1H-indol-2-il)-piridin-3-sulfonamida.

^{1}H RMN (400 MHz, DMSO-d_6) δ ppm 1.10 (t, *J*=7.1 Hz, 6 H), 3.29 (d, *J*=7.1 Hz, 4 H), 3.80 (s, 3 H), 6.85 (s, 1 H), 7.08 - 7.14 (m, 1 H), 7.26 (td, *J*=7.71, 1.26 Hz, 1 H), 7.56 (dd, *J*=8.3, 0.5 Hz, 1 H), 7.63 (d, *J*=7.8 Hz, 1 H), 8.33 (t, *J*=2.1 Hz, 1 H), 9.00 (d, *J*=2.0 Hz, 1 H), 9.10 (d, *J*=2.2 Hz, 1 H). HRMS: (ESI) m/z 344.1428 [(M+H)$^+$ Calculado para $C_{18}H_{22}N_3O_2S$ 344.1427].

Ejemplo 242

N-etil-5-(1-metil-1H-indol-2-il)-piridin-3-sulfonamida



La *N*-etil-5-(1-metil-1H-indol-2-il)-piridin-3-sulfonamida se procesa de acuerdo con el método descrito en el Ejemplo 241c, para dar la *N*-etil-5-(1-metil-1H-indol-2-il)-piridin-3-sulfonamida.

^{1}H RMN (400 MHz, DMSO-d_6) δ ppm 1.02 (t, *J*=7.2 Hz, 3 H), 2.92 (q, *J*=7.2 Hz, 2 H), 3.81 (s, 3 H), 6.83 (s, 1 H), 7.12 (t, *J*=7.1 Hz, 1 H), 7.26 (td, *J*=7.6, 1.1 Hz, 1 H), 7.56 (d, *J*=8.3 Hz, 1 H), 7.63 (d, *J*=7.8 Hz, 1 H), 8.31 (t, *J*=2.2 Hz, 1 H), 8.97 (d, *J*=2.3 Hz, 1 H), 9.08 (d, *J*=2.2 Hz, 1 H). HRMS: (ESI) m/z 316.1126 [(M+H)$^+$ Calculado para $C_{16}H_{18}N_3O_2S$ 316.1114].

Ejemplo 243: Ensayo *In-vitro* para la Inhibición de la Sintasa de Aldosterona

Las actividades de un compuesto de acuerdo con la presente invención se pueden evaluar mediante el siguiente métodos *in vitro* bien descrito en la técnica. Véase Fieber, A y colaboradores (2005), "Aldosterone Synthase Inhibitor Ameliorates Angiotensin II–Induced Organ Damage", *Circulation*, 111: 3087-3094.

En particular, la inhibición de la secreción de aldosterona y cortisol se puede determinar *in vitro* mediante el siguiente ensayo.

La línea celular NCI-H295R fue originalmente aislada a partir de un carcinoma adrenocortical, y se ha caracterizado en la literatura a través de la secreción estimulable de hormonas esteroideas y la presencia de las enzimas esenciales para la estereoidogénesis. Las células muestran la propiedad fisiológica de las células adrenocorticales fetales humanas zonalmente no diferenciadas que, sin embargo, tienen la capacidad para producir las hormonas esteroideas que se forman en las tres zonas fenotípicamente distinguibles en la corteza suprarrenal adulta. Por consiguiente, las células NCI-H295R tienen CYP11B2 (sintasa de aldosterona) y CYP11B1 (11-hidroxilasa esteroidea).

La línea celular de carcinoma adrenocortical humano NCI-H295R se obtiene en la American Type Culture Collection (Manassas, VA). El suplemento de insulina/transferrina/selenio (ITS)-A (100x), DMEM/F-12, antibiótico/antimicótico (100x), y el suero fetal de becerro (FCS) se adquieren en invitrogen (Carlsbad, CA). Las perlas del ensayo de proximidad de cintilación PVT anti-ratón (SPA) y las placas NBS de 96 pozos, se obtienen en Amersham

(Piscataway, NJ), y en Corning (Acton, MA), respectivamente. Las placas de fondo plano de 96 pozos de fondo transparente se adquieren en Costar (Corning, NY). La aldosterona y la angiotensina (Ang II) se adquieren en Sigma (St. Louis, MO). La D-[1,2,6,7-^{3}H(N)]aldosterona y el [1,2,6,7-^{3}H(N)]-cortisol se adquieren en PerkinElmer (Boston, MA). El suero-Nu es un producto de BD Biosciences (Franklin Lakes, NJ).

Para la medición *in vitro* de la actividad de aldosterona y cortisol, se siembran las células de carcinoma adrenocortical humano NCI-H295R en placas NBS de 96 pozos, en una densidad de 25,000 células/pozo en 100 microlitros de un medio de cultivo que contiene DMEM/F12 complementado con suero fetal de becerro al 10 por ciento, suero-Nu al 2.5 por ciento, 1 microgramo de ITS/mililitro, y antibiótico/antimicótico 1x. El medio se cambia después de cultivar durante 3 días a 37°C bajo una atmósfera de CO_2 al 5 por ciento / aire al 95 por ciento. Al día siguiente, las células se enjuagan con 100 microlitros de DMEM/F12, y se incuban en pozos cuadruplicados a 37°C durante 24 horas con 100 microlitros del medio de tratamiento que contiene un estimulante de células y un compuesto en diferentes concentraciones. La sustancia de prueba se agrega en un intervalo de concentración de 0.2 nanomolar a 16 micromolar. Los estimulantes de células que se pueden utilizar son angiotensina-II (1 micromolar), iones de potasio (16 milimolar), forskolina (10 micromolar), o una combinación de dos estimulantes. Al final de la incubación, se puede detectar la excreción de aldosterona y cortisol

en el medio de cultivo mediante anticuerpos monoclonales específicos comercialmente disponibles en radioinmunoensayos de acuerdo con las instrucciones del fabricante.

La medición de aldosterona también se puede llevar a cabo utilizando un formato de placa de 96 pozos. Cada muestra de prueba se incuba con 0.02 µCi de D-[1,2,6,7-^{3}H(N)]aldosterona y 0.3 microgramos de anticuerpo anti-aldosterona en suero regulado con fosfato (PBS) que contiene Triton X-100 al 0.1 por ciento, albúmina de suero bovino al 0.1 por ciento, y glicerol al 12 por ciento, en un volumen total de 200 microlitros, a temperatura ambiente, durante 1 hora. Entonces se agregan las perlas PVT SPA anti-ratón (50 microlitros) a cada pozo, y se incuban durante la noche a temperatura ambiente antes de contarse en un contador de placas Microbeta. La cantidad de aldosterona en cada muestra se calcula comparando con una curva estándar generada utilizando cantidades conocidas de la hormona. La medición de cortisol se puede llevar a cabo de una manera similar a aquélla de a aldosterona, excepto que se utiliza el [1,2,6,7-^{3}H(N)-cortisol.

La inhibición de la liberación de un esteroide se puede utilizar como una medida de la inhibición de la enzima respectiva mediante los compuestos de prueba añadidos. La inhibición de la actividad enzimática dependiente de la dosis mediante un compuesto, se calcula por medio de una gráfica de inhibición, la cual se caracteriza por una IC_{50}. Los valores IC_{50} para los compuestos de prueba activos se aseveran mediante un simple análisis de regresión lineal, con el

objeto de construir gráficas de inhibición sin ponderación de los datos. La gráfica de inhibición se calcula mediante el ajuste de una función logística de 4 parámetros a los puntos de datos brutos, empleando el método de mínimos cuadrados. La ecuación de la función logística de 4 parámetros se calcula como sigue: Y = (d-a) / ((1 + (x/c)-(b) + a) en donde: a = mínima, b = inclinación , c= IC_{50}, d = máxima, x = concentraciones de inhibidor.

Tabla 1

Actividad Inhibidora de los Compuestos

Ejemplo	**Secreción de aldosterona de las células IC_{50} (nM)**	**Secreción de Cortisol de las células IC_{50} (nM)**
6	1	7
15	27	447
33	14	662
42	30	600
65	10	240
90	40	400
101	2	37

Ejemplo	Secreción de aldosterona de las células IC_{50} (nM)	Secreción de Cortisol de las células IC_{50} (nM)
106	85	530
107	9	220
123	78	650
138	43	326
171	3	168
180	2	3
186	21	390
192	4	20
196	3	19
206	2	213
209	23	788
214	56	377
216 (un enantiómero)	32	600

Ejemplo	Secreción de aldosterona de las células IC_{50} (nM)	Secreción de Cortisol de las células IC_{50} (nM)
216 (otro enantiómero)	35	1230
217	4	22
226	36	345
228	105	> 1000
229	5	125
231	2	51
236	21	1100
237	5	1611
238	44	> 1000
242	23	> 1000

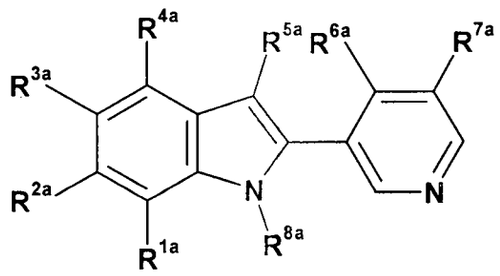
Equivalentes

Los expertos en este campo reconocerán, o podrán aseverar empleando no más que la experimentación de rutina, numerosos equivalentes a los procedimientos específicos descritos en la

presente. Se considera que tales equivalentes están dentro del alcance de la presente invención, y son cubiertos por las siguientes reivindicaciones. Se pueden seleccionar los componentes, procesos, y métodos apropiados a partir de las patentes, solicitudes, y otros documentos para la presente invención y las modalidades de la misma.

REIVINDICACIONES

1. Un compuesto de la fórmula I:



(I)

en donde:

R^{1a}, R^{2a}, R^{3a}, y R^{4a} son cada uno independientemente hidrógeno, halógeno, ciano, hidroxilo, alcoxilo, alquilo, alquenilo, o alcoxi-carbonilo;

R^{5a} es hidrógeno, halógeno, ciano, alquilo, alquenilo, aril-alquilo, heteroaril-alquilo, amino-carbonilo, alquil-amino-carbonilo, carboxilato, alcoxi-carbonilo, heterociclil-carbonilo, arilo, o heteroarilo;

R^{6a} y R^{7a} son cada uno independientemente hidrógeno, halógeno, hidroxilo, alcoxilo, amino, alquilo, sulfonilo, -O-sulfonilo, alquil-amino, heterociclilo, amino-carbonilo, carboxilato, o alcoxi-carbonilo;

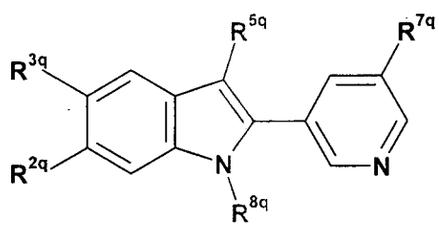
R^{8a} es hidrógeno, alquilo, aril-alquilo, heteroaril-alquilo, alcoxi-carbonilo, sulfonilo, aroílo, arilo, o heteroarilo;

y las sales farmacéuticamente aceptables, polimorfos, rotámeros, pro-fármacos, enantiómeros, hidratos, y solvatos del mismo;

con la condición de que cuando menos uno de R^{1a}-R^{8a} es diferente de hidrógeno; y cuando R^{3a} es alquilo inferior o halógeno, entonces cuando menos uno de R^{1a}, R^{2a} y R^{4a}-R^{8a} es diferente de hidrógeno; y cuando R^{5a} es ciano o alquilo inferior opcionalmente sustituido con ciano, -C(O)-piperidina, amino, alquil-amino, dialquil-amino, carboxilato, alcoxi-carbonilo, amino-carbonilo, o heterociclilo, entonces cuando menos uno de R^{1a}-R^{4a} y R^{6a}-R^{8a} es diferente de hidrógeno; y cuando R^{7a} es imidazolilo, entonces cuando menos uno de R^{1a}-R^{6a} y R^{8a} es diferente de hidrógeno; y cuando R^{8a} es alquilo inferior, aril-alquilo o alcoxi-carbonilo, entonces cuando menos uno de R^{1a}-R^{7a} es diferente de hidrógeno; y cuando R^{5a} es alquilo inferior, y R^{8a} es alquilo sustituido con carboxilato o $PO_3R^{21}R^{22}$ en donde R^{21} y R^{22} son cada uno independientemente hidrógeno o alquilo inferior, entonces cuando menos uno de R^{1a}-R^{4a} y R^{6a} y R^{7a} es diferente de hidrógeno; y cuando R^{3a} es halógeno y R^{5a} y R^{8a} son independientemente alquilo inferior opcionalmente sustituido con carboxilato, alcoxi-carbonilo, o -C(O)-piperidina, entonces cuando menos uno de R^{1a}, R^{2a}, R^{4a}, R^{6a} y R^{7a} es diferente de hidrógeno; y cuando R^{5a} es alquenilo inferior sustituido con heteroarilo, y R^{8a} es alquilo inferior, entonces cuando menos uno de R^{1a}-R^{4a}, R^{6a} y R^{7a} es diferente de hidrógeno; y cuando R^{3a} es halógeno, o alquilo inferior, y R^{5a} es alquilo inferior sustituido con dialquil-amino, dialquil-amino-carbonilo, carboxilato, alcoxi-carbonilo o amino-carbonilo, entonces cuando menos uno de R^{1a}, R^{2a}, R^{4a}, y R^{6a}-R^{8a} es diferente de hidrógeno; y cuando R^{3a} es –O-bencilo y R^{5a} es alquil-NH_2, entonces

cuando menos uno de R^{1a}, R^{2a}, R^{4a}, y R^{6a}-R^{8a} es diferente de hidrógeno; y cuando R^{2a} y R^{3a} son cada uno alcoxilo y R^{5a} es ciano, entonces cuando menos uno de R^{1a}, R^{4a}, y R^{6a}-R^{8a} es diferente de hidrógeno; y cuando R^{1a} y R^{3a} son cada uno halógeno y R^{5a} es alquil–NH_2, entonces cuando menos uno de R^{2a}, R^{4a}, y R^{6a}-R^{8a} es diferente de hidrógeno; y cuando R^{2a} es alcoxi-carbonilo y R^{4a} es halógeno, entonces cuando menos uno de R^{1a}, R^{3a}, R^{5a} y R^{6a}-R^{8a} es diferente de hidrógeno; y cuando R^{5a} es alquilo y R^{7a} es -OCH_2-(N-metil-pirrolidina), entonces cuando menos uno de R^{1a}-R^{4a}, R^{6a} y R^{8a} es diferente de hidrógeno; y cuando R^{3a} es cicloalquilo y R^{5a} es alquil–NH_2, entonces cuando menos uno de R^{1a}, R^{2a}, R^{4a}, y R^{6a}-R^{8a} es diferente de hidrógeno; y cuando R^{3a} es alquilo sustituido con aroílo, y R^5 y R^8 son cada uno independientemente hidrógeno o alquilo inferior, entonces cuando menos uno de R^{1a}, R^{2a}, y R^{4a} es diferente de hidrógeno.

2. Un compuesto de la fórmula II:



(II)

en donde:

R^{2q} es hidrógeno o halógeno;

R^{3q} es hidrógeno, halógeno, o ciano;

R^{5q} es hidrógeno, alquilo, o ciano;

R^{7q} es hidrógeno, halógeno, alcoxilo, -OSO_2-heterociclilo, -O-aril-alquilo, -NR'-SO_2-alquilo, -NR'-C(O)-alquilo, -NR'-C(O)-NR'-alquilo, -NR'-C(O)-O-alquilo, halo-alquilo, o alquilo opcionalmente sustituido con heterociclilo, –NR'-SO_2-alquilo, -NR'-SO_2-halo-alquilo, NR'-C(O)-alquilo, NR'-C(O)-heterociclilo, -NR'-C(O)-NR'-alquilo, o -NR'-C(O)-O-alquilo;

R^{8q} es hidrógeno, alquilo, hidroxi-alquilo, -alquil-OC(O)-alquilo, carboxilato, alcoxi-carbonilo, o aril-alquilo sustituido con alquilo, o aroílo sustituido con ciano y/o alquilo, o -alquil-O-arilo sustituido con alcoxi-carbonilo;

cada R' es independientemente hidrógeno, alquilo de 1 a 4 átomos de carbono, o cicloalquilo de 3 a 6 átomos de carbono;

y las sales farmacéuticamente aceptables, polimorfos, rotámeros, pro-fármacos, enantiómeros, hidratos, y solvatos del mismo;

con la condición de que cuando menos uno de R^{2q}, R^{3q}, R^{5q}, R^{7q} y R^{8q} es diferente de hidrógeno; y cuando R^{8q} es alquilo inferior o alcoxi-carbonilo, entonces cuando menos uno de R^{2q}, R^{3q}, R^{5q} y R^{7q} es diferente de hidrógeno; y cuando R^{5q} es ciano, entonces cuando menos uno de R^{2q}, R^{3q}, y R^{8q} es diferente de hidrógeno.

3. El compuesto de acuerdo con la reivindicación 2, en donde R^{7q} es alcoxilo o alquilo sustituido con heterociclilo, y R^{8q} es alquilo.

4. El compuesto de acuerdo con la reivindicación 2, en donde:

R^{2q} es hidrógeno o halógeno;

R^{3q} es hidrógeno o halógeno;

R^{5q} es hidrógeno o ciano;

R^{7q} es alquilo opcionalmente sustituido con heterociclilo, –NR'-SO_2-alquilo, -NR'-SO_2-halo-alquilo, NR'-C(O)-alquilo, NR'-C(O)-heterociclilo, -NR'-C(O)-NR'-alquilo, o -NR'-C(O)-O-alquilo;

R' es independientemente hidrógeno, alquilo de 1 a 4 átomos de carbono, o cicloalquilo de 3 a 6 átomos de carbono; y

R^{8q} es hidrógeno, o alquilo de 1 a 6 átomos de carbono.

5. El compuesto de acuerdo con la reivindicación 2 ó 4, en donde:

R^{2q} es hidrógeno o halógeno;

R^{3q} es hidrógeno o halógeno;

R^{5q} es hidrógeno o ciano;

R^{7q} es alquilo de 1 a 4 átomos de carbono opcionalmente sustituido con heterociclilo, –NR'-SO_2-alquilo de 1 a 4 átomos de carbono, -NR'-SO_2-haloalquilo de 1 a 4 átomos de carbono, NR'-C(O)-alquilo de 1 a 4 átomos de carbono, NR'-C(O)-heterociclilo, -NR'-C(O)-NR'-alquilo de 1 a 4 átomos de carbono, o -NR'-C(O)-O-alquilo de 1 a 4 átomos de carbono;

R' es independientemente hidrógeno, o alquilo de 1 a 4 átomos de carbono; y

R^{8q} es hidrógeno, o alquilo de 1 a 6 átomos de carbono.

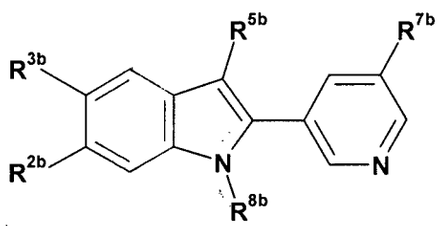
6. El compuesto de acuerdo con las reivindicaciones 2 a 5, en donde:

R^{7q} es alquilo de 1 a 4 átomos de carbono sustituido con –NR'-SO_2-alquilo de 1 a 4 átomos de carbono, -NR'-SO_2-haloalquilo de 1 a 4 átomos de carbono, o NR'-C(O)-alquilo de 1 a 4 átomos de carbono;

R' es independientemente hidrógeno, o alquilo de 1 a 4 átomos de carbono; y

R^{8q} es hidrógeno, metilo, o etilo.

7. Un compuesto de la fórmula III:



(III)

en donde:

R^{2b} es hidrógeno o halógeno;

R^{3b} es hidrógeno, halógeno, o ciano;

R^{5b} es alquilo;

R^{7b} es hidrógeno, halógeno, alcoxilo, -OSO_2-heterociclilo, -O-aril-alquilo, -NR'-SO_2-alquilo, -NR'-C(O)-alquilo, -NR'-C(O)-NR'-alquilo, -NR'-C(O)-O-alquilo, halo-alquilo, o alquilo opcionalmente sustituido con heterociclilo, –NR'-SO_2-alquilo, -NR'-SO_2-halo-alquilo, NR'-C(O)-alquilo, -NR'-C(O)-NR'-alquilo, NR'-C(O)-heterociclilo, o -NR'-C(O)-O-alquilo;

R^{8b} es hidrógeno, alquilo, hidroxi-alquilo, -alquil-OC(O)-alquilo, carboxilato, alcoxi-carbonilo, o aril-alquilo sustituido con

alquilo, o aroílo sustituido con ciano y/o alquilo, o -alquil-O-arilo sustituido con alcoxi-carbonilo;

cada R' es independientemente hidrógeno, alquilo de 1 a 4 átomos de carbono, o cicloalquilo de 3 a 6 átomos de carbono;

y las sales farmacéuticamente aceptables, polimorfos, rotámeros, pro-fármacos, enantiómeros, hidratos, y solvatos del mismo.

8. El compuesto de acuerdo con la reivindicación 7, en donde:

R^{2b} es hidrógeno o halógeno;

R^{3b} es hidrógeno, halógeno, o ciano;

R^{5b} es alquilo de 1 a 4 átomos de carbono;

R^{7b} es hidrógeno, halógeno, alcoxilo de 1 a 4 átomos de carbono, -OSO_2-heterociclilo, -O-aril-alquilo, -NR'-SO_2-alquilo de 1 a 4 átomos de carbono, -NR'-C(O)-alquilo de 1 a 4 átomos de carbono, -NR'-C(O)-NR'-alquilo de 1 a 4 átomos de carbono, -NR'-C(O)-O-alquilo, halo-alquilo, o alquilo de 1 a 4 átomos de carbono opcionalmente sustituido con heterociclilo, –NR'-SO_2-alquilo de 1 a 4 átomos de carbono, -NR'-SO_2-halo-alquilo de 1 a 4 átomos de carbono, NR'-C(O)-alquilo de 1 a 4 átomos de carbono, -NR'-C(O)-NR'-alquilo de 1 a 4 átomos de carbono, NR'-C(O)-heterociclilo, o -NR'-C(O)-O-alquilo de 1 a 4 átomos de carbono;

R^{8b} es hidrógeno, alquilo de 1 a 4 átomos de carbono, hidroxi-alquilo, -alquilo de 1 a 4 átomos de carbono-OC(O)-alquilo de 1 a 4 átomos de carbono, carboxilato, alcoxi-carbonilo, o aril-alquilo

sustituido con alquilo de 1 a 4 átomos de carbono, o aroílo sustituido con ciano y/o alquilo de 1 a 4 átomos de carbono, o -alquilo de 1 a 4 átomos de carbono-O-arilo sustituido con alcoxi-carbonilo;

cada R' es independientemente hidrógeno, alquilo de 1 a 4 átomos de carbono, o cicloalquilo de 3 a 6 átomos de carbono;

y las sales farmacéuticamente aceptables, polimorfos, rotámeros, pro-fármacos, enantiómeros, hidratos, y solvatos del mismo.

9. El compuesto de acuerdo con la reivindicación 7 u 8, en donde:

R^{2b} es hidrógeno o halógeno;

R^{3b} es hidrógeno, halógeno, o ciano;

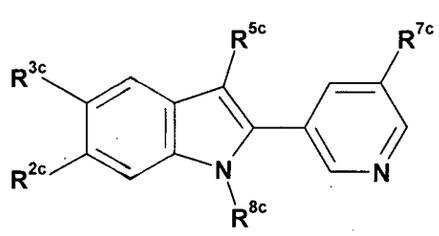
R^{5b} es metilo, etilo, o isopropilo;

R^{7b} es alquilo de 1 a 4 átomos de carbono sustituido con –NR'-SO_2-alquilo de 1 a 4 átomos de carbono, -NR'-SO_2-haloalquilo de 1 a 4 átomos de carbono, NR'-C(O)-alquilo de 1 a 4 átomos de carbono, o -NR'-C(O)-NR'-alquilo de 1 a 4 átomos de carbono;

R^{8b} es hidrógeno, metilo, o etilo;

cada R' es independientemente hidrógeno, o alquilo de 1 a 4 átomos de carbono.

10. Un compuesto de la fórmula IV:



(IV)

en donde:

R^{2c} es hidrógeno o halógeno;

R^{3c} es hidrógeno, halógeno, o ciano;

R^{5c} es ciano; y

R^{7c} es hidrógeno, halógeno alcoxilo, -OSO_2-heterociclilo, -O-aril-alquilo, -NR'-SO_2-alquilo, -NR'-C(O)-alquilo, -NR'-C(O)-NR'-alquilo, -NR'-C(O)-O-alquilo o alquilo opcionalmente sustituido con heterociclilo, –NR'-SO_2-alquilo, -NR'-SO_2-halo-alquilo, NR'-C(O)-alquilo, NR'-C(O)-heterociclilo, -NR'-C(O)-NR'-alquilo, o -NR'-C(O)-O-alquilo;

R^{8c} es alquilo;

cada R' es independientemente hidrógeno, alquilo de 1 a 4 átomos de carbono, o cicloalquilo de 3 a 6 átomos de carbono;

y las sales farmacéuticamente aceptables, polimorfos, rotámeros, pro-fármacos, enantiómeros, hidratos, y solvatos del mismo.

11. El compuesto de acuerdo con la reivindicación 10, en donde:

R^{2c} es hidrógeno o halógeno;

R^{3c} es hidrógeno, halógeno, o ciano;

R^{5c} es ciano; y

R^{7c} es hidrógeno, halógeno, alcoxilo de 1 a 4 átomos de carbono, -OSO_2-heterociclilo, -O-aril-alquilo, -NR'-SO_2-alquilo de 1 a 4 átomos de carbono, -NR'-C(O)-alquilo de 1 a 4 átomos de carbono, -NR'-C(O)-NR'-alquilo de 1 a 4 átomos de carbono, -NR'-C(O)-O-

alquilo de 1 a 4 átomos de carbono o alquilo de 1 a 4 átomos de carbono opcionalmente sustituido con heterociclilo, –NR'-SO_2-alquilo de 1 a 4 átomos de carbono, -NR'-SO_2-halo-alquilo de 1 a 4 átomos de carbono, NR'-C(O)-alquilo de 1 a 4 átomos de carbono, NR'-C(O)-heterociclilo, -NR'-C(O)-NR'-alquilo de 1 a 4 átomos de carbono, o -NR'-C(O)-O-alquilo de 1 a 4 átomos de carbono;

R^{8c} es alquilo de 1 a 4 átomos de carbono; y

cada R' es independientemente hidrógeno, alquilo de 1 a 4 átomos de carbono, o cicloalquilo de 3 a 6 átomos de carbono.

12. El compuesto de acuerdo con la reivindicación 10 u 11, en donde:

R^{2c} es hidrógeno o halógeno;

R^{3c} es hidrógeno, o halógeno;

R^{5c} es ciano; y

R^{7c} es alquilo de 1 a 4 átomos de carbono opcionalmente sustituido con –NR'-SO_2-alquilo de 1 a 4 átomos de carbono, -NR'-SO_2-halo-alquilo de 1 a 4 átomos de carbono, NR'-C(O)-alquilo de 1 a 4 átomos de carbono;

R^{8c} es alquilo de 1 a 4 átomos de carbono;

cada R' es independientemente hidrógeno, metilo, etilo, o propilo.

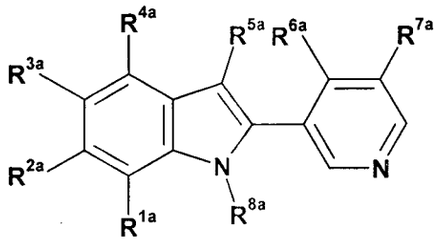
13. El compuesto de acuerdo con las reivindicaciones 10, 11 ó 12, en donde:

R^{7c} es alquilo de 1 a 4 átomos de carbono sustituido con –NR'-SO_2-alquilo de 1 a 4 átomos de carbono, -NR'-SO_2-halo-alquilo

de 1 a 4 átomos de carbono, NR'-C(O)-alquilo de 1 a 4 átomos de carbono; y

cada R' es independientemente hidrógeno o alquilo de 1 a 4 átomos de carbono.

14. Un compuesto de la fórmula I:



(I)

en donde:

R^{1a}, R^{2a}, R^{3a}, y R^{4a} son cada uno independientemente hidrógeno, halógeno, ciano, hidroxilo, alcoxilo, alquilo, alquenilo, o alcoxi-carbonilo;

R^{5a} es hidrógeno halógeno, ciano, alquilo, alquenilo, aril-alquilo, heteroaril-alquilo, amino-carbonilo, alquil-amino-carbonilo, carboxilato, alcoxi-carbonilo, heterociclil-carbonilo, arilo, o heteroarilo;

R^{6a} y R^{7a} son cada uno independientemente hidrógeno, halógeno, hidroxilo, alcoxilo, amino, alquilo, sulfonilo, -O-sulfonilo, alquil-amino, heterociclilo, amino-carbonilo, carboxilato, o alcoxi-carbonilo;

R^{8a} es hidrógeno, alquilo, aril-alquilo, heteroaril-alquilo, alcoxi-carbonilo, sulfonilo, aroílo, arilo, o heteroarilo; y las sales farmacéuticamente aceptables, polimorfos, rotámeros, pro-fármacos,

enantiómeros, hidratos, y solvatos del mismo;

con la condición de que cuando menos uno de R^{1a}-R^{8a} es diferente de hidrógeno; y cuando R^{5a} es ciano o alquilo inferior opcionalmente sustituido con ciano, -C(O)-piperidina, amino, alquil-amino, dialquil-amino, carboxilato, alcoxi-carbonilo, amino-carbonilo, o heterociclilo, entonces cuando menos uno de R^{1a}-R^{4a} y R^{6a}-R^{8a} es diferente de hidrógeno; y cuando R^{7a} es imidazolilo, entonces cuando menos uno de R^{1a}-R^{6a} y R^{8a} es diferente de hidrógeno; y cuando R^{8a} es alquilo, aril-alquilo o alcoxi-carbonilo, entonces cuando menos uno de R^{1a}-R^{7a} es diferente de hidrógeno; y cuando R^{5a} es alquilo inferior, y R^{8a} es alquilo sustituido con carboxilato o $PO_3R^{21}R^{22}$ en donde R^{21} y R^{22} son cada uno independientemente hidrógeno o alquilo inferior, entonces cuando menos uno de R^{1a}-R^{4a} y R^{6a} y R^{7a} es diferente de hidrógeno; y cuando R^{3a} es halógeno y R^{5a} y R^{8a} son independientemente alquilo inferior opcionalmente sustituido con carboxilato, alcoxi-carbonilo, o -C(O)-piperidina, entonces cuando menos uno de R^{1a}, R^{2a}, R^{4a}, R^{6a} y R^{7a} es diferente de hidrógeno; y cuando R^{3a} es halógeno, o alquilo inferior, y R^{5a} es alquilo inferior sustituido con dialquil-amino, dialquil-amino-carbonilo, carboxilato, alcoxi-carbonilo o amino-carbonilo, entonces cuando menos uno de R^{1a}, R^{2a}, R^{4a}, y R^{6a}-R^{8a} es diferente de hidrógeno; y cuando R^{2a} y R^{3a} son cada uno alcoxilo y R^{5a} es ciano, entonces cuando menos uno de R^{1a}, R^{4a}, y R^{6a}-R^{8a} es diferente de hidrógeno; y cuando R^{3a} es alquilo sustituido con aroílo, y R^5 y R^8 son cada uno independientemente hidrógeno o alquilo inferior, entonces cuando menos uno de R^{1a}, R^{2a},

y R^{4a} es diferente de hidrógeno, para utilizarse en terapia.

15. Un método para el tratamiento de un estado asociado con la sintasa de aldosterona en un sujeto, el cual comprende administrar a este sujeto, una cantidad terapéuticamente efectiva del compuesto de las fórmulas I, II, III o IV de acuerdo con las reivindicaciones 1 a 13, de tal manera que se trata dicho estado asociado con la sintasa de aldosterona en el sujeto.

16. El método de la reivindicación 15, en donde el estado asociado con la sintasa de aldosterona en un sujeto se caracteriza por una actividad anormal de la sintasa de aldosterona.

17. El método de la reivindicación 15, en donde el estado asociado con la sintasa de aldosterona en un sujeto se caracteriza por una expresión anormal de la sintasa de aldosterona.

18. El método de la reivindicación 15, en donde el estado asociado con la sintasa de aldosterona es una enfermedad cardiovascular seleccionada a partir de insuficiencia cardíaca, insuficiencia cardíaca congestiva, arritmia, disfunción diastólica, disfunción diastólica de ventrículo izquierdo, insuficiencia cardíaca diastólica, llenado diastólico deteriorado, disfunción sistólica, isquemia, cardiomiopatía hipertrófica, muerte cardíaca repentina, fibrosis de miocardio y vascular, funcionamiento arterial deteriorado, lesiones necróticas de miocardio, daño vascular, infarto de miocardio, hipertrofia de ventrículo izquierdo, fracción de expulsión reducida, lesiones cardíacas, hipertrofia de las paredes vasculares, engrosamiento endotelial, o necrosis fibrinoide de las arterias

coronarias.

19. El método de la reivindicación 15, en donde el estado asociado con la sintasa de aldosterona se selecciona a partir de disfunción renal, enfermedades hepáticas, enfermedades cerebrovasculares, enfermedades vasculares, retinopatía, neuropatía, insulinopatía, edema, disfunción endotelial, disfunción de barorreceptor, migraña, dolores de cabeza, e hipertensión.

20. Un método para el tratamiento de un sujeto para insuficiencia cardíaca, insuficiencia cardíaca congestiva, arritmia, disfunción diastólica, disfunción diastólica de ventrículo izquierdo, insuficiencia cardíaca diastólica, llenado diastólico deteriorado, disfunción sistólica, isquemia, cardiomiopatía hipertrófica, muerte cardíaca repentina, fibrosis de miocardio y vascular, funcionamiento arterial deteriorado, lesiones necróticas de miocardio, daño vascular, infarto de miocardio, hipertrofia de ventrículo izquierdo, fracción de expulsión reducida, lesiones cardíacas, hipertrofia de las paredes vasculares, engrosamiento endotelial, necrosis fibrinoide de las arterias coronarias, disfunción renal, enfermedades hepáticas, enfermedades cerebrovasculares, enfermedades vasculares, retinopatía, neuropatía, insulinopatía, edema, disfunción endotelial, disfunción de barorreceptor, migraña, dolores de cabeza, o hipertensión, el cual comprende:

administrar a este sujeto, una cantidad efectiva del compuesto de la fórmula I, II, III, o IV de acuerdo con las reivindicaciones 1 a 13, de tal manera que se trata al sujeto.

21. El método de cualquiera de las reivindicaciones 15 a 20, en donde el sujeto mencionado es un ser humano.

22. El método de cualquiera de las reivindicaciones 15 a 21, en donde el compuesto mencionado se administra en combinación con un segundo agente.

23. El método de la reivindicación 22, en donde el segundo agente mencionado es un inhibidor de HMG-Co-A-reductasa, un antagonista de los receptores de angiotensina II, un inhibidor de la enzima convertidora de angiotensina (ACE), un bloqueador del canal de calcio (CCB), un inhibidor doble de la enzima convertidora de angiotensina / endopeptidasa neutra (ACE/NEP), un antagonista de endotelina, un inhibidor de renina, un diurético, un mimético de ApoA-I, un agente anti-diabético, un agente reductor de la obesidad, un bloqueador de los receptores de aldosterona, un bloqueador de los receptores de endotelina, o un inhibidor de CETP.

24. Una composición farmacéutica, la cual comprende:

una cantidad efectiva del compuesto de las fórmulas I, II, III, o IV de acuerdo con las reivindicaciones 1 a 13, y

un vehículo o diluyente farmacéuticamente aceptable.

25. La composición farmacéutica de la reivindicación 24, la cual además comprende un segundo agente.

26. La composición farmacéutica de la reivindicación 25, en donde el segundo agente mencionado es un inhibidor de HMG-Co-A-reductasa, un antagonista de los receptores de angiotensina II, un inhibidor de la enzima convertidora de angiotensina (ACE), un

bloqueador del canal de calcio (CCB), un inhibidor doble de la enzima convertidora de angiotensina / endopeptidasa neutra (ACE/NEP), un antagonista de endotelina, un inhibidor de renina, un diurético, un mimético de ApoA-I, un agente anti-diabético, un agente reductor de la obesidad, un bloqueador de los receptores de aldosterona, un bloqueador de los receptores de endotelina, o un inhibidor de CETP

27. El uso de un compuesto de la fórmula (I), (II), (III) o (IV) de acuerdo con las reivindicaciones 1 a 13, para la preparación de una composición farmacéutica para el tratamiento de un trastorno o enfermedad en un sujeto, mediada por la inhibición de la sintasa de aldosterona.

28. Un compuesto de la fórmula (I), (II), (III) o (IV) de acuerdo con las reivindicaciones 1 a 13, para utilizarse como un medicamento.

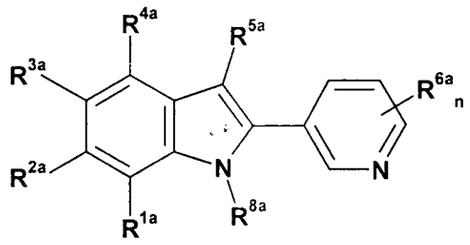
29. La composición farmacéutica de cualquiera de las reivindicaciones 24 a 26, para utilizarse como un medicamento.

30. Un método para el tratamiento de un trastorno o enfermedad mediada por la sintasa de aldosterona en un mamífero, el cual comprende:

administrar al mamífero que lo necesite, una cantidad terapéuticamente efectiva de un compuesto de la fórmula (I), (II), (III) o (IV) de acuerdo con las reivindicaciones 1 a 13.

RESUMEN

La presente invención proporciona compuestos orgánicos novedosos de la fórmula I:



(I),

métodos de uso, y composiciones farmacéuticas de los mismos.

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INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2009/057947

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D213/61 C07D401/04 C07D401/06 C07D401/12 C07D401/14
A61K31/4439 A61P9/00

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

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, BEILSTEIN 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	CH 511 838 A (CIBA GEIGY AG [CH]) 31 August 1971 (1971-08-31) column 1, lines 21-29; examples 1,2,5	1-30
X	US 4 460 777 A (RENFROE HARRIS B [US]) 17 July 1984 (1984-07-17) column 1, lines 34-45; examples	1-30
X	US 4 478 842 A (RENFROE HARRIS B [US]) 23 October 1984 (1984-10-23) column 1, lines 35-46; examples	1-30
A	JP 55 151505 A (KURARAY CO; RIKAGAKU KENKYUSHO) 26 November 1980 (1980-11-26) page 25, table; abstract	1
A	GB 1 224 530 A (MILES LAB [US]) 10 March 1971 (1971-03-10) claim 7; examples	1

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents :

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"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
16 March 2010	24/03/2010

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, Fax: (+31-70) 340-3016	Beyss-Kahana, Ellen

Form PCT/ISA/210 (second sheet) (April 2005)

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2009/057947

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(75) Inventors/Applicants *(for US only)*: **ADAMS, Christopher** [US/US]; Novartis Institutes for BioMedical Research, Inc., 400 Technology Square, Cambridge, Massachusetts 02139 (US). **HU, Qi-Ying** [CN/US]; Novartis Institutes for BioMedical Research, Inc., 400 Technology Square, Cambridge, Massachusetts 02139 (US). **MCQUIRE, Leslie Wighton** [GB/US]; Novartis Institutes for BioMedical Research, Inc., 400 Technology Square, Cambridge, MA 02139 (US). **PAPILLON, Julien** [FR/US]; Novartis Institutes for BioMedical Research, Inc., 400 Technology Square, Cambridge, Massachusetts 02139 (US).

(74) Agent: **VOEGELI-LANGE, Regina**; 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, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PE, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, 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, MK, 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).

Declarations under Rule 4.17:

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

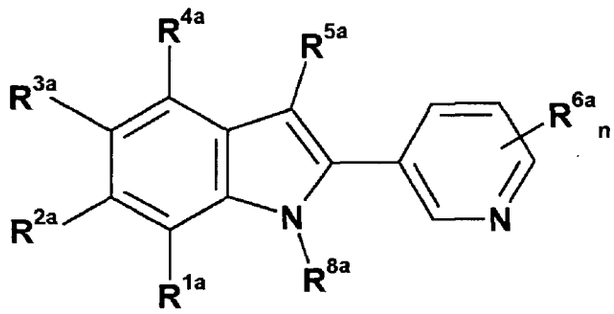
Published:

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

— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments (Rule 48.2(h))*

(88) Date of publication of the international search report:
27 May 2010

(54) Title: ORGANIC COMPOUNDS



(I)

(57) Abstract: The present invention provides novel organic compounds of Formula (I): methods of use, and pharmaceutical compositions thereof.

WO 2009/156462 A3

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D213/61 C07D401/04 C07D401/06 C07D401/12 C07D401/14
A61K31/4439 A61P9/00

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

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, BEILSTEIN 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	CH 511 838 A (CIBA GEIGY AG [CH]) 31 August 1971 (1971-08-31) column 1, lines 21-29; examples 1,2,5	1-30
X	US 4 460 777 A (RENFROE HARRIS B [US]) 17 July 1984 (1984-07-17) column 1, lines 34-45; examples	1-30
X	US 4 478 842 A (RENFROE HARRIS B [US]) 23 October 1984 (1984-10-23) column 1, lines 35-46; examples	1-30
A	JP 55 151505 A (KURARAY CO; RIKAGAKU KENKYUSHO) 26 November 1980 (1980-11-26) page 25, table; abstract	1
A	GB 1 224 530 A (MILES LAB [US]) 10 March 1971 (1971-03-10) claim 7; examples	1

☐ 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
16 March 2010	24/03/2010

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, Fax: (+31-70) 340-3016	Beyss-Kahana, Ellen

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
CH 511838 A	31-08-1971	AT 270636 B	12-05-1969
		BE 707182 A	28-05-1968
		DE 1695047 A1	08-04-1971
		ES 347749 A1	01-03-1969
		FR 7349 M	13-10-1969
		FR 1554803 A	24-01-1969
		GB 1200337 A	29-07-1970
		IL 29024 A	20-10-1971
		NL 6716180 A	30-05-1968
		SE 325029 B	22-06-1970
		US 3468894 A	23-09-1969
US 4460777 A	17-07-1984	NONE	
US 4478842 A	23-10-1984	NONE	
JP 55151505 A	26-11-1980	NONE	
GB 1224530 A	10-03-1971	DE 1901637 A1	04-09-1969
		JP 49031989 B	27-08-1974
		US 3501484 A	17-03-1970

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	**FOR FURTHER ACTION**	see Form PCT/ISA/220 as well as, where applicable, item 5 below.
52533-WO-PCT		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/EP2009/057947	25/06/2009	27/06/2008
Applicant		
NOVARTIS AG		

This international search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This international search report consists of a total of 3 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**
   a. With regard to the **language**, the international search was carried out on the basis of:
      [X] the international application in the language in which it was filed
      [ ] a translation of the international application into _____, which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b))
   b. [ ] This international search report has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43.6*bis*(a)).
   c. [ ] With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, see Box No. I.

2. [ ] **Certain claims were found unsearchable** (See Box No. II)

3. [ ] **Unity of invention is lacking** (see Box No III)

4. With regard to the **title**,
   [X] the text is approved as submitted by the applicant
   [ ] the text has been established by this Authority to read as follows:

5. With regard to the **abstract**,
   [X] the text is approved as submitted by the applicant
   [ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box No. IV. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority

6. With regard to the **drawings**,
   a. the figure of the **drawings** to be published with the abstract is Figure No. _____
      [ ] as suggested by the applicant
      [ ] as selected by this Authority, because the applicant failed to suggest a figure
      [ ] as selected by this Authority, because this figure better characterizes the invention
   b. [ ] none of the figures is to be published with the abstract

International application No
PCT/EP2009/057947

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D213/61 C07D401/04 C07D401/06 C07D401/12 C07D401/14
A61K31/4439 A61P9/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

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"P" document published prior to the international filing date but later than the priority date claimed

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"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
16 March 2010	24/03/2010

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, Fax: (+31-70) 340-3016	Beyss-Kahana, Ellen

1

Form PCT/ISA/210 (second sheet) (April 2005)

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
CH 511838 A	31-08-1971	AT 270636 B	12-05-1969
		BE 707182 A	28-05-1968
		DE 1695047 A1	08-04-1971
		ES 347749 A1	01-03-1969
		FR 7349 M	13-10-1969
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		IL 29024 A	20-10-1971
		NL 6716180 A	30-05-1968
		SE 325029 B	22-06-1970
		US 3468894 A	23-09-1969
US 4460777 A	17-07-1984	NONE	
US 4478842 A	23-10-1984	NONE	
JP 55151505 A	26-11-1980	NONE	
GB 1224530 A	10-03-1971	DE 1901637 A1	04-09-1969
		JP 49031989 B	27-08-1974
		US 3501484 A	17-03-1970

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

No. 10-160879- -00000-0000

Fecha: 2010-12-22 12:59:22 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 350

Industria y Comercio
SUPERINTENDENCIA

LISTA DE CHEQUEO
ADMISIÓN A TRÁMITE – NUEVAS CREACIONES

PATENTE DE INVENCIÓN ☐ **MODELO DE UTILIDAD** ☐ **Art 33 Decisión 486/00**

- ☐ Indicación que se solicita una patente.
- ☐ Datos de identificación del solicitante o de la persona que presenta la solicitud
- ☐ Descripción de la invención
- ☐ Dibujos de ser estos pertinentes
- ☐ Comprobante de pago de las tasas establecidas (De ser el caso formato de descuento)

Completa ☐ Incompleta ☐

PATENTE DE INVENCIÓN PCT ☑ **MODELO DE UTILIDAD PCT** ☐ **Art.33 Decisión 486/00, Circular Única**

- ☑ Indicación que se solicita una PCT
- ☑ Copia de la solicitud en español, tal como fue presentada inicialmente (capítulo descriptivo, reivindicatorio, resumen)
- ☑ Dibujos de ser estos pertinentes
- ☑ Comprobante de pago de las tasas establecidas (de ser el caso formato de descuento)

Completa ☑ Incompleta ☐

DISEÑO INDUSTRIAL ☐ **(Art. 119 Decisión 486/00)**

- ☐ Indicación que se solicita Diseño industrial
- ☐ Datos de identificación del solicitante o de la persona que presenta la solicitud
- ☐ Representación gráfica y fotográfica del Diseño industrial o muestra del material que incorpora el diseño
- ☐ Comprobante de pago de las tasas establecidas

Completa ☐ Incompleta ☐

ESQUEMA DE TRAZADO ☐ **(Art. 92 Decisión 486/00)**

- ☐ Indicación que se solicita un esquema de trazado
- ☐ Datos de identificación del solicitante o de la persona que presenta la solicitud
- ☐ Representación gráfica de un esquema de trazado
- ☐ Comprobante de pago de las tasas establecidas

Completa ☐ Incompleta ☐

Bogotá D.C.,
2020

Doctor(a)
OLARTE GARCIA CARLOS REYNALDO
Apoderado(a) y/o Representante de
NOVARTIS AG

REFERENCIA	Radicación No.	10 160879
	Solicitud internacional	PCT/EP2009/057947
	Fecha inicio fase nacional	27/01/2011
	Trámite	11
	Evento	378
	Actuación	430
	Oficio No.	№ 02235

Como resultado del examen de forma, realizado con fundamento en el artículo 38 de la Decisión 486 de la Comisión de la Comunidad Andina, artículo 27 del Tratado de Cooperación en Materia de Patentes (PCT), regla 51 bis del Reglamento y Circular Única de la Superintendencia de Industria y Comercio, se le comunica que:

1. El solicitante debe presentar un nuevo titulo que permita identificar la materia de la cual trata la solicitud, ya que el titulo relacionado no se encuentra con la precisión necesaria para identificar claramente el objeto de la solicitud de patente. (Regla 4.3 PCT, Art 26-27 D-486, Circular única 5.2.9)

2. La solicitud no contiene la copia del documento en que consta la cesión del derecho a la patente del inventor al solicitante o a su causante, conforme a lo establecido por el artículo 26 literal k) de la Decisión 486 de la Comisión de la Comunidad Andina. Cuando se trate de documentos otorgados en el extranjero, estos deberán legalizarse de conformidad con lo dispuesto por los artículos 259 y 260 del Código de Procedimiento Civil. Cuando se trate de las declaraciones a que hace referencia la Regla 4.17 ii) del Tratado de Cooperación en Materia de Patentes PCT., el alcance de las tales declaraciones se determinará según indiquen claramente una cesión de derechos del inventor al solicitante o su causante, de conformidad con lo dispuesto en el numeral 5.2.15 del Capítulo Quinto, Título X de la Circular Única de Superintendencia de Industria y Comercio.

En cumplimiento de lo dispuesto por el artículo 39 de la Decisión 486, se le requiere para que dentro del término de dos meses siguientes a la fecha de notificación del presente oficio, complete los requisitos anteriormente enunciados. En caso de no dar cumplimiento al presente requerimiento, la solicitud se considerará abandonada y perderá su prelación.

Continua en la página siguiente...

Sede Centro: Carrera 13 No. 27-00 Pisos 2, 5 , 7 y 10 PBX: 5870000
Sede CAN: Av. Cra 50 No. 26-55 int. 2 Tel: 5880070
Call Center 6513240. Linea 01800-910165
Web: www.sic.gov.co e-mail: info@sic.gov.co
Bogotá D.C. - Colombia

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo quinto del título primero de la Circular Unica No.10 de 2001.

JOSE LUIS SALAZAR LOPEZ
Director de Nuevas Creaciones (E)

01 FEB. 2011

El anterior requerimiento fue notificado por fijación en lista de fecha_____.
adpa11

Industria y Comercio
SUPERINTENDENCIA

Bogotá D.C.,
2020

Doctor(a)
OLARTE GARCIA CARLOS REYNALDO
Apoderado(a) y/o Representante de
NOVARTIS AG

REFERENCIA	Radicación No.	10 160879
	Solicitud internacional	PCT/EP2009/057947
	Fecha inicio fase nacional	27/01/2011
	Trámite	11
	Evento	378
	Actuación	430
	Oficio No.	02236

Teniendo en cuenta que el capítulo reivindicatorio presentado excede de diez reivindicaciones, es necesario que cancele la tasa establecida por cada reivindicación adicional presentada, de conformidad con lo dispuesto en la resolución de tasas vigente para la fecha de presentación de la solicitud, so pena de que no sean tenidas en cuenta dentro del presente trámite administrativo.

En consecuencia, con fundamento en lo previsto por el artículo 12 del Código Contencioso Administrativo, se le requiere para que dentro del término de dos (2) meses siguientes a la fecha de notificación del presente oficio atienda el requerimiento aquí señalado. Lo anterior, con el alcance que para tal efecto establece el artículo 13 de la misma codificación, respecto de las reivindicaciones adicionales.

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo quinto del titulo primero de la Circular Única N° 10 de 2001.

JOSE LUIS SALAZAR LOPEZ
Director de Nuevas Creaciones (E)

El anterior requerimiento fue notificado por fijación en lista de fecha 11 FEB. 2011
adpa11