04 123221

Industria y Comercio

SUPERINTENDENCIA

Delegatura de propiedad Industrial

División de Nuevas Creaciones

SOLICITUD

PATENTE DE INVENCIÓN

04/123221

21. **EXPEDIENTE No.** _____

54. **TÍTULO** DERIVADOS DE HETENOARILAMIDA BENZOCONDENZADA DE TIENOPIRIDINAS UTILES COMO AGENTES TERAPEUTICOS COMPOSICIONES FARMACEUTICAS QUE INCLUYEN A LOS MISMOS METODOS PARA SU USO

51. **CLASIFICACIÓN INTERNACIONAL** _____

71. **SOLICITANTE** PFIZER INC

DOMICILIO 235 EAST 42ND STREET NEW YORK N Y 10017 E.U.A.

74. **APODERADO** CARLOS. R. OLARTE

22. **BOGOTÁ, D. C.,** DICIEMBRE 01 2004

(FORMA P-10)

96374 -Imprenta nacional de Colombia- 2004

04/151

OLARTERAISBECK

Industria y Comercio
SUPERINTENDENCIA

SUPERINDUSTRIA Y COMERCIO
Radicacion : 04123221 00000000 Folios 431
Fecha (AMD): 2004-12-09 10:23:17
Tramite : 011 PCT-PATENT 379 FASE NACI 411 PRESENTAC
Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

PETITORIO - FORMULARIO ÚNICO DE SOLICITUD
PATENTE PCT
ENTRADA EN FASE NACIONAL

SOLICITUD DE:

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

[ ] Capítulo I. [X] Capítulo II.

(2) **SOLICITANTE (71)**	**Nombre:** PFIZER INC **Dirección:** 235 East 42nd Street, New York, NY 10017 E.U.A. **Nacionalidad o Domicilio:** ESTADOUNIDENSE **Lugar de Constitución:** Delaware, Estados Unidos de América. **Teléfono:** _____ **Fax:** _____ **E-mail:** _____	**IDENTIFICACIÓN** C.C. [ ] NIT [ ] C.E. [ ] Otro [ ] Cual _____ Número _____
REPRESENTANTE APODERADO	**Nombre:** CARLOS R. OLARTE **Dirección:** Wold Trade Center Torre A, Calle 100 No. 8A-37 Piso 10 **Teléfono:** 601-7700 **Fax:** 601-7799 **E-mail:** office@olarteraisbeck.com	**IDENTIFICACIÓN** C.C. [X] NIT [ ] C.E. [ ] Otro [ ] Cual _____ Número 79782747Bta TP 74.295
INVENTOR (ES) (72)	**Nombre:** VER PAGINA ADJUNTA. **Dirección:** VER PAGINA ADJUNTA. **Nacionalidad o Domicilio:** VER PAGINA ADJUNTA.	

(5) **PCT (86)**

Solicitud Internacional No. PCT/IB03/02393 Fecha Junio 4, 2003

Publicación Internacional No. WO 03/106462 Fecha Diciembre 24, 2003

(6) **Título (54) DERIVADOS DE HETEROARILAMIDA BENZOCONDENSADA DE TIENOPIRIDINAS UTILES COMO AGENTES TERAPEUTICOS, COMPOSICIONES FARMACEUTICAS QUE INCLUYEN A LOS MISMOS, Y METODOS PARA SU USO.**

Clasificación Internacional (51) C07D 495/04.

Prioridad SI [X] NO [ ]

(33) País de Origen	(32) Fecha	(31) Número de Solicitud
US	Junio 14, 2002	60/389,110

(9) **Comprobante de pago No.** 93,909 **Fecha** Diciembre 3, 2004

(0) **ANEX S**

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

(1) **FIGURA CARACTERÍSTICA:**

(2) Solicito la concesión de la patente,

NOMBRE: CARLOS R. OLARTE FIRMA:

C.C. 79.782.747 Btá T.P. 74.295

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

3

INVENTORES SOLICITUD PCT No. PCT/IB03/02393

WILLIAM HENRY ROMINES III
10770 Science Center Drive, San Diego,
California 92121.
Estados Unidos de América.
Nacionalidad: ESTADOUNIDENSE

ROBERT STEVEN KANIA
10770 Science Center Drive, San Diego,
California 92121.
Estados Unidos de América.
Nacionalidad: ESTADOUNIDENSE

JIHONG LOU
10770 Science Center Drive, San Diego,
California 92121.
Estados Unidos de América.
Nacionalidad: CHINA

MICHAEL RAYMOND COLLINS
10770 Science Center Drive, San Diego,
California 92121.
Estados Unidos de América.
Nacionalidad: ESTADOUNIDENSE

STEPHAN JAMES CRIPPS
10770 Science Center Drive, San Diego,
California 92121.
Estados Unidos de América.
Nacionalidad: ESTADOUNIDENSE

MINGYING HE
10770 Science Center Drive, San Diego,
California 92121.
Estados Unidos de América.
Nacionalidad: CHINA

RU ZHOU
10770 Science Center Drive, San Diego,
California 92121.
Estados Unidos de América.
Nacionalidad: CHINA

JUDITH GAIL DEAL
10770 Science Center Drive, San Diego,
California 92121.
Estados Unidos de América.
Nacionalidad: ESTADOUNIDENSE

CYNTHIA LOUISE PALMER
10770 Science Center Drive, San Diego,
California 92121.
Estados Unidos de América.
Nacionalidad: ESTADOUNIDENSE

5

SUPERINDUSTRIA Y COMERCIO
Radicacion : 041E3221 00000000 Folios: 431
Fecha (AMD): 2004-12-09 10:23:17
Tramite : 011 PCT-PATENT 379 FASE NACI 411 PRESENTAC
Dependencia: 2000 DIVISION DE NUEVAS CREACIONES

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 04 - 93,909
FECHA : DICIEMBRE 3 DE 2004

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

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PAG	Vr. PAGO
JOSE SANTOS	CONSIGNACION	BANCO POPULAR	050-00110-6	33693624	02/12/2004	5,212,000.00

***** 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	422,000.00
		TOTAL : $	422,000.00

SON: CUATROCIENTOS VEINTIDOS MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No._____

Traducción oficial del Inglés por Marlén Neira Castro, resolución 2117 del Ministerio de Justicia de Colombia

6

APOSTILLA EN PODER DE REPRESENTACIÓN DE

PFIZER INC.

Bilingüe inglés- español otorgado en Nueva York, Estados Unidos el 14 de julio de 2003 y firmado por J. Trevor Lumb, Vicepresidente de Pfizer Products Inc.

CERTIFICACION NOTARIAL

Bilingüe inglés- español, el 14 de julio de 2003 el suscrito notario Kenneth Greenwood certifica que J. Trevor Lumb, domiciliado en Nueva York ejercía funciones de Asistente General Consejero de Patentes la Compañía Pfizer Inc., con sede en Nueva York, Nueva York, Estados Unidos.

Firma del notario: Kenneth Greenwood

Sello notarial: certificado, verificado y autenticado en la Localidad de Egham en Surrey, 14 julio, 2003 por el Notario Kenneth Greenwood-Horne Engall & Freeman Sello Notario Público en alto relieve rojo.

APOSTILLA

REINO UNIDO DE GRAN BRETAÑA E IRLANDA DEL NORTE

1. País :Reino Unido de Gran Bretaña e Irlanda del Norte
   Este documento Público
2. ha sido firmado por K. Greenwood
3. ejerce funciones de Notario Público
4. Lleva el sello de dicho Notario Público

CERTIFICADÓ

5. En Londres 6. El 17 de julio de 2003
7. Por el Secretario de Estado Principal de su Majestad para Asuntos exteriores y de la mancomunidad
8. No. G210434
9. Sello del Secretario de Estado Principal de su Majestad para Asuntos exteriores y de la mancomunidad
10. Firma de R. Bawden - Por Secretario de Estado

Si el documento se usa en un país que no es parte de la convención de la Haya del 5 de octubre 1961, debe presentarse en sección consular de la misión que representa el país.

Es traducción fiel del inglés, con copia archivo para confrontación. Bogotá 25 de julio-2003. Marlen Neira C

MARLEN NEIRA CASTRO
Traductor e Intérprete Oficial
Inglés - Español - Inglés
Resolución No. 2117 del 7 Oct 1987

OLARTERAISBECK

OLARTE RAISBECK & FRIERI, LTDA.
LEGAL & PROFESSIONAL SERVICES

WORLD TRADE CENTER – TORRE C
CALLE 100 NO. 8A-55 PISO 10
BOGOTA, COLOMBIA
TELEPHONE: +57-1 638-6200
FAX: +57-1 638-6201

www.olarteraisbeck.com

Power of Attorney

The undersigned,

domiciled in

by means of these presents hereby grants to **Carlos R. Olarte, J. Ian Raisbeck and Ana María Frieri** full and sufficient Power of Attorney to file, prosecute, obtain, defend and enforce any and all of the company's Patents, Utility Models and Industrial Designs 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, appeals, 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.

Poder

El suscrito,

Pfizer Inc.

domiciliado en

235 East 42nd Street, New York, NY 10017 USA

por medio del presente otorga a **Carlos R. Olarte, J. Ian Raisbeck y Ana María Frieri** poder especial, amplio y suficiente para presentar, tramitar, obtener, defender y hacer respetar todas y cualquiera de Patentes, Modelos de Utilidad y Diseños Industriales 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, apelaciones, 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: _____

Date/Fecha: July 14, 2003

City,Country/Ciudad,País: New York, USA

OLARTERAISBECK

OLARTE RAISBECK & FRIERI, LTDA.
LEGAL & PROFESSIONAL SERVICES

WORLD TRADE CENTER – TORRE C
CALLE 100 NO. 8A-55 PISO 10
BOGOTA, COLOMBIA
TELEPHONE: +57-1 638-6200
FAX: +57-1 638-6201

www.olarteraisbeck.com

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Notarial Certification

On this date,
July 14, 2003
The undersigned Notary Public certifies:

1. That J. Trevor Lumb
of legal age and domiciled in New York, USA
signed the foregoing document.

2. That the grantor has executed the foregoing document as Assistant General Patent Counsel of Pfizer Inc.

3. That Pfizer Inc.,
having its principal place of business located in
New York, New York, U.S.A.
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. That the grantor has the authority to execute the Power of Attorney and that his/her representation is legal.

5. The foundation for my certifications contained in points 2, 3 and 4 was the exhibition of the following authentic document(s):

Certificación Notarial

En esta fecha,

el Notario Público suscrito certifica:

1. Que
J. Trevor Lumb
mayor de edad y domiciliado
New York
suscribió el documento que antecede.

2. Que el otorgante ha suscrito el referido documento en su carácter de
de

4. Que
con sede principal ubicada en

está legalmente constituida, que tiene existencia legal vigente y que los propósitos para los cuales se otorga el poder se encuentra dentro de los que comprenden su objeto social.

4. Que el otorgante tiene la representación para suscribir el poder, y que ésta es legítima.

5. El fundamento de mis certificaciones contenidas en los puntos 2, 3 y 4 fue la exhibición de los (del) siguiente(s) documento(s) auténtico(s):

NOTARY PUBLIC (Signature):

EXECUTION
Certified Verified and Authenticated
In The Town Of Egham In Surrey
This 14th Day Of July 2003

KENNETH GREENWOOD
NOTARY PUBLIC
NORNE ENGALU AND FREEMAN



APOSTILLE
(Hague Convention of 5 October 1961 / Convention de La Haye du 5 octobre 1961)

UNITED KINGDOM OF GREAT BRITAIN AND NORTHERN IRELAND

1. Country: United Kingdom of Great Britain and Northern Ireland
   Pays: Royaume-Uni de Grande-Bretagne et d'Irlande du Nord

   This public document / Le présent acte public

2. Has been signed by K Greenwood
   a été signé par

3. Acting in the capacity of Notary Public
   agissant en qualité de

4. Bears the seal/stamp of The Said Notary Public
   est revêtu du sceau/timbre de

   Certified/Attesté

5. at London/à Londres 6. the/le 17 July 2003

7. by Her Majesty's Principal Secretary of State for Foreign and Commonwealth Affairs /
   par le Secrétaire d'Etat Principal de Sa Majesté aux Affaires Etrangères et du Commonwealth.

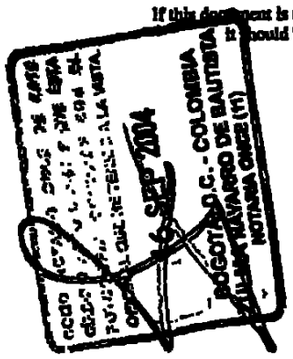
8. Number/sous No **G210434**

9. Stamp:
   timbre:

10. Signature: R. Bawden

For the Secretary of State / Pour le Secrétaire d'Etat

If this document is to be used in a country which is not party to the Hague Convention of 5 October 1961, it should be presented to the consular section of the mission representing that country.



CESION

Por contraprestación valiosa pagada a nosotros por PFIZER INC, sociedad constituida en virtud de las leyes del Estado de Delaware, Estados Unidos de América, cuya dirección postal completa es 235 East 42nd Street, NewYork, New Cork 10017, Estados Unidos de América, por el presente vendemos y traspasamos a la citada PFIZER INC, todo nuestro derecho, titulo e interés en y sobre nuestro invento de una nueva y útil mejora en DERIVADOS DE HETEROARILAMIDA BENZOCONDENSADA DE TIENOPIRIDINAS UTILES COMO AGENTES TERAPEUTICOS, COMPOSICIONES FARMACEUTICAS QUE INCLUYEN LOS MISMOS, Y METODOS PARA SU USO., en cuanto respecta a la República de Colombia, tal como se indica y describe plenamente en la especificación y por el presente autorizamos y solicitamos al Comisionado de Patentes de Colombia expedir dicha patente a nombre de la citada PFIZER INC, de conformidad con esta Cesión.

En fe de lo cual, firmamos de nuestro puño y letra,

SAN DIEGO, CA 92121 21 de Septiembre de 2004, (Fdo)William Henry ROMINES, III.
Lugar, fecha y firma William Henry ROMINES, III.

SAN DIEGO, CA 92121 21 de Septiembre de 2004, (Fdo) Robert Steven KANIA
Lugar, fecha y firma Robert Steven KANIA

SAN DIEGO, CA 21 de Septiembre de 2004, (Fdo) Jihong LOU .
Lugar, fecha y firma Jihong LOU

SAN DIEGO, CA 21 de Septiembre de 2004, (Fdo) Michael Raymond COLLINS .
Lugar, fecha y firma Michael Raymond COLLINS

SAN DIEGO, CA 21 de Septiembre de 2004, (Fdo) Stephan James CRIPPS .
Lugar, fecha y firma Stephan James CRIPPS

SAN DIEGO, CA 21 de Septiembre de 2004, (Fdo) Mingying HE .
Lugar, fecha y firma Mingying HE

10

SAN DIEGO, CA 21 de Septiembre de 2004. (Fdo) Ru ZHOU .
Lugar, fecha y firma Ru ZHOU

SAN DIEGO, CA 22 de Septiembre de 2004. (Fdo) Cynthia Louise PALMER .
Lugar, fecha y firma Cynthia Louise PALMER

SAN DIEGO, CA 22 de Septiembre de 2004. (Fdo) Judith Gail DEAL .
Lugar, fecha y firma Judith Gail DEAL

El suscrito KENNETH GREENWOOD, Notario Público de Town de Egham en Surrey, debidamente autorizado bajo juramento por el presente certifico que las firmas del documento precedente son auténticas.

EN FE DE LO CUAL firmo y de mi puño y letra y estampo mi Sello oficial en Town of Egham el 22 de octubre de 2004.

(Fdo) Kenneth Greenwood, Notario Público con cargo vitalicio.

(Sello Oficial)

12

APOSTILLA

(Convención de la Haya del 5 de Octubre de 1961)

REINO UNIDO DE GRAN BRETAÑA E IRLANDA DEL NORTE

1. País: Reino Unido de Gran Bretaña e Irlanda del Norte

   Este es documento público

2. Ha sido firmado por **K. Greenwood**

3. Actuando en calidad de **Notario Público**

4. Lleva el sello/estampilla de **El antedicho Notario Público**

   Certificado

5. En Londres 6. El **25 de octubre de 2004**

7. Por el Secretario de Estado Principal de Su Majestad para Asuntos Exteriores y de la Mancomunidad.

8. Número **G541469**

9. Sello/Estampilla

(Sello de la Oficina de Asuntos Exteriores y de la Mancomunidad)

10. Firma

(Fdo) **S. Gardiner**
Por el secretario de Estado.

HORNE ENGALL & FREEMAN
Solicitors • Commissioners for Oaths • Notaries Public

Kenneth Greenwood - Notary Public
Nicholas D. Jamieson - Notary Public
Conveyancer
Francois Bothe

47A HIGH STREET
EGHAM • SURREY
TW20 9ES
Telephone - 01784 432282

FAX No. 01784-431984 DX 53100 Egham

COLOMBIA 13

Our Ref | Your Ref | Date

I, KENNETH GREENWOOD, Notary Public of the Town of Egham in Surrey, duly admitted and sworn, practising in the said Town,

DO HEREBY CERTIFY AND ATTEST:

THAT the signatures set and subscribed at the foot of the hereunto annexed document are genuine.

IN TESTIMONY WHEREOF I have hereunto set my hand and affixed my Seal of Office in the Town of Egham aforesaid, this 22nd **day of** Oct **Two Thousand and Four**

NOTARY PUBLIC
MY COMMISSION IS PERMANENT

2598

APOSTILLE
(Hague Convention of 5 October 1961 / Convention de La Haye du 5 octobre 1961)

UNITED KINGDOM OF GREAT BRITAIN AND NORTHERN IRELAND

1 Country: United Kingdom of Great Britain and Northern Ireland
Pays: Royaume-Uni de Grande-Bretagne et d'Irlande du Nord

This public document / Le présent acte public

2 Has been signed by: K Greenwood
a été signé par:

3 Acting in the capacity of: Notary Public
agissant en qualité de:

4 Bears the seal/stamp of: The Said Notary Public
est revêtu du sceau/timbre de:

Certified/Attesté

5 at London/à Londres

6 the/le 25 October 2004

7 by Her Majesty's Principal Secretary of State for Foreign and Commonwealth Affairs /
par le Secrétaire d'Etat Principal de Sa Majesté aux Affaires Etrangères et du Commonwealth

8 Number/sous N: **G541469**

9 Stamp
timbre

10. Signature: S. Gardiner

For the Secretary of State / Pour le Secrétaire d'Etat

If this document is to be used in a country which is not party to the Hague Convention of 5 October 1961 it should be presented to the consular section of the mission representing that country. An apostille or legalisation certificate only confirms that the signature, seal or stamp on the document is genuine. It does not mean that the contents of the document are correct or that the Foreign & Commonwealth Office approves of the contents.

PCAG191

CO-1

ASSIGNMENT

For valuable consideration paid to me (us) by **PFIZER INC.** a corporation organized under the laws of the State of Delaware, United States of America whose full post office address is 235 East 42nd Street, New York, New York 10017, United States of America, I (we) do hereby sell and assign to the said **PFIZER INC.**, all my (our) right, title and interest in and to my (our) invention for a new and useful Improvement in **BENZOFUSED HETEROARYL AMIDE DERIVATIVES OF THIENOPYRIDINES USEFUL AS THERAPEUTIC AGENTS, PHARMACEUTICAL COMPOSITIONS INCLUDING THE SAME, AND METHODS FOR THEIR USE** so far as the Republic of Colombia is concerned, as fully set forth and described in the specification, and I (we) do hereby authorize and request the Commissioner of Patents of Colombia to issue said patent to the said **PFIZER INC.** in accordance with this assignment.

In witness whereof I (we) have hereunto set my (our) hand(s) this

San Diego CA 92121 Sept 21 2004 William H Romines III

Place, date and signature - William Henry ROMINES, III

San Diego CA 92121 9/21/04

Place, date and signature - Robert Steven KANIA

San Diego CA 92121 9/21/04

Place, date and signature - Jihong LOU

San Diego CA 9.21.04 Michael R. Collins

Place, date and signature - Michael Raymond COLLINS

San Diego CA Sept 21 2004

Place, date and signature - Stephan James CRIPPS

San Diego CA Sept 21 2004

Place, date and signature - Mingying HE

San Diego CA 9/21/2004

Place, date and signature - Ru ZHOU

San Diego CA 9/22/04

Place, date and signature - Cynthia Louise PALMER

San Diego CA 9/22/04

Place, date and signature - Judith Gail DEAL

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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
24 December 2003 (24.12.2003)

PCT

(10) International Publication Number
WO 03/106462 A1

(51) International Patent Classification⁷: C07D 495/04, A61K 31/4365, A61P 35/00

(21) International Application Number: PCT/IB03/02393

(22) International Filing Date: 4 June 2003 (04.06.2003)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/389,110 14 June 2002 (14.06.2002) US

(71) Applicant (*for all designated States except US*): PFIZER INC. [US/US]; 235 East 42nd Street, New York, NY 10017 (US).

(72) Inventors; and

(75) Inventors/Applicants (*for US only*): ROMINES, William, Henry, III [US/US]; Pfizer Global Research and Development, 10770 Science Center Drive, San Diego, CA 92121 (US). KANIA, Robert, Steven [US/US]; Pfizer Global Research and Development, 10770 Science Center Drive, San Diego, CA 92121 (US). LOU, Jiheng [CN/US]; Pfizer Global Research and Development, 10770 Science Center Drive, San Diego, CA 92121 (US). COLLINS, Michael, Raymond [US/US]; Pfizer Global Research and Development, 10770 Science Center Drive, Sand Diego, CA 92121 (US). CRIPPS, Stephan, James [US/US]; Pfizer Global Research and Development, 10770 Science Center Drive, San Diego, CA 92121 (US). HE, Mingying [CN/US]; Pfizer Research and Development, 10770 Science Center Drive,, San Diego, CA 92121 (US). ZHOU, Ru [CN/US]; Pfizer Research and Development, 10770 Science Center Drive, San Diego, CA 92121 (US). PALMER, Cynthia, Louise [US/US]; Pfizer Global Research and Development, 10770 Science Center Drive, San Diego, CA 92121 (US). DEAL, Judith, Gail [US/US]; Pfizer Global Research and Development, 10770 Science Center Drive, San Diego, CA 92121 (US).

(74) Agents: LUMB, J., Trevor et al.; Pfizer Inc., 201 Tabor Road, Morris Plains, NJ 07950 (US).

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

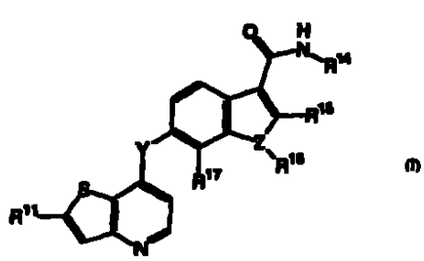
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(54) Title: BENZOFUSED HETEROARYL AMIDE DERIVATIVES OF THIENOPYRIDINES USEFUL AS THERAPEUTIC AGENTS, PHARMACEUTICAL COMPOSITIONS INCLUDING THE SAME, AND METHODS FOR THEIR USE



(I)

(57) Abstract: The invention relates to compounds represented by the formula I and to prodrugs or metabolites thereof, or pharmaceutically acceptable salts or solvates of said compounds, said prodrugs, and said metabolites, wherein Z, Y, R^{11} and R^{14}, R^{15}, R^{16}, and R^{17} are as defined herein. The invention also relates to pharmaceutical compositions containing the compounds of formula I and to methods of treating hyperproliferative disorders in a mammal by administering the compounds of formula I.

BENZOFUSED HETEROARYL AMIDE DERIVATIVES OF THIENOPYRIDINES USEFUL AS THERAPEUTIC AGENTS PHARMACEUTICAL COMPOSITIONS INCLUDING THE SAME AND METHODS FOR THEIR USE

The present patent application claims priority to United States Serial No. 60/389 110 filed June 14, 2002 which is hereby incorporated by reference in its entirety for all purposes

Field of the Invention

This invention relates to novel thienopyridine and thienopyridine derivatives that are useful in the treatment of hyperproliferative diseases, such as cancers, in mammals This invention also relates to a method of using such compounds in the treatment of hyperproliferative diseases in mammals, especially humans, and to pharmaceutical compositions containing such compounds.

Background of the Invention

It is known that a cell may become cancerous by virtue of the transformation of a portion of its DNA into an oncogene (i.e a gene that upon activation leads to the formation of malignant tumor cells) Many oncogenes encode proteins that are aberrant tyrosine kinases capable of causing cell transformation. Alternatively the overexpression of a normal proto-oncogenic tyrosine kinase may also result in proliferative disorders, sometimes resulting in a malignant phenotype.

Receptor tyrosine kinases are large enzymes that span the cell membrane and possess an extracellular binding domain for growth factors such as epidermal growth factor a transmembrane domain, and an intracellular portion that functions as a kinase to phosphorylate a specific tyrosine residue in proteins and hence to influence cell proliferation. The foregoing tyrosine kinases may be classified as growth factor receptor (e.g. EGFR PDGFR FGFR and erbB2) or non-receptor (e g c-src and bcr-abl) kinases It is known that such kinases are often aberrantly expressed in common human cancers such as breast cancer gastrointestinal cancer such as colon, rectal or stomach cancer leukemia and ovarian, bronchial or pancreatic cancer Aberrant erbB2 activity has been implicated in breast, ovarian non-small cell lung, pancreatic, gastric and colon cancers. It has also been shown that epidermal growth factor receptor (EGFR) is mutated or overexpressed in many human cancers such as brain, lung, squamous cell, bladder gastric, breast, head and neck, oesophageal, gynecological and thyroid cancers. Thus, it is believed that inhibitors of receptor tyrosine kinases, such as the compounds of the present invention, are useful as selective inhibitors of the growth of mammalian cancer cells.

It has also been shown that EGFR inhibitors may be useful in the treatment of pancreatitis and kidney disease (such as proliferative glomerulonephritis and diabetes-induced renal disease) and may reduce successful blastocyte implantation and therefore may be useful

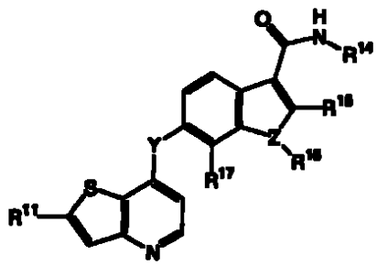
as a contraceptive. See PCT International application publication number WO 95/19970 (published July 27, 1995), hereby incorporated by reference in its entirety.

It is known that polypeptide growth factors such as vascular endothelial growth factor (VEGF) having a high affinity to the human kinase insert-domain-containing receptor (KDR) or the murine fetal liver kinase 1 (FLK-1) receptor have been associated with the proliferation of endothelial cells and more particularly vasculogenesis and angiogenesis. See PCT International application publication number WO 95/21613 (published August 17, 1995), hereby incorporated by reference in its entirety. Agents, such as the compounds of the present invention, that are capable of binding to or modulating the KDR/FLK-1 receptor may be used to treat disorders related to vasculogenesis or angiogenesis such as diabetes, diabetic retinopathy, age related macular degeneration, hemangioma, glioma, melanoma, Kaposi's sarcoma and ovarian, breast, lung, pancreatic, prostate, colon and epidermoid cancer.

Compounds that are useful in the treatment of hyperproliferative diseases are also disclosed in the following patents and applications: PCT International patent application publication number WO 00/38665 (published July 6, 2001), PCT International patent application publication number WO 97/49688 (published December 31, 1997), PCT International patent application publication number WO 98/23613 (published June 4, 1998), United States patent application number 60/360,952 (filed March 1, 2002), United States patent application number 60/299,879 (filed June 21, 2001), United States patent application number 09/502,129 (filed February 10, 2000), United States patent application number 60/209,686 (filed June 6, 2000), United States patent application number 60/214,373 (filed June 28, 2000), United States patent application number 08/953,078 (filed October 17, 1997), United States Patent No. 6,071,935 issued June 6, 2000, PCT International patent application publication number WO 98/30347 (published October 3, 1998), PCT International patent application publication number WO 98/40142 (published December 19, 1998), PCT International patent application publication number WO 97/13771 (published April 17, 1997), and PCT International patent application publication number WO 95/23141 (published August 31, 1995). The foregoing patent and applications are each incorporated herein by reference in their entirety.

Summary Of The Invention

In one of the aspects, the present invention relates to a compound represented by the formula I:



I

wherein:

Y is –NH-, -O-, -S-, or –CH_2-;

Z is -O-, -S-, or -N-;

R^{14} is a C_1-C_8 alkyl, C_1-C_8 alkylamino, C_1-C_8 alkylhydroxy, C_3-C_{10} cycloalkylamino, or methylureido group;

R^{16} and R^{17} are independently H, halo, or a C_1-C_8 alkyl group unsubstituted or substituted by one or more R^5 groups;

R^{15} is H or a C_1-C_8 alkyl group, preferably methyl, when Z is N, and R^{15} is absent when Z is –O- or –S-;.

R^{11} is H, C_1-C_8 alkyl, C_3-C_{10} cycloalkyl, -C(O)$NR^{12}R^{13}$, -C(O)(C_6-C_{10} aryl), -$(CH_2)_t$(C_6-C_{10} aryl), -$(CH_2)_t$(5 to 10 membered heterocyclic), -$(CH_2)_tNR^{12}R^{13}$, -$SO_2NR^{12}R^{13}$ or -CO_2R^{12}, wherein said C_1-C_8 alkyl, -C(O)(C_6-C_{10} aryl), -$(CH_2)_t$(C_6-C_{10} aryl), and -$(CH_2)_t$(5 to 10 membered heterocyclic) moieties of the said R^{11} groups are unsubstituted or substituted by one or more R^5 groups;

each R^5 is independently selected from halo, cyano, nitro, trifluoromethoxy, trifluoromethyl, azido, -C(O)R^6, -C(O)OR^6, -OC(O)R^6, -OC(O)OR^6, -$NR^6C(O)R^7$, -C(O)NR^6R^7, -NR^6R^7, -OR^6, -$SO_2NR^6R^7$, C_1-C_8 alkyl, C_3-C_{10} cycloalkyl, C_1-C_8 alkylamino, -$(CH_2)_tO(CH_2)_qNR^6R^7$, -$(CH_2)_tO(CH_2)_qOR^6$, -$(CH_2)_tOR^6$, -S(O)$_t$(C_1-C_8 alkyl), -$(CH_2)_t$(C_6-C_{10} aryl), -$(CH_2)_t$(5 to 10 membered heterocyclic), -C(O)$(CH_2)_t$(C_6-C_{10} aryl), -$(CH_2)_tO(CH_2)_t$(C_6-C_{10} aryl), -$(CH_2)_tO(CH_2)_t$(5 to 10 membered heterocyclic), -C(O)$(CH_2)_t$(5 to 10 membered heterocyclic), -$(CH_2)_tNR^7(CH_2)_qNR^6R^7$, -$(CH_2)_tNR^7CH_2C(O)NR^6R^7$, -$(CH_2)_tNR^7(CH_2)_qNR^6C(O)R^6$, $(CH_2)_tNR^7(CH_2)_tO(CH_2)_qOR^6$, -$(CH_2)_tNR^7(CH_2)_qS(O)_t$($C_1$-$C_8$ alkyl), -$(CH_2)_tNR^7(CH_2)_tR^6$, -$SO_2(CH_2)_t$(C_6-C_{10} aryl), and -$SO_2(CH_2)_t$(5 to 10 membered heterocyclic), the -$(CH_2)_q$- and -$(CH_2)_t$- moieties of the said R^5 groups optionally include a carbon-carbon double or triple bond where t is an integer between 2 and 6, and the alkyl, aryl and heterocyclic moieties of the said R^5 groups are unsubstituted or substituted with one or more substituents independently selected from halo, cyano, nitro, trifluoromethyl, azido, -OH, -C(O)R^6, -C(O)OR^6, -OC(O)R^6, -OC(O)OR^6, -$NR^6C(O)R^7$, -C(O)NR^6R^7, -$(CH_2)_tNR^6R^7$, C_1-C_8 alkyl, C_3-C_{10} cycloalkyl, -$(CH_2)_t$(C_6-C_{10} aryl), -$(CH_2)_t$(5 to 10 membered heterocyclic), -$(CH_2)_tO(CH_2)_qOR^6$, and -$(CH_2)_tOR^6$;

each R^6 and R^7 is independently selected from H, OH, C_1-C_8 alkyl, C_3-C_{10} cycloalkyl, -$(CH_2)_t$(C_6-C_{10} aryl), -$(CH_2)_t$(5 to 10 membered heterocyclic), -$(CH_2)_tO(CH_2)_qOR^9$, -$(CH_2)_tCN(CH_2)_tOR^9$, -$(CH_2)_tCN(CH_2)_tR^9$ and -$(CH_2)_tOR^9$, and the alkyl, aryl and heterocyclic moieties of the said R^6 and R^7 groups are unsubstituted or substituted with one or more substituents independently selected from hydroxy, halo, cyano, nitro, trifluoromethyl, azido, -$C(O)R^8$, -$C(O)OR^8$, -$CO(O)R^8$, -$OC(O)OR^8$, -$NR^9C(O)R^{10}$, -$C(O)NR^9R^{10}$, -NR^9R^{10}, C_1-C_8 alkyl, -$(CH_2)_t$(C_6-C_{10} aryl), -$(CH_2)_t$(5 to 10 membered heterocyclic), -$(CH_2)_tO(CH_2)_qOR^9$, and -$(CH_2)_tOR^9$, where when R^6 and R^7 are both attached to the same nitrogen, then R^6 and R^7 are not both bonded to the nitrogen directly through an oxygen;

each R^8 is independently selected from H, C_1-C_{10} alkyl, C_3-C_{10} cycloalkyl, -$(CH_2)_t$(C_6-C_{10} aryl), and -$(CH_2)_t$(5 to 10 membered heterocyclic);

each R^9 and R^{10} is independently selected from H, -OR^8, C_1-C_8 alkyl, and C_3-C_{10} cycloalkyl;

wherein j is an integer from 0 to 2, t is an integer from 0 to 6, q is an integer from 2 to 6; and

each R^{12} and R^{13} is independently selected from H, C_1-C_8 alkyl, C_3-C_{10} cycloalkyl, -$(CH_2)_t$(C_3-C_{10} cycloalkyl), -$(CH_2)_t$(C_6-C_{10} aryl), -$(CH_2)_t$(5 to 10 membered heterocyclic), -$(CH_2)_tO(CH_2)_qOR^9$, and -$(CH_2)_tOR^9$, and the alkyl, aryl and heterocyclic moieties of the said R^{12} and R^{13} groups are unsubstituted or substituted with one or more substituents independently selected from R^6, or R^{12} and R^{13} are taken together with the nitrogen to which they are attached to form a C_5-C_9 azabicyclic, aziridinyl, azetidinyl, pyrrolidinyl, piperidyl, piperazinyl, morpholinyl, thiomorpholinyl, isoquinolinyl, or dihydroisoquinolinyl ring, wherein said C_5-C_9 azabicyclic, aziridinyl, azetidinyl, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, thiomorpholinyl, isoquinolinyl, or dihydroisoquinolinyl rings are unsubstituted or substituted with one or more R^8 substituents, where R^{12} and R^{13} are not both bonded to the nitrogen directly through an oxygen;

or prodrugs thereof, or pharmaceutically acceptable salts or solvates of said compounds and said prodrugs.

In one embodiment of the compound of formula I, R^{11} is -$(CH_2)_t$(5 to 10 membered heterocyclic), -$C(O)NR^{12}R^{13}$, -$SO_2NR^{12}R^{13}$ and -CO_2R^{12}, wherein said R^{11} group -$(CH_2)_t$(5 to 10 membered heterocyclic) is unsubstituted or substituted by one or more R^6 groups and wherein each R^{12} and R^{13} is independently selected from H, C_1-C_8 alkyl, C_3-C_{10} cycloalkyl, -$(CH_2)_t$(C_3-C_{10} cycloalkyl), -$(CH_2)_t$(C_6-C_{10} aryl), -$(CH_2)_t$(5 to 10 membered heterocyclic), -$(CH_2)_tO(CH_2)_qOR^9$, -$(CH_2)_tOR^9$, and the alkyl, aryl and heterocyclic moieties of said R^{12} and R^{13} groups are unsubstituted or substituted by one or more substituents independently selected from R^6, or R^{12} and R^{13} are taken together with the nitrogen to which they are attached to form a C_5-C_9 azabicyclic, aziridinyl, azetidinyl, pyrrolidinyl, piperidinyl, piperazinyl,

morpholinyl, thiomorpholinyl, isoquinolinyl, or dihydroisoquinolinyl ring, wherein said C_5-C_9 azabicyclic, aziridinyl, azetidinyl, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, thiomorpholinyl, isoquinolinyl, or dihydroisoquinolinyl ring are unsubstituted or substituted by one or more R^5 substituents, where said R^{12} and R^{13} are not both bonded to the nitrogen directly through an oxygen.

In another embodiment of the compound of formula I, R^{11} is -$(CH_2)_t$(5 to 10 membered heterocyclic), and -$C(O)NR^{12}R^{13}$.

In still another embodiment of the compound of formula I, R^{11} is -$C(O)NR^{12}R^{13}$, wherein R^{12} and R^{13} are independently selected from H, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, -$(CH_2)_t$(C_3-C_{10} cycloalkyl), -$(CH_2)_t$(C_6-C_{10} aryl), -$(CH_2)_t$(5 to 10 membered heterocyclic), -$(CH_2)_qO(CH_2)_qOR^9$, -$(CH_2)_qOR^9$, wherein t is an integer from 0 to 6, q is an integer from 2 to 6, and the alkyl, aryl and heterocyclic moieties of said R^{12} and R^{13} groups are unsubstituted or substituted with one or more substituents independently selected from R^5, or R^{12} and R^{13} are taken together with the nitrogen to which they are attached to form a C_5-C_9 azabicyclic, aziridinyl, azetidinyl, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, thiomorpholinyl, isoquinolinyl, or dihydroisoquinolinyl ring, wherein said C_5-C_9 azabicyclic, aziridinyl, azetidinyl, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, thiomorpholinyl, isoquinolinyl, or dihydroisoquinolinyl ring are unsubstituted or substituted with 1 to 5 R^5 substituents, where R^{12} and R^{13} are not both bonded to the nitrogen directly through an oxygen.

In another embodiment of the compound of formula I, R^{11} is -$C(O)NR^{12}R^{13}$, wherein R^{12} and R^{13} are taken together with the nitrogen to which they are attached to form a C_5-C_9 azabicyclic, aziridinyl, azetidinyl, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, thiomorpholinyl, isoquinolinyl, or dihydroisoquinolinyl ring, wherein said C_5-C_9 azabicyclic, aziridinyl, azetidinyl, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, thiomorpholinyl, isoquinolinyl, or dihydroisoquinolinyl ring are unsubstituted or substituted with 1 to 5 R^5 substituents.

In still another embodiment of the compound of formula I, R^{11} is -$C(O)NR^{12}R^{13}$, wherein R^{12} and R^{13} are taken together with the nitrogen to which they are attached to form a pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, thiomorpholinyl, isoquinolinyl, or dihydroisoquinolinyl ring, wherein said pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, thiomorpholinyl, isoquinolinyl, or dihydroisoquinolinyl ring are unsubstituted or substituted with 1 to 5 R^5 substituents.

In still another embodiment of the compound of formula I, R^{11} is -$C(O)NR^{12}R^{13}$, wherein R^{12} and R^{13} are taken together with the nitrogen to which they are attached to form a pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, or thiomorpholinyl ring, wherein said pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, or thiomorpholinyl rings are unsubstituted or substituted with 1 to 5 R^5 substituents.

In still another embodiment of the compound of formula I, R^{11} is $-C(O)NR^{12}R^{13}$, wherein R^{12} and R^{13} are taken together with the nitrogen to which they are attached to form a pyrrolidinyl or piperidinyl ring, wherein said pyrrolidinyl or piperidinyl ring are unsubstituted or substituted with 1 to 5 R^5 substituents.

In still another embodiment of the compound of formula I, R^{11} is $-C(O)NR^{12}R^{13}$, wherein R^{12} and R^{13} are taken together with the nitrogen to which they are attached to form a pyrrolidinyl ring, wherein said pyrrolidinyl is unsubstituted or substituted with 1 to 5 R^5 substituents.

In still another embodiment of the compound of formula I, R^{11} is $-C(O)NR^{12}R^{13}$, wherein R^{12} and R^{13} are taken together with the nitrogen to which they are attached to form a pyrrolidin-1-yl ring, wherein said pyrrolidin-1-yl is unsubstituted or substituted by 1 to 5 R^5 substituents.

In still another embodiment of the compound of formula I, R^{11} is $-(CH_2)_t$(5 to 10 membered heterocyclic) group, wherein said $-(CH_2)_t$(5 to 10 membered heterocyclic) group is unsubstituted or substituted by 1 to 5 R^5 groups.

In still another embodiment of the compound of formula I, R^{11} is $-(CH_2)_t$(5-8 membered heterocyclic) group, said $-(CH_2)_t$(5-8 membered heterocyclic) group is unsubstituted or substituted by 1 to 5 R^5 groups.

In still another embodiment of the compound of formula I, R^{11} is $-(CH_2)_t$(5 or 6 membered heterocyclic) group, said $-(CH_2)_t$(5 or 6 membered heterocyclic) group is unsubstituted or substituted by 1 to 5 R^5 groups.

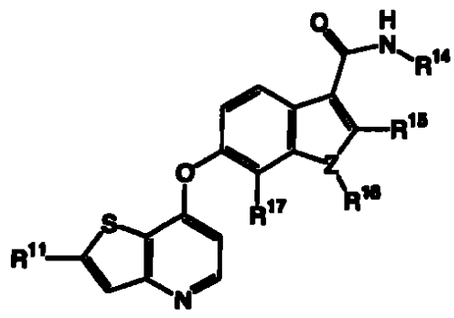
In still another embodiment of the compound of formula I, R^{11} is $-(CH_2)_t$(5 membered heterocyclic) group, said $-(CH_2)_t$(5 membered heterocyclic) group is unsubstituted or substituted by 1 to 5 R^5 groups.

In still another embodiment the compound of formula I, R^{11} is $-(CH_2)_t$thiazolyl, wherein t is an integer from 0 to 6, said $-(CH_2)_t$thiazolyl is unsubstituted or substituted by 1 to 5 R^5 groups.

In still another embodiment, the compound of formula I, R^{11} is a thiazolyl, said thiazolyl is unsubstituted or substituted by 1 to 5 R^5 groups.

In still another embodiment, the compound of formula I, R^{11} is an imidazolyl, said imidazolyl is unsubstituted or substituted by 1 to 5 R^5 groups.

The present invention also relates to compounds represented by formula II:



II

wherein:

Z is -O-, -S-, or -N- ;

R^{14} is a C_1-C_6 alkyl, C_1-C_6 alkylamino, C_1-C_6 alkylhydroxy, C_3-C_{10} cycloalkylamino, or methylureido group;

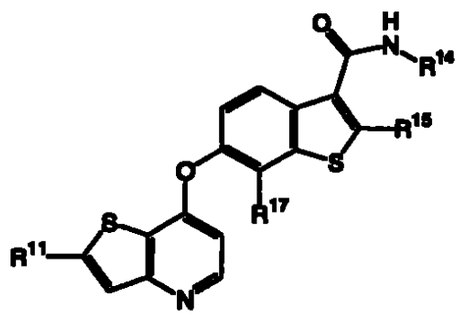
R^{15} and R^{17} are independently H, halo, or a C_1-C_6 alkyl group;

R^{16} is H or a C_1-C_6 alkyl group when Z is N; and R^{16} is absent when Z is –O- or –S-; and wherein R^{11} are as defined for said compounds, prodrug, metabolite, salt or solvate of formula I or prodrugs or metabolites thereof, pharmaceutically acceptable salts or solvates of said compounds, said prodrugs, and said metabolites.

In one embodiment, R^{16} is methyl.

In another embodiment, R^{14} is methyl.

The present invention further relates to compounds represented by the formula III:



III

wherein:

R^{14} is a C_1-C_6 alkyl, C_1-C_6 alkylamino, C_1-C_6 alkylhydroxy, C_3-C_{10} cycloalkylamino, or methylureido group;

R^{15} and R^{17} are independently H or a C_1-C_6 alkyl group; and

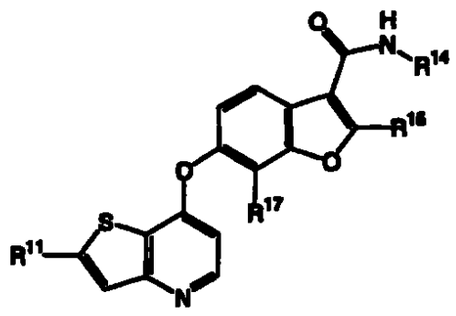
R^{11} is a heterocyclic or a heteroaryl group unsubstituted or substituted by one or more groups selected from $-C(O)OR^5$, C_1-C_6 alkyl, and $-(CH_2)_tOR^5$, wherein t is an integer from 0 to 6;

each R^5 is independently selected from H, C_1-C_{10} alkyl, C_3-C_{10} cycloalkyl,

$-(CH_2)_t(C_5-C_{10}$ aryl), and $-(CH_2)_t$(5 to 10 membered heterocyclic), wherein t is an integer from 0 to 6;

each R^9 is independently selected from H, C_1-C_6 alkyl, and C_3-C_{10} cycloalkyl; or prodrugs thereof, pharmaceutically acceptable salts or solvates of said compounds and said prodrugs.

In another embodiment, the present invention is a compound represented by the formula IV:



IV

wherein:

R^{14} is a C_1-C_6 alkyl, C_1-C_6 alkylamino, C_1-C_6 alkylhydroxy, C_3-C_{10} cycloalkylamino, or methylureido group;

R^{15} and R^{17} are independently H or a C_1-C_6 alkyl group; and

R^{11} is a heterocyclic or a heteroaryl group unsubstituted or substituted by one or more groups selected from $-C(O)OR^9$, C_1-C_6 alkyl, and $-(CH_2)_tOR^9$, wherein t is an integer from 0 to 6;

each R^9 is independently selected from H, C_1-C_{10} alkyl, C_3-C_{10} cycloalkyl, $-(CH_2)_t(C_5-C_{10}$ aryl), and $-(CH_2)_t$(5 to 10 membered heterocyclic), wherein t is an integer from 0 to 6;

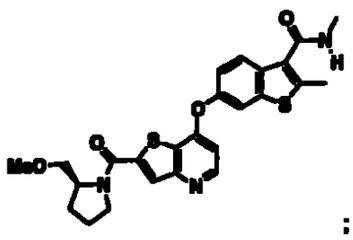
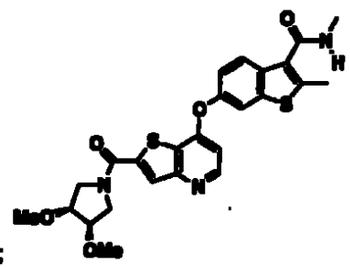
each R^9 is independently selected from H, C_1-C_6 alkyl, and C_3-C_{10} cycloalkyl;

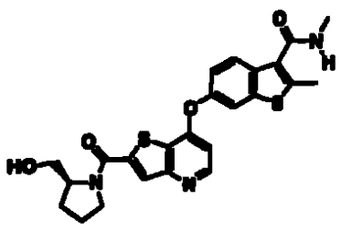
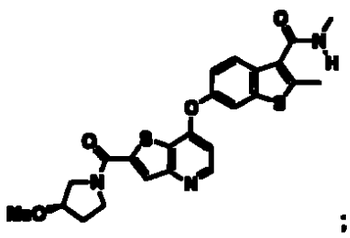
or prodrugs or metabolites thereof, pharmaceutically acceptable salts or solvates of said compounds, said prodrugs, and said metabolites.

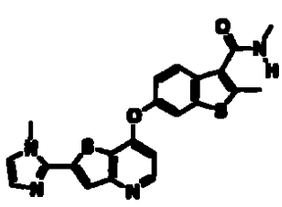
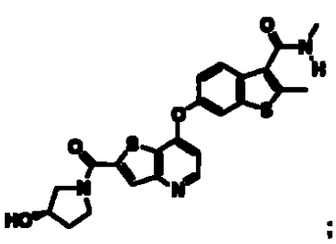
The above compounds of formulas II, III, and IV may be used to prepare the above compounds represented by formula I.

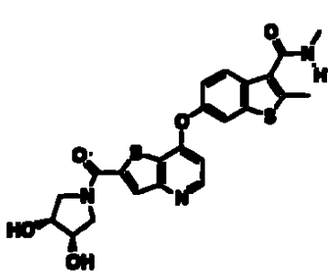
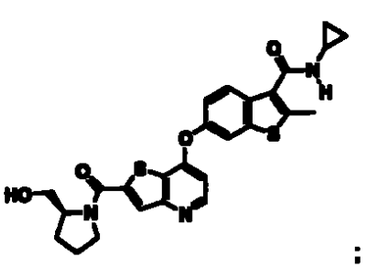
In another embodiment, the present invention comprises compounds selected from the group consisting of:

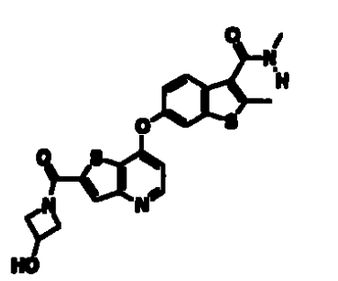
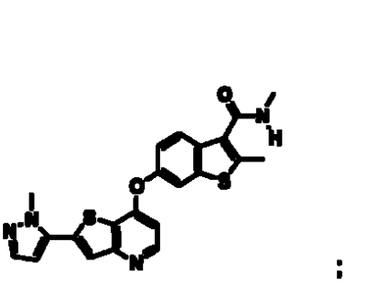
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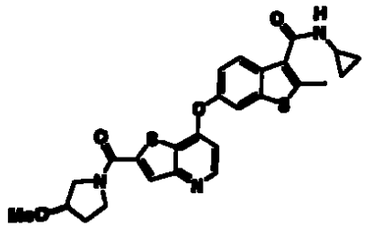
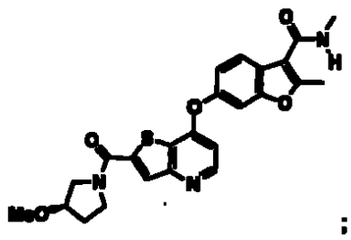

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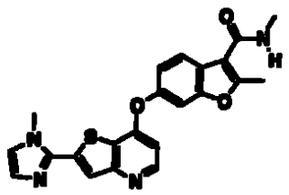
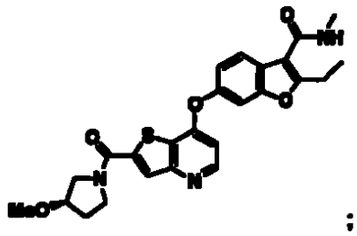

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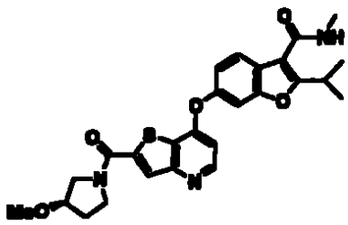
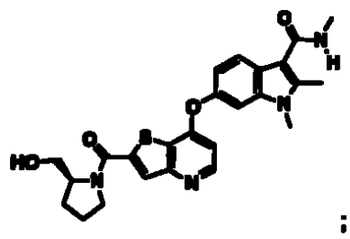

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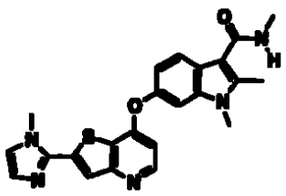
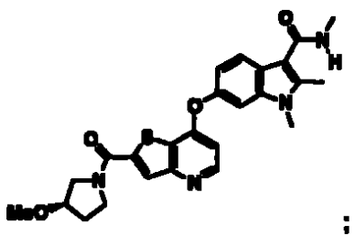
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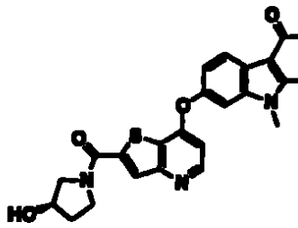
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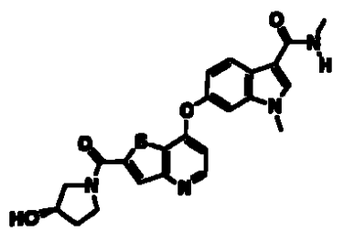
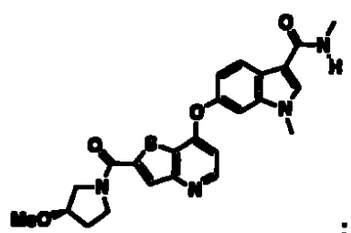
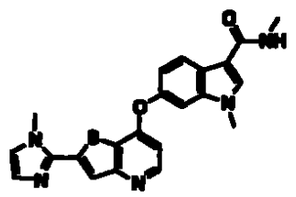
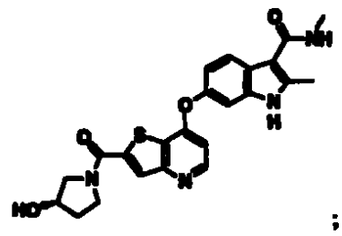

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prodrugs or metabolites thereof, or pharmaceutically acceptable salts or solvates of said compounds, said prodrugs, and said metabolites.

Patients that can be treated with the compounds of formula I, and prodrugs thereof, pharmaceutically acceptable salts or solvates of said compounds and said prodrugs, according to the methods of this invention include, for example, patients that have been diagnosed as having psoriasis, BPH, lung cancer, eye cancer, bone cancer, pancreatic cancer, skin cancer, cancer of the head and neck, cutaneous or intraocular melanoma, uterine cancer, ovarian cancer, rectal cancer, cancer of the anal region, stomach cancer, colon cancer, breast cancer, gynecologic tumors (e.g., uterine sarcomas, carcinoma of the fallopian tubes, carcinoma of the endometrium, carcinoma of the cervix, carcinoma of the vagina or carcinoma of the vulva), Hodgkin's disease, cancer of the esophagus, cancer of the small intestine, cancer of the endocrine system (e.g., cancer of the thyroid, parathyroid or adrenal glands), sarcomas of soft tissues, cancer of the urethra, cancer of the penis, prostate cancer, chronic or acute leukemia, solid tumors of childhood, lymphocytic lymphomas, cancer of the bladder, cancer of the kidney or ureter (e.g., renal cell carcinoma, carcinoma of the renal pelvis), or neoplasms of the central nervous system (e.g., primary CNS lymphoma, spinal axis tumors, brain stem gliomas or pituitary adenomas).

This invention also relates to pharmaceutical compositions containing and methods for treating abnormal cell growth through administering prodrugs of compounds of the formula I. Compounds of formula I having free amino, amido, hydroxy or carboxylic groups that can be converted into prodrugs.

The invention also relates to a pharmaceutical composition for the treatment of a hyperproliferative disorder in a mammal which comprises a therapeutically effective amount of a compound of formula I, or prodrugs thereof, pharmaceutically acceptable salts or solvates of said compounds and said prodrugs, and a pharmaceutically acceptable carrier. In one

embodiment, said pharmaceutical composition is for the treatment of cancer such as brain, lung, ophthalmic, squamous cell, bladder, gastric, pancreatic, breast, head, neck, renal, kidney, ovarian, prostate, colorectal, oesophageal, gynecological or thyroid cancer. In another embodiment, said pharmaceutical composition is for the treatment of a non-cancerous hyperproliferative disorder such as benign hyperplasia of the skin (e.g., psoriasis) or prostate (e.g., benign prostatic hypertropy (BPH)).

The invention also relates to a pharmaceutical composition for the treatment of pancreatitis or kidney disease (including proliferative glomerulonephritis and diabetes-induced renal disease) in a mammal which comprises a therapeutically effective amount of a compound of formula I, or prodrugs thereof, pharmaceutically acceptable salts or solvates of said compounds and said prodrugs, and a pharmaceutically acceptable carrier.

The invention also relates to a pharmaceutical composition for the prevention of blastocyte implantation in a mammal which comprises a therapeutically effective amount of a compound of formula I, or prodrugs thereof, pharmaceutically acceptable salts or solvates of said compounds and said prodrugs, and a pharmaceutically acceptable carrier.

The invention also relates to a pharmaceutical composition for treating a disease related to vasculogenesis or angiogenesis in a mammal which comprises a therapeutically effective amount of a compound of formula I, or prodrugs thereof, pharmaceutically acceptable salts or solvates of said compounds and said prodrugs, and a pharmaceutically acceptable carrier. In one embodiment, said pharmaceutical composition is for treating a disease selected from the group consisting of tumor angiogenesis, chronic inflammatory disease such as rheumatoid arthritis, atherosclerosis, skin diseases such as psoriasis, exzema, and scleroderma, diabetes, diabetic retinopathy, retinopathy of prematurity, age-related macular degeneration, hemangioma, glioma, melanoma, Kaposi's sarcoma and ovarian, breast, lung, pancreatic, prostate, colon and epidermoid cancer.

The invention also relates to a method of treating a hyperproliferative disorder in a mammal which comprises administering to said mammal a therapeutically effective amount of the compound of formula I, or prodrugs thereof, pharmaceutically acceptable salts or solvates of said compounds and said prodrugs. In one embodiment, said method relates to the treatment of cancer such as brain, ophthalmic, squamous cell, bladder, gastric, pancreatic, breast, head, neck, oesophageal, prostate, colorectal, lung, renal, kidney, ovarian, gynecological or thyroid cancer. In another embodiment, said method relates to the treatment of a non-cancerous hyperproliferative disorder such as benign hyperplasia of the skin (e.g., psoriasis) or prostate (e.g., benign prostatic hypertropy (BPH)).

The invention also relates to a method for the treatment of a hyperproliferative disorder in a mammal which comprises administering to said mammal a therapeutically effective amount of a compound of formula I, or prodrugs thereof, pharmaceutically acceptable salts or solvates

of said compounds and said prodrugs, in combination with an anti-tumor agent selected from the group consisting of mitotic inhibitors, alkylating agents, anti-metabolites, intercalating antibiotics, growth factor inhibitors, cell cycle inhibitors, enzymes, topoisomerase inhibitors, biological response modifiers, anti-hormones, and anti-androgens.

The treatment of a hyperproliferative disorder in a mammal which comprises administering to said mammal a therapeutically effective amount of a VEGF receptor tyrosine kinase inhibitor may lead to a sustained increase in blood pressure. The compounds of the present invention may be used in conjunction with an anti-hypertensive, such as NORVASC or PROCARDIA XL, commercially available from Pfizer, for use in the treatment of a hyperproliferative disorder in a mammal.

This invention also relates to a pharmaceutical composition for treating a disease related to vasculogenesis or angiogenesis in a mammal comprising a therapeutically effective amount of a compound, prodrug, metabolite, salt or solvate of claim 1, a therapeutically effective amount of a compound, prodrug, metabolite, salt or solvate of an antihypertensive agent, and a pharmaceutically acceptable carrier.

This invention also relates to a pharmaceutical composition for inhibiting abnormal cell growth in a mammal, including a human, comprising an amount of a compound of the formula I as defined above, or prodrug thereof, pharmaceutically acceptable salt or solvate of said compound and said prodrug, that is effective in inhibiting farnesyl protein transferase, and a pharmaceutically acceptable carrier.

This invention also relates to a pharmaceutical composition for inhibiting abnormal cell growth in a mammal which comprises an amount of a compound of formula I, or prodrug thereof, pharmaceutically acceptable salt or solvate of said compound and said prodrug, in combination with an amount of a chemotherapeutic, wherein the amounts of the compound, salt, solvate, or prodrug, and of the chemotherapeutic are together effective in inhibiting abnormal cell growth. Many chemotherapeutics are presently known in the art. In one embodiment, the chemotherapeutic is selected from the group consisting of mitotic inhibitors, alkylating agents, anti-metabolites, intercalating antibiotics, growth factor inhibitors, cell cycle inhibitors, enzymes, topoisomerase inhibitors, biological response modifiers, anti-hormones, *e.g.* anti-androgens.

This invention further relates to a method for inhibiting abnormal cell growth in a mammal which method comprises administering to the mammal an amount of a compound of formula I, or prodrug thereof, pharmaceutically acceptable salt or solvate of said compound and said prodrug, in combination with radiation therapy, wherein the amount of the compound, salt, solvate or prodrug is in combination with the radiation therapy effective in inhibiting abnormal cell growth in the mammal. Techniques for administering radiation therapy are known in the art, and these techniques can be used in the combination therapy described

herein. The administration of the compound of the invention in this combination therapy can be determined as described herein.

It is believed that the compounds of formula I can render abnormal cells more sensitive to treatment with radiation for purposes of killing and/or inhibiting the growth of such cells. Accordingly, this invention further relates to a method for sensitizing abnormal cells in a mammal to treatment with radiation which comprises administering to the mammal an amount of a compound of formula I or prodrug thereof, pharmaceutically acceptable salt or solvate of said compound and said prodrug, which amount is effective in sensitizing abnormal cells to treatment with radiation. The amount of the compound, salt, solvate or prodrug in this method can be determined according to the means for ascertaining effective amounts of such compounds described herein.

This invention also relates to a method of and to a pharmaceutical composition for inhibiting abnormal cell growth in a mammal which comprises an amount of a compound of formula I, or prodrug thereof, pharmaceutically acceptable salt or solvate of said compound and said prodrug, or an isotopically-labelled derivative thereof, and an amount of one or more substances selected from anti-angiogenesis agents, signal transduction inhibitors, and antiproliferative agents.

Anti-angiogenesis agents, such as MMP-2 (matrix-metalloprotienase 2) inhibitors, MMP-9 (matrix-metalloprotienase 9) inhibitors, and COX-II (cyclooxygenase II) inhibitors, can be used in conjunction with a compound of formula I and pharmaceutical compositions described herein. Examples of useful COX-II inhibitors include CELEBREX™ (alecoxib), valdecoxib, and rofecoxib. Examples of useful matrix metalloproteinase inhibitors are described in WO 96/33172 (published October 24, 1996), WO 96/27583 (published March 7, 1996), European Patent Application No. 97304971.1 (filed July 8, 1997), European Patent Application No. 99308617.2 (filed October 29, 1999), WO 98/07697 (published February 26, 1998), WO 98/03516 (published January 29, 1998), WO 98/34918 (published August 13, 1998), WO 98/34915 (published August 13, 1998), WO 98/33768 (published August 6, 1998), WO 98/30566 (published July 16, 1998), European Patent Publication 606,046 (published July 13, 1994), European Patent Publication 931,788 (published July 28, 1999), WO 90/05719 (published May 31, 1990), WO 99/52910 (published October 21, 1999), WO 99/52889 (published October 21, 1999), WO 99/29667 (published June 17, 1999), PCT International Application No. PCT/IB98/01113 (filed July 21, 1998), European Patent Application No. 99302232.1 (filed March 25, 1999), Great Britain patent application number 9912961.1 (filed June 3, 1999), United States Provisional Application No. 60/148,464 (filed August 12, 1999), United States Patent 5,863,949 (issued January 26, 1999), United States Patent 5,861,510 (issued January 19, 1999), and European Patent Publication 780,386 (published June 25, 1997), all of which are incorporated herein in their entireties by reference. Preferred MMP-2

and MMP-9 inhibitors are those that have little or no activity inhibiting MMP-1. More preferred, are those that selectively inhibit MMP-2 and/or MMP-9 relative to the other matrix-metalloproteinases (*i.e.* MMP-1, MMP-3, MMP-4, MMP-5, MMP-6, MMP-7, MMP-8, MMP-10, MMP-11, MMP-12, and MMP-13).

Some specific examples of MMP inhibitors useful in the present invention are Prinomastat, RO 32-3555, RS 13-0830, and the compounds recited in the following list: 3-[[4-(4-fluoro-phenoxy)-benzenesulfonyl]-(1-hydroxycarbamoyl-cyclopentyl)-amino]-propionic acid; 3-exo-3-[4-(4-fluoro-phenoxy)-benzenesulfonylamino]-8-oxa-bicyclo[3.2.1]octane-3-carboxylic acid hydroxyamide; (2R, 3R) 1-[4-(2-chloro-4-fluoro-benzyloxy)-benzenesulfonyl]-3-hydroxy-3-methyl-piperidine-2-carboxylic acid hydroxyamide; 4-[4-(4-fluoro-phenoxy)-benzenesulfonylamino]-tetrahydro-pyran-4-carboxylic acid hydroxyamide; 3-[[4-(4-fluoro-phenoxy)-benzenesulfonyl]-(1-hydroxycarbamoyl-cyclobutyl)-amino]-propionic acid; 4-[4-(4-chloro-phenoxy) -benzenesulfonylamino]-tetrahydro-pyran-4-carboxylic acid hydroxyamide; (R) 3-[4-(4-chloro-phenoxy)-benzenesulfonylamino]-tetrahydro-pyran-3-carboxylic acid hydroxyamide; (2R, 3R) 1-[4-(4-fluoro-2-methyl-benzyloxy)-benzenesulfonyl]-3-hydroxy-3-methyl-piperidine-2-carboxylic acid hydroxyamide; 3-[[4-(4-fluoro-phenoxy)-benzenesulfonyl]-(1-hydroxycarbamoyl-1-methyl-ethyl)-amino]-propionic acid; 3-[[4-(4-fluoro-phenoxy)-benzenesulfonyl]-(4-hydroxycarbamoyl-tetrahydro-pyran-4-yl)-amino]-propionic acid; 3-exo-3-[4-(4-chloro-phenoxy)-benzenesulfonylamino]-8-oxa-bicyclo[3.2.1]octane-3-carboxylic acid hydroxyamide; 3-endo-3-[4-(4-fluoro-phenoxy)-benzenesulfonylamino]-8 -oxa-bicyclo[3.2.1]octane-3-carboxylic acid hydroxyamide; and (R) 3-[4-(4-fluoro-phenoxy)-benzenesulfonylamino]-tetrahydro-furan-3-carboxylic acid hydroxyamide;
and pharmaceutically acceptable salts and solvates of said compounds. Other anti-angiogenesis agents, including other COX-II inhibitors and other MMP inhibitors, can also be used in the present invention.

This invention further relates to a method for treating a disease related to vasculogenesis or angiogenesis in a mammal comprising administering to said mammal a therapeutically effective amount of a compound, prodrug, metabolite, salt or solvate of claim 1 in conjunction with a therapeutically effective amount of an anti-hypertensive agent.

A compound of formula I, can also be used with signal transduction inhibitors, such as agents that can inhibit EGFR (epidermal growth factor receptor) responses, such as EGFR antibodies, EGF antibodies, and molecules that are EGFR inhibitors; VEGF (vascular endothelial growth factor) inhibitors, such as VEGF receptors and molecules that can inhibit VEGF; and erbB2 receptor inhibitors, such as organic molecules or antibodies that bind to the erbB2 receptor, for example, HERCEPTIN™ (Genentech, Inc. of South San Francisco, California, USA).

EGFR inhibitors are described in, for example in WO 95/19970 (published July 27, 1995), WO 98/14451 (published April 9, 1998), WO 98/02434 (published January 22, 1998), and United States Patent 5,747,498 (issued May 5, 1998), and such substances can be used in the present invention as described herein. EGFR-inhibiting agents include, but are not limited to, the monoclonal antibodies C225 and anti-EGFR 22Mab (ImClone Systems Incorporated of New York, New York, USA), the compounds ZD-1839 (AstraZeneca), BIBX-1382 (Boehringer Ingelheim), MDX-447 (Medarex Inc. of Annandale, New Jersey, USA), and OLX-103 (Merck & Co. of Whitehouse Station, New Jersey, USA), VRCTC-310 (Ventech Research) and EGF fusion toxin (Seragen Inc. of Hopkinton, Massachusetts). These and other EGFR-inhibiting agents can be used in the present invention.

VEGF inhibitors, for example SU-5416 and SU-6668 (Sugen Inc. of South San Francisco, California, USA), can also be combined with the compound of the present invention. VEGF inhibitors are described in, for example in WO 99/24440 (published May 20, 1999), PCT International Application PCT/IB99/00797 (filed May 3, 1999), in WO 95/21613 (published August 17, 1995), WO 99/61422 (published December 2, 1999), United States Patent 5,834,504 (issued November 10, 1998), WO 98/50356 (published November 12, 1998), United States Patent 5,883,113 (issued March 16, 1999), United States Patent 5,886,020 (issued March 23, 1999), United States Patent 5,792,783 (issued August 11, 1998), WO 99/10349 (published March 4, 1999), WO 97/32856 (published September 12, 1997), WO 97/22596 (published June 26, 1997), WO 98/54093 (published December 3, 1998), WO 98/02438 (published January 22, 1998), WO 99/16755 (published April 8, 1999), and WO 98/02437 (published January 22, 1998), all of which are incorporated herein in their entireties by reference. Other examples of some specific VEGF inhibitors useful in the present invention are IM862 (Cytran Inc. of Kirkland, Washington, USA); anti-VEGF monoclonal antibody of Genentech, Inc. of South San Francisco, California; and angiozyme, a synthetic ribozyme from Ribozyme (Boulder, Colorado) and Chiron (Emeryville, California). These and other VEGF inhibitors can be used in the present invention as described herein.

ErbB2 receptor inhibitors, such as GW-282974 (Glaxo Wellcome plc), and the monoclonal antibodies AR-209 (Aronex Pharmaceuticals Inc. of The Woodlands, Texas, USA) and 2B-1 (Chiron), can furthermore be combined with the compound of the invention, for example those indicated in WO 98/02434 (published January 22, 1998), WO 99/35146 (published July 15, 1999), WO 99/35132 (published July 15, 1999), WO 98/02437 (published January 22, 1998), WO 97/13760 (published April 17, 1997), WO 95/19970 (published July 27, 1995), United States Patent 5,587,458 (issued December 24, 1996), and United States Patent 5,877,305 (issued March 2, 1999), which are all hereby incorporated herein in their entireties by reference. ErbB2 receptor inhibitors useful in the present invention are also described in United States Provisional Application No. 60/117,341, filed January 27, 1999, and in United States

Provisional Application No. 60/117,346, filed January 27, 1999, both of which are incorporated in their entireties herein by reference. The erbB2 receptor inhibitor compounds and substance described in the aforementioned PCT applications, U.S. patents, and U.S. provisional applications, as well as other compounds and substances that inhibit the erbB2 receptor, can be used with the compounds of the present invention.

The compounds of the invention can also be used with other agents useful in treating abnormal cell growth or cancer, including, but not limited to, agents capable of enhancing antitumor immune responses, such as CTLA4 (cytotoxic lymphocyte antigen 4) antibodies, and other agents capable of blocking CTLA4; and anti-proliferative agents such as other farnesyl protein transferase inhibitors, and the like. Specific CTLA4 antibodies that can be used in the present invention include those described in United States Provisional Application 60/113,647 (filed December 23, 1998) that is incorporated by reference in its entirety, however other CTLA4 antibodies can be used in the present invention.

The subject invention also includes isotopically-labelled compounds, which are identical to those recited in formula I, but for the fact that one or more atoms are replaced by an atom having an atomic mass or mass number different from the atomic mass or mass number usually found in nature. Examples of isotopes that can be incorporated into compounds of the invention include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorous, fluorine and chlorine, such as ^{2}H, ^{3}H, ^{13}C, ^{14}C, ^{15}N, ^{18}O, ^{17}O, ^{31}P, ^{32}P, ^{35}S, ^{18}F, and ^{36}Cl, respectively. Compounds of the present invention, prodrugs thereof, and pharmaceutically acceptable salts of said compounds or of said prodrugs which contain the aforementioned isotopes and/or other isotopes of other atoms are within the scope of this invention. Certain isotopically-labelled compounds of the present invention, for example those into which radioactive isotopes such as ^{3}H and ^{14}C are incorporated, are useful in drug and/or substrate tissue distribution assays. Tritiated, i.e., ^{3}H, and carbon-14, i.e., ^{14}C, isotopes are particularly preferred for their ease of preparation and detectability. Further, substitution with heavier isotopes such as deuterium, i.e., ^{2}H, can 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. Isotopically labelled compounds of formula I, II, III, or IV of this invention and prodrugs thereof can generally be prepared by carrying out the procedures disclosed in the Schemes and/or in the Examples below, by substituting a readily available isotopically labelled reagent for a non-isotopically labelled reagent. The compounds of formula I and their pharmaceutically acceptable salts and solvates can each independently also be used in a palliative neo-adjuvant/adjuvant therapy in alleviating the symptoms associated with the diseases recited herein as well as the symptoms associated with abnormal cell growth. Such therapy can be a monotherapy or can be in a combination with chemotherapy and/or immunotherapy.

The terms "abnormal cell growth" and "hyperproliferative disorder" are used interchangeably in this application.

"Abnormal cell growth", as used herein, refers to cell growth that is independent of normal regulatory mechanisms (*e.g.*, loss of contact inhibition), including the abnormal growth of normal cells and the growth of abnormal cells. This includes, but is not limited to, the abnormal growth of: (1) tumor cells (tumors), both benign and malignant, expressing an activated Ras oncogene; (2) tumor cells, both benign and malignant, in which the Ras protein is activated as a result of oncogenic mutation in another gene; (3) benign and malignant cells of other proliferative diseases in which aberrant Ras activation occurs. Examples of such benign proliferative diseases are psoriasis, benign prostatic hypertrophy, human papilloma virus (HPV), and restinosis. "Abnormal cell growth" also refers to and includes the abnormal growth of cells, both benign and malignant, resulting from activity of the enzyme farnasyl protein transferase.

The term "treating", as used herein, unless otherwise indicated, means reversing, alleviating, inhibiting the progress of, or preventing the disorder or condition to which such term applies, or one or more symptoms of such disorder or condition. The term "treatment", as used herein, refers to the act of treating, as "treating" is defined immediately above.

The term "halo", as used herein, unless otherwise indicated, means fluoro, chloro, bromo or iodo. Preferred halo groups are fluoro, chloro and bromo.

The term "alkyl", as used herein, unless otherwise indicated, means saturated monovalent hydrocarbon radicals having straight, cyclic or branched moieties. Said "alkyl" group may include an optional carbon-carbon double or triple bond where said alkyl group comprises at least two carbon atoms. It is understood that for cyclic moieties at least three carbon atoms are required in said alkyl group.

The term "alkoxy", as used herein, unless otherwise indicated, means O-alkyl groups wherein "alkyl" is as defined above.

The term "aryl", as used herein, unless otherwise indicated, means an organic radical derived from an aromatic hydrocarbon by removal of one hydrogen, such as phenyl or naphthyl.

The term "hetero cyclic group", as used herein, includes aromatic and non-aromatic heterocyclic groups. Unless otherwise indicated, preferred heterocyclic groups include groups having from 3 to 13 ring atoms, more preferably from 5 to 10 ring atoms, and still more preferably from 5 to 6 ring atoms. In addition, preferred heterocyclic groups include groups containing one to four heteroatoms each selected from O, S and N. The heterocyclic groups include benzo-fused ring systems and ring systems substituted with one or two oxo (=O) moieties such as pyrrolidin-2-one. An example of a 5 membered heterocyclic group is thiazolyl, an example of a 10 membered heterocyclic group is quinolinyl, and an example of a 13 membered heterocyclic group is a carbazole group. Examples of non-aromatic heterocyclic

groups include pyrrolidinyl, piperidino, morpholino, thiomorpholino and piperazinyl. Examples of aromatic heterocyclic groups include pyridinyl, imidazolyl, pyrimidinyl, pyrazolyl, triazolyl, pyrazinyl, tetrazolyl, furyl, thienyl, isoxazolyl and thiazolyl. Heterocyclic groups having a fused benzene ring include benzimidazolyl, benzofuranyl, and benzo[1,3]dioxolyl.

The phrase "pharmaceutically acceptable salt(s)", as used herein, unless otherwise indicated, means salts of acidic or basic groups which may be present in the compounds or prodrugs of formula I. The compounds and prodrugs of formula I that are basic in nature are capable of forming a wide variety of salts with various inorganic and organic acids. The acids that may be used to prepare pharmaceutically acceptable acid addition salts of such basic compounds and prodrugs of formula I are those that form non-toxic acid addition salts, i.e., salts containing pharmacologically acceptable anions, such as the hydrochloride, hydrobromide, hydroiodide, nitrate, sulfate, bisulfate, phosphate, acid phosphate, isonicotinate, acetate, lactate, salicylate, citrate, acid citrate, tartrate, pantothenate, bitartrate, ascorbate, succinate, maleate, gentisinate, fumarate, gluconate, glucaronate, saccharate, formate, benzoate, glutamate, methanesulfonate, ethanesulfonate, benzenesulfonate, p-toluenesulfonate and pamoate [i.e., 1,1'-methylene-bis-(2-hydroxy-3-naphthoate)] salts.

Those compounds and prodrugs of the formulas I that are acidic in nature, are capable of forming base salts with various pharmacologically acceptable cations. Examples of such salts include the alkali metal or alkaline earth metal salts and particularly, the sodium and potassium salts.

The compounds of the present invention may have asymmetric carbon atoms. Such diastereomeric mixtures can be separated into their individual diastereomers on the basis of their physical chemical differences by methods known to those skilled in the art, for example, by chromatography or fractional crystallization. Enantiomers can be separated by converting the enantiomeric mixtures into a diastereomric mixture by reaction with an appropriate optically active compound (e.g., alcohol), separating the diastereomers and converting (e.g., hydrolyzing) the individual diastereomers to the corresponding pure enantiomers. All such isomers, including diastereomer mixtures and pure enantiomers are considered as part of the invention.

The compounds of present invention may in certain instances exist as tautomers. This invention relates to the use of all such tautomers and mixtures thereof.

The term "prodrug", as used herein, unless otherwise indicated, means compounds that are drug precursors, which following administration, release the drug *in vivo* via some chemical or physiological process (e.g., a prodrug on being brought to the physiological pH is converted to the desired drug form).

Prodrugs include compounds wherein an amino acid residue, or a polypeptide chain of two or more (e.g., two, three or four) amino acid residues is covalently joined through an amide or ester bond to a free amino, hydroxy or carboxylic acid group of compounds of

formula I. The amino acid residues include but are not limited to the 20 naturally occurring amino acids commonly designated by three letter symbols and also includes 4-hydroxyproline, hydroxylysine, demosine, isodemosine, 3-methylhistidine, norvalin, beta-alanine, gamma-aminobutyric acid, citrulline homocysteine, homoserine, ornithine and methionine sulfone. Additional types of prodrugs are also encompassed. For instance, free carboxyl groups can be derivatized as amides or alkyl esters. Free hydroxy groups may be derivatized using groups including but not limited to hemisuccinates, phosphate esters, dimethylaminoacetates, and phosphoryloxymethyloxycarbonyls, as outlined in Advanced Drug Delivery Reviews, 1996, 19, 115. Carbamate prodrugs of hydroxy and amino groups are also included, as are carbonate prodrugs, sulfonate esters and sulfate esters of hydroxy groups. Derivatization of hydroxy groups as (acyloxy)methyl and (acyloxy)ethyl ethers wherein the acyl group may be an alkyl ester, optionally substituted with groups including but not limited to ether, amine and carboxylic acid functionalities, or where the acyl group is an amino acid ester as described above, are also encompassed. Prodrugs of this type are described in J. Med. Chem. 1996, 39, 10. Free amines can also be derivatized as amides, sulfonamides or phosphonamides. All of these prodrug moieties may incorporate groups including but not limited to ether, amine and carboxylic acid functionalities.

It will be appreciated that any solvate (e.g. hydrate) form of compounds of formula I and prodrugs thereof can be used for the purpose of the present invention.

The terms "comprising" and "including" are used herein in their open, non-limiting sense.

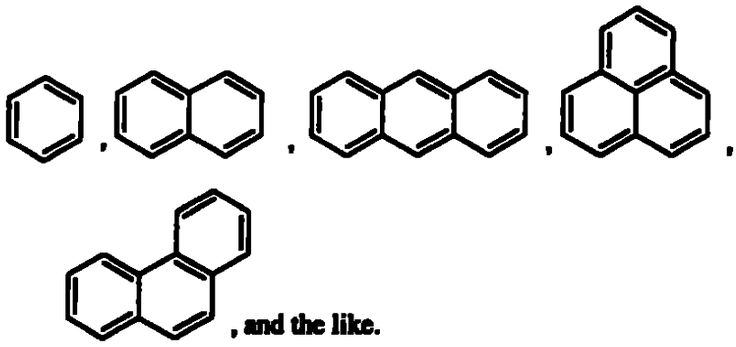
The term "alkyl" as used herein refers to straight- and branched-chain alkyl groups having from one to twelve carbon atoms, preferably from 1 to 6 carbons, and more preferably from 1 to 3 carbons. Exemplary alkyl groups include methyl (Me), ethyl, *n*-propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl (tBu), pentyl, isopentyl, tert-pentyl, hexyl, isohexyl, and the like.

The term "heteroalkyl" as used herein refers to straight- and branched-chain alkyl groups containing one or more heteroatoms selected from S, O, and N.

The term "alkenyl" refers to straight- and branched-chain alkenyl groups having from two to twelve carbon atoms, preferably from 2 to 6 carbons, and more preferably from 2 to 4 carbons. Illustrative alkenyl groups include prop-2-enyl, but-2-enyl, but-3-enyl, 2-methylprop-2-enyl, hex-2-enyl, and the like.

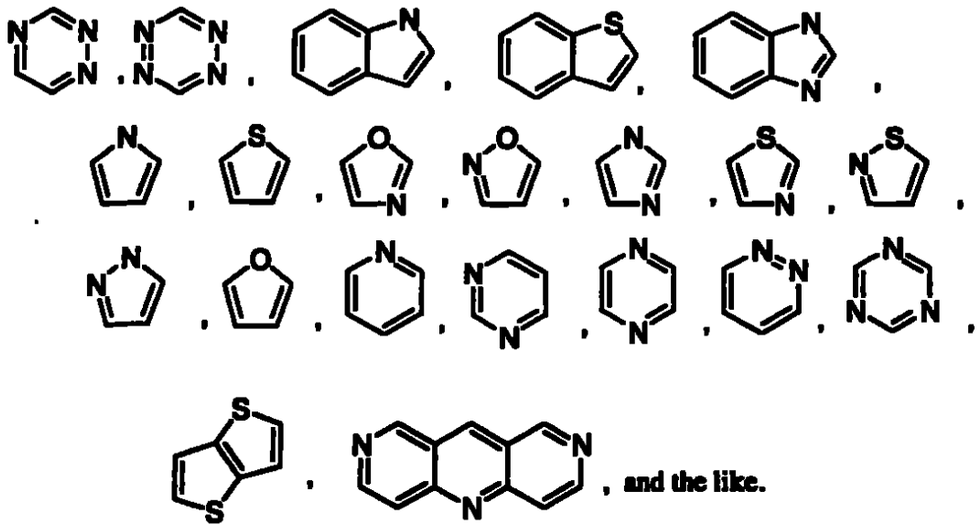
The term "alkynyl" refers to straight- and branched-chain alkynyl groups having from two to twelve carbon atoms, preferably from 2 to 6 carbons, and more preferably from 2 to 4 carbons. Illustrative alkynyl groups include prop-2-ynyl, but-2-ynyl, but-3-ynyl, 2-methylbut-2-ynyl, hex-2-ynyl, and the like.

The term "aryl" (Ar) refers to monocyclic and polycyclic aromatic ring structures containing only carbon and hydrogen. Preferred aryl groups have from 4 to 20 ring atoms, and more preferably from 6 to 14 ring atoms. Illustrative examples of aryl groups include the following moieties:



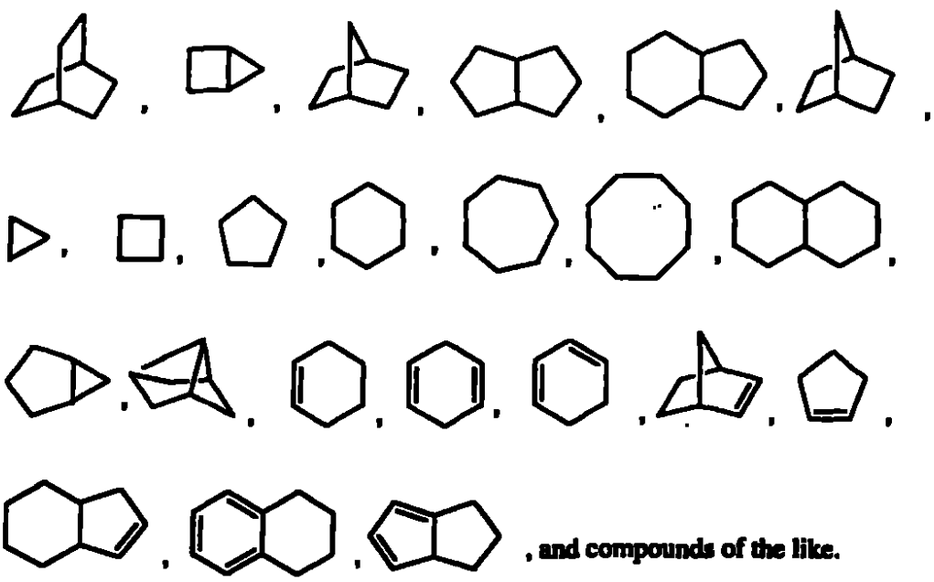
, and the like.

The term "heteroaryl" (heteroAr) refers to an aryl group that includes one or more ring heteroatoms selected from nitrogen, oxygen and sulfur. The polycyclic heteroaryl group may be fused or non-fused. Illustrative examples of aryl groups include the following moieties:



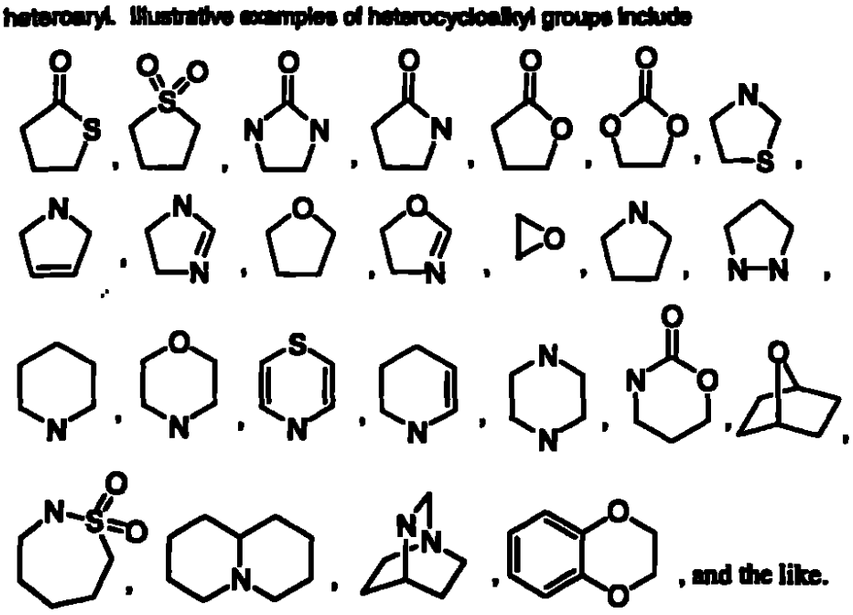
, and the like.

The term "cycloalkyl" refers to a monocyclic or polycyclic radical which contain only carbon and hydrogen, and may be saturated, partially unsaturated, or fully unsaturated. Preferred cycloalkyl groups include groups having from three to twelve ring atoms, more preferably from 5 to 10 ring atoms, and still more preferably from 5 to 6 ring atoms. Illustrative examples of cycloalkyl groups include the following moieties:



, and compounds of the like.

A "heterocycloalkyl" group refers to a cycloalkyl group that includes at least one heteroatom selected from nitrogen, oxygen and sulfur. The radicals may be fused with an aryl or heteroaryl. Illustrative examples of heterocycloalkyl groups include



, and the like.

The term "heterocyclic" comprises both heterocycloalkyl and heteroaryl groups.

The term "alkoxy" refers to the radical –O-R where R is an alkyl as defined above. Examples of alkoxy groups include methoxy, ethoxy, propoxy, and the like.

The term "halogen" represents chlorine, fluorine, bromine or iodine. The term "halo" represents chloro, fluoro, bromo or iodo.

The term "alcohol" refers to the radical –R-OH where R is alkyl, alkenyl, alkynyl, Ar, heteroaryl, heterocycloalkyl, or cycloalkyl as defined above. Examples of alcohols include methanol, ethanol, propanol, phenol and the like.

The term "acyl" represents –C(O)R, -C(O)OR, -OC(O)R or -OC(O)OR where R is alkyl, alkenyl, alkynyl, Ar, heteroaryl, heterocycloalkyl, or cycloalkyl as defined as above.

The term "amide" refers to the radical –C(O)N(R')(R") where R' and R" are each independently selected from hydrogen, alkyl, alkenyl, alkynyl, -OH, alkoxy, cycloalkyl, heterocycloalkyl, heteroaryl, aryl as defined above; or R' and R" cyclize together with the nitrogen to form a heterocycloalkyl or heteroaryl as defined above.

The term "substituted" as used herein means that the group in question , e.g., alkyl group, etc., may bear one or more substituents.

The alkyl, cycloalkyl, aryl, heterocycloalkyl and heteroaryl groups and the substituents containing these groups, as defined hereinabove, may be optionally substituted by at least one other substituent. The term "optionally substituted" is intended to expressly indicate that the specified group is unsubstituted or substituted by one or more substituents as defined herein. Various groups may be unsubstituted or substituted (i.e., they are optionally substituted) as indicated.

If the substituents themselves are not compatible with the synthetic methods of this invention, the substituent may be protected with a suitable protecting group that is stable to the reaction conditions used in these methods. The protecting group may be removed at a suitable point in the reaction sequence of the method to provide a desired intermediate or target compound. Suitable protecting groups and the methods for protecting and de-protecting different substituents using such suitable protecting groups are well known to those skilled in the art; examples of which may be found in T. Greene and P. Wuts, Protecting Groups in Chemical Synthesis (3rd ed.), John Wiley & Sons, NY (1999), which is incorporated herein by reference in its entirety. In some instances, a substituent may be specifically selected to be reactive under the reaction conditions used in the methods of this invention. Under these circumstances, the reaction conditions convert the selected substituent into another substituent that is either useful in an intermediate compound in the methods of this invention or is a desired substituent in a target compound.

Some of the inventive compounds may exist in various stereoisomeric or tautomeric forms. The present invention encompasses all such cell proliferation-inhibiting compounds, including active compounds in the form of single pure enantiomers (i.e., essentially free of other stereoisomers), racemates, mixtures of enantiomers and/or

diastereomers, and/or tautomers. Preferably, the inventive compounds that are optically active are used in optically pure form.

As generally understood by those skilled in the art, an optically pure compound having one chiral center (i.e., one asymmetric carbon atom) is one that consists essentially of one of the two possible enantiomers (i.e., is enantiomerically pure), and an optically pure compound having more than one chiral center is one that is both diastereomerically pure and enantiomerically pure.

Preferably, the compounds of the present invention are used in a form that is at least 90% optically pure, that is, a form that contains at least 90% of a single isomer (80% enantiomeric excess ("e.e.") or diastereomeric excess ("d.e.")), more preferably at least 95% (90% e.e. or d.e.), even more preferably at least 97.5% (95% e.e. or d.e.), and most preferably at least 99% (98% e.e. or d.e.).

Additionally, the formulas are intended to cover solvated as well as unsolvated forms of the identified structures. For example, Formula I includes compounds of the indicated structure in both hydrated and non-hydrated forms. Additional examples of solvates include the structures in combination with isopropanol, ethanol, methanol, DMSO, ethyl acetate, acetic acid, or ethanolamine.

In addition to compounds of Formula I, the invention includes pharmaceutically acceptable prodrugs, pharmaceutically active metabolites, and pharmaceutically acceptable salts of such compounds and metabolites.

The term "pharmaceutically acceptable" means pharmacologically acceptable and substantially non-toxic to the subject being administered the agent.

"A pharmaceutically acceptable prodrug" is a compound that may be converted under physiological conditions or by solvolysis to the specified compound or to a pharmaceutically acceptable salt of such compound. "A pharmaceutically active metabolite" is intended to mean a pharmacologically active product produced through metabolism in the body of a specified compound or salt thereof. Prodrugs and active metabolites of a compound may be identified using routine techniques known in the art. See, e.g., Bertolini et al., *J. Med. Chem.*, 40, 2011-2016 (1997); Shan et al., *J. Pharm. Sci.*, 86 (7), 765-767; Bagshawe, *Drug Dev. Res.*, 34, 220-230 (1995); Bodor, *Advances in Drug Res.*, 13, 224-331 (1984); Bundgaard, *Design of Prodrugs* (Elsevier Press 1985); and Larsen, *Design and Application of Prodrugs, Drug Design and Development* (Krogsgaard-Larsen et al., eds., Harwood Academic Publishers, 1991).

"A pharmaceutically acceptable salt" is intended to mean a salt that retains the biological effectiveness of the free acids and bases of the specified compound and that is not biologically or otherwise undesirable. A compound of the invention may possess a sufficiently acidic, a sufficiently basic, or both functional groups, and accordingly react with any of a

number of inorganic or organic bases, and inorganic and organic acids, to form a pharmaceutically acceptable salt. Exemplary pharmaceutically acceptable salts include those salts prepared by reaction of the compounds of the present invention with a mineral or organic acid or an inorganic base, such as salts including sulfates, pyrosulfates, bisulfates, sulfites, bisulfites, phosphates, monohydrogenphosphates, dihydrogenphosphates, metaphosphates, pyrophosphates, chlorides, bromides, iodides, acetates, propionates, decanoates, caprylates, acrylates, formates, isobutyrates, caproates, heptanoates, propiolates, oxalates, malonates, succinates, suberates, sebacates, fumarates, maleates, butyne-1,4-dioates, hexyne-1,6-dioates, benzoates, chlorobenzoates, methylbenzoates, dinitrobenzoates, hydroxybenzoates, methoxybenzoates, phthalates, sulfonates, xylenesulfonates, phenylacetates, phenylpropionates, phenylbutyrates, citrates, lactates, γ-hydroxybutyrates, glycolates, tartrates, methane-sulfonates, propanesulfonates, naphthalene-1-sulfonates, naphthalene-2-sulfonates, and mandelates.

If the inventive compound is a base, the desired pharmaceutically acceptable salt may be prepared by any suitable method available in the art, for example, treatment of the free base with an inorganic acid, such as hydrochloric acid, hydrobromic acid, sulfuric acid, sulfamic acid, nitric acid, phosphoric acid and the like, or with an organic acid, such as acetic acid, phenylacetic acid, propionic acid, stearic acid, lactic acid, ascorbic acid, maleic acid, hydroxymaleic acid, isethionic acid, succinic acid, mandelic acid, fumaric acid, malonic acid, pyruvic acid, oxalic acid, glycolic acid, salicylic acid, a pyranosidyl acid, such as glucuronic acid or galacturonic acid, an alpha-hydroxy acid, such as citric acid or tartaric acid, an amino acid, such as aspartic acid or glutamic acid, an aromatic acid, such as benzoic acid, 2-acetoxybenzoic acid or cinnamic acid, a sulfonic acid, such as p-toluenesulfonic acid, methanesulfonic acid or ethanesulfonic acid, or the like.

If the inventive compound is an acid, the desired pharmaceutically acceptable salt may be prepared by any suitable method, for example, treatment of the free acid with an inorganic or organic base, such as an amine (primary, secondary or tertiary), an alkali metal hydroxide or alkaline earth metal hydroxide, or the like. Illustrative examples of suitable salts include organic salts derived from amino acids, such as glycine and arginine, ammonia, carbonates, bicarbonates, primary, secondary, and tertiary amines, and cyclic amines, such as benzylamines, pyrrolidines, piperidine, morpholine and piperazine, and inorganic salts derived from sodium, calcium, potassium, magnesium, manganese, iron, copper, zinc, aluminum and lithium.

Pharmaceutical compositions according to the invention may, alternatively or in addition to a compound of Formula I, comprise as an active ingredient pharmaceutically acceptable prodrugs, pharmaceutically active metabolites, and pharmaceutically acceptable

salts of such compounds and metabolites. Such compounds, prodrugs, multimers, salts, and metabolites are sometimes referred to herein collectively as "active agents" or "agents."

In the case of agents that are solids, it is understood by those skilled in the art that the inventive compounds and salts may exist in different crystal or polymorphic forms, all of which are intended to be within the scope of the present invention and specified formulas.

Therapeutically effective amounts of the active agents of the invention may be used to treat diseases mediated by modulation or regulation of protein kinases. An "effective amount" is intended to mean that amount of an agent that significantly inhibits proliferation and/or prevents de-differentiation of a eukaryotic cell, e.g., a mammalian, insect, plant or fungal cell, and is effective for the indicated utility, e.g., specific therapeutic treatment.

The amount of a given agent that will correspond to such an amount will vary depending upon factors such as the particular compound, disease condition and its severity, the identity (e.g., weight) of the subject or host in need of treatment, but can nevertheless be routinely determined in a manner known in the art according to the particular circumstances surrounding the case, including, e.g., the specific agent being administered, the route of administration, the condition being treated, and the subject or host being treated. "Treating" is intended to mean at least the mitigation of a disease condition in a subject such as mammal (e.g., human), that is affected, at least in part, by the activity of one or more kinases, for example protein kinases such as tyrosine kinases, and includes: preventing the disease condition from occurring in a mammal, particularly when the mammal is found to be predisposed to having the disease condition but has not yet been diagnosed as having it; modulating and/or inhibiting the disease condition; and/or alleviating the disease condition.

Agents that potently regulate, modulate, or inhibit cell proliferation are preferred. For certain mechanisms, inhibition of the protein kinase activity associated with CDK complexes, among others, and those which inhibit angiogenesis and/or inflammation are preferred. The present invention is further directed to methods of modulating or inhibiting protein kinase activity, for example in mammalian tissue, by administering an inventive agent. The activity of agents as anti-proliferatives is easily measured by known methods, for example by using whole cell cultures in an MTT assay. The activity of the inventive agents as modulators of protein kinase activity, such as the activity of kinases, may be measured by any of the methods available to those skilled in the art, including in vivo and/or in vitro assays. Examples of suitable assays for activity measurements include those described in International Publication No. WO 99/21845; Parast et al., *Biochemistry*, 37, 16788-16801 (1998); Connell-Crowley and Harper, *Cell Cycle: Materials and Methods*, (Michele Pagano, ed. Springer, Berlin, Germany)(1995); International Publication No. WO 97/34876; and International Publication No. WO

98/14843. These properties may be assessed, for example, by using one or more of the biological testing procedures set out in the examples below.

The active agents of the invention may be formulated into pharmaceutical compositions as described below. Pharmaceutical compositions of this invention comprise an effective modulating, regulating, or inhibiting amount of a compound of Formula I or Formula II and an inert, pharmaceutically acceptable carrier or diluent. In one embodiment of the pharmaceutical compositions, efficacious levels of the inventive agents are provided so as to provide therapeutic benefits involving anti-proliferative ability. By "efficacious levels" is meant levels in which proliferation is inhibited, or controlled. These compositions are prepared in unit-dosage form appropriate for the mode of administration, e.g., parenteral or oral administration.

An inventive agent can be administered in conventional dosage form prepared by combining a therapeutically effective amount of an agent (e.g., a compound of Formula I) as an active ingredient with appropriate pharmaceutical carriers or diluents according to conventional procedures. These procedures may involve mixing, granulating and compressing or dissolving the ingredients as appropriate to the desired preparation.

The pharmaceutical carrier employed may be either a solid or liquid. Exemplary of solid carriers are lactose, sucrose, talc, gelatin, agar, pectin, acacia, magnesium stearate, stearic acid and the like. Exemplary of liquid carriers are syrup, peanut oil, olive oil, water and the like. Similarly, the carrier or diluent may include time-delay or time-release material known in the art, such as glyceryl monostearate or glyceryl distearate alone or with a wax, ethylcellulose, hydroxypropylmethylcellulose, methylmethacrylate and the like.

A variety of pharmaceutical forms can be employed. Thus, if a solid carrier is used, the preparation can be tableted, placed in a hard gelatin capsule in powder or pellet form or in the form of a troche or lozenge. The amount of solid carrier may vary, but generally will be from about 25 mg to about 1 g. If a liquid carrier is used, the preparation will be in the form of syrup, emulsion, soft gelatin capsule, sterile injectable solution or suspension in an ampoule or vial or non-aqueous liquid suspension.

To obtain a stable water-soluble dose form, a pharmaceutically acceptable salt of an inventive agent can be dissolved in an aqueous solution of an organic or inorganic acid, such as 0.3M solution of succinic acid or citric acid. If a soluble salt form is not available, the agent may be dissolved in a suitable cosolvent or combinations of cosolvents. Examples of suitable cosolvents include, but are not limited to, alcohol, propylene glycol, polyethylene glycol 300, polysorbate 80, glycerin and the like in concentrations ranging from 0-60% of the total volume. In an exemplary embodiment, a compound of Formula I is dissolved in DMSO and diluted with water. The composition may also be in the form of a solution of a salt form of the

active ingredient in an appropriate aqueous vehicle such as water or isotonic saline or dextrose solution.

It will be appreciated that the actual dosages of the agents used in the compositions of this invention will vary according to the particular complex being used, the particular composition formulated, the mode of administration and the particular site, host and disease being treated. Optimal dosages for a given set of conditions can be ascertained by those skilled in the art using conventional dosage-determination tests in view of the experimental data for an agent. For oral administration, an exemplary daily dose generally employed is from about 0.001 to about 1000 mg/kg of body weight, with courses of treatment repeated at appropriate intervals. Administration of prodrugs is typically dosed at weight levels that are chemically equivalent to the weight levels of the fully active form.

The compositions of the invention may be manufactured in manners generally known for preparing pharmaceutical compositions, e.g., using conventional techniques such as mixing, dissolving, granulating, dragee-making, levigating, emulsifying, encapsulating, entrapping or lyophilizing. Pharmaceutical compositions may be formulated in a conventional manner using one or more physiologically acceptable carriers, which may be selected from excipients and auxiliaries that facilitate processing of the active compounds into preparations that can be used pharmaceutically.

Proper formulation is dependent upon the route of administration chosen. For injection, the agents of the invention may be formulated into aqueous solutions, preferably in physiologically compatible buffers such as Hanks's solution, Ringer's solution, or physiological saline buffer. For transmucosal administration, penetrants appropriate to the barrier to be permeated are used in the formulation. Such penetrants are generally known in the art.

For oral administration, the compounds can be formulated readily by combining the compounds with pharmaceutically acceptable carriers known in the art. Such carriers enable the compounds of the invention to be formulated as tablets, pills, dragees, capsules, liquids, gels, syrups, slurries, suspensions and the like, for oral ingestion by a patient to be treated. Pharmaceutical preparations for oral use can be obtained using a solid excipient in admixture with the active ingredient (agent), optionally grinding the resulting mixture, and processing the mixture of granules after adding suitable auxiliaries, if desired, to obtain tablets or dragee cores. Suitable excipients include: fillers such as sugars, including lactose, sucrose, mannitol, or sorbitol; and cellulose preparations, for example, maize starch, wheat starch, rice starch, potato starch, gelatin, gum, methyl cellulose, hydroxypropylmethyl-cellulose, sodium carboxymethylcellulose, or polyvinylpyrrolidone (PVP). If desired, disintegrating agents may be added, such as crosslinked polyvinylpyrrolidone, agar, or alginic acid or a salt thereof such as sodium alginate.

Dragee cores are provided with suitable coatings. For this purpose, concentrated sugar solutions may be used, which may optionally contain gum arabic, polyvinyl pyrrolidone, Carbopol gel, polyethylene glycol, and/or titanium dioxide, lacquer solutions, and suitable organic solvents or solvent mixtures. Dyestuffs or pigments may be added to the tablets or dragee coatings for identification or to characterize different combinations of agents.

Pharmaceutical preparations that can be used orally include push-fit capsules made of gelatin, as well as soft, sealed capsules made of gelatin and a plasticizer, such as glycerol or sorbitol. The push-fit capsules can contain the agents in admixture with fillers such as lactose, binders such as starches, and/or lubricants such as talc or magnesium stearate, and, optionally, stabilizers. In soft capsules, the agents may be dissolved or suspended in suitable liquids, such as fatty oils, liquid paraffin, or liquid polyethylene glycols. In addition, stabilizers may be added. All formulations for oral administration should be in dosages suitable for such administration. For buccal administration, the compositions take the form of tablets or lozenges formulated in conventional manners.

For administration intranasally or by inhalation, the compounds for use according to the present invention are conveniently delivered in the form of an aerosol spray presentation from pressurized packs or a nebuliser, with the use of a suitable propellant, e.g., dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, carbon dioxide or other suitable gas. In the case of a pressurized aerosol the dosage unit may be determined by providing a valve to deliver a metered amount. Capsules and cartridges of gelatin for use in an inhaler or insufflator and the like may be formulated containing a powder mix of the compound and a suitable powder base such as lactose or starch.

The compounds may be formulated for parenteral administration by injection, e.g., by bolus injection or continuous infusion. Formulations for injection may be presented in unit-dosage form, e.g., in ampoules or in multi-dose containers, with an added preservative. The compositions may take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilizing and/or dispersing agents.

Pharmaceutical formulations for parenteral administration include aqueous solutions of the agents in water-soluble form. Additionally, suspensions of the agents may be prepared as appropriate oily injection suspensions. Suitable lipophilic solvents or vehicles include fatty oils such as sesame oil, or synthetic fatty acid esters, such as ethyl oleate or triglycerides, or liposomes. Aqueous injection suspensions may contain substances that increase the viscosity of the suspension, such as sodium carboxymethyl cellulose, sorbitol, or dextran. Optionally, the suspension may also contain suitable stabilizers or agents that increase the solubility of the compounds to allow for the preparation of highly concentrated solutions.

For administration to the eye, the agent is delivered in a pharmaceutically acceptable ophthalmic vehicle such that the compound is maintained in contact with the ocular surface for a sufficient time period to allow the compound to penetrate the corneal and internal regions of the eye, for example, the anterior chamber, posterior chamber, vitreous body, aqueous humor, vitreous humor, cornea, iris/ciliary, lens, choroid/retina and sclera. The pharmaceutically acceptable ophthalmic vehicle may be an ointment, vegetable oil, or an encapsulating material. A compound of the invention may also be injected directly into the vitreous and aqueous humor.

Alternatively, the agents may be in powder form for constitution with a suitable vehicle, e.g., sterile pyrogen-free water, before use. The compounds may also be formulated in rectal compositions such as suppositories or retention enemas, e.g. containing conventional suppository bases such as cocoa butter or other glycerides.

In addition to the formulations described above, the agents may also be formulated as a depot preparation. Such long-acting formulations may be administered by implantation (for example, subcutaneously or intramuscularly) or by intramuscular injection. Thus, for example, the compounds may be formulated with suitable polymeric or hydrophobic materials (for example, as an emulsion in an acceptable oil) or ion-exchange resins, or as sparingly soluble derivatives, for example, as a sparingly soluble salt.

An exemplary pharmaceutical carrier for hydrophobic compounds is a cosolvent system comprising benzyl alcohol, a nonpolar surfactant, a water-miscible organic polymer, and an aqueous phase. The cosolvent system may be a VPD co-solvent system. VPD is a solution of 3% w/v benzyl alcohol, 8% w/v of the nonpolar surfactant polysorbate 80, and 65% w/v polyethylene glycol 300, made up to volume in absolute ethanol. The VPD co-solvent system (VPD:5W) contains VPD diluted 1:1 with a 5% dextrose in water solution. This co-solvent system dissolves hydrophobic compounds well, and itself produces low toxicity upon systemic administration. Naturally, the proportions of a co-solvent system may be varied considerably without destroying its solubility and toxicity characteristics. Furthermore, the identity of the co-solvent components may be varied: for example, other low-toxicity nonpolar surfactants may be used instead of polysorbate 80; the fraction size of polyethylene glycol may be varied; other biocompatible polymers may replace polyethylene glycol, e.g. polyvinyl pyrrolidone; and other sugars or polysaccharides may be substituted for dextrose.

Alternatively, other delivery systems for hydrophobic pharmaceutical compounds may be employed. Liposomes and emulsions are known examples of delivery vehicles or carriers for hydrophobic drugs. Certain organic solvents such as dimethylsulfoxide also may be employed, although usually at the cost of greater toxicity. Additionally, the compounds may be delivered using a sustained-release system, such as semi-permeable matrices of solid hydrophobic polymers containing the therapeutic agent. Various sustained-release materials

have been established and are known by those skilled in the art. Sustained-release capsules may, depending on their chemical nature, release the compounds for a few weeks up to over 100 days. Depending on the chemical nature and the biological stability of the therapeutic reagent, additional strategies for protein stabilization may be employed.

The pharmaceutical compositions also may comprise suitable solid- or gel-phase carriers or excipients. Examples of such carriers or excipients include calcium carbonate, calcium phosphate, sugars, starches, cellulose derivatives, gelatin, and polymers such as polyethylene glycols.

Some of the compounds of the invention may be provided as salts with pharmaceutically compatible counter ions. Pharmaceutically compatible salts may be formed with many acids, including hydrochloric, sulfuric, acetic, lactic, tartaric, malic, succinic, etc. Salts tend to be more soluble in aqueous or other protonic solvents than are the corresponding free-base forms.

The agents of the invention may be useful in combination with known anti-cancer treatments such as: DNA interactive agents such as cisplatin or doxorubicin; topoisomerase II inhibitors such as etoposide; topoisomerase I inhibitors such as CPT-11 or topotecan; tubulin interacting agents such as paclitaxel, docetaxel or the epothilones; hormonal agents such as tamoxifen; thymidilate synthase inhibitors such as 5-fluorouracil; and anti-metabolites such as methotrexate. They may be administered together or sequentially, and when administered sequentially, the agents may be administered either prior to or after administration of the known anticancer or cytotoxic agent.

The agents may be prepared using the reaction routes and synthesis schemes as described below, employing the general techniques known in the art using starting materials that are readily available. The preparation of preferred compounds of the present invention is described in detail in the following examples, but the artisan will recognize that the chemical reactions described may be readily adapted to prepare a number of other anti-proliferatives or protein kinase inhibitors of the invention. For example, the synthesis of non-exemplified compounds according to the invention may be successfully performed by modifications apparent to those skilled in the art, e.g., by appropriately protecting interfering groups, by changing to other suitable reagents known in the art, or by making routine modifications of reaction conditions. Alternatively, other reactions disclosed herein or generally known in the art will be recognized as having applicability for preparing other compounds of the invention.

DETAILED DESCRIPTION OF THE INVENTION

EXAMPLES

In the examples described below, unless otherwise indicated, all temperatures are set forth in degrees Celsius and all parts and percentages are by weight. Reagents were purchased from commercial suppliers such as Aldrich Chemical Company or Lancaster

Synthesis Ltd. and were used without further purification unless otherwise indicated. Tetrahydrofuran (THF), N,N-dimethylformamide (DMF), dichloromethane, toluene, and dioxane were purchased from Aldrich in Sure seal bottles and used as received. All solvents were purified using standard methods readily known to those skilled in the art, unless otherwise indicated.

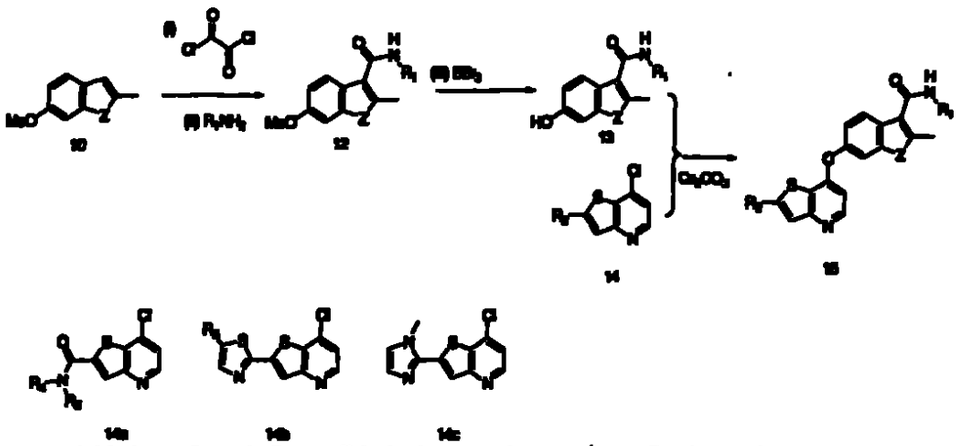
The reactions set forth below were done generally under a positive pressure of argon or nitrogen or with a drying tube, at ambient temperature (unless otherwise stated), in anhydrous solvents, and the reaction flasks were fitted with rubber septa for the introduction of substrates and reagents via syringe. Glassware was oven dried and/or heat dried. Analytical thin layer chromatography (TLC) was performed on glass-backed silica gel 60 F 254 plates Analtech (0.25 mm) and eluted with the appropriate solvent ratios (v/v), and are denoted where appropriate. The reactions were assayed by TLC and terminated as judged by the consumption of starting material.

Visualization of the TLC plates was done with a *p*-anisaldehyde spray reagent or phosphomolybdic acid reagent (Aldrich Chemical 20 wt % in ethanol) and activated with heat. Work-ups were typically done by doubling the reaction volume with the reaction solvent or extraction solvent and then washing with the indicated aqueous solutions using 25% by volume of the extraction volume unless otherwise indicated. Product solutions were dried over anhydrous Na_2SO_4 prior to filtration and evaporation of the solvents under reduced pressure on a rotary evaporator and noted as solvents removed *in vacuo*. Flash column chromatography (Still et al., *J. Org. Chem.*, 43, 2923 (1978)) was done using Baker grade flash silica gel (47-61 μm) and a silica gel: crude material ratio of about 20:1 to 50:1 unless otherwise stated. Hydrogenolysis was done at the pressure indicated in the examples or at ambient pressure.

^{1}H-NMR spectra were recorded on a Bruker instrument operating at 300 MHz and ^{13}C-NMR spectra were recorded operating at 75 MHz. NMR spectra were obtained as $CDCl_3$ solutions (reported in ppm), using chloroform as the reference standard (7.25 ppm and 77.00 ppm) or CD_3OD (3.4 and 4.8 ppm and 49.3 ppm), or internally tetramethylsilane (0.00 ppm) when appropriate. Other NMR solvents were used as needed. When peak multiplicities are reported, the following abbreviations are used: s (singlet), d (doublet), t (triplet), m (multiplet), br (broadened), dd (doublet of doublets), dt (doublet of triplets). Coupling constants, when given, are reported in Hertz (Hz).

Infrared (IR) spectra were recorded on a Perkin-Elmer FT-IR Spectrometer as neat oils, as KBr pellets, or as $CDCl_3$ solutions, and when given are reported in wave numbers (cm^{-1}). The mass spectra were obtained using LSIMS or electrospray. All melting points (mp) are uncorrected.

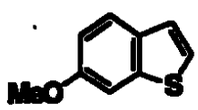
In one general synthetic process, compounds of Formula I are prepared according to the following reaction scheme:



6-Methoxy-2-methylbenzo[b]thiophene or the corresponding benzofuran (compound 10), which are known in the literature, are acylated with oxalyl chloride in the presence of aluminum trichloride. Treatment of the resulting acid chloride with an excess of the appropriate amine, e.g. methylamine, provides the requisite amide derivative of formula 12. Demethylation with a suitable reagent, such as boron tribromide, gives compounds of formula 13. Compounds of formula 13 and 14 are combined by heating them with base, preferably Cs_2CO_3, in a solvent such as DMSO, DMF or acetonitrile to form compounds of formula 15. Alternatively to using compounds of formula 14a , 14b and 14c, compounds of formula 14 where R_2 is a carboxylic acid may be used in the coupling reaction that generates compounds of formula 15. Amide formation may then be the final step.

Indole analogs may be made in a similar fashion as described above for benzofurans and benzothiophenes.

Example (1a): 6-methoxybenzo[b]thiophene



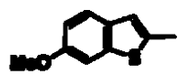
A mixture of 3-methoxybenzenethiol (10 ml, 11.30 g, 80 mmole), K_2CO_3 (11.15 g, 80 mmole) and bromoacetaldehyde diethyl acetal (12 ml, 15.72 g, 80 mmole) in acetone (100 ml) was stirred at ambient temperature for 16 hours, then filtered. The filtrate was subsequently concentrated, *in vacuo*. The residue obtained was partitioned between H_2O (150 ml) and Et_2O (150 ml). The layers were separated and the aqueous phase was extracted with Et_2O (150 ml). The combined organic extracts were washed with 0.5 M KOH (aq), H_2O and brine, then

dried over Na_2SO_4 and concentrated, in vacuo, to give 20.4 g of an amber oil which was used directly in the subsequent cyclization without any further purification.

Method A: A solution of this crude 1-(2,2-diethoxyethylsulfanyl)-3-methoxybenzene (6.41 g, 25 mmole) in CH_2Cl_2 (50 ml) was added, dropwise, to a solution of boron trifluoride etherate (3.4 ml, 3.81 g, 27 mmole) in CH_2Cl_2 (500 ml). The resultant solution was stirred at ambient temperature for an additional 30 minutes. Aqueous saturated $NaHCO_3$ (200 ml) was added and the two-phase mixture was stirred for another hour. The layers were separated and the aqueous phase was extracted with CH_2Cl_2 (150 ml). The combined organic extracts were dried over Na_2SO_4 and concentrated, in vacuo, to give 4.3 g of a red oil which was purified by silica gel chromatography. Elution with hexane: Et_2O (98:2) and evaporation of the appropriate fractions gave 1.82 g (39%) of a colourless oil.

Method B: A solution of the crude 1-(2,2-diethoxyethylsulfanyl)-3-methoxybenzene (8.27 g, 32.3 mmole) in hexane (100 ml) was added, dropwise, to a solution of methanesulfonic acid (1.05 ml, 1.55 g, 16.1 mmole) in hexane (1000 ml) containing 16.5 g of celite (2 wt. eq.). The resultant solution was heated at reflux for one hour. After cooling to room temperature, the reaction was quenched by addition of Et_3N (4.5 ml, 3.26 g, 32.3 mmole). The crude reaction mixture was filtered and the filtrate was concentrated, *in vacuo*, to give a red oil which was purified by silica gel chromatography. Elution with hexane: Et_2O (98:2) and evaporation of the appropriate fractions gave 3.35 g (83%) of a colorless oil. ^1H NMR (DMSO-d_6) δ 7.74 (1H, d, J = 8.7 Hz), 7.56 (1H, d, J = 2.3 Hz), 7.52 (1H, d, J = 5.3Hz), 7.33 (1H, d, J = 5.3Hz), 6.99 (1H, dd, J = 2.3, 8.7 Hz), 3.81 (3H, s). *Anal.* Calcd. for C_9H_8OS: C, 65.82; H, 4.91; S, 19.53. Found: C, 66.01; H, 5.00; S, 19.40.

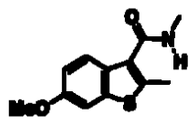
Example 1(b): 6-methoxy-2-methylbenzo[b]thiophene



A 2.5 M solution of n-butyllithium in hexanes (20 ml, 50 mmole) was added under argon to a solution of 6-methoxybenzo[b]thiophene 1a (3.68 g, 22.4 mmole) in THF (150 ml) at -75°. After stirring at -75° for a further 30 minutes, the cooling bath was exchanged and the reaction warmed to -10°C prior to addition of CH_3I (4.2 ml, 9.58 g, 67 mmole). The resultant mixture was stirred at 0°C for an additional 30 minutes, then allowed to gradually warm to room temperature before diluting with saturated $NaHCO_3$ (150 ml). The layers were separated and the aqueous phase was extracted with EtOAc (2 x 100 ml). The combined organic extracts were dried over Na_2SO_4 and concentrated, in vacuo, to give 4.2 g of an amber oil which was purified by silica gel chromatography. Elution with hexane: Et_2O (98:2) and evaporation of the appropriate fractions gave 3.63 g (91%) of a colourless oil. ^1H NMR (DMSO-d_6) δ 7.57 (1H, d, J = 8.7 Hz), 7.43 (1H, d, J = 2.4 Hz), 6.99 (1H, s), 6.92 (1H, dd, J =

2.4, 8.7 Hz), 3.78 (3H, s), 2.50 (3H, s). *Anal.* Calcd. for $C_{10}H_{10}OS$: C, 67.38; H, 5.66; S, 17.99. Found: C, 67.42; H, 5.74; S, 17.87.

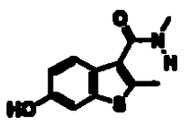
Example 1(c): 6-methoxy-2-methylbenzo[b]thiophene-3-carboxylic acid methylamide



A 2.0 M solution of oxalyl chloride in CH_2Cl_2 (10 ml, 20 mmole) was added to a slurry of $AlCl_3$ (2.69 g, 20 mmole) in CH_2Cl_2 (20 ml) at 0°. After stirring at 0° for a further 30 minutes, a solution of 6-methoxy-2-methylbenzo[b]thiophene 1b (725 mg, 4.1 mmole) in CH_2Cl_2 (40 ml) was added over a 10 minute interval. The cooling bath was removed and the reaction was stirred at ambient temperature for 3 hours prior to addition of crushed ice (50 ml). The layers were separated and the aqueous phase was extracted with CH_2Cl_2 (3 x 50 ml). The combined organic extracts were dried over Na_2SO_4 and concentrated, in vacuo, to give 950 mg of an amber resin which was employed without further purification.

A solution of this crude 6-methoxy-2-methylbenzo[b]thiophene-3-carbonyl chloride in THF (50 ml) was combined with a 2.0 M solution of CH_3NH_2 in THF (20 ml, 40 mmole). The resultant reaction mixture was stirred at ambient temperature for 3 hours. The solvent was removed by concentration, in vacuo, and the residue obtained was partitioned between H_2O (50 ml) and CH_2Cl_2 (50 ml). The layers were separated and the aqueous phase was extracted with CH_2Cl_2 (2 x 30 ml). The combined organic extracts were dried over Na_2SO_4 and concentrated, in vacuo, to give 0.8 g of an amber solid which was purified by silica gel chromatography. Elution with CH_2Cl_2: EtOAc (80:20) and evaporation of the appropriate fractions gave 693 mg (72%) of an off-white solid. ^{1}H NMR (DMSO-d6) δ 8.15 (1H, q, J = 4.6 Hz), 7.62 (1H, d, J = 8.9 Hz), 7.47 (1H, d, J = 2.4 Hz), 6.97 (1H, dd, J = 2.4, 8.9 Hz), 3.79 (3H, s), 2.80 (3H, d, J = 4.6 Hz), 2.53 (3H, s). *Anal.* Calcd. for $C_{12}H_{13}NO_2S$: C, 61.25; H, 5.57; N, 5.95; S, 13.63. Found: C, 60.97; H, 5.56; N, 5.85; S, 13.44.

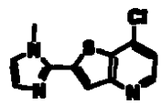
Example 1(d): 6-hydroxy-2-methylbenzo[b]thiophene-3-carboxylic acid methylamide



A 1.0 M solution of BBr_3 in CH_2Cl_2 (6 ml, 6 mmole) was added to a solution of 6-methoxy-2-methylbenzo[b]thiophene-3-carboxylic acid methylamide 1c (683 mg, 2.9 mmole) in CH_2Cl_2 (60 ml) at 0°. The reaction was left stirring for 14 hours, gradually warming to ambient temperature, then poured onto crushed ice (~70 g). The layers were separated and the aqueous phase was extracted with EtOAc (2 x 50 ml). The combined organic extracts were dried over Na_2SO_4 and concentrated, *in vacuo*, to give 623 mg (97%)of a beige solid

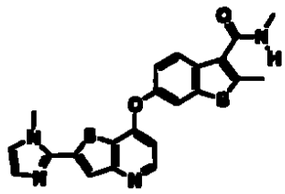
which was employed without further purification. ^{1}H NMR (DMSO-d6) δ 9.56 (1H, s), 8.11 (1H, q, J = 4.4 Hz), 7.53 (1H, d, J = 8.7 Hz), 7.18 (1H, d, J = 2.3 Hz), 6.83 (1H, dd, J = 2.3, 8.7 Hz), 2.79 (3H, d, J = 4.4 Hz), 2.50 (3H, s).

Example 1(e): 7-chloro-2-(1-methyl-1H-imidazol-2-yl)thieno[3,2-b]pyridine



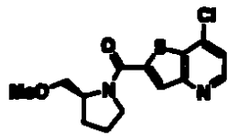
The title compound was prepared by the method described in PCT application WO-99/24440, Example 149; incorporated herein by reference.

Example 1: 2-methyl-6-(2-[1-methyl-1H-imidazol-2-yl]thieno[3,2-b]pyridin-7-yloxy)benzo[b]thiophene-3-carboxylic acid methylamide

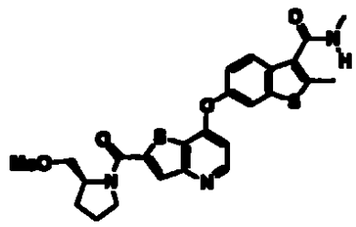


A solution of 7-chloro-2-(1-methyl-1H-imidazol-2-yl)thieno[3,2-b]pyridine 1e (100 mg, 0.4 mmole) and 6-hydroxy-2-methylbenzo[b]thiophene-3-carboxylic acid methylamide 1d (133 mg, 0.6 mmole) in DMSO (10 ml) was purged with argon for minutes at ambient temperature prior to addition of freshly crushed Cs_2CO_3 (651 mg, 2 mmole). The resultant reaction mixture was heated at 110° for 2 hours. After cooling to room temperature, the crude reaction mixture was poured into cold water (60 ml). The precipitate that formed was collected by filtration and purified by silica gel chromatography. Elution with CH_2Cl_2: CH_3OH (95:5) and evaporation of the appropriate fractions gave 89 mg (40%) of an off-white solid. . ^{1}H NMR (DMSO-d6): δ 8.52 (1H, d, J = 5.4 Hz), 8.29 (1H, q, J = 4.6 Hz), 7.95 (1H, d, J = 2.3 Hz), 7.88 (1H, s), 7.85 (1H, d, J = 8.8 Hz), 7.40 (1H, d, J = 0.8 Hz), 7.32 (1H, dd, J = 2.3, 8.8 Hz), 7.02 (1H, d, J = 0.8 Hz), 6.70 (1H, d, J = 5.4 Hz), 3.98 (3H, s), 2.83 (3H, d, J = 4.6 Hz), 2.60 (3H, s). *Anal.* Calcd. for $C_{22}H_{18}N_4O_2S_2$•0.3 CH_2Cl_2•0.2 CH_3OH: C, 57.94; H, 4.19; N, 12.01. Found: C, 57.67; H, 4.13; N, 12.04.

Example 2(a): 7-chloro-2-[(S)-2-(methoxymethyl)pyrrolidine-1-carbonyl]thieno[3,2-b]pyridine

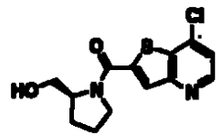


To a mixture of lithium 7-chlorothieno[3,2-b]pyridine-2-carboxylate (6.59 g, 30 mmole) in DMF (100 ml) were added diisopropylethylamine, (6 ml, 4.45 g, 34.4 mmole), benzotriazol-1-yloxytris(pyrrolidino)phosphonium hexafluorophosphate (16.16 g, 31 mmole) and S-(+)-2-(methoxymethyl)pyrrolidine (3.73 g, 32.4 mmole). The resultant reaction mixture was stirred at ambient temperature for 16 hours. The crude reaction mixture was poured into water (600 ml) and extracted with EtOAc (3 x 200 ml). The combined organic extracts were washed with water (4 x 200 ml), dried over Na_2SO_4 and concentrated, *in vacuo*, to give 8.8 g of an amber oil, which was purified by silica gel chromatography. Elution with Et_2O:EtOAc (67:33) and evaporation of the appropriate fractions gave 6.89 g (74%) of an orange syrup. ^{1}H NMR (DMSO-d6): δ 8.62 (1H, d, J = 5.0 Hz), 7.88 (1H, s), 7.35 (1H, d, J = 5.0 Hz), 4.54-4.47 (1H, m), 3.93-3.75 (2H, m), 3.71-3.55 (2H, m), 3.37 (3H, s), 2.15-1.92 (4H, m). *Anal.* Calcd. for $C_{14}H_{15}N_2O_2SCl$: C, 54.10; H, 4.87; N, 9.01; S, 10.32; Cl, 11.41. Found: C, 53.96; Example 2: 6-(2-[(S)-2-(methoxymethyl)pyrrolidine-1-carbonyl]thieno[3,2-b]pyridin-7-yloxy)- 2-methylbenzo[b]thiophene-3-carboxylic acid methylamide



This material was prepared by the reaction of 7-chloro-2-[(S)-2-(methoxymethyl)pyrrolidine-1-carbonyl]thieno[3,2-b]pyridine 2a (153 mg, 0.5 mmole) with 6-hydroxy-2-methylbenzo[b]thiophene-3-carboxylic acid methylamide 1d (164 mg, 0.7 mmole) and Cs_2CO_3 (888 mg, 2.7 mmole) in a manner as previously described for example 1 to give 178 mg (73%) of a yellow solid. ^{1}H NMR (DMSO-d_6): δ 8.57 (1H, d, J = 5.4 Hz), 8.29 (1H, q, J= 4.5 Hz), 8.02 (1H, s), 7.95 (1H, d, J = 2.2 Hz), 7.85 (1H, d, J = 8.8 Hz), 7.32 (1H, dd, J = 2.2, 8.8 Hz), 6.75 (1H, d, J = 5.4 Hz), 4.37-4.23 (1H, m), 3.95-3.74 (2H, m), 3.60-3.48 (2H, m), 3.27 (3H, s), 2.83 (3H, d, J = 4.5 Hz), 2.60 (3H, s), 2.08-1.81 (4H, m). *Anal.* Calcd. for $C_{25}H_{25}N_3O_4S_2$: C, 60.58; H, 5.08; N, 8.48; S, 12.94. Found: C, 60.55; H, 5.33; N, 8.27; S, 12.68.

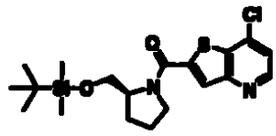
Example 2(a): 7-chloro-2-[(S)-2-(hydroxymethyl)pyrrolidine-1-carbonyl]thieno [3,2-b]pyridine



This material was prepared by the coupling of lithium 7-chlorothieno[3,2-b]pyridine-2-carboxylate and S-(+)-2-(hydroxymethyl)pyrrolidine in a manner as previously described for example 2a to give 4.95 g (55%) of an off-white solid. ^{1}H NMR (DMSO-d_6): δ 8.72 (1H, d, J = 5.1 Hz), 8.08 (1H, s), 7.88 (1H, d, J = 5.1 Hz), 4.27-4.13 (1H, m), 3.94-3.73 (2H, m), 3.67-3.44 (2H, m), 2.09-1.79 (4H, m).

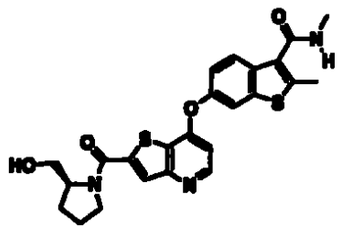
Anal. Calcd. for $C_{13}H_{13}N_2O_2SCl$: C, 52.81; H, 4.42; N, 9.44; S, 10.80; Cl, 11.95. Found: C, 52.61; H, 4.52; N, 9.62; S, 10.59; Cl, 11.96.

Example 3(b): 7-chloro-2-[(S)-2-([t-butyldimethylsilyloxy]methyl)pyrrolidine-1-carbonyl]thieno[3,2-b]pyridine



To a stirred solution of 7-chloro-2-[(S)-2-(hydroxymethyl)pyrrolidine-1-carbonyl]thieno[3,2-b]pyridine 3a (4.50 g, 15 mmole) were added t-butyldimethylchlorosilane (3.18 g, 21 mmole) and triethylamine (3.4 ml, 2.47 g, 24 mmole). The resultant reaction mixture was stirred at ambient temperature for 16 hours. The crude reaction mixture was poured into water (150 ml) and extracted with CH_2Cl_2 (150 ml). The combined organic extracts were washed with brine (150 ml), dried over Na_2SO_4 and concentrated, *in vacuo*, to give 7.8 g of an orange syrup, which was purified by silica gel chromatography. Elution with Et_2O:hexane (67:33) and evaporation of the appropriate fractions gave 5.73 g (92%) of an off-white solid. . ^{1}H NMR (DMSO-d_6): δ 8.72 (1H, d, J = 5.0 Hz), 8.07 (1H, s), 7.88 (1H, d, J = 5.0 Hz), 4.30-4.15 (1H, m), 3.94-3.67 (4H, m), 2.12-1.81 (4H, m), 0.85 (9H, s), 0.03 (3H, s), 0.00 (3H, s). *Anal.* Calcd. for $C_{19}H_{27}N_2O_2SClSi$: C, 55.52; H, 6.62; N, 6.82; S, 7.80; Cl, 8.63. Found: C, 55.49; H, 6.46; N, 6.92; S, 7.80; Cl, 8.88.

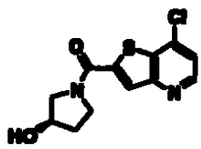
Example 3: 6-(2-[(S)-2-(hydroxymethyl)pyrrolidine-1-carbonyl]thieno[3,2-b]pyridin-7-yloxy)-2-methylbenzo[b]thiophene-3-carboxylic acid methylamide



Example 3 was prepared by the reaction of 7-chloro-2-[(S)-2-((t-butyldimethylsilyloxy)methyl)-pyrrolidine-1-carbonyl]thieno[3,2-b]pyridine 3b (812 mg, 2 mmole) with 6-hydroxy-2-methylbenzo[b]thiophene-3-carboxylic acid methylamide 1d (656 mg, 3 mmole) and Cs_2CO_3 (3.47 g, 11 mmole) in a manner as previously described for example 1 to give 302 mg (32%) of a yellow solid. ^{1}H NMR (DMSO-d_6): δ 8.57 (1H, d, J = 5.3 Hz), 8.29 (1H, q, J= 4.5 Hz), 8.01 (1H, s), 7.96 (1H, d, J = 2.2 Hz), 7.85 (1H, d, J = 8.8 Hz), 7.32 (1H, dd, J = 2.2, 8.8 Hz), 6.75 (1H, d, J = 5.3 Hz), 4.81 (1H, t, J = 5.9 Hz), 4.24-4.12 (1H, m), 3.92-374 (2H, m), 3.63-3.44 (2H, m), 2.83 (3H, d, J = 4.5 Hz), 2.60 (3H, s), 2.08-1.81 (4H, m).

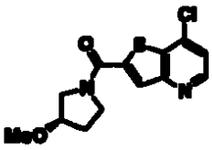
Anal. Calcd. for $C_{24}H_{23}N_3O_4S_2$•0.4 CH_2Cl_2: C, 56.84; H, 4.65; N, 8.15; S, 12.44. Found: C, 56.81; H, 4.78; N, 7.99; S, 12.49.

Example 4(a): 7-chloro-2-[(R)-3-hydroxypyrrolidine-1-carbonyl]thieno[3,2-b]pyridine



This material was prepared by the coupling of lithium 7-chlorothieno[3,2-b]pyridine-2-carboxylate and (R)-3-hydroxypyrrolidine in a manner as previously described for example 2a to give 3.06 g (36%) of an off-white solid. ^{1}H NMR (DMSO-d_6): δ 8.73 (1H, d, J = 5.1 Hz), 8.15, 8.09 (1H, s), 7.69 (1H, d, J = 5.1 Hz), 5.10-5.06 (1H, m), 4.43-4.29 (1H, m), 4.05-3.89 (2H, m), 3.72-3.43 (2H, m), 2.08-1.79 (2H, m).

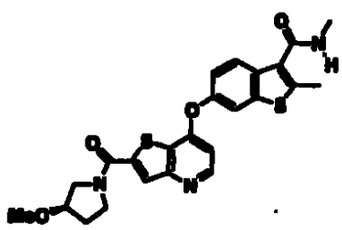
Example 4(b): 7-chloro-2-[(R)-3-methoxypyrrolidine-1-carbonyl]thieno[3,2-b]pyridine



A solution of 7-chloro-2-[(R)-3-hydroxypyrrolidine-1-carbonyl]thieno[3,2-b]pyridine 4a (1.86 g, 6.6 mmole) in THF (150 ml) was cooled to –10° prior to addition of NaH (920 mg, 23 mmole as a 60% by wt. mineral oil dispersion). The resultant mixture was stirred at 0° for 40 minutes. Iodomethane (4 ml, 9.12 g, 64 mmole) was then added to the reaction which was stirred for another 3 hours, gradually warming to room temperature. The crude reaction mixture was quenched with saturated NaHCO3 (150 ml), then extracted with EtOAc (2 x 100

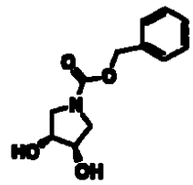
ml). The combined organic extracts were dried over Na_2SO_4 and concentrated, *in vacuo*, to give 2.4 g of an amber paste, which was purified by silica gel chromatography. Elution with CH_2Cl_2: CH_3OH (98:2) and evaporation of the appropriate fractions gave 1.64 g (84%) of a yellow solid. ^1H NMR (DMSO-d_6): δ 8.73 (1H, d, J = 5.1 Hz), 8.15 (1H, s), 7.69 (1H, d, J = 5.1 Hz), 4.11-3.83 (3H, m), 3.69-3.47 (2H, m), 3.27, 3.24 (3H, s), 2.18-1.93 (2H, m). *Anal.* Calcd. for $C_{15}H_{15}N_2O_3SCl$: C, 52.61; H, 4.42; N, 9.44; S, 10.80; Cl, 11.95. Found: C, 52.78; H, 4.47; N, 9.38; S, 10.84; Cl, 12.01.

Example 4: 6-(2-[(R)-3-methoxypyrrolidine-1-carbonyl]thieno[3,2-b]pyridin-7-yloxy)-2-methylbenzo[b]thiophene-3-carboxylic acid methylamide



This material was prepared by the reaction of 7-chloro-2-[(R)-3-methoxypyrrolidine-1-carbonyl]thieno[3,2-b]pyridine 4b (257 mg, 0.9 mmole) with 6-hydroxy-2-methylbenzo[b]thiophene-3-carboxylic acid methylamide 1d (299 mg, 1.4 mmole) and Cs_2CO_3 (1.47 g, 4.5 mmole) in a manner as previously described for example 1 to give 358 mg (82%) of a yellow solid. ^1H NMR (DMSO-d_6): 8.58 (1H, d, J = 5.4 Hz), 8.29 (1H, q, J= 4.6 Hz), 8.06 (1H, s), 7.96 (1H, d, J = 2.3 Hz), 7.85 (1H, d, J = 8.7 Hz), 7.32 (1H, dd, J = 2.3, 8.7 Hz), 6.75 (1H, d, J = 5.4 Hz), 4.11-3.82 (3H, m), 3.68-3.45 (2H, m), 3.27, 3.24 (3H, s), 2.83 (3H, d, J = 4.6 Hz), 2.60 (3H, s), 2.17-1.93 (2H, m). *Anal.* Calcd. for $C_{24}H_{23}N_3O_4S_2 \cdot 0.4\ H_2O$: C, 58.97; H, 4.91; N, 8.60; S, 13.12. Found: C, 58.98; H, 4.98; N, 8.40; S, 13.37.

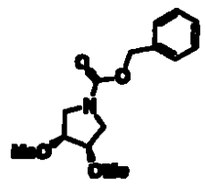
Example 5(a): 3,4-*cis*-dihydroxy-pyrrolidine-1-carboxylic acid benzyl ester



To a solution of benzyl 3-pyrroline-1-carboxylate (15 g, 90%, 68.4 mmole) in THF (100 ml) and water (25 ml) was added osmium tetroxide (10 ml, 2.5 wt. % solution in 2-methyl-2-propanol, 0.8 mmole) and 4-methylmorpholine N-oxide (8.56 g, 73 mmole) as solid. The mixture was stirred at room temperature overnight and concentrated, *in vacuo*. The residue was re-dissolved in EtOAc (300 ml) and washed with aqueous Na_2SO_3 (1.5 g in 100 ml water) solution, aqueous $NaHCO_3$ solution and brine. The combined aqueous layer was extracted once with EtOAc (100 ml). The combined organic extracts were dried over Na_2SO_4

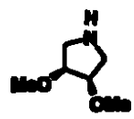
and concentrated, *in vacuo*. The crude was further purified by flash column chromatography eluting with 4-5 % MeOH in CH_2Cl_2 to give 15.26 g (97%) of a white solid. ^1H NMR (300 MHz, $CDCl_3$) δ 7.34 (5H, m), 5.11 (2H, bs), 4.28 (2H, m), 3.66 (2H, m), 3.41 (2H, m), 1.56 (2H, bs).

Example 5(b): 3,4-cis-dimethoxy-pyrrolidine-1-carboxylic acid benzyl ester



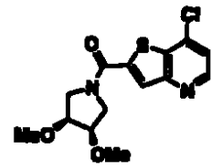
To a stirred solution of 3,4-*cis*-dihydroxy-pyrrolidine-1-carboxylic acid benzyl ester 5a (15.2 g, 64.3 mmole) in anhydrous THF (130 ml) was added Iodomethane (36 g, 257 mmole) at 0°; sodium hydride (6.4 g, 60% in mineral oil, 160 mmole) was then added slowly as at 0°. The mixture was allowed to warm to room temperature and stirred at room temperature for 3 hours. Aqueous 1N HCl (30 ml) was then added to the mixture which was concentrated, *in vacuo*, to remove THF. The residue was re-dissolved in EtOAc (300 ml) and washed with water and brine. The organic layer was dried over Na_2SO_4, filtered, and concentrated, *in vacuo*. The crude was further purified by flash column chromatography eluting with 5-25 % EtOAc in CH_2Cl_2 to give 17 g (99%) of a yellow oil. ^1H NMR (300 MHz, $CDCl_3$) δ 7.35 (5H, m), 5.12 (2H, m), 3.87 (2H, m), 3.55 (2H, m), 3.42 (6H, bs), 1.58 (2H, s).

Example 5(c): 3,4-cis-Dimethoxy-pyrrolidine



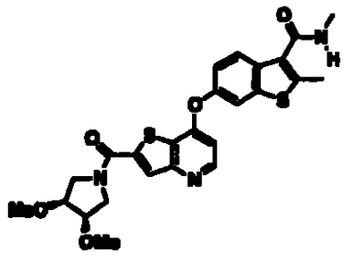
To a stirred solution of 3,4-*cis*-dimethoxy-pyrrolidine-1-carboxylic acid benzyl ester 5b (16.95 g, 63.9 mmole) in MeOH (150 ml) was added 10% Pd on C (1.3 g). The mixture was stirred under H_2 balloon at room temperature for 3 hours and filtered through celite. The filtrate was concentrated, *in vacuo*, re-dissolved in CH_2Cl_2 and dried over Na_2SO_4. The solution was concentrated to give 8.3 g (99%) of a yellow oil. ^1H NMR (300 MHz, $CDCl_3$) δ 3.80 (2H, m), 3.47 (2H, bs), 3.41 (6H, s), 3.01 (2H, bs).

Example (5d): 7-chloro-2-[meso-3,4-dimethoxypyrrolidine-1-carbonyl]thieno [3,2-b]pyridine



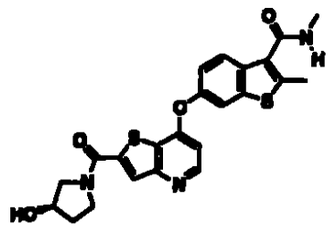
This material was prepared by the coupling of lithium 7-chlorothieno[3,2-b]pyridine-2-carboxylate and 3,4-cis-dimethoxypyrrolidine 5c in a manner as previously described for example 2a to give a pale yellow syrup. ^1H NMR (CD_3OD): δ 8.70 (1H, d, J = 5.1 Hz), 8.03 (1H, s), 7.61 (1H, d, J = 5.1 Hz), 4.20-4.07 (2H, m), 3.97-3.75 (2H, m), 3.52 (3H, s), 3.48 (3H, s), 3.35-3.29 (2H, m).

Example (5): 6-(2-[meso-3,4-dimethoxypyrrolidine-1-carbonyl]thieno[3,2-b]pyridin-7-yloxy)-2-methylbenzo[b]thiophene-3-carboxylic acid methylamide



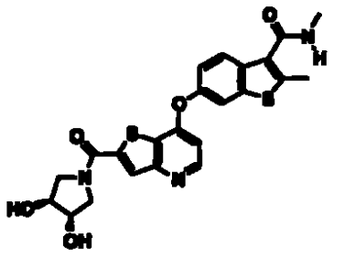
This material was prepared by the reaction of 7-chloro-2-[meso-3,4-dimethoxypyrrolidine-1-carbonyl]thieno[3,2-b]pyridine 5d (164 mg, 0.5 mmole) with 6-hydroxy-2-methylbenzo[b]thiophene-3-carboxylic acid methylamide 1d (164 mg, 0.7mmole) and Cs_2CO_3 (568 mg, 2.7 mmole) in a manner as previously described for example 1 to give 123 mg (48%) of an off-white solid. ^1H NMR (DMSO-d_6): δ 8.59 (1H, d, J = 5.4 Hz), 8.29 (1H, q, J= 4.7 Hz), 8.07 (1H, s), 7.98 (1H, d, J = 2.3 Hz), 7.85 (1H, d, J = 8.8 Hz), 7.32 (1H, dd, J = 2.3, 8.8 Hz), 6.76 (1H, d, J = 5.4 Hz), 4.12-3.98 (3H, m), 3.83 (1H, dd, J = 3.6, 9.1 Hz), 3.66 (1H, dd, J = 4.8, 12.9 Hz), 3.51 (1H, dd, J = 4.2, 12.9 Hz), 3.36 (6H, s), 2.83 (3H, d, J = 4.7 Hz), 2.60 (3H, s). *Anal.* Calcd. for $C_{25}H_{25}N_3O_5S_2 \cdot 0.6\ H_2O$: C, 57.47; H, 5.06; N, 8.04; S, 12.28. Found: C, 57.35; H, 5.02; N, 7.89; S, 12.37.

Example 6: 6-(2-[(R)-3-hydroxypyrrolidine-1-carbonyl]thieno[3,2-b]pyridin-7-yloxy)-2-methylbenzo[b]thiophene-3-carboxylic acid methylamide



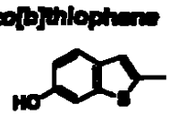
This material was prepared from 6-(2-[(R)-3-methoxypyrrolidine-1-carbonyl]thieno[3,2-b]pyridin-7-yloxy)-2-methylbenzo[b]thiophene-3-carboxylic acid methylamide 4 (172 mg, 0.4 mmole) by treatment with BBr_3 in a manner as previously described for example 1d to give 108 mg (65%) of an off-white solid. ^1H NMR (DMSO-d_6): δ 8.58 (1H, d, J = 5.3 Hz), 8.29 (1H, q, J= 4.4 Hz), 8.06 (1H, s), 7.98 (1H, d, J = 1.2 Hz), 7.85 (1H, d, J = 8.7 Hz), 7.33 (1H, dd, J = 1.2, 8.7 Hz), 6.75 (1H, d, J = 5.3 Hz), 4.44-4.27 (1H,m), 4.05-3.88 (1H, m), 3.71-3.42 (3H, m), 2.83 (3H, d, J = 4.4 Hz), 2.60 (3H, s), 2.10-1.77 (2H, m). *Anal.* Calcd. for $C_{23}H_{21}N_3O_4S_2$•1.0 CH_3OH: C, 57.70; H, 5.04; N, 8.41; S, 12.84. Found: C, 57.41; H, 4.96; N, 8.42; S, 12.63.

Example 7: 6-(2-[meso-3,4-dihydroxypyrrolidine-1-carbonyl]thieno[3,2-b]pyridin-7-yloxy)-2-methylbenzo[b]thiophene-3-carboxylic acid methylamide



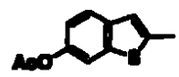
Example 7 was prepared from 6-(2-[meso-3,4-dimethoxypyrrolidine-1-carbonyl]thieno[3,2-b]pyridin-7-yloxy)-2-methylbenzo[b]thiophene-3-carboxylic acid methylamide 5 (74 mg, 0.1 mmole) by treatment with BBr_3 in a manner as previously described for example 1d to give 51 mg (73%) of an off-white solid. ^1H NMR (DMSO-d_6): δ 8.58 (1H, d, J = 5.4 Hz), 8.29 (1H, q, J= 4.6 Hz), 7.99 (1H, s), 7.98 (1H, d, J = 2.3 Hz), 7.85 (1H, d, J = 8.8 Hz), 7.32 (1H, dd, J = 2.3, 8.8 Hz), 6.75 (1H, d, J = 5.4 Hz), 5.1- (2H, d, J = 5.3 Hz), 4.18-4.07 (2H, m), 4.02 (1H, dd, J = 5.6, 10.2 Hz), 3.66 (1H, dd, J = 4.9, 10.2 Hz), 3.62 (1H, dd, J = 5.1, 12.8 Hz), 3.40 (1H, dd, J = 4.4, 12.8 Hz), 2.83 (3H, d, J = 4.7 Hz), 2.60 (3H, s). *Anal.* Calcd. for $C_{23}H_{23}N_3O_5S_2$•0.5 NaBr•H_2O: C, 49.95; H, 4.19; N, 7.60; S, 11.60. Found: C, 49.93; H, 4.15; N, 7.44; S, 11.44.

Example 8a: 6-hydroxy-2-methylbenzo[b]thiophene



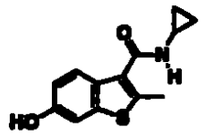
This material was prepared from 6-methoxy-2-methylbenzo[b]thiophene 1b (2.92 g, 16.4 mmole) by treatment with BBr_3 in a manner as previously described for example 1d to give 2.51 g (93%) of a white solid. ^1H NMR (DMSO-d_6) δ 9.43 (1H, s), 7.47 (1H, d, J = 8.5 Hz), 7.14 (1H, d, J = 2.2 Hz), 6.92 (1H, s), 6.78 (1H, dd, J = 2.2, 8.5 Hz), 2.46 (3H, s). *Anal.* Calcd. for C_9H_8OS: C, 65.82; H, 4.91; S, 19.53. Found: C, 65.96; H, 5.11; S, 19.69.

Example 8(b): 6-acetoxy-2-methylbenzo[b]thiophene



Acetyl chloride (1.5 ml, 1.66 g, 21 mmole) and Et_3N (3 ml, 2.18 g, 21.5 mmole) were added, sequentially, to a solution of 6-hydroxy-2-methylbenzo[b] thiophene 8a (2.51 g, 15 mmole) in THF (120 ml) at 0°. The reaction was left stirring for 14 hours, gradually warming to ambient temperature, then diluted with EtOAc (100 ml) and washed with H_2O (100 ml) and brine (100 ml). The combined aqueous layers were extracted with EtOAc (100 ml). The combined organic extracts were subsequently dried over Na_2SO_4 and concentrated, *in vacuo*, to give 3.9 g of a yellow solid which was purified by silica gel chromatography. Elution with hexane: Et_2O (90:10) and evaporation of the appropriate fractions gave 2.93 g (93%) of a white solid. ^1H NMR (DMSO-d_6) δ 7.70 (1H, d, J = 8.8 Hz), 7.66 (1H, d, J = 2.2 Hz), 7.12 (1H, s), 7.07 (1H, dd, J = 2.2, 8.8 Hz), 2.54 (3H, s), 2.27 (3H, s). *Anal.* Calcd. for $C_{11}H_{10}O_2S$: C, 64.05; H, 4.89; S, 15.55. Found: C, 63.84; H, 4.93; S, 15.57.

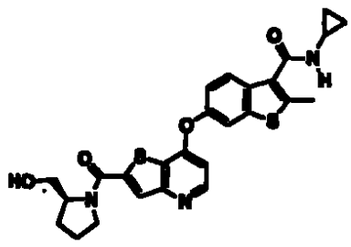
Example (8c): 6-hydroxy-2-methylbenzo[b]thiophene-3-carboxylic acid cyclopropylamide



This material was prepared from 6-acetoxy-2-methylbenzo[b]thiophene 8b (413 mg, 2 mmole) by acylation with oxalyl chloride in the presence of $AlCl_3$, followed by treatment with cyclopropylamine in a manner as previously described for example 1c to give 384 mg (78%) of a pale yellow solid. ^1H NMR (DMSO-d_6) δ 9.56 (1H, s), 8.29 (1H, d, J = 4.3 Hz), 7.48 (1H, d, J = 8.7 Hz), 7.17 (1H, d, J = 2.2 Hz), 6.83 (1H, dd, J = 2.2, 8.7 Hz), 2.92-2.81 (1H, m), 2.46 (3H, s), 0.74-0.66 (2H, m), 0.58-0.51 (2H, m). *Anal.* Calcd. for $C_{13}H_{13}NO_2S$•0.2 H_2O: C, 62.23; H, 5.36; N, 5.60. Found: C, 62.22; H, 5.36; N, 5.60.

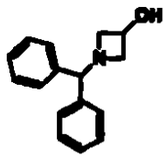
Example 8: 6-(2-[(S)-2-(hydroxymethyl)pyrrolidine-1-carbonyl]thieno[3,2-b]pyridin-7-yloxy)-2-methylbenzo[b]thiophene-3-carboxylic acid cyclopropylamide

60



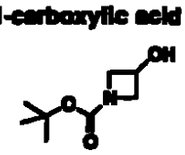
This material was prepared by the reaction of 7-chloro-2-[(S)-2-[[t-butyldimethylsilyloxy]methyl]-pyrrolidine-1-carbonyl]thieno[3,2-b]pyridine 3b (206 mg, 0.5 mmole) with 6-hydroxy-2-methylbenzo[b]thiophene-3-carboxylic acid cyclopropylamide 8c (186 mg, 0.75 mmole) and Cs_2CO_3 (869 mg, 2.7 mmole) in a manner as previously described for example 1 to give 132 mg (52%) of a yellow solid. ^{1}H NMR (DMSO-d_6): δ 8.58 (1H, d, J = 5.4 Hz), 8.46 (1H, d, J= 4.3 Hz), 8.00 (1H, s), 7.95 (1H, d, J = 2.3 Hz), 7.80 (1H, d, J = 8.8 Hz), 7.32 (1H, dd, J = 2.3, 8.8 Hz), 6.75 (1H, d, J = 5.4 Hz), 4.90-4.72 (1H, m), 4.24-4.11 (1H, m), 3.92-374 (2H, m), 3.64-3.43 (2H, m), 2.95-2.84 (1H, m), 2.57 (3H, s), 2.09-1.80 (4H, m) 0.77-0.67 (2H, m), 0.60-0.52 (2H, m). *Anal.* Calcd. for $C_{24}H_{23}N_3O_4S_2$•0.4 CH_2Cl_2•0.4 CH_3OH: C, 58.06; H, 4.98; N, 7.58. Found: C, 58.03; H, 4.98; N, 7.52.

Example 9(a): 1-benzhydrylazetidin-3-ol



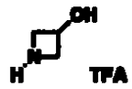
A mixture of (diphenylmethyl)amine (2.2 ml, 12.8 mmole), 2-chloromethyloxirane (2.0 ml, 25.6mmole) in DMF (25 ml) were heated at 95 °C for 72 hours. The resultant yellow solution was cooled to 0° and treated with 0.5 M HCl (250 ml). The aqueous layer was washed with methyl *tert*-butyl ether (3 x 150 ml), and the organic layers were discarded. The aqueous layer was made basic with NaOH and the resultant milky white suspension was extracted with methyl *tert*-butyl ether (3 x 150 ml). The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated, *in vacuo*, to a clear oil (3.1 g). The oil was triturated with cyclohexane and methyl *tert*-butyl ether and provided a white solid (2.3 g, 74%): TLC (4% methanol-chloroform with 0.1% ammonium hydroxide) R_f 0.3; ^{1}H-NMR (DMSO-d_6, 400 MHz) δ 7.40-7.38 (4H, m), 7.27-7.23 (4H, m), 7.17-7.13 (2H, m), 5.28 (1H, d, J = 6.3 Hz), 4.34 (1H, s), 4.22-4.18 (1H,m), 3.36-3.34 (2H,m), 2.69-2.66 (2H,m).

Example 9(b): 3-hydroxyazetidine-1-carboxylic acid tert-butyl ester



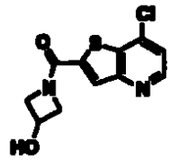
1-Benzhydryl-azetidin-3-ol 9a (4.0 g, 16.7 mmole), EtOAc (150 ml), di-*tert*-butyl dicarbonate (4.4 g, 20.1 mmole) and 20% $Pd(OH)_2$ on carbon (0.8 g, 20 wt.%) were sequentially added to a round bottom flask. The mixture was degassed and purged with hydrogen. The hydrogenolysis was completed after 24 hours at one atmosphere. The reaction mixture was filtered through celite and concentrated, *in vacuo*, to a clear oil (7.0 g). The crude product was dissolved in CH_2Cl_2 (10 ml) and purified over a silica gel plug (35 g), which was eluted with CH_2Cl_2 (150 ml) followed by EtOAc (150 ml). The EtOAc fractions were concentrated, *in vacuo*, to a clear oil (3.1 g, >100%): TLC (50% ethyl acetate-cyclohexane) R_f 0.4 (I_2 stain); ^{1}H-NMR (DMSO-d_6, 300 MHz) δ 5.62 (1H, d, J = 6.4 Hz), 4.39-4.32 (1H, m), 3.97 (2H, t, J = 7.8 Hz), 3.57 (2H, t, J = 4.4 Hz), 1.35 (9H, s).

Example 9(c): Azetidin-3-ol trifluoroacetic acid salt



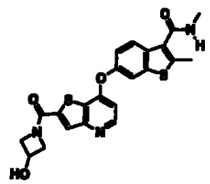
3-Hydroxy-azetidine-1-carboxylic acid tert-butyl ester 9b (0.73 g, 4.2 mmole) was dissolved in CH_2Cl_2 (2 ml) and trifluoroacetic acid (2 ml). CAUTION: The deprotection generated a rapid evolution of gas. The clear solution was stirred for 75 minutes and the solvent was removed, *in vacuo*, to a clear oil (1.4 g, >100%): ^{1}H-NMR (DMSO-d_6, 400 MHz) δ 8.63 (2H, br. s), 4.55-4.48 (1H, m), 4.09-4.02 (2H, m), 3.76-3.68 (2H, m).

Example 9(d): 7-Chloro-2-[3-hydroxyazetidin-1-carbonyl]thieno[3,2-*b*]pyridine



A mixture of the lithium salt of 7-chlorothieno[3,2-*b*]pyridine-2-carboxylic acid (0.92 g, 4.2 mmole), CH_2Cl_2 (40 ml) and thionyl chloride (0.92 ml, 12.6 mmole) was heated to reflux. The resultant white slurry gave rise to an amber solution upon the addition of DMF (5 ml). After 60 minutes the reaction mixture was concentrated, *in vacuo*, to a white slurry. The acid chloride was suspended in CH_2Cl_2 (40 ml) and treated with a solution of azetidin-3-ol trifluoroacetic acid salt 9c (0.78 g, 4.2 mmole) and Et_3N (0.58 ml, 4.2 mmole) in DMF (2 ml). After 60 minutes the CH_2Cl_2 layer was removed, *in vacuo*, and the resultant beige residue was poured into saturated $NaHCO_3$ (100 ml). The aqueous layer was extracted with EtOAc (3 x 100 mL). The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated, *in vacuo*, to a beige slurry (1.7 g). The slurry was triturated with methyl *tert*-butyl ether and provided a beige solid (0.23 g, 21%): TLC (5% methanol-dichloromethane) R_f 0.4; ^{1}H-NMR (DMSO-d_6, 400 MHz) δ 8.74 (1H, d, J = 5.1 Hz), 7.99 (1H, s), 7.70 (1H, d, J = 4.8 Hz), 5.88 (1H,d, J = 6.3 Hz), 4.80-4.78 (1H, m), 4.60-4.56 (1H, m), 4.37-4.34 (2H, m), 3.86-3.84 (1H, m); ESIMS *m/z* 269 $(M + H)^+$.

Example 9 6-(2-[3-Hydroxyazetidine-1-carbonyl]thieno[3,2-*b*]pyridin-7-yloxy)-2-methylbenzo[*b*]thiophene-3-carboxylic acid methylamide



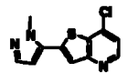
A slurry of 7-chloro-2-[3-hydroxyazetidin-1-carbonyl]thieno[3,2-*b*]pyridine 9d (120 mg 0.45 mmole) 6-hydroxy-2-methylbenzo[*b*]thiophene-3-carboxylic acid methylamide 1d (100 mg, 0.45 mmole) and Cs_2CO_3 (0.73 g, 2.2 mmole) in acetonitrile (15 ml) was heated to 70 ° After 30 hours both starting materials remained, but the reaction was stopped. The reaction mixture was poured into a solution of 50% saturated $NaHCO_3$ (150 ml) The aqueous layer was extracted with 10% isopropanol-chloroform (3 x 150 ml) The combined organic layers were dried with brine magnesium sulfate filtered and concentrated, *in vacuo*, to a white solid (0.18 g) The crude product was purified by silica gel radial chromatography and the gradient mobile phase was 5-10% CH_3OH-$CH2Cl_2$ with 0 1% NH_4OH. The product was triturated with ethyl acetate – cyclohexane and isolated as a white solid (40 mg 20%)· TLC (5% CH_3OH-$CH2Cl_2$) R_f 0.2; ^{1}H-NMR (DMSO-d_6, 400 MHz) δ 8.58 (1H, d, J = 5.3 Hz) δ 30-8.27 (1H, m) 7 96-7 84 (3H m) 7.32 (1H d J = 8.9 Hz) 6.75 (1H, d J = 5 3 Hz) 5.88 (1H d, J = 6.6 Hz) 4.80-4.78 (1H m) 4.58-4.55 (1H m) 4.35-4.30 (2H, m), 3.87-3.82 (1H, m) 2.84 (3H, d J = 4.3 Hz) 2 60 (3H, s) ESIMS *m/z* 454 $(M + H)^+$ mp 237-239 °C. *Anal.* Calcd for $C_{22}H_{19}N_3O_4S_2$·0.9 H_2O· C, 56.25; H 4.46, N 8.95 S 13.65. Found C 56.36· H 4.22; N 9.00; S, 13.51

Example 10(a) 1-Methyl-5-trimethylstannanyl-1*H*-pyrazole



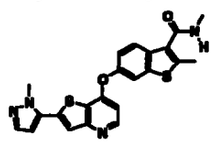
A solution of 1-methyl-1*H*-pyrazole (1.6 g 20.0 mmole) in Et_2O was treated with n-butyllithium (12.5 ml, 1.6 M in hexanes, 20.0 mmole) over a period of 10 minutes at room temperature. The yellow slurry was stirred for a further 90 minutes. Subsequently trimethyltin chloride (4.0 g 20.0 mmole) was added in one portion. The brown slurry was stirred for 30 minutes filtered and the filtrate was concentrated *in vacuo*, to a black oil (5.0 g). The product was isolated by distillation at 1.5 Torr (67 72 °C) as a clear oil (2.1 g, 42%). ^{1}H-NMR (DMSO-d_6, 400 MHz) δ 7.40 (1H, d, J = 1.5 Hz) 6.27 (1H d J = 1 7 Hz) 3.84 (3H, s) 0.34 (9H, s). ESIMS *m/z* 243-247 ion cluster $(M + H)^+$

Example 10(b): 7-Chloro-2-(2-methyl-2*H*-pyrazol-3-yl)thieno[3,2-*b*]pyridine



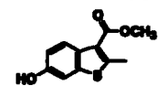
A mixture of 1-methyl-5-trimethylstannanyl-1*H*-pyrazole 10a (2 1 g 8.5 mmole) 7 chloro-2-iodo-thieno[3,2-*b*]pyridine (2 5 g, 8.5 mmole) tetrakis(triphenylphosphine)palladium(0) (0.5 g, 0.4 mmole 5mol%) in *o*-xylene (85 ml) was degassed purged with nitrogen and heated to 120 ° which gave an orange solution. After 14 hours the black reaction mixture was diluted with toluene (100 ml) and extracted with 1.2 M HCl (3 x 60 ml) The combined aqueous layers were washed with toluene (100 ml) The organic layers were discarded and the aqueous layer was treated with NaOH to pH 14 The resultant white solid was collected (1 1 g 52%) TLC (6% methanol-dichloromethane) R_f 0.8 ^{1}H-NMR (DMSO-d_6, 400 MHz) δ 8.70 (1H d J = 5.3 Hz) 8.00 (1H s) 7 63 (1H,d, J = 5.3 Hz) 7 58 (1H d, J = 2.0 Hz), 6.79 (1H, d J = 2.0 Hz) 4 09 (3H s) ESIMS *m/z* 250 (M + H)

Example 10· 2-Methyl-6-(2-[2-methyl-2*H*-pyrazol-3-yl]thieno[3,2-*b*]pyridin-7 yloxy)benzo[*b*]thiophene-3-carboxylic acid methylamide



Example 10 was prepared by the reaction of 7-Chloro-2-(2-methyl-2*H*-pyrazol-3-yl)thieno[3,2-*b*]pyridine 10b with 6-hydroxy-2-methylbenzo[b]thiophene-3-carboxylic acid methylamide 1d and Cs_2CO_3 in a manner as previously described for example 1 to give 115 mg of a beige solid (60%) TLC (6% methanol-dichloromethane) R_f 0.6, ^{1}H-NMR (DMSO-d_6 400 MHz) δ 8.54 (1H d J = 5.5 Hz) 8.28 (1H, q J = 4.5 Hz) 7.98 (1H d J = 2.3 Hz) 7 92 (1H s) 7.86 (1H, d, J = 8.8 Hz), 7.54 (1H, d J = 2.0 Hz) 7 33 (1H dd, J = 2.3, 8.8 Hz), 6.72 (1H d, J = 2.0 Hz), 6.68 (1H d J = 5.5 Hz) 4.08 (3H s) 2.84 (1H, d, J = 4.5 Hz) 2.60 (3H, s) ESIMS *m/z* 435 (M + H) mp 210-212 °C *Anal.* Calcd for $C_{20}H_{18}N_4O_2S_2$•1.3 H_2O· C, 57 70; H, 4.53; N 12.23; S, 14 00. Found C, 57 75 H, 4.55, N, 12.21 S 14.13.

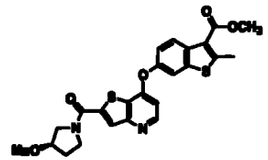
Example 11(a). Methyl 6-hydroxy-2-methylbenzo[b]thiophene-3-carboxylate



This material was prepared from 6-acetoxy-2-methylbenzo[b]thiophene 8b (500 mg, 2.42 mmole) by acylation with oxalyl chloride in the presence of $AlCl_3$ as previously described for example 1c. A solution of the crude 6-methoxy-2-methylbenzo[b]thiophene-3-carbonyl

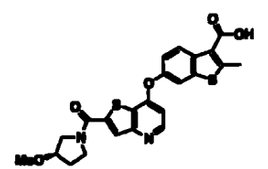
chloride in MeOH (24 ml) was cooled to 0 °C prior to the addition of K_2CO_3 (351 mg 2.66 mmole) The reaction was warmed to ambient temperature and stirred 3 hours The solvent was removed *in vacuo*, and the resulting residue was diluted with CH_2Cl_2 (75 ml) and H_2O (25 ml). The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (50 ml) The combined organics were washed with brine (25 ml) dried (Na_2SO_4) filtered and concentrated *in vacuo* to afford the 468 mg (87%) of a pale brown solid. ^{1}H NMR (300 MHz, DMSO-d6) δ 9 66 (1H, s) 8.06 (1H, d, *J* = 8.9 Hz) 7.23 (1H d *J* = 2.3 Hz) 6.91 (1H, dd, *J* = 2.3, 8.9 Hz)

Example 11(b) Methyl 6-[(2-[[(3*R*)-3-methoxypyrrolidin-1-yl]carbonyl]thieno[3,2-*b*]pyridin-7-yl)oxy]-2-methylbenzo[b]thiophene-3-carboxylate



Example 11(b) was prepared by the reaction of 7-chloro-2-[(*R*)-3-methoxypyrrolidine-1-carbonyl]thieno[3,2-b]pyridine 4b (417 mg 1.40 mmole) with methyl 6-hydroxy-2-methylbenzo[b]thiophene-3-carboxylate 11a (417 mg 2.11 mmole) and Cs_2CO_3 (2.28 g 7.02 mmole) in a manner as previously described for example 1 to give 290 mg (43%) of a yellow solid ^{1}H NMR (DMSO-d_6) 88.58 (1H, d *J* = 5.4 Hz) 8.39 (1H d *J* = 9.0 Hz), 8.07 (1H s) 8.02 (1H d *J* = 2.3 Hz) 7.42 (1H, dd *J* = 2.3, 9.0 Hz) 6.79 (1H d, *J* = 5.4 Hz) 4.08-3.99 (3H m), 3.67 3.86 (2H m) 3.91 (3H s) 3.84-3.59 (2H m) 3.27 3.24 (3H, s) 2.62 (3H, s).

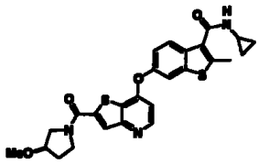
Example 11(c) 6-[(2-[[(3*R*)-3-methoxypyrrolidin-1-yl]carbonyl]thieno[3,2-*b*]pyridin-7-yl)oxy]-2-methylbenzo[b]thiophene-3-carboxylic acid



To a solution of methyl 6-[(2-[[(3*R*)-3-methoxypyrrolidin-1-yl]carbonyl]thieno[3,2-*b*]pyridin-7-yl)oxy]-2-methylbenzo[b]thiophene-3-carboxylate 11b (258 mg, 0.535 mmole) in a mixture of THF/MeOH/H_2O (3:2.1 6 ml) was added LiOH-H_2O (224 mg, 5.35 mmole) The reaction was stirred 24 hours at ambient temperature The mixture was diluted with H_2O (10 ml) and acidified to pH 1 with 1 M HCl The precipitate was collected by vacuum filtration, rinsed with MeOH and dried at 50 °C under vacuum to afford 116 mg (45%) of a pale brown

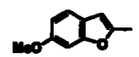
solid ^{1}H NMR (DMSO-d_6) δ 8.58 (1H, d *J* = 5.4 Hz) 8.44 (1H d, *J* = 8.9 Hz) 8.07 (1H s) 8.00 (1H d *J* = 2.4 Hz) 7.39 (1H dd, *J* = 2.4 8.9 Hz) 6.78 (1H d, *J* = 5.4 Hz) 4.10-3.81 (3H, *m*) 3.69-3.54 (4H m), 3.27 3.24 (3H, s) 2.81 (3H s)

Example 11 6-[(2-[[(3*R*)-3-methoxypyrrolidin-1-yl]carbonyl}thieno[3,2-*b*]pyridin-7-yl)oxy]-2-methylbenzo[b]thiophene-3-carboxylic acid cyclopropylamide



Thionyl chloride (31 µl 0.427 mmole) was added to a suspension of 6-[(2-[[(3*R*)-3-methoxypyrrolidin-1-yl]carbonyl}thieno[3,2-*b*]pyridin-7-yl)oxy]-2-methylbenzo[b]thiophene-3-carboxylic acid 11c (40 mg, 0.085 mmole) in dichloroethane (1 ml) The reaction mixture was heated to reflux for 90 minutes, cooled to room temperature and concentrated *in vacuo*. The yellow residue was dissolved in CH_2Cl_2 (1 ml) and cyclopropylamine (30 µl 0.427 mmole) was added The resulting mixture was stirred at ambient temperature for 16 hours diluted with CH_2Cl_2 (10 ml) and washed with H_2O (5 ml) The aqueous layer was extracted with CH_2Cl_2 (2 x 5ml) and the combined organics were dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The crude mixture was purified by silica gel chromatography (5% MeOH / EtOAc) to afford 20 mg (46%) of a pale yellow solid. ^{1}H NMR (DMSO-d_6, 300 MHz) δ 8.58 (1H, d, *J* = 5.3 Hz) 8.46 (1H d, *J* = 4.5 Hz) 8.06 (1H, s) 7.96 (1H d, *J* = 2.3 Hz) 7.81 (1H *J* = 8.7 Hz), 7.32 (1H dd *J* = 2.3, 8.7 Hz) 6.75 (1H d, *J* = 5.3 Hz) 4.10-3.82 (4H m) 3.61 (2H m) 3.27 3.24 (3H s) 2.91 (1H, m) 2.72 (1H m) 2.57 (3H, s) 0.78-0.70 (2H m) 0.50-0.55 (2H, m) *Anal.* Calcd for $C_{25}H_{23}N_3O_4S_2$. C 61.52, H 4.96 N, 8.28 S, 12.63 Found: C, 59.30; H 4.78 N 7.95, S 12.23.

Example 12(a) 6-methoxy-2-methylbenzofuran

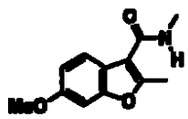


A pressure tube was charged with a stir bar 2-Iodo-5-methoxyphenol (500mg 2.0mmol) (prepared according to Heterocycles 45, (8) 1997 1137) $Cl_2Pd(PPh_3)_2$ (70mg 0.1mmol) CuI (19mg, 0.1mmol) 1 1,3,3-Tetramethylguanidine (2.5ml, 20.0mmol) and DMF (10 ml) then cooled to –78° while propyne gas was condensed. The tube was sealed and allowed to warm to room temperature After 18 hours the contents of the tube were poured into sat NaCl solution and extracted with EtOAc (2x) The combined organic layers were washed with brine (3x) dried ($MgSO_4$) and concentrated under reduced pressure The residue was flash chromatographed on silica gel eluting 3.1 (hexanes/ethyl acetate) to give

66

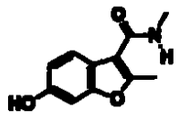
239mg (74%) of an amber liquid. ^{1}H NMR (DMSO-d_6) δ 7.31 (1H, d, J = 8.3 Hz), 6.95 (1H, d, J = 2.2 Hz), 6.80 (1H, dd, J = 2.2, 8.3 Hz), 6.27 (1H, s), 3.85 (3H, s), 2.40 (3H, s). *Anal.* Calcd for $C_{10}H_{10}O_2 \cdot 0.05$ hexanes: C, 74.30; H, 6.48. Found: C, 74.63; H, 6.48.

Example 12(b): 6-methoxy-2-methylbenzofuran-3-carboxylic acid methylamide



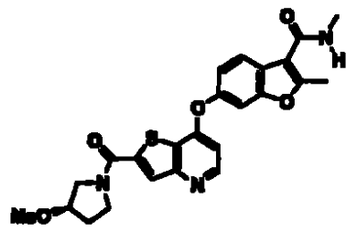
This material was prepared from 6-methoxy-2methylbenzofuran 11a (500mg, 3.1mmole) by acylation with oxalyl chloride in the presence of $AlCl_3$, followed by treatment with methylamine in a manner as previously described for example 1c to give 541mg (80%) of an off-white solid. ^{1}H NMR ($CDCl_3$) δ (as a pair of rotamers) 7.48, 7.41 (1H, d, J = 8.6 Hz), 6.98, 6.55 (1H, s), 6.89, 6.71 (1H, dd, J = 2.3, 8.6 Hz), 6.22, 5.83 (1H, bs), 3.84, 3.82 (3H, s,), 3.03, 2.93 (3H, d, J = 4.8 Hz), 2.69, 2.38 (3H, s,). *Anal.* Calcd for $C_{12}H_{13}NO_3$: C, 65.74; H, 5.98; N, 6.39. Found: C, 65.86; H, 5.96; N, 6.35.

Example (12c): 6-hydroxy-2-methylbenzofuran-3-carboxylic acid methylamide



This material was prepared from 6-methoxy2methylbenzo[b]furan-3-carboxylic acid methylamide 11b (516mg, 2.35mmol) by treatment with BBr_3 in a manner as previously described for example 1d to give 429mg (89%) of an off-white solid. ^{1}H NMR (DMSO-d_6) δ 9.54 (1H, s), 7.80 (1H, d, J = 4.5 Hz), 7.50 (1H, d, J = 8.3 Hz), 6.88 (1H, s), 6.72 (1H, d, J = 8.3 Hz), 2.79 (3H, d, J = 4.5 Hz), 2.57 (3H, s). Anal. Calcd for $C_{11}H_{11}NO_3 \cdot 0.1$ EtOAc: C, 63.97; H, 5.58; N, 6.54. Found: C, 63.87; H, 5.88; N, 6.45.

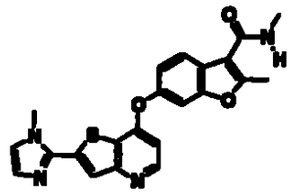
Example 12: 6-(2-[3-methoxypyrrolidine-1-carbonyl]thieno[3,2-b]pyridin-7-yloxy)-2-methylbenzofuran-3-carboxylic acid methylamide



This material was prepared by the reaction of 7-chloro-2-[(*R*)-3-methoxypyrrolidine-1-carbonyl]thieno[3,2-b]pyridine 4b (144 mg, 0.5 mmole) with 6-hydroxy-2-methylbenzo[b]furan-3-carboxylic acid methylamide 11c (120 mg, 0.6 mmole) and Cs_2CO_3 (794 mg, 2.4 mmole) in

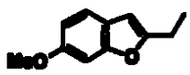
a manner as previously described for example 1 to give 134mg (59%) of an off-white solid. ^{1}H NMR (DMSO-d_6) δ 8.58 (1H, d, J = 5.3 Hz), 8.07 (1H, s), 7.97 (1H, d, J = 4.5 Hz), 7.83 (1H, d, J = 8.6 Hz), 7.65 (1H, d, J = 2.0 Hz), 7.24 (1H, dd, J = 2.0, 8.6 Hz), 6.72 (1H, d, J = 5.3 Hz), 4.25-3.75 (3H, m), 3.65-3.45 (2H, m), 3.27, 3.24 (3H, s), 2.82 (3H, d, J = 4.3 Hz), 2.62 (3H, s), 2.15-1.95 (2H, m). *Anal.* Calcd for $C_{24}H_{22}N_5O_3S \cdot 0.5\ H_2O$: C, 60.74; H, 5.10; N, 8.88; S, 6.76. Found: C, 60.89; H, 5.16; N, 8.89; S, 6.58.

Example 13: 2-methyl-6-[2-(1-methyl-1H-imidazol-2-yl)-thieno[3,2-b]pyridin-7-yloxy]-benzofuran-3-carboxylic acid methylamide



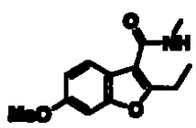
This material was prepared by the reaction of 7-chloro-2-(1-methyl-1H-imidazol-2-yl)thieno[3,2-b]pyridine 1e with 6-hydroxy-2-methylbenzo[b]furan-3-carboxylic acid methylamide 11c and Cs_2CO_3 in a manner as previously described for example 1to give a 51% yield of a light yellow solid. ^{1}H NMR (DMSO-d_6) δ 8.50 (1H, d, J = 5.6 Hz), 8.01 (1H, d, J = 4.5 Hz), 7.88 (1H, s), 7.82 (1H, d, J = 8.6 Hz), 7.64 (1H, s), 7.40 (1H, s), 7.25 (1H, d, J = 8.3 Hz), 7.03 (1H, s), 6.66 (1H, d, J = 5.6 Hz), 3.97 (3H, s), 2.81 (3H, d, J = 4.5 Hz), 2.64 (3H,s). *Anal.* Calcd for $C_{22}H_{18}N_4O_3S \cdot 0.25\ H_2O$: C, 62.47; H, 4.41; N, 13.25; S, 7.29. Found: C, 62.57; H, 4.37; N, 13.05; S, 7.29.

Example 14(a): 6-methoxy-2-ethylbenzofuran



This material was prepared from 2-Iodo-5-methoxyphenol (1 g, 4 mmole) and 1-butyne in a manner as previously described for example 12a to give 570 mg (81%) of a brown oil. ^{1}H NMR ($CDCl_3$) δ 7.33 (1H, d, J = 8.6 Hz), 6.97 (1H, d, J = 2.2 Hz), 6.80 (1H, dd, J = 2.2, 8.6 Hz), 6.26 (1H, s), 3.83 (3H, s), 3.04 (2H, q, J = 7.3 Hz), 1.28 (3H, t, J = 7.3 Hz).

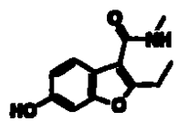
Example 14(b): methoxy-2-ethylbenzofuran-3-carboxylic acid methylamide



Example 14(b) was prepared from 6-methoxy-2-ethylbenzofuran 14a (522 mg, 2.96 mmole) by acylation with oxalyl chloride in the presence of $AlCl_3$, followed by treatment with

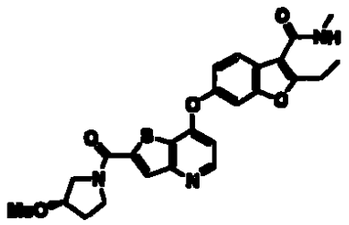
methylamine in a manner as previously described in Example 1c to give 433 mg (83%) of an off-white solid. ^{1}H NMR (DMSO-d_6) δ 7.83 (1H, d, J = 4.8 Hz), 7.56 (1H, d, J = 8.8 Hz), 7.23 (1H, d, J = 2.3 Hz) , 6.83 (1H, dd, J = 2.3, 8.8 Hz), 3.78 (3H, s), 3.05 (2H, q, J = 7.2 Hz),, 2.80 (3H, d, J = 4.8 Hz), 1.26 (3H, t, J = 7.2 Hz). *Anal.* Calcd for $C_{13}H_{15}NO_3$: C, 66.93; H, 6.48; N, 6.00. Found: C, 66.96; H, 6.46; N, 5.95.

Example (14c): 6-hydroxy-2-ethylbenzofuran-3-carboxylic acid methylamide



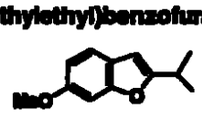
Example 14(c) was prepared from 6-methoxy-2-ethylbenzo[b]furan-3-carboxylic acid methylamide 14b (401mg, 1.72 mmole) by treatment with BBr_3 in a manner as previously described for example 1d to give 318mg (84%) of an off-white solid. ^{1}H NMR (DMSO-d_6) δ 9.53 (1H, s), 7.79 (1H, d, J = 4.6 Hz), 7.45 (1H, d, J = 8.6 Hz), 6.88 (1H, d, J = 2.0 Hz), 6.74 (1H, dd, J = 2.0, 8.6 Hz), 3.03 (2H, q, J = 7.3 Hz), 2.77 (3H, d, J = 4.6 Hz), 1.24 (3H, t, J = 7.3 Hz). *Anal.* Calcd for $C_{13}H_{13}NO_3$: C, 65.74; H, 5.96; N, 6.39. Found: C, 65.61; H, 6.06; N, 6.32.

Example 14: 6-(2-[3-methoxypyrrolidine-1-carbonyl]thieno[3,2-b]pyridin-7-yloxy)-2-ethylbenzofuran-3-carboxylic acid methylamide



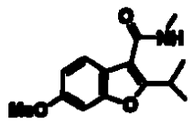
Example 14 was prepared by the reaction of 7-chloro-2-[(R)-3-methoxypyrrolidine-1-carbonyl]thieno[3,2-b]pyridine 4b (135 mg, 0.46 mmole) with 6-hydroxy-2-ethylbenzo[b]furan-3-carboxylic acid methylamide 14c (120 mg, 0.55 mmole) and Cs_2CO_3 (594 mg, 1.82 mmole) in a manner as previously described for example 1 to give 75 mg (34%) of an off-white solid. ^{1}H NMR (DMSO-d_6) δ 8.57 (1H, d, J = 5.4 Hz), 8.07 (1H, s), 8.01 (1H, d, J = 4.5 Hz), 7.83 (1H, d, J = 8.6 Hz), 7.68 (1H, d, J = 2.0 Hz), 7.26 (1H, dd, J = 2.0, 8.6 Hz), 6.73 (1H, d, J = 5.4 Hz), 4.11-3.82 (3H, m), 3.69-3.43 (2H, m), 3.27, 3.24 (3H, s), 3.05 (2H, q, J = 7.5 Hz), 2.82 (3H, d, J = 4.5 Hz), 2.18-1.94 (2H, m), 1.27 (3H, t, J = 7.5 Hz). *Anal.* Calcd for $C_{25}H_{25}N_3O_5S$•0.2 CH_2Cl_2•0.25 hexane: C, 61.90; H, 5.62; N, 8.11; S, 6.19. Found: C, 61.88; H, 5.84; N, 8.03; S, 6.11.

Example 15(a): 6-methoxy-2-(1-methylethyl)benzofuran



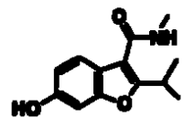
Example 15(a) was prepared from 2-iodo-5-methoxyphenol (896 mg, 3.6 mmole) and 3-methyl-1-butyne in a manner as previously described for example 12a to give 265 mg (38%) of an amber oil. ^{1}H NMR ($CDCl_3$) δ 7.33 (1H, d, J = 8.6 Hz), 6.97 (1H, d, J = 2.2 Hz), 6.80 (1H, dd, J = 2.2, 8.6 Hz), 6.26 (1H, s), 3.83 (3H, s), 3.07-3.01 (1H, m), 1.31 (6H, d, J = 7.1 Hz).

Example 15(b): 6-methoxy-2-(1-methylethyl)benzofuran-3-carboxylic acid methylamide



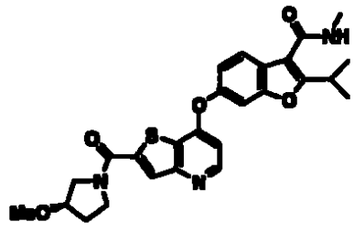
Example 15(b) was prepared from 6-methoxy-2-(1-methylethyl)benzofuran 15a (263 mg, 1.36 mmole) by acylation with oxalyl chloride in the presence of $AlCl_3$, followed by treatment with methylamine in a manner as previously described for example 1c to give 200 mg (60%) of an off-white solid. ^{1}H NMR (DMSO-d_6) δ 7.83 (1H, d, J = 4.8 Hz), 7.56 (1H, d, J = 8.8 Hz), 7.20 (1H, d, J = 2.3 Hz) , 6.89 (1H, dd, J = 2.3, 8.8 Hz), 3.78 (3H, s), 3.68-3.61 (1H, m), 2.78 (3H, d, J = 4.8 Hz), 1.26 (6H, d, J = 6.8 Hz).

Example 15(c): 6-hydroxy-2-(1-methylethyl)benzofuran-3-carboxylic acid methylamide



This material was prepared from 6-methoxy-2-(1-methylethyl) benzo[b]furan-3-carboxylic acid methylamide 15b (173 mg, 0.84 mmole) by treatment with BBr_3 in a manner as previously described for example 1d to give 157 mg (80%) of a crisp foam. ^{1}H NMR (DMSO-d_6) δ 9.54 (1H, s), 7.76 (1H, d, J = 4.8 Hz), 7.45 (1H, d, J = 8.6 Hz), 6.88 (1H, d, J = 2.0 Hz), 6.74 (1H, dd, J = 2.0, 8.6 Hz), 3.68-3.61 (1H, m), 2.75 (3H, d, J = 4.8 Hz), 1.24 (6H, d, J = 7.1 Hz).

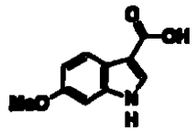
Example 15: 6-(2-[3-methoxypyrrolidine-1-carbonyl]thieno[3,2-b]pyridin-7-yloxy)-2-(1-methylethyl)benzofuran-3-carboxylic acid methylamide



This material was prepared by the reaction of 7-chloro-2-[(R)-3-methoxypyrrolidine-1-carbonyl]thieno[3,2-b]pyridine 4b (122 mg, 0.41 mmole) with 6-hydroxy-2-(1-methylethyl)benzo[b]furan-3-carboxylic acid methylamide 15c (125 mg, 0.53 mmole) and Cs_2CO_3 (200 mg, 0.61 mmole) in a manner as previously described for example 1 to give 82

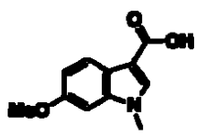
mg (40%) of a white solid. ^{1}H NMR (DMSO-d_6) δ 8.56 (1H, d, J = 5.3 Hz), 8.06 (1H, s), 8.01 (1H, d, J = 4.6 Hz), 7.79 (1H, d, J = 8.6 Hz), 7.68 (1H, d, J = 2.2 Hz), 7.25 (1H, dd, J = 2.2, 8.6 Hz), 6.73 (1H, d, J = 5.3 Hz), 4.15-3.85 (3H, m), 3.70-3.45 (3H, m), 3.27, 3.24 (3H, s), 2.82 (3H, d, J = 4.6 Hz), 2.15-1.95 (2H, m), 1.30 (6H, d, J = 7.1 Hz). *Anal.* Calcd for $C_{28}H_{37}N_3O_5S \cdot 0.2\ H_2O/0.2$ MTBE: C, 62.99; H, 5.84; N, 8.186; S, 6.23. Found: C, 62.92; H, 5.93; N, 7.97; S, 6.07.

Example 16(a): 6-methoxy-1H-indole-3-carboxylic acid



The preparation of the title compound was adapted from work previously published by Swain et al (*J. Med. Chem.* 1992, *35*, 1019-1031). To a stirring solution of 6-methoxy-1H-indole (10g, 68 mmole) in DMF (100ml) at 0°C was added trifluoroacetic anhydride (21.4ml, 150mmole) dropwise. After the addition, the mixture was heated at 165° for 18hours. The mixture was removed from heat and added dropwise to ice water (1L). The resulting precipitate was collected by filtration, washed with water then suspended in 20% aq. NaOH (200ml). The suspension was heated at 90° until homogeneous (~2hr). The dark mixture was allowed to cool to RT and was washed with Et_2O (200ml). The aqueous layer was washed with CH_2Cl_2. A precipitate formed during the extraction which was collected by filtration. The filtrate was divided into layers and the aqueous layer acidified to pH 3 using 6N HCl resulting in the formation of a precipitate. The previously collected solids were added to the suspension and the mixture was stirred for 3hours. The mixture was acidified to pH 2 using 6N HCl and the solids collected by filtration. The solids were washed with water and dried in air to give 10.08g (77%) of an off-white solid which was carried on without further purification. ^{1}H NMR (DSMO-d_6) δ 11.53 (1H, broad s), 7.88 (1H, d, J = 8.7 Hz), 7.75 (1H, s), 6.91 (1H, d, J = 2.0 Hz), 6.74 (1H, dd, J = 2.0, 8.7 Hz), 3.75 (3H, s).

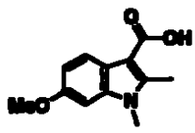
Example 16(b): 6-methoxy-1-methyl-1H-indole-3-carboxylic acid



To a stirring solution of 6-methoxy-1H-indole-3-carboxylic acid 16a (8.0g, 41.2 mmole) in anhydrous DMF (100ml) at 0° was added NaH (60% dispersion in oil, 4.12g, 103 mmole) in a single portion. After stirring at 0°C for 1.3 hour, iodomethane (7.5 ml, 120 mmole) was added via syringe. The resultant mixture was stirred for 18hours, gradually warming to room temperature, then poured into 0.2N NaOH (1L) and extracted with EtOAc (3

x 250ml). The combined extracts were washed sequentially with 1N NaOH (50 ml), water (3 x 50 ml), and brine (50 ml) then dried over Na_2SO_4 and concentrated, *in vacuo*. The resulting crude 6-methoxy-1-methyl-1H-indole-3-carboxylic acid methyl ester was triturated with hexanes and collected by filtration. This material was suspended in aqueous KOH (3.38g, 60mmol in 150 ml) and the resulting suspension heated at reflux for 3.5 hours. The mixture was then poured onto 200 g of ice and washed with CH_2Cl_2 (2 x 50 ml). The aqueous layer was acidified with 6N HCl to pH 2 resulting in a white precipitate which was collected by filtration, washed with water and air dried to yield 7.25 g (66%) of the title compound which was carried on without any further purification. ^{1}H NMR (DMSO-d_6) δ 11.84 (1H, broad s), 7.88 (1H, s), 7.84 (1H, d, J = 8.7 Hz), 7.02 (1H, d, J = 2.2 Hz), 6.82 (1H, dd, J = 2.2, 8.7 Hz), 3.81 (3H, s), 3.79 (3H, s). *Anal.* Calcd. for $C_{11}H_{11}NO_3$•0.2 H_2O: C, 63.27; H, 5.50; N, 6.71. Found: C, 63.36; H, 5.35; N,6.63.

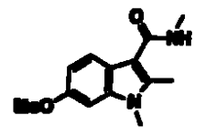
Example 16(c): 1,2-dimethyl-6-methoxy-1H-indole-3-carboxylic acid



The preparation of the title compound was adapted from work previously published by Buttery et al (*J. Chem. Soc. Perkin Trans.* 1993, 1425-1431). A solution of 6-methoxy-1-methyl-1H-indole-3-carboxylic acid 16b (5.2 g, 25.4 mmole) in anhydrous THF (100ml) was added dropwise over 30 minutes to a stirring solution of LDA [made from n-BuLi (69mmole) and diisopropylamine (60mmole)] in anhydrous THF (50ml) at –78°C. The resulting mixture was allowed to warm to –10°C over 30 minutes, then cooled to –78°C prior to addition of iodomethane (8ml, 128.5mmole) via syringe. The resulting amber mixture was allowed to warm to 15°C over 3 hours, then was washed with 1N NaOH (100ml). A precipitate formed during the separation that was collected by filtration. The filtrate was separated into layers. The organic layer was washed again with 1N NaOH (50ml). The solids were suspended in water and the resulting suspension acidified to pH 3 using 0.5 N HCl. The resulting thick suspension was sonicated and stirred for 15 minutes, then the solids were collected by filtration and washed with water. The combined NaOH layers from above were acidified to pH 4 using 6N HCl to yield another batch of solids which was collected by filtration and washed with water. The first batch of solids was suspended in hot $CHCl_3$:MeOH (3:1) and the insoluble material collected by filtration. This isolate was found to be desired product. The filtrate was concentrated to dryness under reduced pressure and the residue triturated twice with warm $CHCl_3$ to yield a second crop of product. The solids obtained from acidification of the basic aqueous layer were triturated three times with warm $CHCl_3$ to yield a third crop of product. The three crops were combined, triturated with MTBE and filtered to give 3.13g (56%) of a white solid. This material was of suitable purity to be carried on without further

purification. ^{1}H NMR (DMSO-d_6) δ 11.83 (1H, broad s), 7.81 (1H, d, J = 8.6 Hz), 7.03 (1H,d, J = 2.3 Hz), 6.76 (1H, dd, J = 2.3, 8.6 Hz), 3.79 (3H, s), 3.67 (3H, s), 2.67 (3H, s). *Anal.* calcd for $C_{13}H_{15}NO_2$•0.2 H_2O: C, 64.66; H, 6.06; N, 6.29. Found: C: 64.89; H, 5.91; N, 6.29.

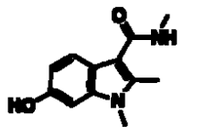
Example 16(d): 6-methoxy-1,2-dimethyl-1H-indole-3-carboxylic acid methylamide



To a stirring solution of the carboxylate 16c (700 mg, 3.2 mmole) in anhydrous CH_2Cl_2 (15 ml) at 0°C was added a drop of DMF, followed by oxalyl chloride (0.55 ml, 6.4 mmole) via syringe. After stirring at 0°C for 15 minutes, the ice bath was removed and the mixture was stirred at ambient temperature for 55 minutes. The mixture was diluted with benzene and concentrated to dryness under reduced pressure. The residue was dissolved in CH_2Cl_2 (10ml) and added via syringe to a 2 M solution of methylamine in THF (30 ml). After observing a slight exotherm upon the start of the addition, the mixture was cooled to 0° for the remainder of the addition. The reaction was stirred for a further 16 hours, gradually warming to room temperature, then partitioned between CH_2Cl_2 (100ml) and 1N NaOH (100ml). The organic layer was washed sequentially with 1N NaOH (50ml), brine (50ml), then dried over Na_2SO_4 and concentrated, *in vacuo*. The crude residue was triturated with MTBE and filtered to give 590 mg (79%) of a white solid. ^{1}H NMR (DMSO-d_6) δ 7.60 (1H, d, J = 8.6 Hz), 7.39-7.35 (1H, m), 7.00 (1H,d, J = 2.3 Hz), 6.72 (1H, dd, J = 2.3, 8.6 Hz), 3.79 (3H, s), 3.63 (3H, s), 2.78 (3H, d, J = 4.6 Hz), 2.53 (3H, s).

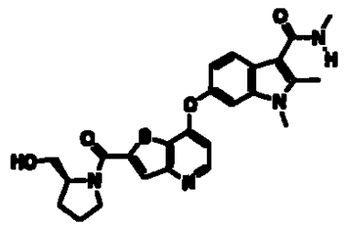
Anal. Calcd. for $C_{13}H_{16}N_2O_2$: C, 67.22; H, 6.54; N,12.08. Found: C, 67.00; H, 6.95; N, 11.99.

Example 16(e): 6-hydroxy-1,2-dimethyl-1H-indole-3-carboxylic acid methylamide



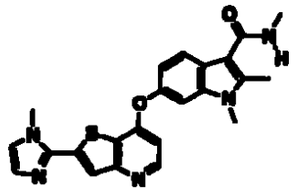
Example 16(e) was prepared from 6-methoxy-1,2-dimethyl-1H-indole-3-carboxylic acid methylamide 16d (560 mg, 2.4 mmole) by treatment with BBr_3 in a manner as previously described for example 1d to obtain 380 mg (73%) of white solid. ^{1}H NMR (DMSO-d_6) δ 9.05 (1H, s), 7.50 (1H, d, J = 8.59 Hz), 7.35-7.28 (1H, m), 6.73 (1H,d, J = 1.77 Hz), 6.80 (1H, dd, J = 8.5, 2.27 Hz), 3.54 (3H, s), 2.75 (3H, d, J = 4.55 Hz), 2.53 (3H, s). *Anal.* Calcd. for $C_{12}H_{14}N_2O_2$•0.3 H_2O: C, 64.44; H, 6.58; N, 12.53. Found: C, 64.55; H, 6.49; N,12.35.

Example 16: 6-[2-(2-Hydroxymethyl-pyrrolidine-1-carbonyl)-thieno[3,2-b]pyridin-7-yloxy]-1,2-dimethyl-1H-indole-3-carboxylic acid methylamide



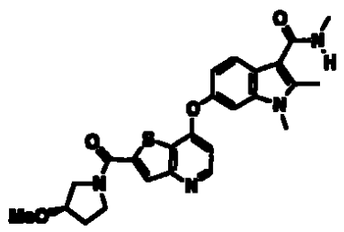
This material was prepared by the reaction of 7-chloro-2-[(S)-2-([t-butyldimethylsilyloxy]methyl)-pyrrolidine-1-carbonyl]thieno[3,2-b]pyridine 3b (76 mg, 0.3 mmole) with 6-hydroxy-1,2-dimethyl-1H-indole-3-carboxylic acid methylamide 16e (100 mg, 0.46 mmole) and Cs_2CO_3 (488 mg, 1.5 mmole) in a manner as previously described for example 1 to give 53mg (43%) of an off-white solid. ^{1}H NMR (DMSO-d_6) δ 8.54 (1H, d, J = 5.48 Hz), 7.99 (1H, s), 7.83 (1H, d, J = 8.67 Hz), 7.81-7.55 (1H, m), 7.54 (1H, d, J = 2.07 Hz), 7.03(1H, dd, J = 8.48, 2.07 Hz), 6.64 (1H, d, J = 5.27 Hz), 5.10-4.80 (1H, 2m), 4.41-4.16 (1H, 2m), 3.91-3.77 (1H, m), 3.67 (3H, s), 3.64-3.47 (2H, m), 2.80 (3H, d, J = 4.52 Hz), 2.60 (3H, s), 2.04-1.81 (4H, m). *Anal.* Calcd for $C_{25}H_{28}N_4O_4S$•0.4 H_2O•0.2 EtOAc: C, 61.56; H, 5.89;

Example 17: 1,2-dimethyl-6-(2-[1-methyl-1H-imidazol-2-yl]thieno[3,2-b]pyridin-7-yloxy)-1H-indole-3-carboxylic acid methylamide



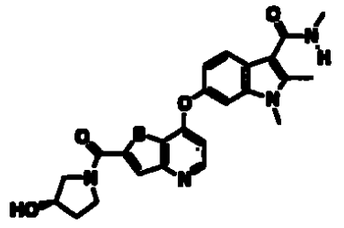
This material was prepared by the reaction of 7-chloro-2-(1-methyl-1H-imidazol-2-yl)thieno[3,2-b]pyridine 1e (76mg, 0.3mmole) with 6-hydroxy-1,2-dimethyl-1H-indole-3-carboxylic acid methylamide 16e (100mg, 0.46 mmole) and Cs_2CO_3 (488mg, 1.5 mmole) in a manner as previously described for example 1 to give 51mg (39%) of product as an off-white solid. ^{1}H NMR (DMSO-d_6) δ 8.48 (1H, d, J = 5.5 Hz), 7.88 (1H, s), 7.83 (1H, d, J = 8.6 Hz), 7.81-7.55 (1H, m), 7.53 (1H, t, J = 2.3 Hz), 7.41(1H, d, J = 1.0 Hz), 7.0-6.99 (2H, m), 6.59 (1H, d, J = 5.5 Hz), 3.98 (3H, s), 3.67 (3H, s) , 2.80 (3H, d, J = 4.6 Hz), 2.60 (3H, s). *Anal.* Calcd for $C_{23}H_{21}N_5O_2S$•0.3 H_2O•0.1 EtOAc: C:63.05; H:5.07; N:15.71; S:7.19. Found: C:63.06; H:5.06; N:15.56; S:6.96.

Example 18: 1,2-dimethyl-6-(2-[3-methoxy-pyrrolidine-1-carbonyl]thieno[3,2-b]pyridin-7-yloxy)-1H-indole-3-carboxylic acid methylamide



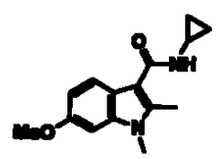
This material was prepared by the reaction of 7-chloro-2-[(R)-3-methoxypyrrolidine-1-carbonyl]thieno[3,2-b]pyridine 4b (157 mg, 0.5 mmole) with 6-hydroxy-1,2-dimethyl-1H-indole-3-carboxylic acid methylamide 16e (150 mg, 0.7 mmole) and Cs_2CO_3 (673 mg, 2.1 mmole) in a manner as previously described for example 1 to give 51mg (39%) of a crisp foam. ^1H NMR (DMSO-d_6) δ 8.54 (1H, dd, J = 5.5, 1.13 Hz), 8.05 (1H, s), 7.84 (1H, d, J = 8.6 Hz), 7.61-7.55 (1H, m), 7.54 (1H, d, J = 2.1 Hz), 7.03(1H, dd, J = 2.1, 8.6 Hz), 6.64 (1H, d, J = 5.5 Hz), 4.12-3.51 (5H, m), 3.67 (3H, s), 3.27, 3.24 (3H, 2s) , 2.80 (3H, d, J = 4.5 Hz), 2.60 (3H, s), 2.35-1.95 (2H, m). *Anal.* Calcd for $C_{25}H_{28}N_4O_4S$•0.9 H_2O•0.2 EtOAc: C, 60.47; H, 5.78; N, 10.93; S, 6.26. Found: C, 60.46; H, 5.56; N, 10.81; S, 6.34.

Example 19: 1,2-dimethyl-6-(2-[3-hydroxy-pyrrolidine-1-carbonyl]thieno[3,2-b]pyridin-7-yloxy)-1H-indole-3-carboxylic acid methylamide



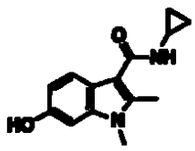
This material was prepared from 1,2-dimethyl-6-(2-[3-methoxy-pyrrolidine-1-carbonyl]thieno[3,2-b]pyridin-7-yloxy)-1H-indole-3-carboxylic acid methylamide 18 (126mg, 0.27mmole) by treatment with BBr_3 in a manner as previously described for example 1d to give 70mg (56%) of a white solid. ^1H NMR (DMSO-d_6) δ 8.54 (1H, dd, J = 5.3, 1.1 Hz), 8.05, 7.99 (1H, 2s), 7.83 (1H, d, J = 8.6 Hz), 7.61-7.55 (1H, m), 7.54 (1H, d, J = 2.2 Hz), 7.03(1H, dd, J = 2.2, 8.6 Hz), 6.64 (1H, dd, J = 5.3, 1.1 Hz), 5.10-5.05 (1H, m), 4.41-4.31 (1H, m), 4.00-3.90 (1H, m), 3.67 (3H, s), 3.66-3.42 (3H, m), 2.80 (3H, d, J = 4.5 Hz), 2.60 (3H, s), 2.06-1.92 (2H, m). *Anal.* Calcd for $C_{24}H_{24}N_4O_4S$•0.9 H_2O: C, 59.96; H, 5.41; N, 11.65; S, 6.67. Found: C, 59.87; H, 5.19; N, 11.51; S, 6.48.

Example 20(a): 6-Methoxy-1,2-dimethyl-1H-indol-3-carboxylic acid cyclopropylamide



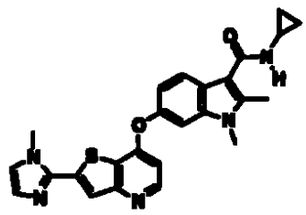
This material was prepared from 1,2-dimethyl-6-methoxy1H-indole-3-carboxylic acid 16c (500 mg, 2.3 mmole), oxalyl chloride (0.4 ml, 4.6 mmole) and cyclopropylamine (1.6 ml, 23 mmole) in a manner as previously described for example 16d to give 480mg (82%) of a white solid. ^{1}H NMR (DMSO-d_6 δ 7.57 (1H, d, J = 3.8 Hz), 7.50 (1H, d, J = 8.8 Hz), 6.99 (1H, d, J = 2.3 Hz), 6.71 (1H, dd , J = 2.3, 8.8 Hz), 3.78 (3H, s), 3.63 (3H, s), 2.83-2.80 (1H, m), 2.51 (3H, s), 0.68-0.62 (2H, m), 0.57-0.53 (2H, m).

Example 20(b): 6-Hydroxy-1,2-dimethyl-1H-indol-3-carboxylic acid cyclopropylamide



This material was prepared from 6-methoxy-1,2-dimethyl-1H-indole-3-carboxylic acid cyclopropylamide 20a (655mg, 2.5 mmole) by treatment with BBr_3 in a manner as previously described for example 1d to give 130mg (21%) of a white solid. ^{1}H NMR (DMSO-d_6) δ 9.08 (1H, s), 7.51 (1H, d, J = 4.0 Hz), 7.41 (1H, d, J = 8.5 Hz), 6.73 (1H, d, J = 1.8 Hz), 6.60 (1H, dd, J = 1.8, 8.5 Hz), 3.56 (3H, s), 2.82 (1H, m), 2.50 (3H, s), 0.62 (2H, m), 0.52 (2H, m).

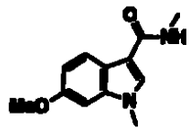
Example 20: 1,2-Dimethyl-6-[2-(1-methyl-1H-imidazol-2-yl)-thieno[3,2-b]pyridin-7-yloxy]-1H-indole-3-carboxylic acid cyclopropylamide



This material was prepared by the reaction of 7-chloro-2-(1-methyl-1H-imidazol-2-yl)thieno[3,2-b]pyridine 1e (79 mg, 0.3mmole) with 1,2-dimethyl-6-hydroxy-1H-indole-3-carboxylic acid cyclopropylamide 20b (93 mg, 0.4 mmole) and Cs_2CO_3 (517 mg, 1.6 mmole) in a manner as previously described for example 1 to give 84 mg (58%) of a white solid. ^{1}H NMR (DMSO-d_6) δ 8.47 (1H, d, J = 4.9 Hz), 7.87 (1H, s), 7.78 (1H, d, J = 3.7 Hz), 7.72 (1H, d, J = 8.5 Hz), 7.52 (1H, s), 7.40 (1H, s), 7.02 (1H, s), 7.01 (1H, d, J = 8.9 Hz), 6.58 (1H, d, J = 5.3 Hz), 3.98 (3H, s), 3.67 (3H, s), 2.85 (1H, m), 2.57 (3H, s), 0.68 (2H, m), 0.58 (2H, m).

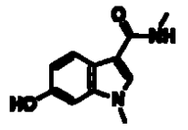
Anal. Calcd for $C_{25}H_{23}N_5O_2S$•0.5 MeOH: C, 64.67; H, 5.32; N, 14.78; S, 6.77.
Found: C, 64.57; H, 5.24; N, 14.72; S, 6.81

Example 21(a): 6-methoxy-1-methyl-*1H*-indole-3-carboxylic acid methylamide



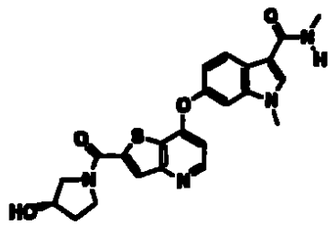
This material was prepared from 6-methoxy-1-methyl-indole-3-carboxylic acid 16b (515 mg, 2.5 mmole), oxalyl chloride (0.9 ml, 12.6 mmole) and methylamine (7.5 mmole) in a manner as previously described for example 16d to give 457 mg of a pale brown solid (83%). ^{1}H NMR (CD_3OD) δ 7.83 (1H, d, J = 8.7 Hz), 7.51 (1H, s), 6.81 (1H, d, J = 2.3 Hz), 6.72 (1H, dd, J = 2.3, 8.7 Hz), 3.75 (3H, s), 3.67 (3H, s), 2.80 (3H, s); ESIMS (MH^+): 219.05.

Example 21(b): 6-hydroxy-1-methyl-*1H*-indole-3-carboxylic acid methylamide



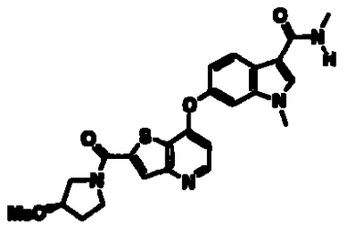
This material was prepared from 6-methoxy-1-methyl-1H-indole-3-carboxylic acid methylamide 21a (453 mg, 2.1 mmol) by treatment with BBr_3 in a manner as previously described for example 1d to give 219 mg (51%) of a pale orange solid. ^{1}H NMR (CD_3OD) δ 7.75 (1H, d, J = 8.5 Hz), 7.47 (1H, s), 6.61-6.66 (2H, m), 3.62 (3H, s), 3.24 (1H, s), 2.79 (3H, s). ESIMS (MH^+): 205.10.

Example 21: 6-[2-[3-(R)-hydroxy-pyrrolidine-1-carbonyl]thieno[3,2-*b*]pyridin-7-yloxy]-1-methyl-1*H*-indole-3-carboxylic acid methylamide



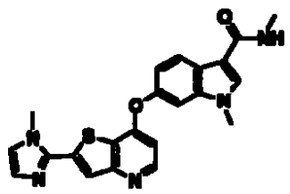
This material was prepared by the reaction of 7-chloro-2-[(R)-3-hydroxypyrrolidine-1-carbonyl]thieno[3,2-b]pyridine 4a (152 mg, 0.5 mmole) with 6-hydroxy-1-methyl-1H-indole-3-carboxylic acid methylamide 21b (110 mg, 0.5 mmole) and Cs_2CO_3 (176 mg, 0.5 mmole) in a manner as previously described for example 1 to give 65 mg (27%) of a white solid. ^{1}H NMR (CD_3OD) δ 8.39 (1H, d, J = 5.5 Hz), 8.12 (1H, d, J = 8.7 Hz), 7.77 (1H, d, J = 17.33 Hz), 7.72 (1H, s), 7.32 (2H, m), 6.99 (dd, 1H, J_1 = 6.59 Hz, J_2 = 2.08 Hz), 6.60 (1H, d, J = 5.5 Hz), 4.43 (m, 1H), 3.95 (1H, m), 3.73 (3H, s), 3.59-3.69 (3H, m), 2.83 (3H, s), 2.01 (2H, m). ESIMS (MH^+): 451.10; *Anal.* Calcd. For $C_{22}H_{22}N4O_4S$•0.6 CH_3OH•0.2 CH_2Cl_2: C, 57.91; H, 5.02; N, 11.35. Found: C, 57.68; H, 5.06; N, 11.43.

Example 22: 6-[2-(3-methoxypyrroildine-1-carbonyl)-thieno[3,2-b]pyridin-7-yloxy]-1-methyl-1H-indole-3-carboxylic acid methylamide



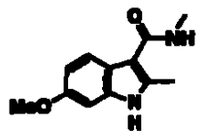
This material was prepared by the reaction of 7-chloro-2-[(R)-3-methoxypyrrolidine-1-carbonyl]thieno[3,2-b]pyridine 4b with 6-hydroxy-1-methyl-1H-indole-3-carboxylic acid methylamide 21b and Cs_2CO_3 in a manner as previously described for example 1. ^1H NMR (300 MHz, CD_3OD) δ 8.53 (1H, d, J = 5.5 Hz), 8.25 (1H, d, J = 8.7 Hz), 7.96 (1H, d, J = 6.2 Hz), 7.86 (1H, s), 7.46 (1H, d, J = 1.9 Hz), 7.12 (1H, d, J = 8.5 Hz), 6.74 (1H, d, J = 5.5 Hz), 4.19-4.11 (1H, m), 4.05-3.95 (2H, m), 3.38 (3H, s), 3.85-3.72 (2H, m), 3.40 (3H, d, J= 13.9 Hz), 2.96 (3H, s), 2.30-2.09 (2H, m). LCMS (ESI+) [M+H]/z Calc'd 465, found 465. *Anal.* ($C_{24}H_{24}N_4O_4S$•0.4CH_2Cl_2) C, H, N.

Example 23: 1-Methyl-6-[2-(1-methyl-1H-imidazol-2-yl)-thieno[3,2-b]pyridin-7-yloxy]-1H-indole-3-carboxylic acid methylamide



This material was prepared by the reaction of 7-chloro-2-(1-methyl-1H-imidazol-2-yl)thieno[3,2-b]pyridine 1e with 6-hydroxy-1-methyl-1H-indole-3-carboxylic acid methylamide 21b and Cs_2CO_3 in a manner as previously described for example 1. ^1H NMR (300 MHz, $CDCl_3$) δ 8.43 (1H, d, J = 5.5 Hz), 8.05 (1H, d, J = 8.7 Hz), 7.67 (1H, s), 7.61 (1H, s), 7.17 (1H, d, J = 2.1 Hz), 7.13 (1H, s), 7.08 (1H, dd, J = 2.1, 8.7 Hz), 7.02 (1H, s), 6.54 (1H, d, J = 5.5 Hz), 3.95 (3H, s), 3.75 (3H, s), 3.01 (3H, s). LCMS (ESI+) [M+H]/z Calc'd 418, found 418. *Anal.* ($C_{22}H_{19}N_5O_2S$•0.25EtOAc) C, H, N.

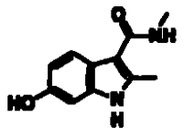
Example 24(a): 6-Methoxy-2-methyl-1H-indol-3-carboxylic acid methylamide



To a stirred solution of 6-methoxy-2-methyl-1H-indole (500mg, 3.1 mmol) (prepared according to JACS 1988, 110, 2242) in 8 mL anhydrous THF maintained at room temperature was added methylmagnesium bromide (1.13 ml, 3.0 M solution in diethyl ether, 3.41 mmol). After stirring for 1 hour at room temperature, a solution of 0.5M zinc chloride in THF (7.44 ml, 3.72 mmol) was introduced and the mixture was stirred for 1 hour at room temperature before

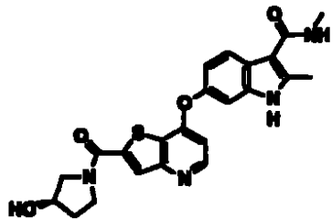
addition of methyl isocyanate (424 mg, 7.44 mmol). The resulting mixture was stirred at ambient temperature overnight, quenched with water, and extracted with EtOAc. The combined organic layer was washed with brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by flash column chromatography eluting with 2-5% MeOH in CH_2Cl_2 to give 200 mg product (30% yield). ^1H NMR (300 MHz, CD_3OD) δ 7.55 (1H, d, J=8.6 Hz), 6.78 (1H, d, J = 2.2 Hz), 6.70 (1H, dd, J = 2.2, 8.6 Hz), 3.73 (3H, s), 2.80 (3H, s), 2.52 (3H, s). LCMS (ESI+) [M+H]/z Calc'd 219, found 219.

Example 24(b): 6-Hydroxy-2-methyl-1H-indol-3-carboxylic acid methylamide



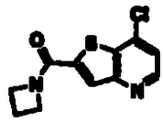
This material was prepared from 6-methoxy-2-methyl-1H-indol-3-carboxylic acid methylamide 24a by treatment with BBr_3 in a manner as previously described for example 1d. ^1H NMR (300 MHz, CD_3OD) δ 7.52 (1H, d, J = 8.7 Hz), 6.72 (1H, d, J = 2.3 Hz), 6.65 (1H, dd, J = 2.3, 8.7 Hz), 2.93 (3H, s), 2.55 (3H, s). LCMS (ESI+) [M+H]/z Calc'd 205, found 205.

Example 24: 6-[2-(3-Hydroxy-pyrrolidine-1-carbonyl)-thieno[3,2-b]pyridin-7-yloxy]-2-methyl-1H-indole-3-carboxylic acid methylamide



This material was prepared by the reaction of 7-chloro-2-[(R)-3-hydroxypyrrolidine-1-carbonyl]thieno[3,2,-b]pyridine 4a with 6-hydroxy-2-methyl-1H-indol-3-carboxylic acid methylamide and Cs_2CO_3 in a manner as previously described for Example 1. ^1H NMR (300 MHz, CD_3OD) δ 8.46 (1H, d, J = 5.5 Hz), 7.91 (1H, d, J = 17.3 Hz), 7.86 (1H, d, J = 8.6 Hz), 7.21 (1H, s), 7.00 (1H, d, J = 8.6 Hz), 6.89 (1H, d, J = 5.5 Hz), 4.50 (1H, m), 4.05-3.70 (4H, m), 2.97 (3H, s), 2.63 (3H, s), 2.40-1.90 (2H, m). LCMS (ESI+) [M+H]/z Calc'd 451, found 451.

Example 25 (a): 2-(Azetidin-1-ylcarbonyl)-7-chlorothieno[3,2-*b*]pyridine

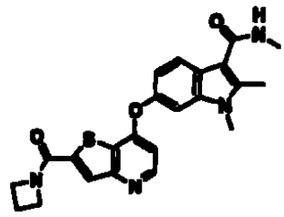


This material was prepared from lithium 7-chlorothieno[3,2-*b*]pyridine-2-carboxylate (100 mg, 0.47 mmole) by treatment with thionyl chloride followed by coupling with azetidine, in a manner as previously described for example 9d to afford 98 mg (83%) of a dark yellow

solid. ^{1}H NMR (DMSO-d_6) δ 8.72 (1H, d, J = 5.1 Hz), 7.96 (1H, s), 7.70 (1H, d, J = 5.1 Hz), 4.62 (2H, t, J = 7.4 Hz), 4.12 (2H, t, J = 7.7 Hz), 2.34 (2H, tt, J = 7.4, 7.7 Hz).

Anal. Calcd for $C_{11}H_9N_2OSCl$: C, 52.28; H, 3.59; Cl, 14.03; N, 11.09; S, 12.69. Found: C, 52.39; H, 3.63; Cl, 14.29; N, 10.99; S, 12.74.

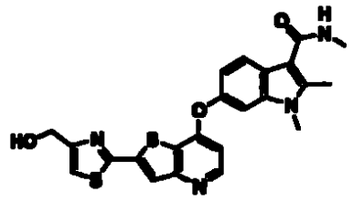
Example 25: 6-[2-(Azetidine-1-carbonyl)-thieno[3,2-*b*]pyridin-7-yloxy]-1,2-dimethyl-3*H*-indole-3-carboxylic acid methylamide



This material was prepared by the reaction of 2-(azetidin-1-ylcarbonyl)-7-chlorothieno[3,2-*b*]pyridine 25a with 6-hydroxy-1,2-dimethyl-1H-indole-3-carboxylic acid methylamide 16e and Cs_2CO_3 in a manner as previously described for example 1. ^{1}H NMR (300 MHz, CD_3OD) δ 8.41 (1H, d, *J* = 5.5 Hz), 7.80 (1H, d, *J* = 3.20 Hz), 7.74 (1H, d, *J* = 11.88 Hz), 7.30 (1H, s), 6.94 (1H, d, *J* = 8.88 Hz), 6.62 (1H, d, *J* = 5.5 Hz), 4.64-4.59 (2H, m), 4.20-4.15 (2H, m), 3.63 (3H, s), 2.85 (3H, s), 2.57 (3H, s), 2.44-2.36 (2H, m). LCMS (ESI+) [M+H]/z Calc'd 435, found 435.

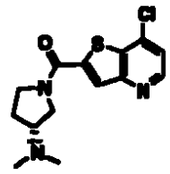
Anal. ($C_{23}H_{22}N_4O_3S$•0.35CH_2Cl_2) C, H, N.

Example 26: 1,2-Dimethyl-6-(2-[4-(hydroxymethyl)thiazol-2-yl]thieno[3,2-*b*]pyridin-7-yloxy)-1*H*-indole-3-carboxylic acid methylamide



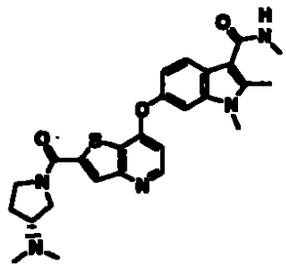
This material was prepared by the reaction of [2-(7-chloro-thieno[3,2-*b*]pyridin-2-yl)-thiazol-4-yl]-methanol with 6-hydroxy-1,2-dimethyl-1*H*-indole-3-carboxylic acid methyl amide 16e and Cs_2CO_3 in a manner as previously described for example 1. ^{1}H NMR (300 MHz, DMSO- d_6) δ 8.52 (1H, d, *J* = 5.5 Hz), 8.14 (1H, s), 7.83 (1H, d, *J* = 8.8 Hz), 7.83 (1H, s), 7.58 (1H, d, *J* = 4.7 Hz), 7.54 (1H, d, *J* = 2.0 Hz), 7.04 (1H, dd, *J* = 2.0, 8.8 Hz), 6.84 (1H, d, *J* = 5.5 Hz), 4.60 (2H, s), 3.67 (3H, s), 2.80 (3H, d, *J* = 4.3 Hz), 2.61 (3H, s). LCMS (ESI+) [M+H]/z Calc'd 465, found 465. *Anal.* ($C_{23}H_{20}N_4O_3S_2$•0.6CH_3OH) C, H, N.

Example 27(a): (3*R*)-1-[(7-Chlorothieno[3,2-*b*]pyridin-2-yl)carbonyl]-*N*,*N*-dimethylpyrrolidin-3-amine



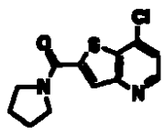
This material was prepared from lithium 7-chlorothieno[3,2-*b*]pyridine-2-carboxylate (0.214 g, 1.0 mmole) by treatment with thionyl chloride followed by reaction of the resultant acyl chloride with (3*R*)-*N*,*N*-dimethylpyrrolidin-3-amine (0.114g, 1.0 mmole) and Et_3N (0.139 ml, 1.0 mmole), in a manner as previously described for example 9d to give a brown solid (0.134g, 43%). ^1H NMR (300 MHz, CD_3OD) δ 7.24 (1H, d, *J* = 5.1 Hz), 6.57 (1H, d, *J* = 8.48 Hz), 6.15 (1H, d, *J* = 5.1 Hz), 2.70 (1H, m), 2.51 (2H, m), 2.24 (1H, m), 2.04 (1H, m), 1.49 (1H, m), 0.93 (3H, s), 0.90 (3H, s), 0.52 (1H, m); ESIMS (MH^+): 310.10.

Example 27: 6-[(2-[[(3*R*)-3-(Dimethylamino)pyrrolidin-1-yl]carbonyl]thieno[3,2-*b*]pyridin-7-yl)oxy]-*N*,1,2-trimethyl-1*H*-indole-3-carboxamide



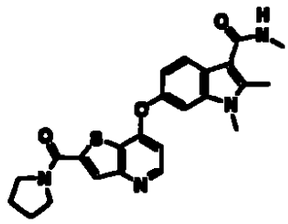
This material was prepared by the reaction (3*R*)-1-[(7-chlorothieno[3,2-*b*]pyridin-2-yl)carbonyl]-*N*,*N*-dimethylpyrrolidin-3-amine 27a (0.138g, 0.44 mmole) with 6-hydroxy-*N*,1,2-trimethyl-1*H*-indole-3-carboxamide 18e (0.064g, 0.294 mmole) and Cs_2CO_3 (0.096g, 0.29 mmole) in a manner as previously described for example 1 to give a brown colored foam (0.059g, 17%). ^1H NMR (300 MHz, CD_3OD) δ 8.40 (1H, d, *J* = 5.46 Hz), 7.84 (1H, d, *J* = 8.59 Hz), 7.76 (1H, d, *J* = 8.67 Hz), 7.29 (1H, d, *J* = 2.07 Hz), 6.95 (1H, dd, *J* = 8.57, 2.17 Hz), 6.82 (1H, d, *J* = 5.65 Hz), 4.06 (1H, m), 3.87 (2H, m), 3.83 (3H, s) 3.03 (2H, m), 2.88 (3H, s), 2.57 (3H, s), 2.37 (3H, s), 2.32 (3H, s), 2.23 (1H, m), 1.95 (1H, m); HRMS (MH^+): Calcd: 492.2085; Found: 492.2069.

Example 28(a): (7-Chloro-thieno[3,2-*b*]pyridin-2-yl)-pyrrolidin-1-yl-methanone



This material was prepared from the coupling of 7-chlorothieno[3,2-*b*]pyridine-2-carboxylic acid and pyrrolidine in a manner as previously described for example 9d. ^{1}H NMR (300 MHz, CD_3OD) δ 8.60 (1H, d, *J* = 5.1 Hz), 7.84 (1H, s), 7.32 (1H, d, *J* = 5.1 Hz), 3.82 (2H, t, *J* = 6.4 Hz), 3.70 (2H, t, *J* = 6.6 Hz), 2.02 (4H, m). LCMS (ESI+) [M+H]/z Calc'd 267, found 267.

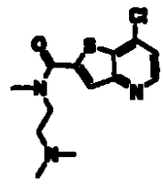
Example 28: 1,2-Dimethyl-6-[2-(pyrrolidine-1-carbonyl)-thieno[3,2-*b*]pyridin-7-yloxy]-1H-indole-3-carboxylic acid methylamide



This material was prepared from the reaction of (7-chloro-thieno[3,2-*b*]pyridin-2-yl)-pyrrolidin-1-yl-methanone 28a with 6-hydroxy-1,2-dimethyl-1*H*-indole-3-carboxylic acid methylamide 16e and Cs_2CO_3 in a manner as previously described for example 1. ^{1}H NMR (300 MHz, CD_3OD) D 8.47 (1H, d, *J* = 5.3 Hz), 7.82 (1H, s), 7.74 (1H, d, *J* = 8.4 Hz), 7.14 (1H, d, *J* = 1.7 Hz), 7.02 (1H, dd, *J* = 1.7, 8.4 Hz), 6.55 (1H, d, *J* = 5.3 Hz), 5.91 (1H, bs), 3.84 (2H, m), 3.70 (2H, m), 3.65 (3H, s), 3.05 (3H, d, *J* = 4.5 Hz), 2.72 (3H, s), 2.02 (4H, m). LCMS (ESI+) [M+H]/z Calc'd 449, found 449.

Anal. ($C_{24}H_{28}N_4O_3S$•0.5CH_3OH) C, H, N.

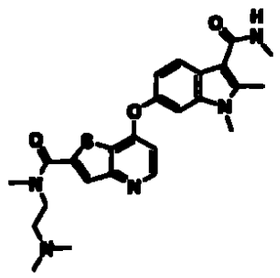
Example 29(a): 7-Chloro-*N*-[2-(dimethylamino)ethyl]-*N*-methylthieno[3,2-*b*]pyridine-2-carboxamide



This material was prepared from lithium 7-chlorothieno[3,2-*b*]pyridine-2-carboxylate (0.957 g, 4.48 mmole) by treatment with thionyl chloride followed by reaction of the resultant acyl chloride with *N,N,N'*-trimethylethane-1,2-diamine (0.640 ml, 4.93 mmole) and Et_3N (0.624

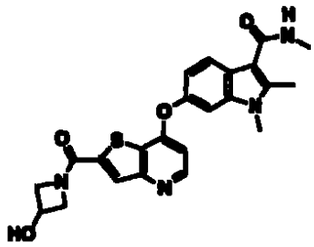
ml, 4.48 mmole), in a manner as previously described for example 9d to give a brown solid (0.167 g, 13%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.60 (1H, d, *J* = 5.1 Hz), 7.74 (1H, s), 7.32 (1H, d, *J* = 5.1 Hz), 3.66 (2H, t, *J* = 6.4 Hz), 3.26 (3H, s), 2.57 (2H, t, *J* = 6.4 Hz), 2.25 (6H, s); ESIMS (MH^+): 298.05.

Example 29: *N*-[2-(Dimethylamino)ethyl]-7-({1,2-dimethyl-3-[(methylamino)carbonyl]-1*H*-indol-6-yl}oxy)-*N*-methylthieno[3,2-*b*]pyridine-2-carboxamide



This material was prepared by the reaction of 7-chloro-*N*-[2-(dimethylamino)ethyl]-*N*-methylthieno[3,2-*b*]pyridine-2-carboxamide 28a (0.167g, 0.56 mmole) with 6-hydroxy-*N*,1,2-trimethyl-1*H*-indole-3-carboxamide 16e (0.123g, 0.56 mmole) and Cs_2CO_3 (0.182g, 0.56 mmole) in a manner as previously described for example 1 to give a yellow solid (0.040g, 13%). ^{1}H NMR (400 MHz, CD_3OD) δ 8.71 (1H, d, *J* = 6.8 Hz), 8.06 (1H, s), 7.83 (1H, d, *J* = 8.6 Hz), 7.46 (1H, d, *J* = 2.0 Hz), 7.09 (1H, d, *J* = 6.8 Hz), 7.05 (1H, dd, *J* = 2.0, 8.6 Hz), 3.90 (2H, t, *J* = 5.8 Hz), 3.64 (3H, s), 3.42 (2H, t, *J* = 5.8 Hz), 3.23 (6H, s), 2.93 (3H, s), 2.88 (3H, s), 2.58 (3H, s). HRMS (MH^+): Calcd: 480.2090; Found: 480.2089.

Example 30: 6-[2-(3-Hydroxy-azetidine-1-carbonyl)-thieno[3,2-*b*]pyridin-7-yloxy]-1,2-dimethyl-1*H*-indole-3-carboxylic acid methylamide

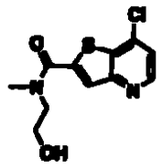


This material was prepared by the reaction of (7-chloro-thieno [3,2-b]pyridin-2-yl)-(3-hydroxy-azetidin-1-yl)-methanone 9d with 6-hydroxy-1,2-dimethyl-1H-indole-3-carboxylic acid methylamide 16e and Cs_2CO_3 in a manner as previously described for example 1. ^{1}H NMR (300 MHz, CD_3OD) δ 8.41 (1H, d, *J* = 5.5 Hz), 7.78-7.74 (2H, m), 7.29 (1H, d, *J* = 2.1Hz), 6.95(1H, dd, *J* = 2.1, 8.6 Hz), 6.62 (1H, d, *J* = 5.5 Hz), 4.76-4.73 (2H, m), 4.63 (1H, bs), 4.35-

4.32 (2H, m), 3.97-3.94(1H, m), 3.62(3H, s), 2.89(3H, s), 2.57 (3H, s). LCMS (ESI+) [M+H]/z Calc'd 451, found 451.

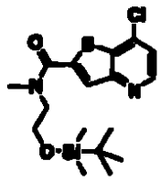
Anal. ($C_{23}H_{22}N_4O_4S \cdot 1.1CH_2Cl_2$) C, H, N.

Example 31(a): 7-Chloro-*N*-(2-hydroxyethyl)-*N*-methylthieno[3,2-*b*]pyridine-2-carboxamide



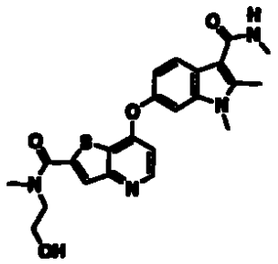
This material was prepared from lithium 7-chlorothieno[3,2-*b*]pyridine-2-carboxylate (1.0 g, 4.68 mmole) by treatment with thionyl chloride followed by reaction of the resultant acyl chloride with 2-(methylamino)ethanol (0.414 ml, 5.15 mmole) and Et_3N (0.718 ml, 5.15 mmole), in a manner as previously described for example 9d to give a pale brown solid (0.624g, 49% yield). ^1H NMR (400 MHz, $CDCl_3$) δ 8.61 (1H, d, J = 4.8 Hz), 7.80 (1H, s), 7.33 (1H, d, J = 4.8 Hz), 3.92 (2H, m), 3.76 (2H, t, J = 5.1 Hz), 3.37 (3H, s), 3.19 (1H, s); ESIMS (MH^+): 259.10.

Example 31(b): *N*-(2-[[*tert*-Butyl(dimethyl)silyl]oxy]ethyl)-7-chloro-*N*-methylthieno[3,2-*b*]pyridine-2-carboxamide



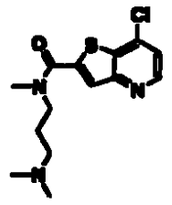
This material was prepared from 7-chloro-*N*-(2-hydroxyethyl)-*N*-methylthieno[3,2-*b*]pyridine-2-carboxamide 31a (1.27 g, 4.68 mmole), t-butyldimethylsilyl chloride (0.705 g, 4.68 mmole) and Et_3N (0.718 ml, 4.68 mmole) in a manner as previously described for 3b to give an orange oil (1.40 g, 78%). ^1H NMR (300 MHz, $CDCl_3$) δ 8.61 (1H, d, J = 5.1 Hz), 7.74 (1H, s), 7.32 (1H, d, J = 5.1 Hz), 3.89 (2H, m), 3.71 (2H, m), 3.37 (3H, s), 0.89 (9H, m), 0.07 (6H, m); ESIMS (MH^+): 385.10.

Example 31: *N*-{(1,2-Dimethyl-3-[(methylamino)carbonyl]-1*H*-inden-6-yl)oxy}-*N*-(2-hydroxyethyl)-*N*-methylthieno[3,2-*b*]pyridine-2-carboxamide



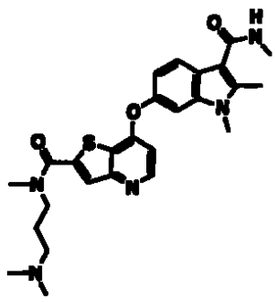
This material was prepared by the reaction of *N*-(2-[[*tert*-butyl(dimethyl)silyl]oxy]ethyl) -7-chloro-*N*-methylthieno[3,2-*b*]pyridine-2-carboxamide 31b (0.133g, 0.35 mmole) with 6-hydroxy-*N*,1,2-trimethyl-1*H*-indole-3-carboxamide 16e (0.76g, 0.35 mmole) and Cs_2CO_3 (0.114g, 0.35 mmole) in a manner as previously described for example 1 to give a mixture of *N*-(2-[[*tert*-butyl(dimethyl)silyl]oxy]ethyl)-7-({1,2-dimethyl-3-[(methylamino)carbonyl]-1*H*-indol-6-yl}oxy)-*N*-methylthieno[3,2-*b*]pyridine-2-carboxamide and 7-({1,2-dimethyl-3-[(methylamino)carbonyl]-1*H*-inden-6-yl}oxy)-*N*-(2-hydroxyethyl)-*N*-methylthieno[3,2-*b*]pyridine-2-carboxamide, which was dissolved in THF (10 ml) and treated with TBAF (0.7 ml) for 2 h. The reaction mixture was quenched with H_2O and partitioned between CH_2Cl_2 (50x2 ml) and H_2O (50 ml). The combined organic layers were dried over $MgSO_4$ and concentrated. The residue was purified by flash column chromatography eluting with 5-8% CH_3OH in CH_2Cl_2 to give an off-white solid (0.064g, 41% yield). ^1H NMR (400 MHz, CD_3OD) δ 8.38 (1H, d, J = 5.4 Hz), 7.76 (2H, m), 7.29 (1H, s), 6.95 (1H, dd, J = 2.1, 8.7 Hz), 6.81 (1H, d, J = 5.4 Hz), 3.72 (2H, m), 3.62 (3H, s), 3.22 (3H, s), 3.12 (2H, m), 2.88 (3H, s), 2.57 (3H, s); HRMS (MH^+): Calcd: 453.1606; Found: 453.1597.

Example 32(a): 7-Chloro-*N*-[3-(dimethylamino)propyl]-*N*-methylthieno[3,2-*b*]pyridine-2-carboxamide



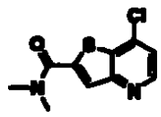
This material was prepared from 7-chlorothieno[3,2-*b*]pyridine-2-carboxylic acid (1.0 g, 4.68 mmole), $SOCl_2$ (10 ml), *N*,*N*,*N*-trimethylpropane-1,3-diamine (0.668 ml, 4.68 mmole) and Et_3N (1.96 ml, 14.04 mmole) in a manner as previously described for example 9d to give a white foam (1.07g, 77%). ^1H NMR (300 MHz, CD_3OD) δ 8.56 (1H, d, J = 5.2 Hz), 7.76 (1H, s), 7.46 (1H, d, J = 5.2 Hz), 3.51 (2H, m), 3.20 (3H, s), 2.33 (2H, m), 2.18 (6H, s), 1.79 (2H, m); ESIMS (MH^+): 312.05.

Example 32: *N*-[3-(Dimethylamino)propyl]-7-({1,2-dimethyl-3-[(methylamino)carbonyl]-1*H*-indol-6-yl}oxy)-*N*-methylthieno[3,2-*b*]pyridine-2-carboxamide



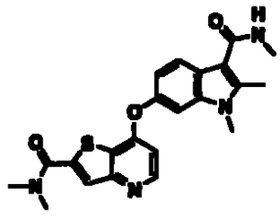
This material was prepared by the reaction of 7-chloro-*N*-[3-(dimethylamino)propyl]-*N*-methylthieno[3,2-*b*]pyridine-2-carboxamide 32a (0.095g, 0.32 mmole) with 6-hydroxy-*N*,1,2-trimethyl-1*H*-indole-3-carboxamide (0.070g, 0.32 mmole) 16e and Cs_2CO_3 (0.104g, 0.32 mmole) in a manner as described previously for example 1 to give a white solid (0.098g, 62%). ^{1}H NMR (300 MHz, CD_3OD) δ 8.53 (1H, d, *J* = 5.3 Hz), 7.91 (2H, m), 7.38 (1H, s), 7.09 (1H, dd, *J* = 2.1, 8.7 Hz), 6.81(1H, d, *J* = 5.3 Hz), 3.73 (3H, s), 3.66 (2H, m), 3.28 (2H, m), 3.01 (3H, s), 2.68 (9H, m), 2.06 (2H, m), 1.94(3H, s); HRMS (MH^+): Calcd: 494.2223; Found: 494.2226.

Example 33(a): 7-Chloro-*N*,*N*-dimethylthieno[3,2-*b*]pyridine-2-carboxamide



This material was prepared from 7-chlorothieno[3,2-*b*]pyridine-2-carboxylic acid (0.57g, 2.67 mmole), $SOCl_2$ (5 ml), 2.0 M *N*,*N*-dimethylamine in THF (1.60 ml, 3.20 mmole) and Et_3N (0.447 ml, 3.20 mmole) in a manner as previously described for example 9d to give a brown solid (0.54g, 84%). ^{1}H NMR (300 MHz, $CDCl_3$) δδ 1H, d, *J* = 5.0 Hz), 7.74 (1H, s), 7.35 (1H, d, *J* = 5.0 Hz), 3.28 (3H, s), 3.22 (3H, s); ESIMS (MH^+): 240.95.

Example 33: 7-({1,2-Dimethyl-3-[(methylamino)carbonyl]-1*H*-indol-6-yl}oxy)-*N*,*N*-dimethylthieno[3,2-*b*]pyridine-2-carboxamide

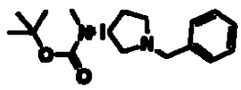


This material was prepared by the reaction 7-chloro-*N*,*N*-dimethylthieno[3,2-*b*]pyridine-2-carboxamide 33a (0.077g, 0.32 mmole) and 6-hydroxy-*N*,1,2-trimethyl-1*H*-indole-3-carboxamide 16e (0.070g, 0.32mmole) and Cs_2CO_3 (0.104g, 0.32 mmole) in a manner as

previously described for example 1 to give a pale yellow solid (0.098g, 73%). ^{1}H NMR (300 MHz, CD_3OD) δ 8.38 (1H, d, *J* = 5.5 Hz), 7.75 (1H, d, *J* = 8.7 Hz), 7.66 (1H, s), 7.28 (1H, d, *J* = 2.1 Hz), 6.94 (1H, dd, *J* = 2.1, 8.7 Hz), 6.60 (1H, d, *J* = 5.5 Hz), 3.61 (3H, s), 3.21 (6H, m), 2.67 (3H, s), 2.56 (3H, s). ESIMS (MH^+): 423.05.

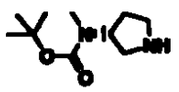
Anal. Calcd. For $C_{22}H_{22}N_4O_3S0.8H_2O$: C, 59.21; H, 5.28; N, 12.44; Found: C, 59.20; H, 5.28; N, 12.44.

Example 34(a): Benzyl (3*R*)-3-[(*tert*-butoxycarbonyl)(methyl)amino]pyrrolidine-1-carboxylate



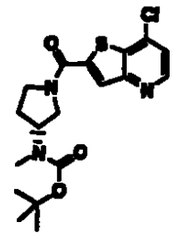
Boc_2O (1.26 g, 5.76 mmole) and DMAP (6.4 mg, 0.053 mmole) was added to a solution of *tert*-butyl methyl[(3*R*)-pyrrolidin-3-yl]carbamate (1.0g, 5.26 mmole). The reaction mixture was stirred at room temperature overnight and was partitioned between CH_2Cl_2 (2x100 ml) and H_2O (100 ml). The combined organic layers were dried over $MgSO_4$ and concentrated. The residue was purified by flash column chromatography eluting with 1-2% CH_3OH in CH_2Cl_2 to give a pale yellow oil (1.51 g, 99%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30 (5H, m), 3.56 (2H, m), 2.82 (3H, s), 2.76 (2H, m), 2.53 (2H, m), 2.33 (1H, m), 2.09 (1H, m), 1.73 (1H, m), 1.42 (9H, m); ESIMS (MH^+): 291.20.

Example 34(b): *tert*-Butyl methyl[(3*R*)-pyrrolidin-3-yl]carbamate



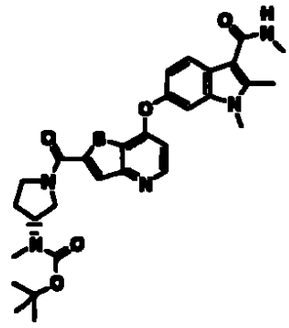
To a stirred solution of benzyl (3*R*)-3-[(*tert*-butoxycarbonyl)(methyl)amino]pyrrolidine-1-carboxylate 34a (1.5 g, 5.17 mmole) in MeOH (10 ml) was added $Pd(OH)_2$ on carbon (150 mg). The reaction mixture was under 1 atmosphere of H_2 overnight, filtered through celite and concentrated, *in vacuo*. The residue obtained was used directly in the subsequent reaction without any further purification, *vide infra*. ^{1}H NMR (300 MHz, CD_3OD) δ 4.47 (1H, m), 3.20 (1H, m), 2.91 (2H, m), 2.76 (1H, m), 2.69 (3H, s), 1.89 (1H, m), 1.68 (1H, m), 1.35 (9H, s).

Example 34(c): *tert*-Butyl (3*R*)-1-[(7-chlorothieno[3,2-*b*]pyridin-2-yl)carbonyl]pyrrolidin-3-yl(methyl)carbamate



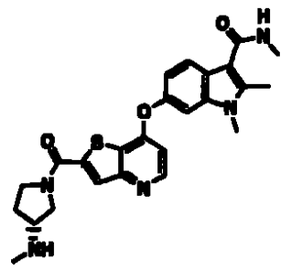
This material was prepared from 7-chlorothieno[3,2-*b*]pyridine-2-carboxylic acid (1.05g, 4.94 mmole), $SOCl_2$ (10 ml), *tert*-butyl methyl[(3*R*)-pyrrolidin-3-yl]carbamate 34b (0.989g, 4.94 mmole) and Et_3N (0.689 ml, 4.94 mmole) in a manner as previously described for example 8d to give a brown oil (0.723g, 0.30%). ^1H NMR (300 MHz, $CDCl_3$) δ 8.62 (1H, d, J = 5.1 Hz), 7.85 (1H, s), 7.35 (1H, d, J = 5.1 Hz), 4.82 (1H, m), 3.93 (3H, m), 3.63 (1H, m), 2.82 (3H, s), 2.12 (2H, m), 1.47 (9H, s); ESIMS (MH^+): 396.05.

Example 34: *tert*-Butyl-(3*R*)-1-[[7-({1,2-dimethyl-3-[(methylamino)carbonyl]-1*H*-indol-6-yl}oxy)thieno[3,2-*b*]pyridin-2-yl]carbonyl]pyrrolidin-3-yl(methyl)carbamate



This material was prepared by the reaction of *tert*-butyl (3*R*)-1-[(7-chlorothieno[3,2-*b*]pyridin-2-yl)carbonyl]pyrrolidin-3-yl(methyl)carbamate 34c (0.181g, 0.46 mmole) with 6-hydroxy-*N*,1,2-trimethyl-1*H*-indole-3-carboxamide 16e (0.10 g, 0.46 mmole) and Cs_2CO_3 (0.149g, 0.46 mmole) in a manner as previously described for example 1 to give a yellow solid (0.105g, 40%). ^1H NMR (300 MHz, $CDCl_3$) δ 8.48 (1H, d, J = 5.4 Hz), 7.82 (1H, s), 7.75 (1H, d, J = 8.7 Hz), 7.15 (1H, d, J = 2.1 Hz), 7.02 (1H, dd, J = 2.1, 8.7 Hz), 6.56 (1H, d, J = 5.4 Hz), 5.91 (1H, d, J = 4.7 Hz), 4.82 (1H, m), 4.07 (2H, m), 3.87 (1H, m), 3.68 (1H, m), 3.65 (3H, s), 3.05 (3H, d, J = 4.7 Hz), 2.84 (3H, s), 2.73 (3H, s), 2.17 (2H, m), 1.45 (9H, s); HRMS (MH^+): Calcd: 578.2450; Found: 578.2437.

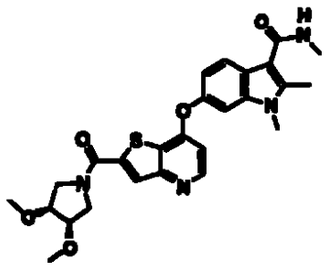
Example 35: 1,2-Dimethyl-6-[2-(3-methylamino-pyrrolidine-1-carbonyl)-thieno[3,2-*b*]pyridin-7-yloxy]-1*H*-indole-3-carboxylic acid methylamide



4N HCl in 1,4-dioxane (1.0 ml) was added to a solution of *tert*-butyl (3*R*)-1-[[7-({1,2-dimethyl-3-[(methylamino)carbonyl]-1*H*-indol-6-yl}oxy)thieno[3,2-*b*]pyridin-2-yl]carbonyl}pyrrolidin-3-yl(methyl)carbamate 34 (0.090 g, 0.16 mmole) in 1,4-dioxane (5 ml). The reaction mixture was stirred at room temperature for 3hr., then concentrated, *in vacuo*. The residue was purified by reverse phase chromatography eluting with 10-60% CH_3CN in H_2O to give a white solid (0.020 g, 26%). ^1H NMR (300 MHz, $CDCl_3$) δ 8.54 (1H, d, J = 5.3 Hz), 8.01 (1H, s), 7.83 (1H, d, J = 8.7 Hz), 7.53-7.57 (2H, m), 7.03 (1H, dd, J = 1.9, 8.7 Hz), 6.63 (1H, d, J = 5.3 Hz), 3.86-3.99 (2H, m), 3.67 (3H, s), 3.61 (1H, m), 3.29 (3H, m), 2.80 (3H, d, J = 4.50 Hz), 2.61 (3H, s), 2.30 (3H, d, J = 10.55 Hz), 1.78-1.83 (1H, m); ESIMS (MH^+): 478.10.

Anal. Calcd. For $C_{25}H_{27}N_5O_2S$•1.2 CH_2Cl_2: C, 54.30; H, 5.11; N, 12.09; Found: C, 53.95; H, 5.52; N, 11.96.

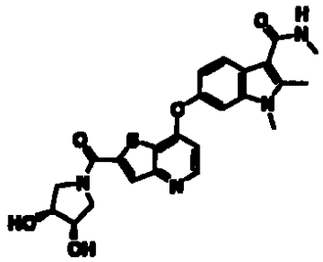
Example 36: 6-[2-(3,4-Dimethoxy-pyrrolidine-1-carbonyl)-thieno[3,2-*b*]pyridin-7-yloxy]-1,2-dimethyl-1*H*-indole-3-carboxylic acid methylamide (36).



This material was prepared by the reaction of 7-chloro-2-[[(3*R*,4*S*)-3,4-dimethoxypyrrolidin-1-yl]carbonyl]thieno[3,2-*b*]pyridine 5d (0.152g, 0.47 mmole) with 6-hydroxy-*N*,1,2-trimethyl-1*H*-indole-3-carboxamide 16e (0.102g, 0.47 mmole) and Cs_2CO_3 (0.153g, 0.47 mmole) in a manner as previously described for example 1 to give an off-white solid (0.093g, 39%). ^1H NMR (300 MHz, $CDCl_3$) δ 8.42 (1H, d, J = 5.3 Hz), 7.84 (1H, s), 7.77 (1H, dd, J = 3.8, 8.7 Hz), 7.31 (1H, d, J = 2.30 Hz), 3.97 (1H, dd, J = 2.3, 8.7 Hz), 6.63 (1H, d, J = 5.3 Hz), 4.04 (4H, m), 3.66 (2H, m), 3.64 (3H, s), 3.42 (3H, s), 3.36 (3H, s), 2.90 (3H, s), 2.69 (3H, s); ESIMS (MH^+): 409.15.

Anal. Calcd. For $C_{28}H_{28}N_4O_5S$•0.2 CH_2Cl_2•0.5EtOAc: C, 59.46; H, 5.73; N, 9.84; Found: C, 59.09; H, 5.95; N, 9.93.

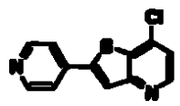
Example 37: 6-[2-(3,4-Dihydroxy-pyrrolidine-1-carbonyl)-thieno[3,2-*b*]pyridin-7-yloxy]-1,2-dimethyl-1*H*-indole-3-carboxylic acid methylamide (37).



This material was prepared by treating 6-[(2-[[(3*R*,4*S*)-3,4-dimethoxypyrrolidin-1-yl]carbonyl)thieno[3,2-*b*]pyridin-7-yl)oxy]-1,2-dimethyl-1*H*-indole-3-carboxylic acid methylamide 36 (0.065g, 0.13 mmole) with 1.0 M BBr_3 in CH_2Cl_2 (0.070 ml, 0.77 mmole) in a manner as described previously for example 1d to give a white solid (0.017g, 33%). ^{1}H NMR (300 MHz, CD_3OD) δ 8.38 (1H, d, *J* = 5.5 Hz), 7.79 (2H, m), 7.28 (1H, d, *J* = 2.1 Hz), 6.94 (1H, dd, *J* = 2.1, 8.7 Hz), 6.60 (1H, d, *J* = 5.5 Hz), 5.07-5.13 (2H, m), 4.41 (1H, m), 3.95 (2H, m), 3.70 (1H, m), 3.61 (3H, s), 2.55 (3H, m), 1.90 (3H, s); ESIMS (MH^+): 481.10.

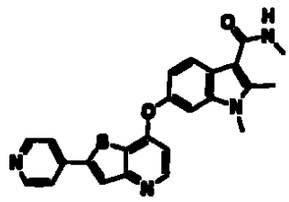
Anal. Calcd. For $C_{24}H_{24}N_4O_5S$•0.2CH_2Cl_2•H_2O: C, 56.38; H, 5.16; N, 10.87; Found: C, 56.36; H, 5.09; N, 10.80.

Example 38(a): 7-Chloro-2-pyridin-4-ylthieno[3,2-*b*]pyridine



Tetrakis(triphenylphosphine)palladium (54 mg, 0.05 mmole) was added to a solution of 4-(tributylstannyl)pyridine (0.432 g, 1.17 mmole) and 7-chloro-2-iodothieno[3,2-*b*]pyridine (0.347 g, 1.17 mmole) in DMF (5ml). The reaction mixture was stirred at reflux for 3h, cooled to room temperature. The mixture was filtered, washed with CH_2Cl_2 and was partitioned between H_2O (50 ml) and CH_2Cl_2 (2x50 ml). The combined organic layers were dried over $MgSO_4$ and concentrated. The residue was purified by flash column chromatography eluting with 30-60% EtOAc in hexane to give pale yellow color solid (0.103 g, 36%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.61 (1H, d, *J* = 5.1 Hz), 7.95 (1H, s), 7.86 (2H, m), 7.44 (2H, m), 7.31 (1H, d, *J* = 5.1 Hz); ESIMS (MH^+): 481.10.

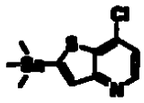
Example 38: 1,2-Dimethyl-6-(2-pyridin-4-yl-thieno[3,2-*b*]pyridin-7-yloxy)-1*H*-indole-3-carboxylic acid methylamide



This material was prepared by the reaction 7-chloro-2-pyridin-4-ylthieno[3,2-*b*]pyridine 38a (0.103g, 0.42 mmole) with 6-hydroxy-*N*,1,2-trimethyl-1*H*-indole-3-carboxamide 16e (0.070g, 0.32 mmole) and Cs_2CO_3 (0.104 g, 0.32 mmole) in a manner as previously described for example 1 to give an off-white solid (0.055g, 31%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.70 (2H, m), 8.52 (1H, m), 8.37 (1H, m), 7.87 (3H, m), 7.56 (2H, m), 7.05 (1H, d, *J* = 8.3 Hz), 6.59 (1H, m), 3.68 (3H, s), 2.80 (3H, s), 2.61 (3H, s); ESIMS (MH^+): 429.05.

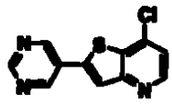
Anal. Calcd. For $C_{24}H_{20}N_4O_2S$•0.5 CH_2Cl_2•0.4 EtOAc: C, 61.82; H, 4.82; N, 11.07; Found: C, 61.93; H, 4.97; N, 10.99.

Example 39(a): 7-Chloro-2-(trimethylstannyl)thieno[3,2-*b*]pyridine



Tereakis(triphenylphosphine)palladium (238 mg, 0.2 mmole) was added to a solution of hexamethyldistannane (1.68 g, 5.1 mmole) and 7-chloro-2-iodothieno[3,2-*b*]pyridine (1.52 g, 5.1 mmole) in 1,4-dioxane (20 ml). The reaction mixture was stirred at 110°C for 3hr. After cooling to room temperature, the mixture was filtered, washed with CH_2Cl_2 and was partitioned between H_2O (100 ml) and CH_2Cl_2 (2 x 100 ml). The combined organic layers were dried over $MgSO_4$ and concentrated. The residue was purified by flash column chromatography eluting with 10-15% EtOAc in hexane to give an orange solid (1.09 g, 63%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.16 (1H, d, *J* = 5.1 Hz), 6.87 (1H, s), 6.82 (1H, d, *J* = 5.1 Hz), 0.06 (9H, m); ESIMS (MH^+): 333.95.

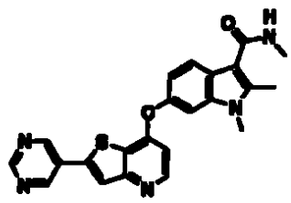
Example 39(b): 7-Chloro-2-pyrimidin-5-ylthieno[3,2-*b*]pyridine



Tereakis(triphenylphosphine)palladium (17 mg) was added to a solution of 5-bromopyrimidine (0.057 g, 0.36 mmole) and 7-chloro-2-(trimethylstannyl)thieno[3,2-*b*]pyridine 38a (0.119 g, 0.36 mmole) in toluene (10 ml). The reaction mixture was stirred at 90°C overnight. After cooling to room temperature, the mixture was filtered, washed with CH_2Cl_2 and was partitioned between H_2O (20 ml) and CH_2Cl_2 (2 x 20 ml). The combined organic layers were dried over $MgSO_4$ and concentrated. The residue was purified by flash column chromatography eluting with 0-1% MeOH in CH_2Cl_2 to give white solid (0.045 g, 51%); ^{1}H

NMR (300 MHz, C_5D_5) δ 9.25 (1H, s), 9.10 (2H, s), 8.64 (1H, d, *J* = 5.1 Hz), 7.89 (1H, s), 7.34 (1H, d, *J* = 5.1 Hz); ESIMS (MH^+): 248.00.

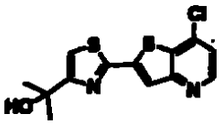
Example 39: 1,2-Dimethyl-6-(2-pyrimidin-5-yl-thieno[3,2-b]pyridin-7-yloxy)-1H-indole-3-carboxylic acid methylamide



This material was prepared by the reaction of 7-chloro-2-pyrimidin-5-ylthieno[3,2-*b*]pyridine 39b (0.045g, 0.18 mmole) with 6-hydroxy-*N*,1,2-trimethyl-1*H*-indole-3-carboxamide 16e (0.040g, 0.18 mmole) and Cs_2CO_3 (0.059g, 0.18 mmole) in a manner as previously described for example 1 to give an off-white solid (0.018g, 23%). ^1H NMR (300 MHz, CD_3OD) δ 9.23 (3H, m), 8.63 (1H, d, *J* = 6.2 Hz), 8.11 (1H, s), 7.82 (1H, d, *J* = 8.5 Hz), 7.43 (1H, s), 7.01 (2H, m), 3.63 (3H, s), 2.88 (3H, s), 2.55 (3H, s); ESIMS (MH^+): 430.10.

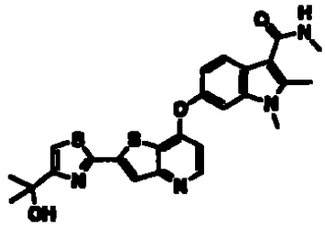
Anal. Calcd. For $C_{24}H_{23}N_4O_2S \cdot 1.0\ CH_2Cl_2 \cdot 1.5\ CH_3OH$: C, 54.45; H, 4.84; N, 12.46; Found: C, 54.12; H, 4.89; N, 12.30.

Example 40(a): 2-[2-(7-Chlorothieno[3,2-*b*]pyridin-2-yl)-1,3-thiazol-4-yl]propan-2-ol



The title compound was prepared by the method described in PC10795A, section A, example 27.

Example 40: 6-[2-[4-(1-Hydroxy-1-methyl-ethyl)-thiazol-2-yl]-thieno[3,2-*b*]pyridin-7-yloxy]-1,2-dimethyl-1*H*-indole-3-carboxylic acid methylamide

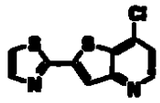


This material was prepared by the reaction of 2-[2-(7-chlorothieno[3,2-*b*]pyridin-2-yl)-1,3-thiazol-4-yl]propan-2-ol 40a (0.099g, 0.32 mmole) with 6-hydroxy-*N*,1,2-trimethyl-1*H*-indole-3-carboxamide 16e (0.071g, 0.32 mmole) and Cs_2CO_3 (0.106g, 0.32 mmole) in a manner as previously described for example 1 to give a yellow color solid (0.116g, 73%). ^1H NMR (300 MHz, DMSO-d_6) δ 8.50 (1H, d, *J* = 5.46 Hz), 8.12 (1H, s), 7.84 (1H, d, *J* = 8.67

Hz), 7.58 (2H, m), 7.54 (1H, d, *J* = 2.07 Hz), 7.04 (1H, dd, *J* = 8.67, 2.26 Hz), 6.59 (1H, d, *J* = 5.46 Hz), 3.88 (3H, s), 2.80 (1H, d, *J* = 4.71 Hz), 2.61 (3H, s), 2.53 (3H, s), 1.50 (6H, s).

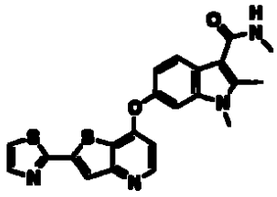
Anal. Calcd. For $C_{25}H_{24}N_4O_3S_2 \cdot 0.45\ CH_2Cl_2 \cdot 1.0\ CH_3OH$: C, 55.64; H, 5.18; N, 9.95; Found: C, 56.37; H, 5.22; N, 9.89.

Example 41(a): 7-Chloro-2-(1,3-thiazol-2-yl)thieno[3,2-*b*]pyridine



This material was prepared by coupling of 7-chloro-2-(trimethylstannyl)thieno[3,2-*b*]pyridine 39a (0.140g, 0.42 mmole) and 2-bromo-1,3-thiazole (0.038 ml, 0.42 mmole) with tetrakis(triphenylphosphine) palladium (0.019g) in a manner as previously described in example 39b to give a yellow solid (0.049g, 46%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.59 (1H, d, *J* = 5.1 Hz), 7.93 (1H, s), 7.89 (1H, d, *J* = 3.4 Hz), 7.45 (1H, d, *J* = 3.4 Hz), 7.30 (1H, d, *J* = 5.1 Hz).

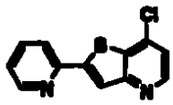
Example 41: 1,2-Dimethyl-6-(2-thiazol-2-yl-thieno[3,2-*b*]pyridin-7-yloxy)-1*H*-indole-3-carboxylic acid methylamide



This material was prepared by the reaction of 7-chloro-2-(1,3-thiazol-2-yl)thieno[3,2-*b*]pyridine 41a (0.049g, 0.19 mmole) with 6-hydroxy-*N*,1,2-trimethyl-1*H*-indole-3-carboxamide 16a (0.043g, 0.19 mmole) and Cs_2CO_3 (0.062g, 0.19 mmole) in a manner as previously described for example 1 to give an off-white solid (0.050g, 60%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.52 (1H, d, *J* = 5.4 Hz), 8.18 (1H, s), 7.93 (2H, m), 7.84 (1H, d, *J* = 8.9 Hz), 7.56 (2H, m), 7.05 (1H, m), 6.63 (1H, d, *J* = 5.4 Hz), 3.88 (3H, s), 2.80 (3H, d, *J* = 4.5Hz), 2.61 (3H, s); ESIMS (MH^+): 430.10.

Anal. Calcd. For $C_{22}H_{19}N_4O_2S_2 \cdot 0.45\ CH_2Cl_2 \cdot 1.0\ CH_3OH$: C, 55.64; H, 5.18; N, 9.95; Found: C, 56.37; H, 5.22; N, 9.89.

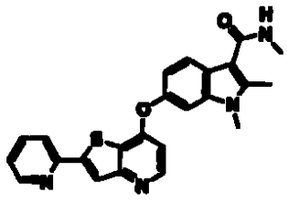
Example 42(a): 7-Chloro-2-pyridin-2-ylthieno[3,2-*b*]pyridine



This material was prepared by coupling 7-chloro-2-(trimethylstannyl)thieno[3,2-*b*]pyridine 39a (0.255g, 0.77 mmole) with 2-bromopyridine (0.121g, 0.77 mmole) using tetrakis(triphenylphosphine) palladium(0) (0.036g) as catalyst in a manner as previously

described in example 39b to give a white solid (0.058g, 31%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.66 (1H, m), 8.57 (1H, d, *J* = 5.1 Hz), 8.00 (1H, s), 7.83 (3H, m), 7.27 (1H, d, *J* = 5.1 Hz); ESIMS (MH^+): 246.95.

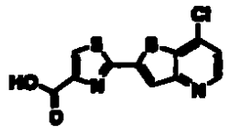
Example 42: 1,2-Dimethyl-6-(2-pyridin-2-yl-thieno[3,2-*b*]pyridin-7-yloxy)-1*H*-indole-3-carboxylic acid methylamide



This material was prepared by the reaction of 7-chloro-2-pyridin-2-ylthieno[3,2-*b*]pyridine (0.100g, 0.41 mmole) 42a with 6-hydroxy-*N*,1,2-trimethyl-1*H*-indole-3-carboxamide 16e (0.089g, 0.41 mmole) and Cs_2CO_3 (0.134g, 0.41 mmole) in a manner as previously described for example 1 to give an off-white solid (0.048g, 27%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.63 (1H, d, *J* = 4.5 Hz), 8.49 (1H, d, *J* = 5.5 Hz), 8.35 (1H, s), 8.28 (1H, d, *J* = 7.72 Hz), 7.95 (1H, t, *J* = 8.4 Hz), 7.84 (1H, d, *J* = 8.6 Hz), 7.58 (1H, d, *J* = 4.5 Hz), 7.54 (1H, d, *J* = 1.9 Hz), 7.43 (1H, m), 7.04 (1H, dd, *J* = 1.9, 8.6 Hz), 6.58 (1H, d, *J* = 5.5 Hz), 3.68 (3H, s), 2.80 (3H, s), 2.62 (3H, s); ESIMS (MH^+): 429.05.

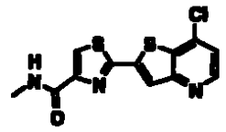
Anal. Calcd. For $C_{24}H_{20}N_4O_2S$•0.8 H_2O: C, 65.08; H, 4.92; N, 12.65; Found: C, 65.16; H, 4.93; N, 12.40.

Example 43(a): 2-(7-Chlorothieno[3,2-*b*]pyridin-2-yl)-1,3-thiazole-4-carboxylic acid



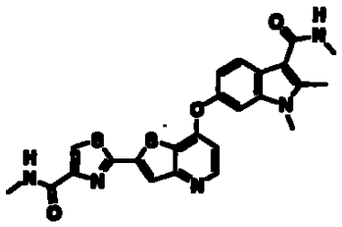
To a solution of methyl 2-(7-chlorothieno[3,2-*b*]pyridin-2-yl)-1,3-thiazole-4-carboxylate (0.200 g, 0.62 mmole), prepared by the method described in PC10795A, section A, example 28, in EtOAc (5 ml) was added 1N aqueous NaOH solution (1.85 ml, 1.85 mmole). The reaction mixture was stirred at 50° C for 1h, cooled to room temperature, diluted with H_2O (10 ml) and acidified with 1N HCl to pH~2. The resulting solution was extracted with 10% MeOH in CH_2Cl_2 (5x10 ml), dried over $MgSO_4$ and concentrated and dried under vacuum to give yellow solid (0.181 g, 98%). ^{1}H NMR (300 MHz, DMSO-d_6) □ 7.67 (1H, d, *J* = 5.09 Hz) 8.41 (1H, s) 8.65 (1H, s) 8.71 (1H, bs); ESIMS (MH^+): 309.95.

Example 43(b): 2-(7-Chlorothieno[3,2-*b*]pyridin-2-yl)-*N*-methyl-1,3-thiazole-4-carboxamide



To a solution of 2-(7-chlorothieno[3,2-*b*]pyridin-2-yl)-1,3-thiazole-4-carboxylic acid 43a (0.123 g, 0.41 mmole) in CH_2Cl_2 cooled at 0° C was added 2.0 M oxalyl chloride in CH_2Cl_2 (0.520 ml, 1.04 mmole) and DMF (2 drops). The reaction mixture was stirred at room temperature for 1h, concentrated and dried. The residue was taken into CH_2Cl_2 (10 ml), and 2.0 M methylamine in CH_2Cl_2 (0.250 ml, 0.492 mmole) was added. The reaction mixture was stirred at room temperature for 1h, and then partitioned between H_2O (100 ml) and CH_2Cl_2 (2x100 ml). The combined organic layers were dried over $MgSO_4$ and concentrated. The residue was purified by flash column chromatography eluting with 2-8% CH_3OH in CH_2Cl_2 to give yellow solid (0.116 g, 91%). ^1H NMR (300 MHz, $CDCl_3$) δ 8.62 (1H, d, J = 5.1 Hz), 8.19 (1H, s), 7.96 (1H, s), 7.33 (1H, d, J = 5.1 Hz), 3.08 (3H, d, J = 4.9 Hz); ESIMS (MH^+): 309.95.

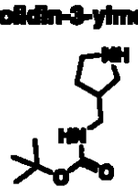
Example 43: 1,2-Dimethyl-6-[2-(4-methylcarbamoyl-thiazol-2-yl)-thieno[3,2-*b*]pyridin-7-yloxy]-1*H*-indole-3-carboxylic acid methylamide



This material was prepared by the reaction of 2-(7-chlorothieno[3,2-*b*]pyridin-2-yl)-*N*-methyl-1,3-thiazole-4-carboxamide 43b (0.125g, 0.403 mmole) with 6-hydroxy-1,2-dimethyl-1*H*-indole-3-carboxylic acid methylamide 16e (0.092g, 0.403 mmole) and Cs_2CO_3 (0.137g, 0.42 mmole) in a manner as previously described for example 1 to give an off-white solid (0.015g, 9%). ^1H NMR (300 MHz, DMSO-d_6) δ 8.54 (1H, d, J = 5.3 Hz), 8.43 (1H, d, J = 4.7 Hz), 8.40 (1H, s), 8.30 (1H, s), 7.84 (1H, d, J = 8.7 Hz), 7.56 (2H, m), 7.05 (1H, dd, J = 2.1, 8.7Hz), 6.63 (1H, d, J = 5.3 Hz), 3.68 (3H, s), 2.81 (6H, m), 2.61 (3H, s); ESIMS (MH^+): 482.05.

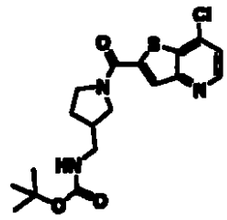
Anal. Calcd. For $C_{24}H_{21}N_4O_3S_2Cl$•0.5 CH_2Cl_2: C, 55.10; H, 4.15; N, 13.11; Found: C, 55.14; H, 4.42; N, 12.99.

Example 44(a): *tert*-Butyl pyrrolidin-3-ylmethylcarbamate



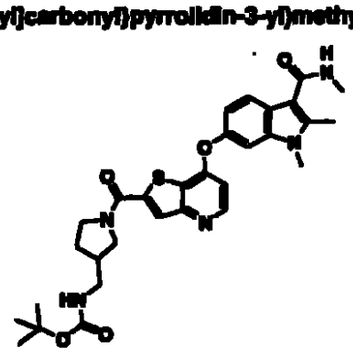
To a solution of *tert*-butyl (1-benzylpyrrolidin-3-yl)methylcarbamate (3.0g, 10.33 mmole) in EtOAc (100 ml) was added $Pd(OH)_2$ on carbon (0.3 g). The mixture was stirred under H_2 balloon at room temperature for 3 h and filtered through Celite. The filtrate was concentrated to give colorless oil (1.87 g, 90%).

Example 44(b): *tert*-Butyl (1-[(7-chlorothieno[3,2-*b*]pyridin-2-yl)carbonyl]pyrrolidin-3-yl)methylcarbamate



This material was prepared from 7-chlorothieno[3,2-*b*]pyridine-2-carboxylic acid lithium salt (2.27g, 10.33 mmole), $SOCl_2$ (10 ml), *tert*-butyl pyrrolidin-3-ylmethylcarbamate 44a (2.07g, 10.33 mmole) and Et_3N (1.44 ml, 10.33 mmole) in a manner as previously described for example 9d to give a yellow solid (2.44g, 60%). ^1H NMR (300 MHz, $CDCl_3$) δ 7.85 (1H, s), 7.34 (1H, d, J = 5.1 Hz), 4.73 (1H, s), 3.96 (1H, m), 3.85 (1H, m), 3.70 (1H, m), 3.55 (1H, m), 3.42 (1H, m), 3.22 (2H, m), 2.54 (1H, m), 2.12 (1H, m), 1.43, 1.41 (9H, s); ESIMS (M^+): 396.05.

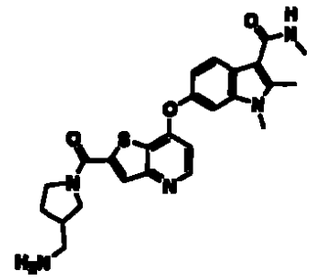
Example 44: *tert*-Butyl (1-[[7-({1,2-dimethyl-3-[(methylamino)carbonyl]-1*H*-indol-6-yl}oxy)thieno[3,2-*b*]pyridin-2-yl]carbonyl}pyrrolidin-3-yl)methylcarbamate



This material was prepared by the reaction of *tert*-butyl (1-[(7-chlorothieno[3,2-*b*]pyridin-2-yl)carbonyl]pyrrolidin-3-yl)methylcarbamate 44b (0.206g, 0.52 mmole) with 6-hydroxy-*N*,1,2-trimethyl-1*H*-indole-3-carboxamide 16e (0.113g, 0.52 mmole) and Cs_2CO_3 (0.169g, 0.52 mmole) in a manner as previously described for example 1 to give an off-white solid (0.168g, 56%). ^1H NMR (300 MHz, $CDCl_3$) δ 8.48 (1H, d, J = 5.3 Hz), 7.82 (1H, s), 7.75 (1H, d, J = 8.7 Hz), 7.25 (1H, s), 7.15 (1H, d, J = 2.0 Hz), 7.02 (1H, dd, J = 2.0, 8.7 Hz), 6.56 (1H, d, J = 5.3 Hz), 5.89 (1H, s), 4.74 (1H, s), 3.97 (1H, m), 3.84 (1H, m), 3.65 (3H, s), 3.44 (1H, m), 3.20 (2H, m), 3.06 (3H, d, J = 4.71 Hz), 2.72 (3H, s), 1.77 (1H, m), 1.44, 1.42 (9H, s), 0.84 (2H, m).

Anal. Calcd. For $C_{20}H_{23}N_5O_2S \cdot 1.0\ H_2O \cdot 1.2$ EtOAc: C, 59.59; H, 6.70; N, 9.96; Found: C, 59.54; H, 6.44; N, 9.85.

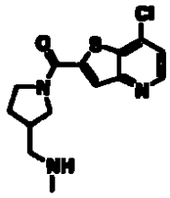
Example 45: 6-[2-(3-Aminomethyl-pyrrolidine-1-carbonyl)-thieno[3,2-*b*]pyridin-7-yloxy]-1,2-dimethyl-1*H*-indole-3-carboxylic acid methylamide



Trifluoroacetic acid (1 ml) was added to a stirred solution of *tert*-butyl (1-[[7-({1,2-dimethyl-3-[(methylamino)carbonyl]-1*H*-indol-6-yl}oxy)thieno[3,2-*b*]pyridin-2-yl]carbonyl} pyrrolidin-3-yl)methyl carbamate 44 (0.145g, 0.25 mmole). The reaction mixture was stirred at room temperature for 15 min and concentrated. The residue was triturated with Et_2O, filtrated to give a yellow solid (0.050g, 40%). ^1H NMR (300 MHz, DMSO-d_6) δ 8.56 (1H, d, *J* = 5.5 Hz), 8.05 (1H, s), 7.84 (3H, m), 7.58 (1H, d, *J* = 4.5 Hz), 7.54 (1H, d, *J* = 1.7 Hz), 7.02 (1H, d, *J* = 8.8 Hz), 6.67 (1H, d, *J* = 5.5 Hz), 4.08 (1H, m), 3.92 (1H, m), 3.78 (1H, m), 3.67 (3H, s), 3.54 (1H, m), 3.36 (1H, m), 2.96 (2H, m), 2.80 (3H, d, *J* = 4.33 Hz), 2.61 (3H, s), 2.09 (1H, m), 1.78 (1H, m); ESIMS (MH^+): 478.10.

Anal. Calcd. For $C_{25}H_{27}N_5O_2S \cdot 1.0\ CF_3CO_2H \cdot 2.7\ CH_2Cl_2$: C, 46.69; H, 4.41; N, 9.17; Found: C, 46.87; H, 4.27; N, 9.06.

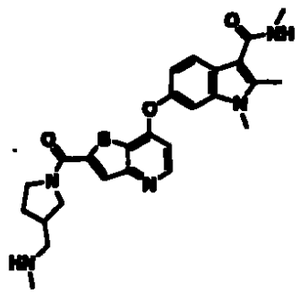
Example 46(a): *N*-({1-[(7-chlorothieno[3,2-*b*]pyridin-2-yl)carbonyl]pyrrolidin-3-yl}methyl)-*N*-methylamine



NaH (0.039 g, 0.82 mmole) and CH_3I (0.064 ml, 1.02 mmole) were added to a solution of *tert*-butyl (1-[(7-chlorothieno[3,2-*b*]pyridin-2-yl)carbonyl]pyrrolidin-3-yl}methyl-carbamate 43 (0.271g, 0.68 mmole) in THF at 0° C. The reaction mixture was stirred and warmed to room temperature overnight and partitioned between H_2O (50 ml) and EtOAc (2 x 50 ml). The combined organic layers were dried over $MgSO_4$ and concentrated. The residue was purified by flash column chromatography eluting with 0-2% CH_3OH in CH_2Cl_2 to give a

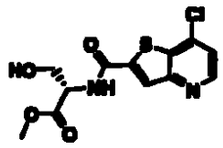
yellow solid (0.283 g, 82%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.62 (1H, d, *J* = 5.1 Hz), 7.85 (1H, s), 7.34 (1H, d, *J* = 5.1 Hz), 4.72 (1H, s), 3.99 (1H, m), 3.77 (2H, m), 3.50 (1H, m), 3.19 (2H, m), 2.88 (3H, d, *J* = 12.06 Hz), 2.62 (1H, m), 2.14 (1H, m), 1.83 (1H, m); ESIMS (MH^+): 310.10.

Example 46: 1,2-Dimethyl-6-[2-(3-methylaminomethyl-pyrrolidine-1-carbonyl)-thieno[3,2-*b*]pyridin-7-yloxy]-1*H*-indole-3-carboxylic acid methylamide



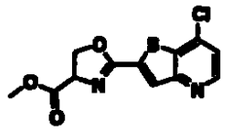
This material was prepared by the reaction of *N*-([1-[(7-chlorothieno[3,2-*b*]pyridin-2-yl)carbonyl]pyrrolidin-3-yl]methyl)-*N*-methylamine 46a (0.115g, 0.41 mmole) with 6-hydroxy-*N*,1,2-trimethyl-1*H*-indole-3-carboxamide 16e (0.090g, 0.41 mmole) and Cs_2CO_3 (0.147g, 0.41 mmole) in a manner as previously described for example 1 to give an off-white solid (0.110g, 54%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.54 (1H, s), 8.01 (1H, s), 7.83 (1H, m), 7.54 (2H, m), 7.02 (1H, s), 6.64 (1H, d, *J* = 5.46 Hz), 3.93 (2H, m), 3.68 (3H, s), 3.54 (2H, m), 3.16 (2H, m), 2.99 (1H, m), 2.80 (3H, s), 2.79 (3H, s), 1.98 (2H, m), 1.65 (1H, m); HRMS (MH^+): Calcd: 492.2084; Found: 492.2048.

Example 47(a): Methyl *N*-[(7-chlorothieno[3,2-*b*]pyridin-2-yl)carbonyl]-L-serinate



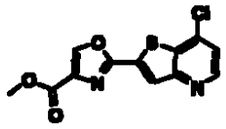
This material was prepared from lithium 7-chlorothieno[3,2-*b*]pyridine-2-carboxylic acid (2.69g, 12.25 mmole), $SOCl_2$ (10 ml), L-serine methyl ester hydrochloride (2.88g, 18.4 mmole) and Et_3N (5.12 ml, 37.7 mmole) in a manner as previously described for example 9d to give a white solid (2.09g, 54%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.61 (1H, d, *J* = 5.1 Hz), 8.02 (1H, s), 7.35 (1H, d, *J* = 5.1 Hz), 4.89 (1H, m), 4.15 (2H, m), 3.84 (3H, m).

Example 47(b): 2-[2-(7-Chlorothieno[3,2-*b*]pyridin-2-yl)-4,5-dihydro-1,3-oxazol-4-yl]propan-2-ol



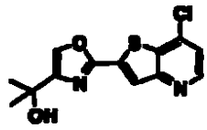
Burgess reagent (0.606g, 2.54 mmole) was added to a stirred solution of methyl *N*-[(7-chlorothieno[3,2-*b*]pyridin-2-yl)carbonyl]-L-serinate 47a (0.728g, 2.31 mmole) in THF (10 ml). The reaction mixture was stirred at reflux for 2h, quenched with MeOH (1 ml) and was partitioned between saturated H_2O (30 ml) and EtOAc (2x30 ml). The combined organic layers were dried over $MgSO_4$ and concentrated. The residue was purified by flash column chromatography eluting with 20-60% EtOAc in hexane to a white solid (0.314 g, 46%). ^1H NMR (300 MHz, $CDCl_3$) δ 8.66 (1H, d, *J* = 5.1 Hz), 8.06 (1H, s), 7.37 (1H, d, *J* = 5.1 Hz), 5.03 (1H, m), 4.61 (1H, t, *J* = 8.4 Hz), 4.70 (1H, m), 3.85 (3H, s); ESIMS (MH^+): 296.95.

Example 47(c): Methyl 2-(7-chlorothieno[3,2-*b*]pyridin-2-yl)-1,3-oxazole-4-carboxylate



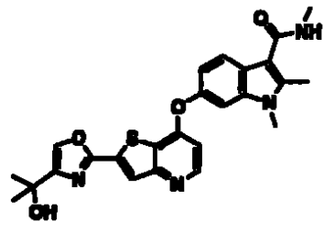
MnO_2 (0.628 mg) was added to a solution of 2-[2-(7-chlorothieno[3,2-*b*]pyridin-2-yl)-4,5-dihydro-1,3-oxazol-4-yl]propan-2-ol 47b (0.314g, 1.08 mmole) in benzene (15 ml). The reaction mixture was heated to reflux for 2hr., then filtered through celite. The filtrate was concentrated and the residue was purified by flash column chromatography eluting with 10-60% EtOAc in hexane to give a white solid (0.220 g, 71%). ^1H NMR (300 MHz, $CDCl_3$) δ 8.65 (1H, d, *J* = 5.0 Hz), 8.35 (1H, s), 8.20 (1H, s), 7.36 (1H, d, *J* = 5.0 Hz),3.97 (3H, s); ESIMS (MH^+): 294.95.

Example 47(d): 2-[2-(7-chlorothieno[3,2-*b*]pyridin-2-yl)-1,3-oxazol-4-yl]propan-2-ol



MeMgBr (0.483 ml, 1.45 mmole) was added to a solution of methyl 2-(7-chlorothieno[3,2-*b*]pyridin-2-yl)-1,3-oxazole-4-carboxylate 47c (0.171g, 0.58 mmole) in THF (10 ml) at 0° C. The reaction mixture was stirred at 0° C for 1h, quenched with saturated NH_4Cl (1 ml) and partitioned between saturated $NaHCO_3$ (20 ml) and EtOAc (2x20 ml). The combined organic layers were dried over $MgSO_4$ and concentrated. The residue was purified by flash column chromatography eluting with 0-2% CH_3OH in 1:1 EtOAc and CH_2Cl_2 to give a off-white solid (0.070 g, 41%). ^1H NMR (300 MHz, $CDCl_3$) δ 8.65 (1H, d, *J* = 5.0 Hz), 8.35 (1H, s), 8.20 (1H, s), 7.36 (1H, d, *J* = 5.0 Hz), 3.97 (6H, s); ESIMS (MH^+): 294.95.

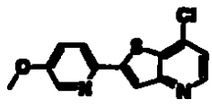
Example 47: 6-{2-[4-(1-Hydroxy-1-methyl-ethyl)-oxazol-2-yl]-thieno[3,2-*b*]pyridin-7-yloxy}-1,2-dimethyl-1*H*-indole-3-carboxylic acid methylamide (47).



This material was prepared by the reaction of 2-[2-(7-chlorothieno[3,2-*b*]pyridin-2-yl)-1,3-oxazol-4-yl]propan-2-ol 47d (0.068g, 0.23 mmole) with 6-hydroxy-*N*,1,2-trimethyl-1*H*-indole-3-carboxamide 16e (0.051g, 0.23 mmole) and Cs_2CO_3 (0.081g, 0.23 mmole) in a manner as previously described for example 1 to give a yellow solid (0.046g, 42%). ^{1}H NMR (300 MHz, CD_3OD) δ 8.39 (1H, d, *J* = 5.3 Hz), 7.94 (1H, d, *J* = 1.0 Hz), 7.79 (1H, s), 7.77 (1H, s), 7.32 (1H, s), 6.98 (1H, d, *J* = 8.8 Hz), 6.82 (1H, d, *J* = 5.3 Hz), 3.83 (3H, s), 2.90 (3H, s), 2.58 (3H, s), 1.51 (6H, s); ESIMS (MH^+): 477.10.

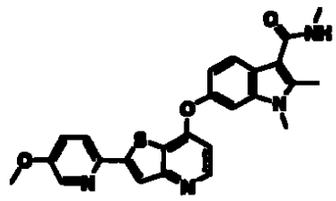
Anal. Calcd. For $C_{25}H_{25}N_4O_4S$•0.25 CH_2Cl_2: C, 60.80; H, 5.15; N, 11.26; Found: C, 60.84; H, 5.21; N, 10.98.

Example 48(a): 7-Chloro-2-(5-methoxypyridin-2-yl)thieno[3,2-*b*]pyridine



This material was prepared by coupling 7-chloro-2-(trimethylstannyl)thieno[3,2-*b*]pyridine 39a (0.214g, 0.64 mmole) with 2-iodo-5-methoxypyridine (0.152g, 0.64 mmole) using tereakis (triphenylphosphine)palladium(0) (30mg) as catalyst in a manner as previously described for example 39b to give a yellow solid (0.060g, 34%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.55 (1H, d, *J* = 5.1 Hz), 8.43 (1H, s), 8.28 (1H, dd, *J* = 1.3, 4.8 Hz), 7.34 (1H, m), 7.29 (1H, m), 7.24 (1H, d, *J* = 5.8 Hz), 4.04 (3H, s).

Example 48: 6-[2-(5-Methoxy-pyridin-2-yl)-thieno[3,2-*b*]pyridin-7-yloxy]-1,2-dimethyl-1*H*-indole-3-carboxylic acid methylamide



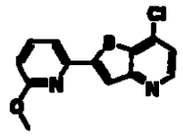
This material was prepared by the reaction 7-chloro-2-(5-methoxypyridin-2-yl)thieno[3,2-*b*]pyridine 48a (0.058g, 0.21 mmole) with 6-hydroxy-*N*,1,2-trimethyl-1*H*-indole-3-carboxamide 16e (0.046g, 0.21 mmole) and Cs_2CO_3 (0.068g, 0.21 mmole) in a manner as previously described for example 1 to give a pale yellow solid (0.014g, 15%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.42 (2H, m), 8.26 (1H, dd, *J* = 1.1, 4.8 Hz), 7.73 (1H, d, *J* = 8.8 Hz), 7.34 (1H, m), 7.27 (1H, d, *J* = 4.8 Hz), 7.15 (1H, d, *J* = 2.0 Hz), 7.05 (1H, dd, *J* = 2.0, 8.8 Hz), 6.49 (1H,

100

d, J = 5.31 Hz), 5.91 (1H, bs), 4.03 (3H, s), 3.64 (3H, s), 3.06 (3H, d, J = 4.8 Hz), 2.72 (3H, s); ESIMS (MH^+): 459.03.

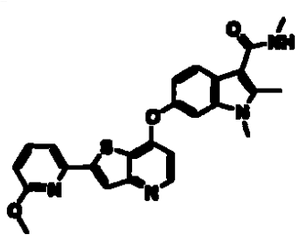
Anal. Calcd. For $C_{25}H_{22}N_4O_3S$•0.7 CH_3OH: C, 64.18; H, 5.20; N, 11.65; Found: C, 64.28; H, 5.27; N, 11.47.

Example 49(a): 7-Chloro-2-(6-methoxypyridin-2-yl)thieno[3,2-*b*]pyridine



This material was prepared by coupling 7-chloro-2-(trimethylstannyl)thieno[3,2-*b*]pyridine 39a (0.478g, 1.44 mmole) with 2-bromo-6-methoxypyridine (0.177ml, 1.44 mmole) using tereakis (triphenylphosphine)palladium(0) (67mg) as catalyst in a manner as previously described for example 39b to give a pale yellow solid (0.249g, 63%). ^1H NMR (300 MHz, $CDCl_3$) δ 8.56 (1H, d, J = 5.1 Hz), 7.98 (1H, s), 7.66 (3H, m), 6.75 (1H, d, J = 8.3 Hz), 4.05 (3H, s); ESIMS (MH^+): 276.95.

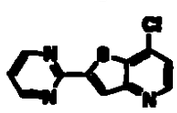
Example 49: 6-[2-(6-Methoxy-pyridin-2-yl)-thieno[3,2-*b*]pyridin-7-yloxy]-1,2-dimethyl-1*H*-indole-3-carboxylic acid methylamide



This material was prepared by the reaction of 7-chloro-2-(6-methoxypyridin-2-yl)thieno[3,2-*b*]pyridine 49a (0.093g, 0.34 mmole) with 6-hydroxy-*N*,1,2-trimethyl-1*H*-indole-3-carboxamide 16e (0.074g, 0.34 mmole) and Cs_2CO_3 (0.111g, 0.34 mmole) in a manner as previously described for example 1 to give a white solid (0.029g, 19%). ^1H NMR (300 MHz, $CDCl_3$) δ 8.43 (1H, d, J = 5.46 Hz), 7.99 (1H, s), 7.76 (1H, d, J = 8.7 Hz), 7.65 (1H, m), 7.45 (1H, d, J = 7.4 Hz), 7.18 (1H, d, J = 2.0 Hz), 7.07 (1H, dd, J = 2.0, 8.7 Hz), 6.73 (1H, d, J = 8.1 Hz), 6.47 (1H, m), 5.87 (1H, s), 4.03 (3H, s), 3.66 (3H, s), 3.07 (3H, d, J = 4.9 Hz), 2.74 (3H, s); ESIMS (MH^+): 459.20.

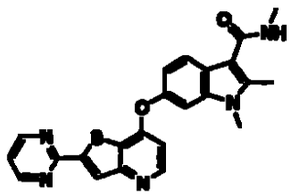
Anal. Calcd. For $C_{25}H_{22}N_4O_3S$•0.85 H_2O: C, 63.37; H, 5.04; N, 11.82; Found: C, 63.48; H, 4.98; N, 11.43.

Example 50(a): 7-Chloro-2-pyrimidin-2-ylthieno[3,2-*b*]pyridine



This material was prepared by coupling 7-chloro-2-(trimethylstannyl)thieno[3,2-*b*]pyridine 39a (0.218g, 0.66 mmole) with 2-bromopyrimidine (0.104g, 0.66 mmole) using tetrakis(triphenylphosphine) palladium(0) (31mg) as catalyst in a manner as previously described for example 39b to give a white solid (0.066g, 40%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.76 (2H, d, *J* = 4.90 Hz), 8.57 (1H, d, *J* = 5.1 Hz), 8.41 (1H, s), 7.28 (1H, d, *J* = 5.1 Hz), 7.20 (1H, m); ESIMS (MH^+): 248.00.

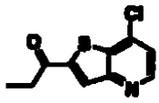
Example 50: 1,2-Dimethyl-6-(2-pyrimidin-2-yl-thieno[3,2-*b*]pyridin-7-yloxy)-1*H*-indole-3-carboxylic acid methylamide



This material was prepared by the reaction of 7-chloro-2-pyrimidin-2-ylthieno[3,2-*b*]pyridine 50a (0.066g, 0.23 mmole) with 6-hydroxy-*N*,1,2-trimethyl-1*H*-indole-3-carboxamide 16e (0.050g, 0.23 mmole) and Cs_2CO_3 (0.075g, 0.23 mmole) in a manner as previously described for example 1 to give a white solid (0.041g, 41%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.90 (2H, d, *J* = 4.9 Hz), 8.50 (1H, d, *J* = 5.3 Hz), 8.29 (1H, s), 7.81 (1H, d, *J* = 8.5 Hz), 7.50 (3H, m), 7.01 (1H, dd, *J* = 2.2, 8.5 Hz), 6.60 (1H, d, *J* = 5.3 Hz), 3.84 (3H, s), 2.76 (3H, d, *J* = 4.5 Hz), 2.57 (3H, s); ESIMS (MH^+): 430.10.

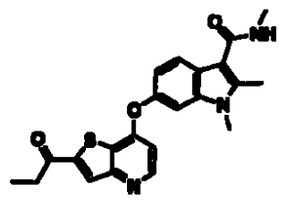
Anal. Calcd. For $C_{23}H_{19}N_5O_2S$•0.75 CH_3OH: C, 62.90; H, 4.89; N, 15.44; Found: C, 62.92; H, 4.81; N, 15.39.

Example 51(a): 1-(7-Chlorothieno[3,2-*b*]pyridin-2-yl)propan-1-one



2.5 M *n*BuLi in hexane (0.619 ml, 1.55 mmole) was added to a solution of 7-chlorothieno[3,2-*b*]pyridine (0.250g, 1.47 mmole) in THF (5 ml) at -78° C. The reaction mixture was stirred at -78° C for 30 min, and then propanoyl chloride (0.162 ml, 1.76 mmole) was added. The reaction mixture stirred at -78° C and slowly warmed to 0° C and quenched with H_2O (10 ml), extracted with EtOAc (2 x 10ml). The organic layer was dried over $MgSO_4$ and concentrated. The residue was purified by flash column chromatography eluting with 10-70% EtOAc in hexane to a off-white solid (0.084 g, 25%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.66 (1H, d, *J* = 4.9 Hz), 8.12 (1H, s), 7.38 (1H, d, *J* = 4.9 Hz), 3.09 (2H, q, *J* = 7.3 Hz), 1.29 (3H, t, *J* = 7.3 Hz,); ESIMS (MH^+): 225.95.

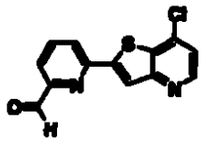
Example 51: 1,2-Dimethyl-6-(2-propionyl-thieno[3,2-*b*]pyridin-7-yloxy)-1*H*-indole-3-carboxylic acid methylamide



This material was prepared by the reaction of 1-(7-chlorothieno[3,2-*b*]pyridin-2-yl)propan-1-one 51a (0.062g, 0.28 mmole) with 6-hydroxy-*N*,1,2-trimethyl-1*H*-indole-3-carboxamide 16e (0.061g, 0.28 mmole) and Cs_2CO_3 (0.091g, 0.28 mmole) in a manner as previously described for example 1 to give an off-white solid (0.035g, 31%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.51 (1H, d, *J* = 5.5 Hz), 8.11 (1H, s), 7.76 (1H, d, *J* = 8.6 Hz), 7.15 (1H, d, *J* = 2.1 Hz), 7.02 (1H, dd, *J* = 2.1, 8.6 Hz), 6.58 (1H, d, *J* = 5.5 Hz), 5.57 (1H, d, *J* = 4.3 Hz), 3.66 (3H, s), 3.10 (2H, m), 3.06 (3H, d, *J* = 4.9 Hz), 2.73 (3H, s), 1.31 (3H, t, *J* = 7.3 Hz); ESIMS (MH^+): 408.05.

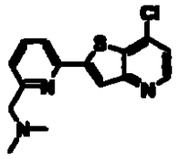
Anal. Calcd. For $C_{22}H_{21}N_3O_3S$•0.15 CH_2Cl_2: C, 63.31; H, 5.11; N, 10.00; Found: C, 63.42; H, 5.03; N, 9.83.

Example 52(a): 6-(7-Chlorothieno[3,2-*b*]pyridin-2-yl)pyridine-2-carbaldehyde



This material was prepared by coupling 7-chloro-2-(trimethylstannyl)thieno[3,2-*b*]pyridine 38a (0.707g, 2.17 mmole) with 6-bromopyridine-2-carbaldehyde (0.396g, 2.17 mmole) using tereakis (triphenylphosphine) palladium(0) (100 mg) as catalyst in a manner as previously described for example 38b to give a white solid (0.161g, 27%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.15 (1H, s), 8.61 (1H, d, *J* = 5.1 Hz), 7.93-8.09 (4H, m) 7.31 (1H, d, *J* = 5.1 Hz); ESIMS (MH^+): 275.00.

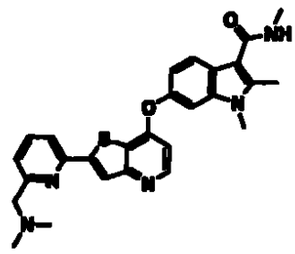
Example 52(b): *N*-[[6-(7-Chlorothieno[3,2-*b*]pyridin-2-yl)pyridin-2-yl]methyl]-*N*,*N*-dimethylamine



To a solution of 6-(7-chlorothieno[3,2-*b*]pyridin-2-yl)pyridine-2-carbaldehyde 52a (0.127g, 0.46 mmole) in THF (20 ml) was added 2.0 M dimethylamine in THF (1.5 ml, 2.3 mmole), $NaCNBH_3$ (0.063g, 0.92 mmole) and NaOAc (0.076g, 0.92 mmole). The reaction mixture was stirred at room temperature overnight and concentrated. The residue was purified by flash column chromatography eluting with 2-10% CH_3OH in $CHCl_3$ to give a yellow

solid (0.066 g, 61%). ^{1}H NMR (300 MHz, CD_3OD) δ 8.50 (1H, d, *J* = 5.3 Hz), 8.11 (1H, s), 8.03 (1H, d, *J* = 7.9 Hz), 7.90 (1H, t, *J* = 7.9 Hz), 7.41 (2H, m), 4.16 (2H, s), 2.71 (6H, s).

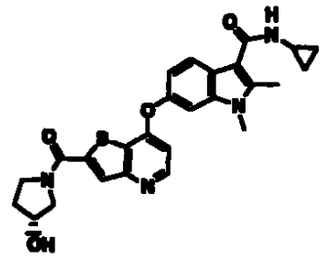
Example 52: 6-[2-(6-Dimethylaminomethyl-pyridin-2-yl)-thieno[3,2-*b*]pyridin-7-yloxy]-1,2-dimethyl-1*H*-indole-3-carboxylic acid methylamide



This material was prepared by the reaction of *N*-[[6-(7-chlorothieno[3,2-*b*]pyridin-2-yl)pyridin-2-yl]methyl]-*N*,*N*-dimethylamine 52b (0.080 0.26 mmole) with 6-hydroxy-*N*,1,2-trimethyl-1*H*-indole-3-carboxamide 16e (0.056 g, 0.26 mmole) and Cs_2CO_3 (0.085g, 0.26 mmole) in a manner as previously described for example 1 to give a white solid (0.016g, 13%). ^{1}H NMR (300 MHz, CD_3OD) δ 8.27 (1H, d, *J* = 5.5 Hz), 7.91 (1H, s), 7.77 (3H, m), 7.31 (1H, d, *J* = 7.0 Hz), 7.24 (1H, d, *J* = 2.0 Hz), 6.83 (1H, dd, *J* = 2.0, 8.6 Hz), 6.49 (1H, d, *J* = 5.5 Hz), 3.57 (5H, m), 2.88 (3H, s), 2.54 (3H, s), 2.26 (6H, s).

Anal. Calcd. For $C_{27}H_{27}N_5O_2S$•1.5 CH_2Cl_2: C, 55.84; H, 4.93; N, 11.43; Found: C, 55.75; H, 5.15; N, 11.01.

Example 53: 6-[2-((R)-3-Hydroxy-pyrrolidine-1-carbonyl)-thieno[3,2-*b*]pyridin-7-yloxy]-1,2-dimethyl-1*H*-indole-3-carboxylic acid cyclopropylamide

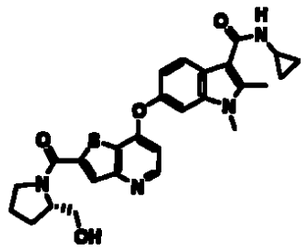


This material was prepared by the reaction of (7-chloro-thieno [3,2-b]pyridin-2-yl)-((R)-3-hydroxy-pyrrolidin-1-yl)-methanone 4a with 6-hydroxy-1,2-dimethyl-1H-indole-3-carboxylic acid cyclopropylamide 20b and Cs_2CO_3 in a manner as previously described for example 1. ^{1}H NMR (300 MHz, CD_3OD) δ 8.50 (1H, d, *J* = 5.5 Hz), 7.93 (1H, d, *J* = 17.33Hz), 7.80 (1H, d, *J* = 8.6Hz), 7.39 (1H, d, *J* = 2.1 Hz), 7.05 (1H, dd, *J* = 2.1, 8.6 Hz), 6.71 (1H, d, *J* = 5.5 Hz), 4.54 (1H, bs), 4.11-4.00 (2H, m), 3.85-3.72(6H, m), 2.93-2.86(1H, m), 2.66 (3H, s), 2.19-2.07 (2H, m), 0.90-0.84 (2H, m), 0.76-0.68 (2H, m). LCMS (ESI+) [M+H]/z Calc'd 491, found 491.

Anal. ($C_{28}H_{30}N_4O_4S$•0.2CH_2Cl_2) C, H, N.

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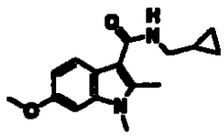
Example 54: *N*-Cyclopropyl-6-[(2-[[(2*S*)-2-(hydroxymethyl)pyrrolidin-1-yl]carbonyl]thieno[3,2-*b*]pyridin-7-yl)oxy]-1,2-dimethyl-1*H*-indole-3-carboxamide



This material was prepared by the reaction of ((2*S*)-1-[(7-chlorothieno[3,2-*b*]pyridin-2-yl)carbonyl]pyrrolidin-2-yl]methanol 3b (0.107g, 0.345 mmole) with *N*-cyclopropyl-6-hydroxy-1,2-dimethyl-1*H*-indole-3-carboxamide 20b (0.055g, 0.23 mmole) and Cs_2CO_3 (0.073g, 0.23 mmole) in a manner as previously described for example 1 to give brown solid (0.059g, 51%). ^{1}H NMR (300 MHz, CD_3OD) δ 8.37 (1H, d, *J* = 5.6 Hz), 7.81 (1H, s), 7.67 (1H, d, *J* = 8.6 Hz), 7.27 (1H, d, *J* = 2.1 Hz), 6.92 (1H, dd, *J* = 2.1, 8.6 Hz), 6.59 (1H, d, *J* = 5.6 Hz), 4.25 (1H, m), 3.82 (3H, m), 3.61 (3H, s), 2.76 (1H, m), 2.54 (3H, s), 2.00 (4H, m), 1.84 (1H, m), 1.14 (2H, m), 0.77 (2H, m). ESIMS (MH^+): 505.15.

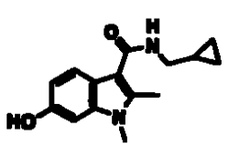
Anal. Calcd. for $C_{27}H_{28}N_4O_4S$•0.45 CH_2Cl_2: C, 60.74; H, 5.37; N, 10.32; Found: C, 60.40; H, 5.56; N, 10.06.

Example 55(a): *N*-(Cyclopropylmethyl)-6-methoxy-1,2-dimethyl-1*H*-indole-3-carboxamide



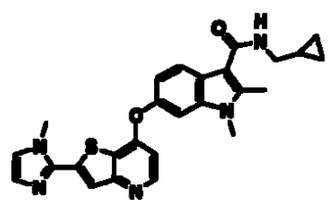
This material was prepared from 6-methoxy-1,2-dimethyl-1*H*-indole-3-carboxylic acid 16c (0.80, 3.65 mmole) with $SOCl_2$ (0.799 ml, 10.95 mmole) and cyclopropylmethylamine (0.38 ml, 4.38 mmole) in a manner as previously described for example 9d to give a pale yellow solid (0.382g, 38%). ^{1}H NMR (300 MHz, CD_3OD) δ 7.50 (1H, d, *J* = 8.7 Hz), 6.81 (1H, d, *J* = 2.2 Hz), 6.69 (1H, dd, *J* = 2.2, 8.7 Hz), 3.74 (3H, s), 3.56 (3H, s), 3.20 (2H, m), 2.50 (3H, m), 1.07 (1H, m), 0.44 (2H, m), 0.21 (2H, m); ESIMS (MH^+): 273.10.

Example 55(b): *N*-(Cyclopropylmethyl)-6-hydroxy-1,2-dimethyl-1*H*-indole-3-carboxamide



This material was prepared by reaction of *N*-(cyclopropylmethyl)-6-methoxy-1,2-dimethyl-1*H*-indole-3-carboxamide 55a (0.38g, 1.4 mmole) with 1.0 M BBr_3 in CH_2Cl_2 (4.19 ml, 4.19 mmole) in a manner as previously described for example 1d to give a pale yellow solid (0.278g, 77%). ^{1}H NMR (400 MHz, CD_3OD) δ 7.55 (1H, d, *J* = 8.5 Hz), 6.77 (1H, s), 6.71 (1H, d, *J* = 8.5 Hz), 3.63 (3H, s), 3.28 (2H, m), 2.61 (3H, s), 1.18 (1H, m), 0.56 (2H, m) ; ESIMS (MH^+): 259.10.

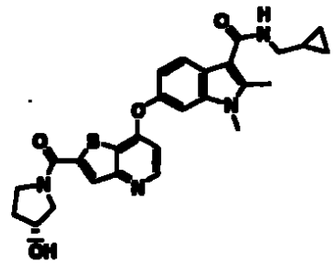
Example 55: *N*-(Cyclopropylmethyl)-1,2-dimethyl-6-[[2-(1-methyl-1*H*-imidazol-2-yl)thieno[3,2-*b*]pyridin-7-yl]oxy]-1*H*-indole-3-carboxamide



This material was prepared by the reaction of 7-chloro-2-(1-methyl-1*H*-imidazol-2-yl)thieno[3,2-*b*]pyridine 1e (0.78g, 0.32 mmole) with 6-hydroxy-*N*,1,2-trimethyl-1*H*-indole-3-carboxamide 55b (0.074g, 0.32 mmole) and Cs_2CO_3 (0.098g, 0.30 mmole) in a manner as previously described for example 1 to give a pale yellow solid (0.060g, 40%). ^{1}H NMR (400 MHz, CD_3OD) δ 8.33 (1H, d, *J* = 5.6 Hz), 7.75 (1H, d, *J* = 8.6 Hz), 7.67 (1H, s), 7.28 (1H, d, *J* = 2.2Hz), 7.21 (1H, d, *J* = 1.1 Hz), 6.99 (1H, d, *J* = 1.1 Hz), 6.95 (1H, dd, *J* = 2.2, 8.6 Hz), 6.57 (1H, d, *J* = 5.6 Hz), 3.92 (3H, s), 3.61 (3H, s), 2.55 (3H, s), 1.06 (1H, m), 0.46 (2H, m), 0.23 (2H, m). ESIMS (MH^+): 472.10.

Anal. Calcd. For $C_{25}H_{29}N_5O_2S$•0.5 CH_3OH: C, 65.27; H, 5.58; N, 14.36; Found: C, 65.52; H, 5.56; N, 14.12.

Example 56: *N*-(Cyclopropylmethyl)-6-[(2-[[(3*R*)-3-hydroxypyrrolidin-1-yl]carbonyl}thieno[3,2-*b*]pyridin-7-yl)oxy]-1,2-dimethyl-1*H*-indole-3-carboxamide

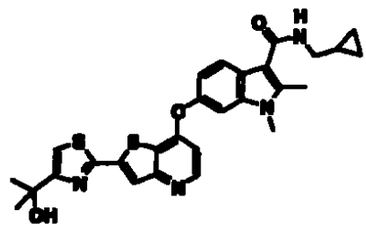


This material was prepared by the reaction of (3*R*)-1-[(7-chlorothieno[3,2-*b*]pyridin-2-yl) carbonyl] pyrrolidin-3-ol 4a (0.083g, 0.29 mmole) with 6-hydroxy-*N*,1,2-trimethyl-1*H*-indole-3-carboxamide 55b (0.075g, 0.29 mmole) and Cs_2CO_3 (0.094g, 0.29 mmole) in a manner as previously described for example 1 to give a pale yellow solid (0.050g, 34%). ^{1}H NMR (300 MHz, CD_3OD) δ 8.50 (1H, d, *J* = 5.3 Hz), 7.83 (1H, s), 7.73 (1H, d, *J* = 8.7 Hz), 7.50 (1H, d, *J* = 4.7 Hz), 7.42 (1H, d, *J* = 2.1 Hz), 6.99 (1H, d, *J* = 2.1, 8.7 Hz), 4.53 (1H, m), 3.96 (2H, m),

3.65 (2H, m), 3.61 (3H, s), 3.10 (4H, m), 2.35 (3H, s),1.09 (1H, m), 0.88 (2H, m), 0.45 (2H, m); ESIMS (MH^+): 505.20.

Anal. Calcd. For $C_{27}H_{28}N_4O_4S$•0.25 CH_2Cl_2: C, 62.24; H, 5.46; N, 10.66; Found: C, 62.10; H, 5.74; N, 10.33.

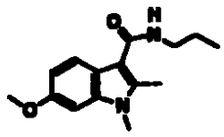
Example 57: 6-[2-[4-(1-Hydroxy-1-methyl-ethyl)-thiazol-2-yl]-thieno[3,2-*b*]pyridin-7-yloxy]-1,2-dimethyl-1*H*-indole-3-carboxylic acid cyclopropylmethyl-amide



This material was prepared by the reaction of 2-[2-(7-chlorothieno[3,2-*b*]pyridin-2-yl)-1,3-thiazol-4-yl]propan-2-ol 40a (0.102g, 0.33 mmole) with *N*-(cyclopropylmethyl)-6-hydroxy-1,2-dimethyl-1*H*-indole-3-carboxamide 55b (0.085g, 0.33 mmole) and Cs_2CO_3 (0.108g, 0.33 mmole) in a manner as previously described for example 1. ^1H NMR (300 MHz, DMSO-d_6) δ 8.50 (1H, d, J = 5.5 Hz), 8.12 (1H, s), 7.83 (1H, d, J = 8.6 Hz), 7.73 (1H, t, J = 5.8 Hz), 7.58 (1H, s), 7.54 (1H, d, J = 2.1Hz), 7.05 (1H, dd, J = 2.1, 8.6 Hz), 6.59 (1H, d, J = 5.5 Hz), 3.68 (3H, s), 3.17 (2H, t, J = 6.1 Hz), 2.61 (3H, s), 1.50 (6H, s), 1.06 (2H, m), 0.43 (2H, m), 0.25 (2H, m); ESIMS (MH^+): 533.15.

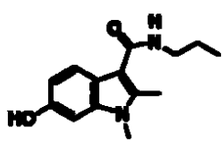
Anal. Calcd. For $C_{29}H_{28}N_4O_3S_2$•0.25 H_2O: C, 62.60; H, 5.35; N, 10.43; Found: C, 62.85; H, 5.37; N, 10.20.

Example 58(a): 6-Methoxy-1,2-dimethyl-1*H*-indol-3-carboxylic acid propylamide



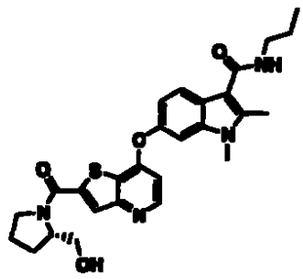
This material was prepared from 1,2-dimethyl-6-methoxy-1H-indole-3-carboxylic acid 16c, thionyl chloride and propylamine in a manner as previously described for example 9d. ^1H NMR (300 MHz, $CDCl_3$) δ 7.55 (1H, d, J = 8.6 Hz), 6.84 (1H, dd, J = 2.2, 8.6 Hz), 6.78 (1H, d, J = 2.2 Hz), 5.87 (1H, bs), 3.87 (3H, s), 3.63 (3H, s), 3.45 (2H, m), 2.69 (3H, s), 1.67 (2H, m), 1.02 (3H, t, J = 7.4 Hz). LCMS (ESI+) [M+H]/z Calc'd 261, found 261.

Example 58(b): 6-Hydroxy-1,2-dimethyl-1*H*-indol-3-carboxylic acid propylamide



This material was prepared from 6-methoxy-1,2-dimethyl-1H-indol-3-carboxylic acid propylamide 58a by treatment with BBr_3 in a manner as previously described for example 1d. ^1H NMR (300 MHz, CD_3OD) δ 7.50 (1H, d, *J* = 8.7 Hz), 6.74 (1H, d, *J* = 1.9 Hz), 6.66 (1H, dd, *J* = 1.9, 8.7 Hz), 3.61 (3H, s), 3.32 (2H, m), 2.58 (3H, s), 1.66 (2H, m), 1.01 (3H, t, *J* = 7.4 Hz). LCMS (ESI+) [M+H]/z Calc'd 247, found 247.

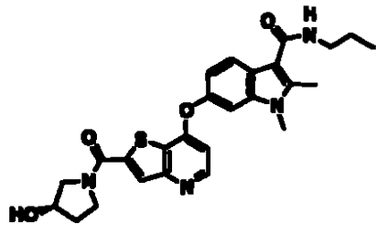
Example 59: 6-[2-[2-(S)Hydroxymethyl-pyrrolidine-1-carbonyl]thieno[3,2-*b*]pyridin-7-yloxy)-1,2-dimethyl-1*H*-indole-3-carboxylic acid propylamide



This material was prepared by the reaction of (7-chloro-thieno[3,2-*b*]pyridin-2-yl)-(3-hydroxymethyl-pyrrolidin-1-yl)-methanone 3a (0.127 g, 0.43 mmole) with 6-hydroxy-1,2-dimethyl-1*H*-indole-3-carboxylic acid propylamide 58b (0.070 g, 0.285 mmole) and Cs_2CO_3 (0.099 g, 0.35 mmole) in a manner as previously described for example 1 to give 30 mg (14% yield) of pale yellow solid. ^1H NMR (CD_3OD) δ 8.33 (1H, d, *J* = 5.1 Hz), 7.69-7.75 (2H, m), 7.24 (1H, s), 6.9 (1H, d, *J* = 8.1 Hz), 6.56 (1H, d, *J* = 5.1 Hz), 4.22 (1H, m), 3.64-3.76 (4H, m), 3.56 (3H, s), 3.20-3.31 (2H, m), 2.52 (3H, s), 1.90-1.96 (4H, m), 1.62-1.55 (2H, m), 0.95-0.90 (3H, m). ESIMS (MH^+): 507.20.

Anal. Calcd. For $C_{27}H_{30}N_4O_4S \cdot 1.0\ CH_3OH$: C, 62.43; H, 6.38; N, 10.40. Found: C, 62.44; H, 6.13; N, 10.13.

Example 59: 6-[2-(3-Hydroxy-pyrrolidine-1-carbonyl)-thieno[3,2-*b*]pyridin-7-yloxy]-1,2-dimethyl-3*H*-indole-3-carboxylic acid propylamide

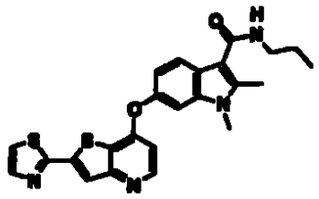


This material was prepared by the reaction of 7-chloro-2-[(R)-3-hydroxypyrrolidine-1-carbonyl]thieno[3,2,-b]pyridine 4a with 6-hydroxy-1,2-dimethyl-1H-indol-3-carboxylic acid propylamide 58b and Cs_2CO_3 in a manner as previously described for example 1. ^1H NMR (300 MHz, CD_3OD) δ 8.50 (1H, d, *J* = 5.6 Hz), 7.96 (1H, d, *J* = 17.3 Hz), 7.86 (1H, d, *J* = 8.7 Hz), 7.40 (1H, s), 7.06 (1H, d, *J* = 10.7 Hz), 6.72 (1H, d, *J* = 5.6 Hz), 4.61-4.53 (1H, m), 4.15-

4.00 (2H, m), 3.91-3.73 (3H, m), 3.73 (3H, s), 3.53-3.40 (2H, m), 2.67 (3H, s), 2.28-2.07 (2H, m), 1.78-1.69 (2H, m), 1,18-1.04 (3H, m). LCMS (ESI+) [M+H]/z Calc'd 493, found 493.

Anal. ($C_{28}H_{32}N_4O_4S$•0.3CH_2Cl_2) C, H, N.

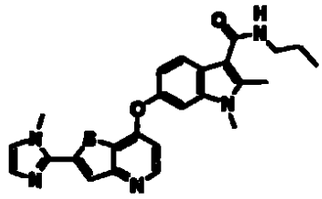
Example 60: 1,2-Dimethyl-6-(2-thiazol-2-yl-thieno[3,2-*b*]pyridin-7-yloxy)-1*H*-indole-3-carboxylic acid propylamide



This material was prepared by the reaction of 7-chloro-2-(1,3-thiazol-2-yl)thieno[3,2-*b*]pyridine 41a (0.078g, 0.314 mmole) with 6-hydroxy-1,2-dimethyl-*N*-propyl-1*H*-indole-3-carboxamide 58b (0.076g, 0.31 mmole) and Cs_2CO_3 (0.101g, 0.31 mmole) in a manner as previously described for example 1 to give a yellow solid (0.035g, 24%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.46 (1H, d, *J* = 5.3 Hz), 7.92 (1H, s), 7.88 (1H, d, *J* = 3.2 Hz), 7.74 (1H, d, *J* = 8.7 Hz), 7.42 (1H, d, *J* = 3.2 Hz), 7.17 (1H, d, *J* = 1.7 Hz), 7.05 (1H, dd, *J* = 1.7, 8.7 Hz), 6.55 (1H, d, *J* = 5.3 Hz), 5.90 (1H, m), 3.66 (3H, s), 3.47 (2H, m), 2.73 (3H, s), 1.69 (2H, m), 1.03 (3H, t, *J* = 7.4 Hz); ESIMS (MH^+): 463.10.

Anal. Calcd. For $C_{24}H_{22}N_4O_2S_2$•0.05 CH_2Cl_2: C, 61.87; H, 4.77; N, 12.00; Found: C, 61.90; H, 4.77; N, 11.90.

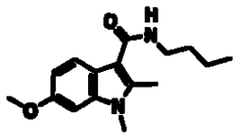
Example 61: 1,2-Dimethyl-6-[2-(1-methyl-1*H*-imidazol-2-yl)-thieno[3,2-*b*]pyridin-7-yloxy]-1*H*-indole-3-carboxylic acid propylamide



This material was prepared from 7-chloro-2-(1-methyl-1H-imidazol-2-yl)thieno[3,2-b]pyridine 1e with 6-hydroxy-1,2-dimethyl-1H-indole-3-carboxylic acid propylamide 58b and Cs_2CO_3 in a manner as previously described for example 1. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.42 (1H, d, *J* = 5.5 Hz), 7.82 (1H, d, *J* = 8.7 Hz), 7.76 (1H, s), 7.37 (1H, d, *J* = 1.8 Hz), 7.30 (1H, s), 7.08 (1H, s), 7.03 (1H, dd, *J* = 1.8, 8.7 Hz), 6.65 (1H, d, *J* = 5.5 Hz), 4.01 (3H, s), 3.70 (3H, s), 3.39 (2H, m), 2.84 (3H, s), 1.70 (2H, m), 1.03 (3H, m). LCMS (ESI+) [M+H]/z Calc'd 460, found 460.

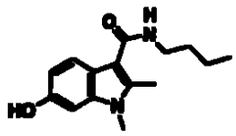
Anal. ($C_{25}H_{29}N_5O_2S$•1.0CH_3OH) C, H, N.

Example 62(a): 6-Methoxy-1,2-dimethyl-1*H*-indole-3-carboxylic acid butylamide



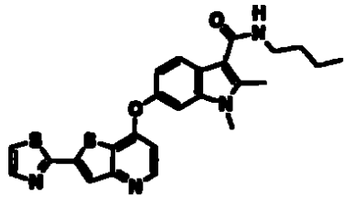
This material was prepared from the reaction of 6-methoxy-1,2-dimethyl-1*H*-indole-3-carboxylic acid (1.12g, 5.11 mmole) 16c with oxalyl chloride (0.682 ml, 13.6 mmole) and butan-1-amine (1.51 ml, 15.33 mmole) in a manner as previously described for example 16d to give a yellow solid (0.990g, 71%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.01 (1H, d, *J* = 8.6 Hz), 7.31 (1H, dd, *J* = 2.3, 8.6 Hz), 7.25 (1H, d, *J* = 2.3 Hz), 6.32 (1H, s), 4.34 (3H, s), 4.09 (3H, s), 3.95 (2H, m), 3.16 (3H, s), 2.10 (2H, m), 1.92 (2H, m), 1.44 (3H, t, *J* = 7.4 Hz); ESIMS (MH^+): 275.15.

Example 62(b): 6-Hydroxy-1,2-dimethyl-1*H*-indole-3-carboxylic acid butylamide



This material was prepared by the reaction of 6-methoxy-1,2-dimethyl-1*H*-indole-3-carboxylic acid butylamide 62a (0.78g, 2.84 mmole) with 1.0 M BBr_3 in CH_2Cl_2 (8.53 ml, 8.53 mmole) in a manner as previously described for example 1d to give an off-white solid (0.623g, 96%). ^{1}H NMR (300 MHz, CD_3OD) δ 7.40 (1H, d, *J* = 8.5 Hz), 6.64 (1H, d, *J* = 2.1 Hz), 6.59 (1H, dd, *J* = 2.1, 8.5 Hz), 3.50 (3H, s), 3.29 (2H, m), 2.48 (3H, s), 1.54 (2H, m), 1.36 (2H, m), 0.90 (3H, t, *J* = 7.3 Hz); ESIMS (MH^+): 261.15.

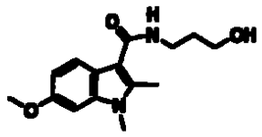
Example 62: 1,2-Dimethyl-6-(2-thiazol-2-yl-thieno[3,2-*b*]pyridin-7-yloxy)-1*H*-indole-3-carboxylic acid butylamide



This material was prepared by the reaction of 7-chloro-2-(1,3-thiazol-2-yl)thieno[3,2-*b*]pyridine 41a (0.085g, 0.33 mmole) with 6-Hydroxy-1,2-dimethyl-1*H*-indole-3-carboxylic acid butylamide 62b (0.087g, 0.33 mmole) and Cs_2CO_3 (0.108g, 0.33 mmole) in a manner as previously described for example 1 to give a yellow solid (0.090g, 57%). ^{1}H NMR (300 MHz, CD_3OD) δ 8.32 (1H, d, *J* = 5.5 Hz), 7.83 (1H, s), 7.78 (1H, d, *J* = 3.2 Hz), 7.72 (1H, d, *J* = 8.7 Hz), 7.63 (1H, d, *J* = 3.2 Hz), 7.28 (1H, d, *J* = 2.0 Hz), 6.94 (1H, dd, *J* = 2.0, 8.7 Hz), 6.56 (1H, d, *J* = 5.5 Hz), 3.59 (3H, s), 3.34 (2H, m), 2.54 (3H, s), 1.57 (2H, m), 1.38 (2H, m), 0.90 (3H, t, *J* = 7.4 Hz); ESIMS (MH^+): 477.05.

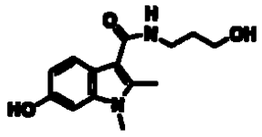
Anal. Calcd. For $C_{28}H_{34}N_4O_2S_2 \cdot 0.7\ H_2O$: C, 61.37; H, 5.23; N, 11.45; Found: C, 61.34; H, 5.22; N, 11.11.

Example 63(a): 6-Methoxy-1,2-dimethyl-1*H*-indole-3-carboxylic acid (3-hydroxy-propyl)-amide



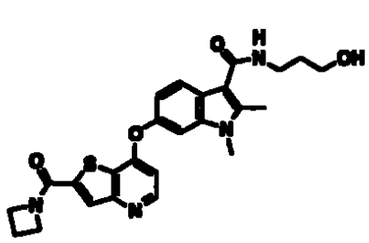
This material was prepared by the reaction of 1,2-dimethyl-6-methoxy-1H-indole-3-carboxylic acid 16c with 3-hydroxy-propyl amine and oxalyl chloride in a manner as previously described for 16d. ^{1}H NMR (300 MHz, CD_3OD) δ 7.52 (1H, d, J = 8.6 Hz), 6.73 (1H, d, J = 2.1 Hz), 6.68 (1H, dd, J = 2.1, 8.6 Hz), 3.69 (2H, t, J = 6.1 Hz), 3.79 (3H, s), 3.63 (3H, s), 3.51 (2H, m), 2.57 (3H, s), 1.85 (2H, m). LCMS (ESI+) [M+H]/z Calc'd 291, found 291.

Example 63(b): 6-Hydroxy-1,2-dimethyl-1*H*-indole-3-carboxylic acid (3-hydroxy-propyl)-amide



This material was prepared from 6-methoxy-1,2-dimethyl-1*H*-indole-3-carboxylic acid (3-methoxy-propyl)-amide 63a by treatment with BBr_3 in a manner as previously described for example 1d. ^{1}H NMR (300 MHz, CD_3OD) δ 7.52 (1H, d, J = 8.6 Hz), 6.73 (1H, d, J = 2.1 Hz), 6.68 (1H, dd, J =2.1, 8.6 Hz), 3.69 (2H, t, J = 6.1 Hz), 3.57 (3H, s), 3.51 (2H, m), 2.57 (3H, s), 1.85 (2H, m). LCMS (ESI+) [M+H]/z Calc'd 263, found 263.

Example 63: 6-[2-(Azetidine-1-carbonyl)-thieno[3,2-*b*]pyridin-7-yloxy]-1,2-dimethyl-1H-indole-3-carboxylic acid (3-hydroxy-propyl)-amide

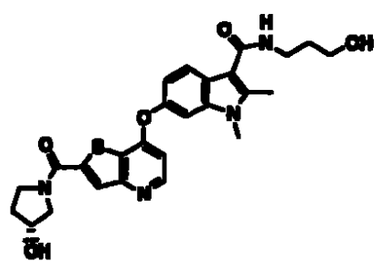


This material was prepared by the reaction of 2-(azetidin-1-ylcarbonyl)-7-chlorothieno[3,2-*b*]pyridine 25a with 6-hydroxy-1,2-dimethyl-1H-indole-3-carboxylic acid (3-hydroxy-propyl)-amide 63b and Cs_2CO_3 in a manner as previously described for example 1. ^{1}H NMR (300 MHz, CD_3OD) δ 8.50 (1H, d, J = 5.5 Hz), 7.89 (1H, d, J = 8.7 Hz), 7.82 (1H, s),

7.40 (1H, s), 7.08 (1H, d, J = 6.6 Hz), 6.72 (1H, d, J = 5.5 Hz), 4.74-4.65 (2H, m), 4.31-3.68 (5H, m), 3.60-3.55(2H, m), 2.68 (3H, s), 2.54-2.46 (2H, m), 1.95-1.87 (2H, m). LCMS (ESI+) [M+H]/z Calc'd 478, found 478.

Anal. ($C_{25}H_{28}N_4O_3S$•0.9CH_2Cl_2) C, H, N.

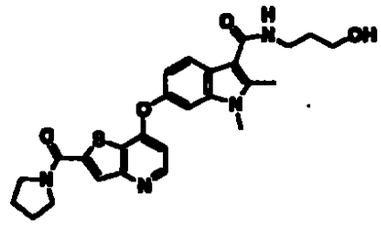
Example 64: 6-[2-((R)-3-Hydroxy-pyrrolidine-1-carbonyl)-thieno[3,2-*b*]pyridin-7-yloxy]-1,2-dimethyl-1*H*-indole-3-carboxylic acid (3-hydroxy-propyl)-amide



This material was prepared by the reaction of (7-chloro-thieno [3,2-*b*] pyridin-2-yl)-((R)-3-hydroxy-pyrrolidin-1-yl)-methanone 4a with 6-hydroxy-1,2-dimethyl-1H-indole-3-carboxylic acid (3-hydroxy-propyl)-amide 63b and Cs_2CO_3 in a manner as previously described for example 1. ^{1}H NMR (300 MHz, CD_3OD) δ 8.38 (1H, d, J = 5.5 Hz), 7.84-7.74 (2H,m), 7.28 (1H, d, J = 2.1 Hz), 6.94 (1H, dd, J = 2.1,8.6 Hz), 6.80 (1H, d, J = 5.5 Hz), 4.45-4.42 (1H, *m*), 3.93-3.91 (2H, *m*), 3.71-3.60 (6H, *m*), 3.45 (2H, *m*), 2.56 (3H, s), 2.02-1.96 (2H, m), 1.72-1.68 (2H, m). LCMS (ESI+) [M+H]/z Calc'd 509, found 509.

Anal. ($C_{26}H_{28}N_4O_3S$•0.8CH_2Cl_2) C, H, N.

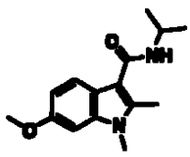
Example 65: 1,2-Dimethyl-6-[2-(pyrrolidine-1-carbonyl)-thieno[3,2-*b*]pyridin-7-yloxy]-1*H*-indole-3-carboxylic acid (3-hydroxy-propyl)-amide



This material was prepared from the reaction of (7-chloro-thieno[3,2-*b*]pyridin-2-yl)-pyrrolidin-1-yl-methanone with 6-hydroxy-1,2-dimethyl-1*H*-indole-3-carboxylic acid (3-hydroxy-propyl)-amide 63b and Cs_2CO_3 in a manner as previously described for example 1. ^{1}H NMR (300 MHz, CD_3OD) δ 8.44 (1H, d, J = 5.5 Hz), 7.85 (1H, s), 7.83 (1H, d, J = 10.0 Hz), 7.35 (1H, d, J = 1.9 Hz), 7.01 (1H, dd, J = 1.9, 8.5 Hz), 6.66 (1H, d, J = 5.5 Hz), 3.86 (2H, m), 3.67 (7H, m), 3.54 (2H, m), 2.63 (3H, s), 1.83-2.10 (6H, m). LCMS (ESI+) [M+H]/z Calc'd 493, found 493.

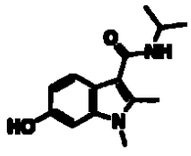
Anal. ($C_{28}H_{32}N_4O_4S$•0.5CH_3OH) C, H, N.

Example 66(a): 6-Methoxy-1,2-dimethyl-1*H*-indole-3-carboxylic acid isopropylamide



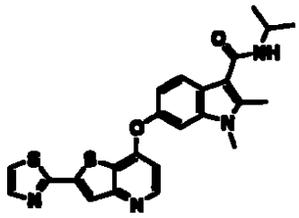
This material was prepared from 1,2-dimethyl-6-methoxy-1H-indole-3-carboxylic acid 16c, oxalyl chloride and isopropylamine in a manner as previously described for example 16d. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.53 (1H, d, *J* = 8.7 Hz), 6.85 (1H, dd, *J* = 2.3, 8.7 Hz), 6.77 (1H, d, *J* = 2.3 Hz), 4.35 (1H, m), 3.87 (3H, s), 3.63 (3H, s), 2.69 (3H, s), 1.30 (3H, s), 1.27 (3H, s). LCMS (ESI+) [M+H]/z Calc'd 261, found 261.

Example 66(b): 6-Hydroxy-1,2-dimethyl-1*H*-indole-3-carboxylic acid isopropylamide



This material was prepared from 6-methoxy-1,2-dimethyl-1H-indol-3-carboxylic acid isopyropylamide 66a by treatment with BBr_3 in a manner as previously described for example 1d. ^{1}H NMR (300 MHz, CD_3OD) δ 7.47 (1H, d, *J* = 8.5 Hz), 6.74 (1H, d, *J* = 2.1 Hz), 6.67 (1H, dd, *J* = 2.1, 8.5 Hz), 4.22 (1H, m), 3.61 (3H, s), 2.56 (3H, s), 1.28 (3H, s), 1.26 (3H, s). LCMS (ESI+) [M+H]/z Calc'd 247, found 247.

Example 66: 1,2-Dimethyl-6-(2-thiazol-2-yl-thieno[3,2-*b*]pyridin-7-yloxy)-1*H*-indole-3-carboxylic acid isopropylamide

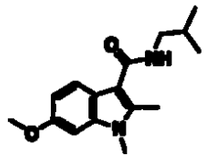


This material was prepared by the reaction 7-chloro-2-(1,3-thiazol-2-yl)thieno[3,2-*b*]pyridine 41a (0.084g, 0.33 mmole) with 6-hydroxy-*N*-isopropyl-1,2-dimethyl-1*H*-indole-3-carboxamide 66b (0.082g, 0.33 mmole) and Cs_2CO_3 (0.116g, 0.33 mmole) to give a off-white solid (0.058g, 38%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.46 (1H, d, *J* = 5.4 Hz), 7.93 (1H, s), 7.88

(1H, d, J = 3.2 Hz), 7.73 (1H, d, J = 8.6 Hz), 7.42 (1H, d, J = 3.2 Hz), 7.17 (1H, d, J = 2..1 Hz), 7.07 (1H, dd, J = 2.1, 8.6 Hz), 6.54 (1H, d, J = 5.4 Hz), 5.71 (1H, d, J = 7.7 Hz), 4.36 (1H, m), 3.68 (3H, s), 2.72 (3H, s), 1.31 (6H, d, J = 6.6 Hz); ESIMS (MH^+): 463.10.

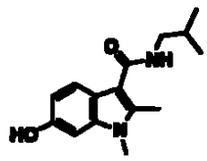
Anal. Calcd. For $C_{24}H_{22}N_4O_2S_2$•0.3 H_2O: C, 61.58; H, 4.87; N, 11.97; Found: C, 61.48; H, 4.67; N, 11.86.

Example 67(a): 6-Methoxy-1,2-dimethyl-1*H*-indole-3-carboxylic acid isobutyl-amide



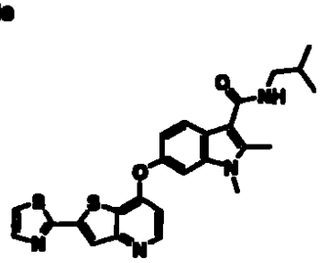
This material was prepared from 1,2-dimethyl-6-methoxy-1H-indole-3-carboxylic acid 18c, oxalyl chloride and isobutylamine in a manner as previously described for example 18d. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.58 (1H, d, J = 8.6 Hz), 6.85 (1H, dd, J = 2.2, 8.6 Hz), 6.78 (1H, d, J = 2.2 Hz), 3.87 (3H, s), 3.63 (3H, s), 3.32 (2H, m), 2.69 (3H, s), 1.93 (1H, m), 1.02 (3H, s), 1.00 (3H, s). LCMS (ESI+) [M+H]/z Calc'd 275, found 275.

Example 67(b): 6-Hydroxy-1,2-dimethyl-1*H*-indole-3-carboxylic acid isobutyl-amide



This material was prepared from 6-methoxy-1,2-dimethyl-1H-indol-3-carboxylic acid isobutyl-amide 67a by treatment with BBr_3 in a manner as previously described for example 1d. ^{1}H NMR (300 MHz, CD_3OD) δ 7.52 (1H, d, J = 8.5 Hz), 6.74 (1H, d, J = 2.3 Hz), 6.68 (1H, dd, J = 2.3, 8.5 Hz), 3.61 (3H, s), 3.22 (2H, m), 2.58 (3H, s), 1.95 (1H, m), 1.02 (3H, s), 1.00 (3H, s). LCMS (ESI+) [M+H]/z Calc'd 261, found 261.

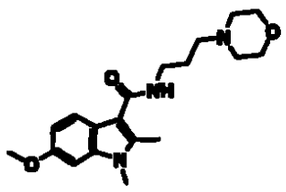
Example 67: 1,2-Dimethyl-6-(2-thiazol-2-yl-thieno[3,2-*b*]pyridin-7-yloxy)-1*H*-indole-3-carboxylic acid isobutyl-amide



This material was prepared by the reaction *tert*-butyl 7-chloro-2-(1,3-thiazol-2-yl)thieno[3,2-*b*]pyridine 41a (0.066 g, 0.34 mmole) with 6-hydroxy-*N*-isobutyl-1,2-dimethyl-1*H*-indole-3-carboxamide 67b (0.087g, 0.34 mmole) and Cs_2CO_3 (0.120g, 0.34 mmole) to give a pale yellow solid (0.065g, 40%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.46 (1H, d, *J* = 5.5 Hz), 7.93 (1H, s), 7.88 (1H, d, *J* = 3.2 Hz), 7.75 (1H, d, *J* = 8.6 Hz), 7.42 (1H, d, *J* = 3.2 Hz), 7.18 (1H, d, *J* = 2.1 Hz), 7.06 (1H, dd, *J* = 2.1, 8.6 Hz), 6.55 (1H, d, *J* = 5.5 Hz), 5.95 (1H, s), 3.88 (3H, s), 3.35 (1H, t, *J* = 6.4 Hz), 2.73 (3H, s), 1.95 (1H, m),1.03 (6H, d, *J* = 6.8 Hz); ESIMS (MH^+): 477.05.

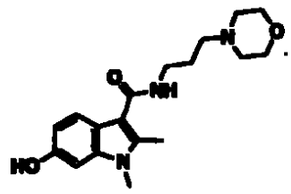
Anal. Calcd. For $C_{25}H_{24}N_4O_2S_2$·0.4 H_2O: C, 62.06; H, 5.17; N, 11.58; Found: C, 61.97; H, 5.00; N, 11.47.

Example 68(a): 6-Methoxy-1,2-dimethyl-*N*-(3-morpholin-4-ylpropyl)-1*H*-indole-3-carboxamide



This material was prepared from 6-methoxy-1,2-dimethyl-1*H*-indole-3-carboxylic acid 18c (0.483g, 2.20 mmole) with 2.0 M oxalyl chloride in CH_2Cl_2 (2.2 ml, 4.4 mmole) and 3-morpholin-4-ylpropylamine in a manner as previously described for example 18d to give a white solid (0.445g, 59%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.80 (1H, d, *J* = 8.6 Hz), 6.82 (1H, dd, *J* = 2.3, 8.6 Hz), 6.77 (1H, d, *J* = 2.3 Hz), 6.71 (1H, s), 3.87 (3H, s), 3.62 (3H, s), 3.57 (6H, m), 2.69 (3H, s), 2.50 (2H, t, *J* = 6.6 Hz), 2.43 (4H, m), 1.81 (2H, m); ESIMS (MH^+): 346.20.

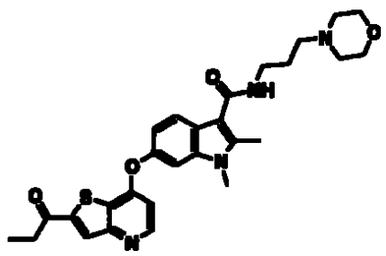
Example 68(b): 6-Hydroxy-1,2-dimethyl-*N*-(3-morpholin-4-ylpropyl)-1*H*-indole-3-carboxamide



This material was prepared from 6-methoxy-1,2-dimethyl-*N*-(3-morpholin-4-ylpropyl)-1*H*-indole-3-carboxamide 68a (0.445g, 1.29 mmole) by treatment with 1.0 M BBr_3 in CH_2Cl_2 (3.86 ml, 3.86 mmole) in a manner as described previously for example 1d to give a white

solid (0.445g, 59%). ^{1}H NMR (300 MHz, CD_3OD) δ 7.49 (1H, d, *J* = 8.6 Hz), 6.71 (1H, s), 6.64 (1H, dd, *J* = 2.2, 8.6 Hz), 3.87 (4H, m), 3.56 (3H, s), 3.47 (2H, t, *J* = 6.4 Hz), 3.10-3.24 (6H, m), 2.55 (3H, s), 2.00 (2H, m); ESIMS (MH^+): 332.15.

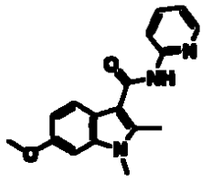
Example 68: 1,2-Dimethyl-6-(2-propionyl-thieno[3,2-*b*]pyridin-7-yloxy)-1*H*-indole-3-carboxylic acid (3-morpholin-4-yl-propyl)-amide



This material was prepared by the reaction of 1-(7-Chlorothieno[3,2-*b*]pyridin-2-yl)propan-1-one 51a (0.074g, 0.33 mmole) with 6-hydroxy-1,2-dimethyl-*N*-(3-morpholin-4-ylpropyl)-1*H*-indole-3-carboxamide 68b (0.110g, 0.33 mmole) and Cs_2CO_3 (0.108g, 0.33 mmole) in a manner as previously described for example 1 to give a white solid (0.019g, 11%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.58 (1H, d, *J* = 5.5 Hz), 8.47 (1H, s), 7.82 (1H, d, *J* = 8.5 Hz), 7.69 (1H, t, *J* = 5.6 Hz), 7.55 (1H, d, *J* = 2.1 Hz), 7.04 (1H, dd, *J* = 2.1, 8.5 Hz), 6.67 (1H, d, *J* = 5.5 Hz), 3.67 (3H, s), 3.54 (4H, m), 3.20 (2H, q, *J* = 7.2 Hz), 2.60 (3H, s), 2.36 (8H, m), 1.71 (2H, m), 1.13 (3H, t, *J* = 7.2 Hz); ESIMS (MH^+): 521.15.

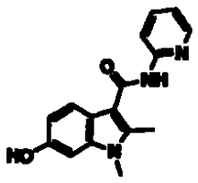
Anal. Calcd. For $C_{28}H_{32}N_4O_4S \cdot 1.5\ H_2O$: C, 61.40; H, 6.44; N, 10.23; Found: C, 61.40; H, 6.13; N, 10.09.

Example 69(a): 6-Methoxy-1,2-dimethyl-1*H*-indole-3-carboxylic acid pyridin-2-ylamide



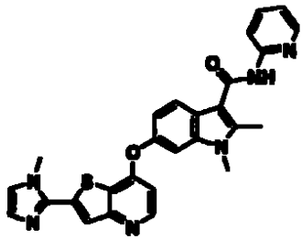
This material was prepared from 1,2-dimethyl-6-methoxy-1H-indole-3-carboxylic acid 16c, oxalyl chloride and propylamine in a manner as previously described for example 16d. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.34-8.37 (2H, m), 8.30 (1H, d, *J* = 5.0 Hz), 7.78 (1H, d, *J* = 8.7 Hz), 7.71 (1H, d, *J* = 8.9 Hz), 7.03 (1H, m), 6.92 (1H, dd, *J* = 2.3, 8.9 Hz), 6.82 (1H, d, *J* = 2.3 Hz), 3.89 (3H, s), 3.68 (3H, s), 2.76 (3H, s). LCMS (ESI+) [M+H]/z Calc'd 296, found 296.

Example 69(b): 6-Hydroxy-1,2-dimethyl-1*H*-indole-3-carboxylic acid pyridin-2-ylamide



This material was prepared from 6-methoxy-1,2-dimethyl-1H-indol-3-carboxylic acid pyridin-2-ylamide 69a by treatment with BBr_3 in a manner as previously described for example 1d. ^1H NMR (300 MHz, CD_3OD) δ 8.29 (1H, m), 8.24 (1H, d, *J* = 8.3 Hz), 7.82 (1H, m), 7.64 (1H, d, *J* = 8.7 Hz), 7.12 (1H, m), 6.82 (1H, d, *J* = 2.2 Hz), 6.76 (1H, dd, *J* = 2.2, 8.7 Hz), 3.86 (3H, s), 2.69 (3H, s). LCMS (ESI+) [M+H]/z Calc'd 282, found 282.

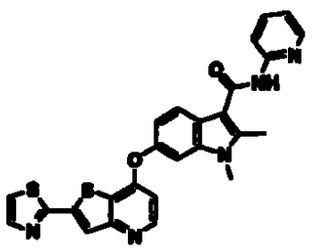
Example 69: 1,2-Dimethyl-6-[2-(1-methyl-1*H*-imidazol-2-yl)-thieno[3,2-*b*]pyridin-7-yloxy]-1*H*-indole-3-carboxylic acid pyridin-2-ylamide



This material was prepared by the reaction of 7-chloro-2-(1-methyl-1H-imidazol-2-yl)thieno[3,2-b]pyridine 1e with 6-hydroxy-1,2-dimethyl-1*H*-indole-3-carboxylic acid pyridin-2-ylamide 69b and Cs_2CO_3 in a manner as previously described for example 1. ^1H NMR (300 MHz, DMSO-d6) δ 8.43 (1H, d, *J* = 5.5 Hz), 8.33 (1H, s), 8.20 (1H, d, *J* = 3.8 Hz), 7.75-7.85 (3H, m), 7.61 (1H, s), 7.40 (1H, s), 7.11 (2H, m), 7.03 (1H, s), 6.60 (1H, d, *J* = 5.5 Hz), 4.05 (3H, s), 3.73 (3H, s), 2.68 (3H, s). LCMS (ESI+) [M+H]/z Calc'd 495, found 495.

Anal. ($C_{27}H_{22}N_6O_2S$•1.0H_2O) C, H, N.

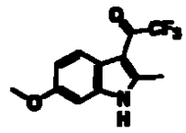
Example 70: 1,2-Dimethyl-6-(2-thiazol-2-yl-thieno[3,2-*b*]pyridin-7-yloxy)-1*H*-indole-3-carboxylic acid pyridin-2-ylamide



This material was prepared by the reaction of 7-chloro-2-(1,3-thiazol-2-yl)thieno[3,2-*b*]pyridine 41a (0.117g, 0.46 mmole) with 6-hydroxy-1,2-dimethyl-*N*-pyridin-2-yl-1*H*-indole-3-carboxamide 69b (0.130g, 0.46 mmole) and Cs_2CO_3 (0.150g, 0.46 mmole) in a manner as previously described for example 1 to give a yellow solid (0.051g, 22%). ^1H NMR (300 MHz, $CDCl_3$) δ 8.48 (1H, d, *J* = 5.5 Hz), 8.38 (1H, s), 8.35 (1H, s), 8.30 (1H, d, *J* = 3.77 Hz), 7.95 (2H, s), 7.88 (1H, d, *J* = 3.2 Hz), 7.75 (1H, m), 7.42 (1H, d, *J* = 3.39 Hz), 7.22 (1H, d, *J* = 1.9 Hz), 7.12 (1H, dd, *J* = 1.9, 8.6 Hz), 7.04 (1H, dd, *J* = 5.1, 8.6 Hz), 6.56 (1H, d, *J* = 5.5 Hz), 3.70 (3H, m), 2.80 (3H, m); ESIMS (MH^+): 498.05.

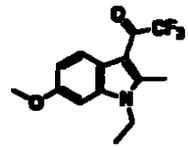
Anal. Calcd. For $C_{25}H_{19}N_5O_2S_2$•0.1 H_2O: C, 62.53; H, 3.88; N, 14.02; Found: C, 62.44; H, 3.96; N, 13.83.

Example 71(a): 2,2,2-Trifluoro-1-(6-methoxy-2-methyl-1*H*-indol-3-yl)-ethanone



To a solution of 6-methoxy-2-methyl-1H-indole (1g, 6.2 mmole) (prepared according to JACS 1988, 110, 2242) in 25 ml of THF was added TFAA (1.56 g, 7.44 mmole) with ice bath cooling. The mixture was warmed to room temperature and stirred for two hours and concentrated *in vacuo*. The residue was further purified by column chromatography (eluting with CH2Cl2) to give 1.34 g product as pale yellow solid (82% yield). ^1H NMR (300 MHz, $CDCl_3$) δ 7.90 (1H, d, J = 8.9 Hz), 6.87 (1H, dd, J = 2.2, 8.9 Hz), 6.80 (1H, d, J = 2.2 Hz), 3.82 (3H, s), 2.69 (3H, s).

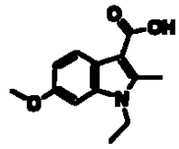
Example 71(b): 1-(1-Ethyl-6-methoxy-2-methyl-1*H*-indol-3-yl)-2,2,2-trifluoro-ethanone



To a solution of 2,2,2-trifluoro-1-(6-methoxy-2-methyl-1*H*-indol-3-yl)-ethanone 71a (1.3 g, 5.05 mmole) in 20 ml anhydrous THF was added ethyl iodide (2.36 g, 15.15 mmole) and sodium hydride (404 mg, 60% in mineral oil, 10.1 mmole) with ice bath cooling. The mixture was warmed slowly to room temperature and stirred for an additional four hours. The reaction was quenched with water and extracted with EtOAc. The combined organic layer was dried over Na_2SO_4, filtered and concentrated under rot vap. The residue was purified by column chromatography (eluting with 20-30% EtOAc in hexanes) to give a brown oil (580 mg,

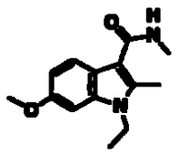
40 % yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.91 (1H, d, *J* = 8.9 Hz), 6.93 (1H, dd, *J* = 2.3, 8.9 Hz), 6.82 (1H, d, *J* = 2.3 Hz), 4.18 (2H, m), 3.88 (3H, s), 2.76 (3H, s), 1.40 (3H, m).

Example 71(c): 1-Ethyl-6-methoxy-2-methyl-1*H*-indole-3-carboxylic acid



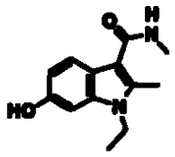
To a solution of 1-(1-ethyl-6-methoxy-2-methyl-1*H*-indol-3-yl)-2,2,2-trifluoro-ethanone 71b (580 mg, 2.03 mmole) in 10 ml ethanol was added a solution of KOH (1.1g, 20 mmole) in 10 ml water. The mixture was heated to reflux for 1 hour and cooled to room temperature. Concentrated HCl was added to adjust pH to 1. The mixture was extracted with EtOAc and the combined organic layer was dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was further purified by column chromatography (eluting with 1-2 % MeOH in CH_2Cl_2) to give 350 mg product as brown solid (74 % yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 (1H, d, *J* = 8.7 Hz), 6.90 (1H, dd, *J* = 2.2, 8.7 Hz), 6.80 (1H, d, *J* = 2.2 Hz), 4.14 (2H, q, *J* = 7.2 Hz), 3.88 (3H, s), 2.77 (3H, s), 1.37 (3H, t, *J* = 7.2 Hz).

Example 71(d): 1-Ethyl-6-methoxy-2-methyl-1*H*-indole-3-carboxylic acid methylamide



This material was prepared from the reaction of 1-ethyl-6-methoxy-2-methyl-1*H*-indole-3-carboxylic acid 71c (350 mg, 1.5 mmole), oxalyl chloride (1.1 ml, 2.0M solution) and methylamine (1.5 ml, 2.0M solution) in a manner as previously described for example 16d to give 350 mg product as beige solid (95% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.58 (1H, d, *J* = 8.7 Hz), 6.84 (1H, dd, *J* = 2.3, 8.7 Hz), 6.80 (1H, d, *J* = 2.3 Hz), 5.84 (1H, be), 4.10 (2H, q, *J* = 7.2 Hz), 3.87 (3H, s), 3.03 (3H, d, *J* = 4.9 Hz), 2.70 (3H, s), 1.33 (3H, t, *J* = 7.2 Hz).

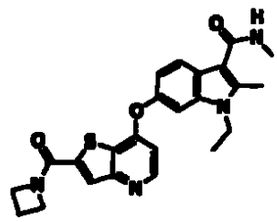
Example 71(e): 1-Ethyl-6-hydroxy-2-methyl-1*H*-indole-3-carboxylic acid methylamide



This material was prepared from 1-ethyl-6-methoxy-2-methyl-1*H*-indole-3-carboxylic acid methylamide 71d (350 mg, 1.42 mmole) by treatment with BBr_3 in a manner as previously described for example 1d to give 280 mg product as white solid (85 % yield). ^{1}H

NMR (400 MHz, $CDCl_3$) δ 7.48 (1H, d, *J* = 8.3 Hz), 6.73-6.77 (2H, m), 6.01 (1H, bs), 4.04 (2H, q, *J* = 7.2 Hz, 3.03 (3H, d, *J* = 4.9 Hz), 2.66 (3H, s), 1.31 (3H, t, *J* = 7.2 Hz).

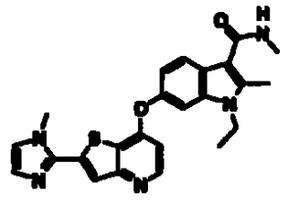
Example 71: 6-[2-(Azetidine-1-carbonyl)-thieno[3,2-*b*]pyridin-7-yloxy]-1-ethyl-2-methyl-1*H*-indole-3-carboxylic acid methylamide



This material was prepared by the reaction of 2-(azetidin-1-ylcarbonyl)-7-chlorothieno[3,2-*b*]pyridine 25a with 1-ethyl-6-hydroxy-2-methyl-1*H*-indole-3-carboxylic acid methylamide 71e and Cs_2CO_3 in a manner as previously described for example 1. ^1H NMR (300 MHz, $CDCl_3$) δ 8.47 (1H, d, *J* = 5.5 Hz), 7.75 (2H, m), 7.16 (1H, d, *J* = 1.7 Hz), 7.01 (1H, dd, *J* = 1.7, 8.4 Hz), 6.56 (1H, d, *J* = 5.5 Hz), 5.91 (1H, bs), 4.59 (2H, m), 4.28 (2H, m), 4.11 (2H, m), 3.05 (3H, d, *J* = 4.0 Hz), 2.72 (3H, s), 2.45 (2H, m), 1.33 (3H, m). LCMS (ESI+) [M+H]/z Calc'd 449, found 449.

Anal. ($C_{24}H_{24}N_4O_2S$·0.5H_2O·0.25MeOH) C, H, N.

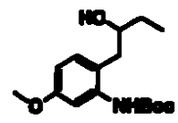
Example 72: 1-Ethyl-2-methyl-6-[2-(1-methyl-1*H*-imidazol-2-yl)-thieno[3,2-*b*]pyridin-7-yloxy]-1*H*-indole-3-carboxylic acid methylamide



This material was prepared by the reaction of 7-chloro-2-(1-methyl-1H-imidazol-2-yl)thieno[3,2-*b*]pyridine 1e with 1-ethyl-6-hydroxy-2-methyl-1*H*-indole-3-carboxylic acid methylamide 71e and Cs_2CO_3 in a manner as previously described for example 1. ^1H NMR (300 MHz, $CDCl_3$) δ 8.44 (1H, d, *J* = 5.4 Hz), 7.74 (1H, d, *J* = 8.7 Hz), 7.68 (1H, s), 7.18 (1H, d, *J* = 1.9 Hz), 7.14 (1H, s), 7.05 (1H, d, *J* = 1.9 Hz), 7.02 (1H, s), 6.54 (1H, d, *J* = 5.4 Hz), 5.92 (1H, bs), 4.11 (2H, m), 3.96 (3H, s), 3.05 (3H, d, *J* = 4.7 Hz), 2.72 (3H, s), 1.33 (3H, m). LCMS (ESI+) [M+H]/z Calc'd 446, found 446.

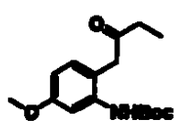
Anal. ($C_{24}H_{23}N_5O_2S$·0.5 H_2O·0.5 MeOH) C, H, N.

Example 73(a): [2-(2-Hydroxy-butyl)-5-methoxy-phenyl]-carbamic acid *t*-butyl ester



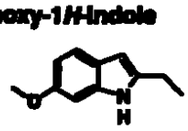
To a solution of (5-methoxy-2-methyl-phenyl)-carbamic acid *t*-butyl ester (6.85 g, 29.3 mmole) in 100 ml THF cooled at –45 °C was added sec-BuLi (45 ml, 58.5 mmole) slowly to keep temperature lower than –45 °C. The reaction mixture was stirred and warmed to –20 °C, then cooled to –45 °C and propionaldehyde (2.67 ml, 36.63 mmole) was added. The reaction mixture was stirred and warmed to room temperature for 1 h, quenched with 1N HCl and extracted with EtOAc, dried over $MgSO_4$ and concentrated. The residue was purified by flash column chromatography (10 – 15% EtOAc in hexane) to give colorless oil (3.40 g, 39%). ^1H NMR ($CDCl_3$) δ 7.96 (1H, s), 7.44 (1H, s), 6.96-7.00 (1H, m), 6.55 (1H, m), 3.80 (3H, s), 2.60-2.78 (2H, *m*), 1.93-1.95 (2H, *m*), 1.50 (9H, s), 0.93-1.01 (4H, *m*). ESIMS (MNa^+): 318.20.

Example 73(b): [5-Methoxy-2-(2-oxo-butyl)-phenyl]-carbamic acid *t*-butyl ester



To a solution of Dess-Martin reagent (2.82 g, 6.68 mmole) in 80 ml THF cooled at 0 °C was added [2-(2-hydroxy-butyl)-5-methoxy-phenyl]-carbamic acid *t*-butyl ester 73a (1.64 g, 5.57 mmole) in 20 ml THF. The reaction mixture was stirred and warmed to room temperature for 2 h, quenched with half saturated $NaHCO_3$, extracted with EtOAc. The organic layer was dried over $MgSO_4$ and concentrated. The residue was purified by flash column chromatography (10 – 15% EtOAc in hexane) to give colorless oil (1.36 g, 84%). ^1H NMR ($CDCl_3$) δ 7.67 (1H, bs), 7.48 (1H, s), 6.99-7.03 (1H, m), 6.56-6.60 (1H, m), 3.79 (3H, s), 3.59 (2H, s), 2.53-2.61 (2H, q, J = 7.2 Hz), 1.51 (9H, s), 1.02 (3H, t, J = 7.2 Hz). ESIMS (MNa^+): 316.10.

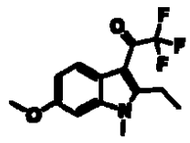
Example 73(a): 2-Ethyl-6-methoxy-1*H*-indole



To a solution of [5-methoxy-2-(2-oxo-butyl)-phenyl]-carbamic acid *t*-butyl ester 73b (1.36 g, 4.65 mmole) in 10 ml THF was added 4 ml TFA. The reaction mixture was stirred at room temperature for 5 h, quenched with 50 ml H_2O and extracted with EtOAc. The organic layer was dried over $MgSO_4$ and concentrated. The residue was purified by flash column chromatography (10 – 15% EtOAc in hexane) to give pale yellow solid (1.36 g, 73%). ^1H NMR

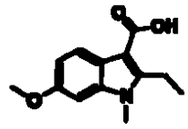
($CDCl_3$) δ 7.75 (1H, bs), 7.49 (1H, d, J = 8.6 Hz), 6.81 (1H, s), 6.73 (1H, d, J = 8.6 Hz), 3.83 (3H, s), 2.75 (2H, q, J = 7.5 Hz), 1.32 (3H, t, J = 7.5 Hz). ESIMS (MH^+): 272.10.

Example 73(d): 1-(2-Ethyl-6-methoxy-1-methyl-1*H*-indol-3-yl)-2,2,2-trifluoro-ethanone



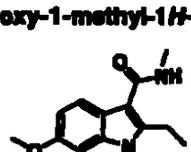
To a solution of 2-ethyl-6-methoxy-*1H*-indole 73c (1.79 g, 10.2 mmole) in 50 ml THF at 0 °C was added TFAA (1.58 ml, 11.22 mmole). The reaction mixture was stirred at 0 °C for 1 h, then concentrated and dried under vacuum, which was used without purification. ESIMS (MH^+): 272.10. The above residue was dissolved in 25 ml THF and cooled to 0 °C, MeI (1.59 ml, 25.5 ml) and NaH (60%, 0.816 g, 20.4 mmole) was added. The reaction was stirred at room temperature for 1h, quenched with H_2O and extracted with EtOAc. The organic layer was dried over $MgSO_4$, and concentrated. The residue was purified by flash column chromatography (25% EtOAc in hexane) to give yellow color solid (2.42 g, 73%). ^1H NMR ($CDCl_3$) δ 7.88 (1H, d, J = 8.9 Hz), 6.94 (1H, dd, J = 2.4, 8.9 Hz), 6.81 (1H, s), 3.88 (3H, s), 3.72 (3H, s), 3.20 (2H, q, J = 7.5 Hz), 1.27 (3H, t, J = 7.5 Hz). ESIMS (MH^+): 286.10

Example 73(e): 2-Ethyl-6-methoxy-1-methyl-1*H*-indole-3-carboxylic acid



KOH (1.9 g, 33.49 mmole) in 20 ml H_2O was added to a solution of 1-(2-ethyl-6-methoxy-1-methyl-*1H*-indol-3-yl)-2,2,2-trifluoro-ethanone 73d (2.42 g, 8.47 mmole) in 20 ml EtOH. The reaction mixture was heated to reflux for 8 h and concentrated. The residue was dissolved in H_2O, acidified with 1N HCl to pH ~ 1 and filtrated. The solid was purified by flash column chromatography (2 - 5% CH_3OH in CH_2Cl_2) to give yellow color solid (1.3 g, 72%). ^1H NMR ($CDCl_3$) δ 11.88 (1H, bs), 7.82 (1H, d, J = 8.7 Hz), 7.04 (1H, s), 6.77 (1H, d, J = 8.7 Hz), 3.80 (3H, s), 3.70 (3H, s), 3.51 (2H, q, J = 7.4 Hz), 1.15 (3H, t, J = 7.4 Hz). ESIMS (MH^+): 234.05.

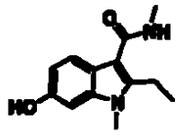
Example 73(f): 2-Ethyl-6-methoxy-1-methyl-1*H*-indole-3-carboxylic acid methylamide



Thionyl chloride (0.383 ml, 4.45 mmole) was added to a solution of 2-ethyl-6-methoxy-1-methyl-*1H*-indole-3-carboxylic acid 73e (0.347 g, 1.48 mmole). The reaction mixture was

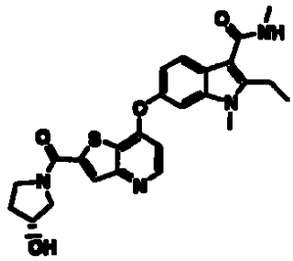
heated to reflux for 30 min and concentrated. The residue was dissolved in 5 ml CH_2Cl_2 and added methylamine (2.0 M in THF, 2.22 ml, 4.44 mmole). The reaction mixture was stirred at room temperature for 1hr, then concentrated. The residue was purified by flash column chromatography (2 - 5% CH_3OH in CH_2Cl_2) to give yellow color solid (0.267 g, 73%). ^1H NMR ($CDCl_3$) δ 7.47 (1H, d, J = 8.7 Hz), 6.80 (1H, s), 6.69 (1H, d, J = 8.7 Hz), 3.47 (3H, s), 3.58 (3H, s), 3.00 (2H, q, J = 7.4 Hz), 2.83 (3H, s), 1.14 (3H, t, J = 7.4 Hz). ESIMS (MH^+): 247.10.

Example 73(g): 2-Ethyl-6-hydroxy-1-methyl-1*H*-indole-3-carboxylic acid methylamide



To a solution of 2-ethyl-6-methoxy-1-methyl-*1H*-indole-3-carboxylic acid methylamide *73f* (0.267 g, 1.08 mmole) in 15 ml CH_2Cl_2 at 0 °C was added BBr_3 (1.0 M in CH_2Cl_2, 3.25 ml, 3.25 mmole). The reaction mixture was stirred at room temperature for 2 h, quenched with saturated NH_4OH to make pH~10. The mixture was diluted with H_2O and extracted with 10% CH_3OH in CH_2Cl_2. The organic layer was dried over $MgSO_4$ and concentrated. The residue purified by flash column chromatography (3 - 5% CH_3OH in CH_2Cl_2) to give pale yellow color solid (0.170 g, 68%). ^1H NMR ($CDCl_3$) δ 7.40 (1H, d, J = 8.5 Hz), 6.85 (1H, s), 6.59 (1H, d, J = 8.5 Hz), 3.53 (3H, s), 3.28 (2H, q, J = 7.5 Hz), 2.82 (3H, s), 1.13 (3H, t, J = 7.5 Hz). ESIMS (MH^+): 233.15.

Example 73: 2-Ethyl-6-[2-(3-hydroxy-pyrrolidine-1-carbonyl)-thieno[3,2-*b*]pyridin-7-yloxy]-1-methyl-1*H*-indole-3-carboxylic acid methylamide

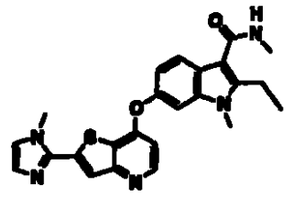


The material was prepared by the reaction of (7-chloro-thieno[3,2-*b*]pyridin-2-yl)-(3-hydroxy-pyrrolidin-1-yl)-methanone 4a (0.148 g, 0.517 mmole) with 2-ethyl-6-hydroxy-1-methyl-*1H*-indole-3-carboxylic acid methylamide 73g (0.080 g, 0.344 mmole) and Cs_2CO_3 (0.112 g, 0.344 mmole) in a manner as previously described for example 1 to give 30 mg (18% yield) of pale yellow solid. ^1H NMR (CD_3OD) δ 8.34 (1H, d, J = 5.5 Hz), 7.69-7.70 (2H, m), 7.28 (1H,

123

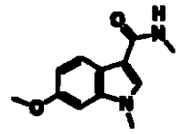
s), 6.91 (1H, d, J = 6.8 Hz), 6.85 (1H, d, J = 5.5 Hz), 4.39 (1H, m), 3.90 (2H, m), 3.67-3.61 (5H, m), 2.99 (2H, m), 2.88 (3H, m), 2.00 (2H, m), 1.14-1.19 (3H, m). ESIMS (MH^+): 479.10. *Anal.* Calcd. For $C_{25}H_{30}N_4O_4S$•0.55 CH_2Cl_2: C, 58.42; H, 5.20; N, 10.67. Found: C, 58.47; H, 5.43; N, 11.31.

Example 74: 2-Ethyl-1-methyl-6-[2-(1-methyl-1*H*-imidazol-2-yl)-thieno[3,2-*b*]pyridin-7-yloxy]-1*H*-indole-3-carboxylic acid methylamide



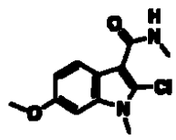
This material was prepared by the reaction 7-chloro-2-(1-methyl-1*H*-imidazol-2-yl)thieno[3,2-*b*]pyridine 1e (0.084g, 0.34 mmole) with 2-ethyl-6-hydroxy-*N*,1-dimethyl-1*H*-indole-3-carboxamide 73g (0.078g, 0.33 mmole) and Cs_2CO_3 (0.111g, 0.34 mmole) in a manner as previously described for example 1 to give an off-white solid (0.058g, 40%). ^{1}H NMR (300 MHz, CD_3OD δ 8.27 (1H, d, J = 5.4 Hz), 7.68 (1H, d, J = 8.6 Hz), 7.59 (1H, s), 7.24 (1H, d, J = 1.9 Hz), 7.17 (1H, s), 6.96 (1H, s), 6.90 (1H, dd, J = 1.9, 8.6 Hz), 6.50 (1H, d, J = 5.4 Hz), 3.87 (3H, s), 3.58 (3H, s), 3.01 (2H, m), 2.85 (3H, s), 1.14 (3H, m). HRMS (MH^+): Calcd: 446.1655; Found: 446.1651.

Example 75(a): 6-Methoxy-1-methyl-1*H*-indole-3-carboxylic acid methylamide



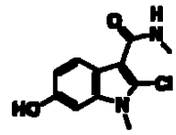
This material was prepared from 6-methoxy-1-methyl-1*H*-indole-3-carboxylic acid 16b (2.39 g, 10.9 mmole), oxalyl chloride and methylamine in a manner as previously described for example 16d to give a brown solid (1.06g, 45%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.97 (1H, d, J = 8.7 Hz), 7.76 (2H, m), 6.99 (1H, d, J = 2.3 Hz), 6.77 (1H, dd, J = 2.3, 8.7 Hz), 3.80 (3H, s), 3.76 (3H, s), 2.74 (3H, s); ESIMS (MH^+): 219.05.

Example 75(b): 2-Chloro-6-methoxy-1-methyl-1*H*-indole-3-carboxylic acid methylamide



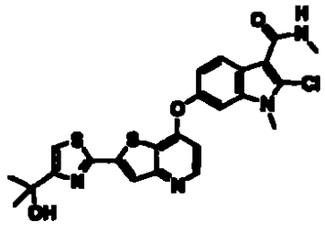
N-Chlorosuccinimide (0.150 g, 1.12 mmole) was added to a solution of 6-methoxy-*N*,1-dimethyl-1*H*-indole-3-carboxamide 75a (0.243 g, 1.11 mmole) in CCl_4 (10 ml) and DMF (3 ml). The reaction mixture was heated to 80°C for 3h and concentrated. The residue was purified by reverse phase chromatography eluting with 0-1% CH_3OH in 1:1 EtOAc and CH_2Cl_2 to give a brown colored oil (0.243 g, 87% yield); ^1H NMR (300 MHz, $CDCl_3$) δ 7.61 (1H, d, *J* = 8.6 Hz), 6.38 (1H, d, *J* = 8.6 Hz), 6.19 (1H, s), 3.35 (3H, s), 2.96 (3H, s), 2.52 (3H, s); ESIMS (MH^+): 253.05.

Example 75(c): 2-Chloro-6-hydroxy-1-methyl-1*H*-indole-3-carboxylic acid methylamide



This material was prepared by reaction of 2-chloro-6-methoxy-*N*,1-dimethyl-1*H*-indole-3-carboxamide 75b (0.38g, 1.4 mmole) with 1.0 M BBr_3 in CH_2Cl_2 (4.19 ml, 4.19 mmole) in a manner as previously described for example 1d to give an off-white solid (0.195g, 85%). ^{1}NMR (300 MHz, CD_3OD) δ 7.61 (1H, d, *J* = 8.3 Hz), 6.65 (1H, s), 6.62 (1H, d, *J* = 2.1 Hz), 3.56 (3H, s) 2.85 (3H, s); ESIMS (MH^+): 239.00.

Example 75: 2-Chloro-6-[2-[4-(1-hydroxy-1-methyl-ethyl)-thiazol-2-yl]-thieno[3,2-*b*]pyridin-7-yloxy]-1-methyl-1*H*-indole-3-carboxylic acid methylamide

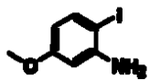


This material was prepared by the reaction of 2-[2-(7-chlorothieno[3,2-*b*]pyridin-2-yl)-1,3-thiazol-4-yl]propan-2-ol 40a (0.102g, 0.33 mmole) with 2-chloro-6-hydroxy-*N*,1-dimethyl-1*H*-indole-3-carboxamide 75c (0.085g, 0.33 mmole) and Cs_2CO_3 (0.108g, 0.33 mmole) in a manner as previously described for example 1 to give an off-white solid (0.039g, 21%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.40 (1H, d, *J* = 5.5 Hz), 8.31 (1H, d, *J* = 8.3 Hz), 7.82 (1H, m), 7.20

(1H, s), 7.14 (1H, s), 7.07 (2H, m), 6.47 (1H, d, J = 5.5 Hz), 6.34 (1H, m), 3.89 (3H, s), 3.01 (3H, d, J = 4.7 Hz), 1.80 (6H, s).

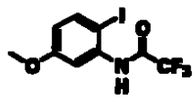
Anal. Calcd. For $C_{24}H_{21}N_4O_3S_2Cl$•0.6 H_2O•1.0 CH_3OH: C, 54.71; H, 4.53; N, 10.36; Found: C, 54.56; H, 4.45; N, 10.17.

Example 76(a): 2-Iodo-5-methoxy-phenylamine



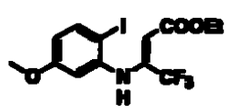
To a solution of 4-Iodo-3-nitroanisole (5g, 17.9 mmole) in 100 ml methanol was added $FeCl_3$ (50mg, 0.3 mmole) and activated carbon (40 mg). The mixture was heated to reflux and hydrazine hydrate (1.75 g, 35 mmole) was added dropwise. The mixture was refluxed for an additional 8 hours and cooled to room temperature, filtered through Celite. The filtrate was concentrated and purified by column chromatography (eluting with 10% EtOAc in hexanes) to give 4.05 g product as pale yellow oil (91% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.47 (1H, d, J = 8.7 Hz), 6.31 (1H, d, J = 2.8 Hz), 6.13 (1H, dd, J = 2.8, 8.7 Hz), 3.73 (3H, s).

Example 76(b): 2,2,2-Trifluoro-*N*-(2-iodo-5-methoxy-phenyl)-acetamide



To a solution of 2-Iodo-5-methoxy-phenylamine 76a (4.05 g, 16.3 mmole) in 10 ml anhydrous CH_2Cl_2 was added TFAA (4.1 g, 19.5 mmole). The mixture was stirred at 38°C overnight, TLC indicated some starting material remained. Additional TFAA (4.1 g, 19.5 mmole) was added and stirred at 38°C for another 24 hours. The mixture was concentrated under rot vap and purified by column chromatography (eluting with 5-10 % EtOAc in hexanes) to give 4.6 g product (81% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.92 (1H, d, J = 2.8 Hz), 7.66 (1H, d, J = 8.9 Hz), 6.59 (1H, dd, J = 2.8, 8.9 Hz), 3.82 (3H, s).

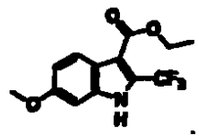
Example 76(c): 4,4,4-Trifluoro-3-(2-iodo-5-methoxy-phenylamino)-but-2-enoic acid ethyl ester



A solution of 2,2,2-trifluoro-N-(2-iodo-5-methoxy-phenyl)-acetamide 76b (4.6 g, 13.3 mmole) and methyl (triphenylphosphoranylidene)acetate (8.7 g, 25 mmole) in 50 ml toluene was brought to reflux for 5 hours and cooled to room temperature. The solution was

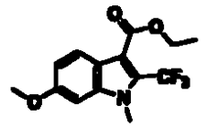
concentrated, *in vacuo* and purified by column chromatography (eluting with 2-6 % EtOAc in hexanes) to give 4.8 g product (87% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.57 (1H, s), 7.68 (1H, d, J = 8.8 Hz), 6.83 (1H, d, J = 2.8 Hz), 6.57 (1H, dd, J = 2.8, 8.8 Hz), 5.43 (1H, s), 4.23 (2H, m), 3.76 (3H, s), 1.55 (3H, s), 1.31 (3H, m).

Example 76(d): 6-Methoxy-2-trifluoromethyl-1*H*-indole-3-carboxylic acid ethyl ester



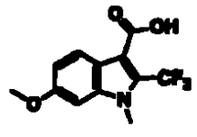
A mixture of 4,4,4-trifluoro-3-(2-iodo-5-methoxy-phenylamino)-but-2-enoic acid ethyl ester 76c (0.5 g, 1.2 mmole), $Pd(OAc)_2$ (22.4 mg, 0.1 mmole), PPh_3 (52.5 mg, 0.2 mmole) and $NaHCO_3$ (505 mg, 6mmole) in 5 ml DMF was heated at 120°C under argon for 24 hours and cooled to room temperature. The mixture was poured into EtOAc/water and washed with brine. The organic layer was dried over Na_2SO_4 and concentrated under rot vap. The residue was purified by column chromatography to give 217 mg product (63% yield). ^{1}H NMR (300 MHz, CD_3OD) δ 8.00 (1H, d, J = 9.0 Hz), 6.96 (1H, d, J = 2.0 Hz), 6.90 (1H, dd, J = 2.0, 9.0 Hz), 4.37 (2H, m), 3.84 (3H, s), 1.40 (3H, m).

Example 76(e): 6-Methoxy-1-methyl-2-trifluoromethyl-1*H*-indole-3-carboxylic acid ethyl ester



This material was prepared from 6-methoxy-2-trifluoromethyl-1*H*-indole-3-carboxylic acid ethyl ester 76d (1.64 g, 5.7 mmole) by treatment with NaH (274 mg, 60% in mineral oil, 6.84 mmole) and methyl iodide (1.21 g, 8.55 mmole) and NaH in a manner as previously described for example 16b to give 1.5 g product (87% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.96 (1H, dd, J = 3.7, 8.8 Hz), 6.94 (1H, dd, J = 2.3, 9.1 Hz), 6.77 (1H, d, J = 2.1 Hz), 4.40 (2H, m), 3.89 (3H, s), 3.86 (3H, s), 1.41 (3H, m).

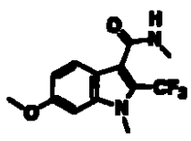
Example 76(f): 6-Methoxy-1-methyl-2-trifluoromethyl-1*H*-indole-3-carboxylic acid



To a solution of 6-methoxy-1-methyl-2-trifluoromethyl-1*H*-indole-3-carboxylic acid ethyl ester 76e (1.5 g, 4.98 mmole) in 10 ml THF and 5ml MeOH was added a solution of KOH (2.8 g, 50 mmole) in 5 ml water with ice bath cooling. The mixture was warmed to room

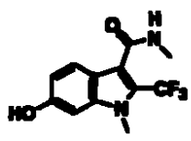
temperature and stirred overnight. Concentrated aqueous HCl solution was added to adjust the pH to 1. The mixture was extracted with EtOAc and the combined organic layer was dried over Na_2SO_4, filtered and concentrated. The residue was further purified by column chromatography (eluting with 1-5% MeOH in CH_2Cl_2) to give 880 mg product (65% yield). ^1H NMR (300 MHz, CD_3OD) δ 7.90 (1H, d, J = 9.0 Hz), 7.01 (1H, d, J = 2.1 Hz), 6.91 (1H, dd, J = 2.1, 9.0 Hz), 3.90 (3H, s), 3.86 (3H, s).

Example 76(g): 6-Methoxy-1-methyl-2-trifluoromethyl-1*H*-indole-3-carboxylic acid methylamide



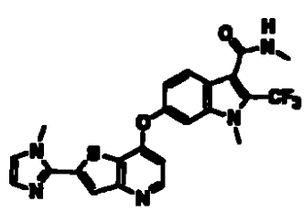
This material was prepared from 6-methoxy-1-methyl-2-trifluoromethyl-1*H*-indole-3-carboxylic acid 78f (880 mg, 3.22 mmole), oxalyl chloride (3 ml, 2.0M solution) and methylamine (5 ml, 2.0M solution) in a manner as previously described for example 16d to give 900 mg product as white solid (98% yield). ^1H NMR (300 MHz, $CDCl_3$) δ 7.62 (1H, d, J = 8.9 Hz), 6.88 (1H, dd, J = 2.1, 8.9 Hz), 6.73 (1H, d, J = 2.1 Hz), 5.80 (1H, bs), 3.88 (3H, s), 3.79 (3H, s), 3.04 (3H, d, J = 4.9 Hz).

Example 76(h): 6-Hydroxy-1-methyl-2-trifluoromethyl-1H-indole-3-carboxylic acid methylamide



This material was prepared from 6-hydroxy-1-methyl-2-trifluoromethyl-1H-indole-3-carboxylic acid methylamide 78g (900 mg, 3.14 mmole) by treatment with BBr_3 in a manner as previously described for example 1d to give 760 mg product as white solid (89% yield). ^1H NMR (300 MHz, CD_3OD) δ 7.44 (1H, d, J = 8.7 Hz), 6.76-6.81 (2H, m), 3.77 (1H, s), 2.93 (3H, s).

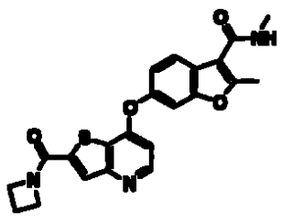
Example 76: 1-Methyl-6-[2-(1-methyl-1*H*-imidazol-2-yl)-thieno[3,2-*b*]pyridin-7-yloxy]-2-trifluoromethyl-1*H*-indole-3-carboxylic acid methylamide



The material was prepared by the reaction of 7-chloro-2-(1-methyl-1H-imidazol-2-yl)thieno[3,2,-b]pyridine 1e with 6-hydroxy-1-methyl-2-trifluoromethyl-1*H*-indole-3-carboxylic acid methylamide 76h and Cs_2CO_3 in a manner as previously described for example 1. ^1H NMR (300 MHz, DMSO-d_6) δ 8.51 (1H, d, *J* = 5.5 Hz), 7.89 (1H, s), 7.78 (1H, s), 7.72 (1H, d, *J* = 8.6 Hz), 7.41 (1H, s), 7.18 (1H, d, *J* = 9.8 Hz), 7.03 (1H, s), 6.66 (1H, d, *J* = 5.4 Hz), 3.99 (3H, s), 3.86 (3H, s), 2.81 (3H, s). LCMS (ESI+) [M+H]/z Calc'd 486, found 486.

Anal. ($C_{25}H_{18}F_3N_5O_2S$•1.3H_2O) C, H, N.

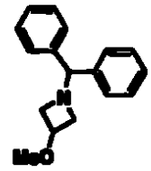
Example 77: 6-[2-(Azetidine-1-carbonyl)-thieno[3,2-b]pyridin-7-yloxy]-2-methyl-benzofuran-3-carboxylic acid methylamide



This material was prepared by the reaction 2-(azetidin-1-ylcarbonyl)-7-chlorothieno[3,2-*b*]pyridine 25a (100 mg, 0.40 mmole) with 6-hydroxy-2-methylbenzofuran-3-carboxylic acid methylamide (100 mg, 0.49 mmole) and Cs_2CO_3 (257 mg, 0.79 mmole) in a manner as previously described for example 1 to give 124mg (74%) of a tan solid. ^1H NMR (DMSO-d_6) δ 8.56 (1H, d, J = 5.6 Hz), 7.99 (1H, d, J = 4.6 Hz), 7.89 (1H, s), 7.83 (1H, d, J = 8.6 Hz), 7.66 (1H, d, J = 2.0 Hz), 7.24 (1H, dd, J = 8.6, 2.3 Hz), 6.70 (1H, d, J = 5.3 Hz), 4.61 (2H, t, J = 7.6 Hz), 4.10 (2H, t, J = 7.3 Hz), 2.81 (3H, d, J = 4.6Hz), 2.63 (3H, s), 2.35 (2H, p, J = 7.7 Hz).

Anal. Calcd for $C_{22}H_{19}N_3O_4S$• 0.5 H_2O: C, 62.03; H, 4.61; N, 9.86; S, 7.53. Found: C, 62.31; H, 4.65; N, 9.60; S, 7.34.

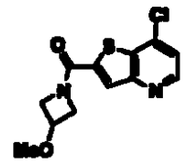
Example 78(a): 1-Benzhydryl-3-methoxy-azetidine



To an ice cold solution of 1-benzhydrylazetidin-3-ol 9a (1.0 g, 4.2 mmole) in DMF (10 ml) was added 60% dispersion NaH in mineral oil (0.25 g, 6.3 mmole). After 30min at 0°C, 5ml more DMF was added along with methyl iodide (0.39 ml, 6.3 mmole). The ice bath was

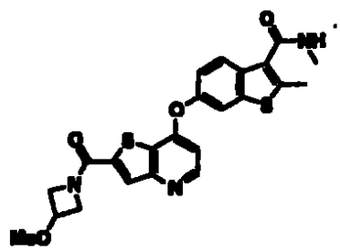
removed, and the reaction was stirred at room temperature (rt). After 1.5hr, the reaction was poured into brine and extracted with Et_2O (2x). The combined organic layers were washed with brine, dried ($MgSO_4$) and concentrated under reduced pressure. The residue was flash chromatographed on silica gel eluting Hexanes/EtOAc (1:1) to give 919mg (92%) of a colorless oil which crystallized on standing. ^1H NMR (DMSO-d_6) δ 7.42 (4H, d, J = 7.3 Hz), 7.27 (4H, t, J = 7.3 Hz), 7.13 (2H, t, J = 7.3 Hz), 4.39 (1H, s), 3.95 (1H, p, J = 5.8 Hz), 3.35 (2H, t, J = 6.3 Hz), 3.11 (3H, s), 2.75 (2H, t, J = 5.6 Hz).

Example 78(b): (7-Chloro-thieno[3,2-b]pyridin-2-yl)-(3-methoxy-azetidin-1-yl)-methanone



A 100 ml round bottom flask was charged with 1-benzhydryl-3-methoxy-azetidine 78a (447 mg, 1.77 mmole), 10%Pd/C (300 mg), trifluoroacetic acid (0.15 ml, 1.94 mmole) and EtOH (30 ml) and placed under 1 atm H_2 and vigorously stirred at rt. After 2hr, the catalyst was removed and washed with MeOH. The filtrate was concentrated under reduced pressure to give the crude azetidine which was dissolved in CH_2Cl_2. To this solution were added triethylamine (0.6 ml, 4.41 mmole) and 7-chloro-thieno[3,2-b]pyridine-2-carbonyl chloride, prepared as previously described in example 25a. After stirring at ambient temperature overnight, the reaction mixture was diluted with more CH_2Cl_2, then washed sequentially with 0.5N HCl, satd. $NaHCO_3$ (aq), and brine. The organic layer was dried ($MgSO_4$) and concentrated to near dryness under reduced pressure, then triturated with hexanes to give 278 mg (56%) of the desired product as a light yellow solid. ^1H NMR (DMSO-d_6) δ 8.73(1H, d, J = 5.1 Hz), 8.00 (1H, s), 7.70 (1H, d, J = 5.1 Hz), 4.77 (1H, m), 4.49 (1H, m), 4.31 (2H, m), 3.90 (1H, m), 3.24 (3H, s). APCI m/z 283/285 $(M + H)^+$.

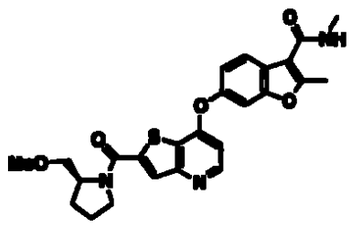
Example 78: Methoxy-azetidine-1-carbonyl)-thieno[3,2-b]pyridin-7-yloxy]-2-methyl-benzofuran-3-carboxylic acid methylamide



This material was prepared by the reaction of (7-Chloro-thieno[3,2-b]pyridin-2-yl)-(3-methoxy-azetidin-1-yl)-methanone 78b (241 mg, 0.85 mmole) with 6-hydroxy-2-methylbenzo[b]furan-3-carboxylic acid methylamide 12c (210 mg, 1.02 mmole) and Cs_2CO_3 (833 mg, 2.56 mmole) in a manner as previously describedin example 1 to give 298 mg (77%) of a yellow solid. ^1H NMR (DMSO-d_6) δ 8.57 (1H, d, J = 5.3 Hz), 7.99 (1H, d, J = 4.7 Hz), 7.94 (1H, s), 7.82 (1H, d, J = 8.5 Hz), 7.66 (1H, d, J = 2.3 Hz), 7.24 (1H, dd, J = 8.5, 2.3 Hz), 6.72 (1H, d, J = 5.5 Hz), 4.76 (1H, m), 4.47 (1H, m), 4.30 (2H, m), 3.90 (1H, m), 3.25 (3H, s), 2.82 (3H, d, J = 4.5 Hz), 2.63 (3H, s).

Anal. Calcd for $C_{22}H_{21}N_3O_5S$•0.4 H_2O: C, 60.22; H, 4.79; N, 9.16; S, 6.99. Found: C, 60.33; H, 4.78; N, 9.13; S, 6.79.

Example 79: 6-(2-[(S)-2-(methoxymethyl)pyrrolidine-1-carbonyl]thieno[3,2-b]pyridin-7-yloxy)-2-methyl-benzofuran-3-carboxylic acid methyl amide

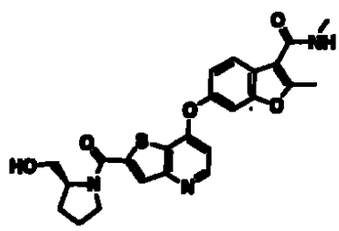


This material was prepared by the reaction of 7-chloro-2-[(R)-2-methoxymethylpyrrolidine-1-carbonyl]thieno[3,2-b]pyridine 2a with 6-Hydroxy-2-methyl-benzofuran-3-carboxylic acid methyl amide 12c and Cs_2CO_3 in a manner as previously described for example 1. ^1H NMR (DMSO-d_6) δ 8.57 (1H,d, J = 5.3 Hz), 8.02 (1H, s), 7.98 (1H, m), 7.83 (1H, d, J = 8.6 Hz), 7.66 (1H, d, J = 2.0 Hz), 7.25 (1H, dd, J = 8.6, 2.0 Hz), 6.72 (1H, d, J = 5.3 Hz), 4.31 (1H,m), 3.94-3.80 (2H, m), 3.60-3.39 (2H, m), 3.28 (3H, s), 2.82 (3H, d, J = 4.6 Hz), 2.63 (3H, s), 2.06-1.85 (4H,m).

Anal. Calcd for $C_{23}H_{23}N_3O_5S$•0.6H_2O• 0.2 Hexanes: C, 61.99; H, 5.76; N, 8.26; S, 6.32. Found: C, 61.94; H, 5.74; N, 8.12; S, 6.32.

Example 80: 6-(2-[(S)-2-(hydroxymethyl)pyrrolidine-1-carbonyl]thieno[3,2-b]pyridin-7-yloxy)-2-methyl-benzofuran-3-carboxylic acid methylamide

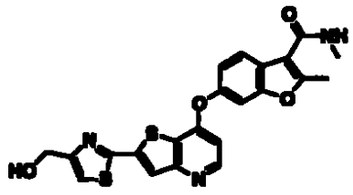
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This material was prepared from 2-methyl-6-[2-(2-methoxymethyl-pyrrolidine-1-carbonyl)-thieno[3,2-b]pyridin-7-yloxy]-benzofuran-3-carboxylic acid methylamide 79 by treatment with BBr_3 in a manner as previously described for example 1d. ^1H NMR (DMSO-d_6) δ 8.56 (1H, d, J = 5.1 Hz), 8.00-7.98 (2H, m), 7.83 (1H, d, J = 8.6 Hz), 7.66 (1H, d, J = 2.0 Hz), 7.25 (1H, dd, J = 8.6, 2.0 Hz), 6.73 (1H, d, J = 5.1 Hz), 4.81 (1H, m), 4.18 (1H, m), 3.91-3.32 (4H, m), 2.81 (3H, d, J = 4.5 Hz), 2.63 (3H, s), 2.05-1.83 (4H, m).

Anal. Calcd for $C_{24}H_{23}N_3O_5S \cdot 2\ H_2O \cdot 0.2$ EtOAc: C, 57.37; H, 5.55; N, 8.09; S, 6.18. Found: C, 57.15; H, 5.24; N, 7.71; S, 6.01.

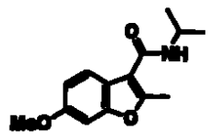
Example 81: 6-[2-(4-Hydroxymethyl-thiazol-2-yl)-thieno[3,2-b]pyridin-7-yloxy]-2-methyl-benzofuran-3-carboxylic acid methylamide



This material was prepared by the reaction of [2-(7-Chloro-thieno[3,2-b]pyridin-2-yl)-thiazol-4-yl]-methanol with 6-hydroxy-2-methyl-benzofuran-3-carboxylic acid methyl amide 12c and Cs_2CO_3 in a manner as previously described for example 1. ^1H NMR (DMSO-d_6) δ 8.55 (1H, d, J = 5.6 Hz), 8.16 (1H, s), 7.98 (1H, m), 7.84 (1H, d, J = 8.6 Hz), 7.67 (1H, d, J = 2.0 Hz), 7.63 (1H, s), 7.26 (1H, dd, J = 8.6, 2.0 Hz), 6.73 (1H, d, J = 5.6 Hz), 5.43 (1H, m), 4.61 (2H,s), 2.82 (3H, d, J = 4.6 Hz) , 2.64 (3H, s).

Anal. Calcd for $C_{22}H_{17}N_3O_4S_2 \cdot 0.6\ H_2O$: C, 57.15; H, 3.97; N, 9.09; S, 13.87. Found: C, 57.13; H, 4.07; N, 8.95; S, 13.67.

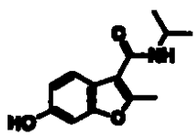
Example 82(a): 6-Methoxy-2-methyl-benzofuran-3-carboxylic acid isopropyl amide



This material was prepared from 6-methoxy-2-methylbenzofuran,12a (500mg, 3.1mmole) by acylation with oxalyl chloride in the presence of $AlCl_3$, followed by treatment with isopropylamine in a manner as previously described for example 1c to give 540mg (71%) of an off-white solid. ^1H NMR (DMSO-d_6) δ 7.80 (1H, d, J = 7.8 Hz), 7.50 (1H, d, J = 8.6 Hz), 7.14 (1H, d, J = 2.2 Hz), 6.89 (1H, dd, J = 8.6, 2.2 Hz), 4.09 (1H, m), 3.76 (3H, s), 2.56 (3H, s), 1.18 (6H, d, J = 6.6 Hz).

Anal. Calcd for $C_{14}H_{17}NO_3$: C, 67.99; H, 6.93; N, 5.66. Found: C, 67.86; H, 6.87; N, 5.60.

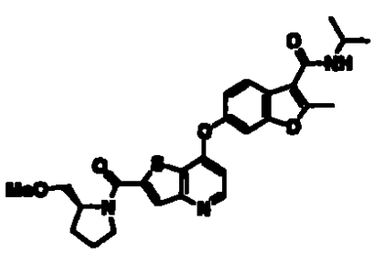
Example 82(b): 6-Hydroxy-2-methyl-benzofuran-3-carboxylic acid isopropyl amide



This material was prepared from 6-methoxy-2-methylbenzofuran-3-carboxylic acid isopropylamide 82a (507mg, 2.05mmole) by treatment with BBr_3 in a manner as previously described for example 1d to give 425mg (89%) of lt. tan solid. ^1H NMR (DMSO-d_6) δ 9.54 (1H, s), 7.71 (1H, d, J = 8.1 Hz), 7.38 (1H, d, J = 8.6 Hz), 6.87 (1H, s), 6.70 (1H, d, J = 8.6 Hz), 4.07 (1H, m), 2.51 (3H, s), 1.17 (6H, d, J = 6.6 Hz).

Anal. Calcd for $C_{13}H_{15}NO_3$• 0.1 MeOH: C, 66.54; H, 6.58; N, 5.92. Found: C, 66.36; H, 6.48; N, 5.93.

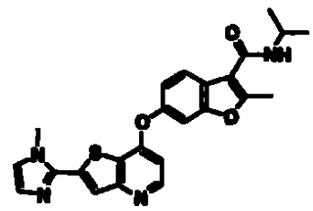
Example 82; 6-(2-[(S)-2-(methoxymethyl)pyrrolidine-1-carbonyl]thieno[3,2-b]pyridin-7-yloxy)-2-methyl-benzofuran-3-carboxylic acid isopropylamide



This material was prepared by the reaction of 7-chloro-2-[(S)-2-(methoxymethyl)pyrrolidine-1-carbonyl]thieno[3,2-b]pyridine 2a (133 mg, 0.43 mmole) 6-

hydroxy-2-methyl-benzofuran-3-carboxylic acid isopropy amide 82b (120 mg, 0.51 mmole) and Cs_2CO_3 (279mg, 0.86 mmole) in a manner as previously described to give 150 mg (69%) of an off-white brittle foam. ^{1}H NMR (DMSO-d6): δ 8.56 (1H, d, J = 5.3 Hz), 8.03 (1H, s), 7.96 (1H, d, J = 8.1 Hz), 7.75 (1H, d, J = 8.3 Hz), 7.65 (1H, d, J = 2.3Hz), 7.24 (1H, dd, J = 8.6, 2.3 Hz), 6.72 (1H, d, J = 5.3 Hz), 4.30 (1H, m), 4.12 (1H, m), 3.85 (2H, m), 3.56 (1H, m), 3.42 (1H, m), 3.25 (3H, s), 2.59 (3H, s), 2.08-1.81 (4H, m), 1.20 (6H, d, J = 6.6 Hz). Anal. Calcd for $C_{27}H_{28}N_4O_3S$• 0.3 EtOAc: C, 63.42; H, 5.93; N, 7.87; S, 6.00. Found: C, 63.20; H, 5.90; N, 7.85; S, 6.03.

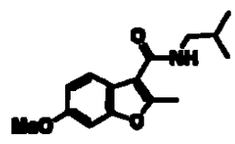
Example 83: 2-Methyl-6-[2-(1-methyl-1H-imidazol-2-yl)-thieno[3,2-b]pyridin-7-yloxy]-benzofuran-3-carboxylic acid isopropyl amide



This material was prepared by the reaction of 7-chloro-2-(1-methyl-1H-imidazol-2-yl)thieno[3,2-b]pyridine 1e (89mg, 0.36mmole) with 6-hydroxy-2-methylbenzo[b]furan-3-carboxylic acid isopropylamide 82a (100mg, 0.43mmole) and Cs_2CO_3 (233mg, 0.72mmole) in a manner as previously described for example 1 to give a 37% yield of a light yellow solid. ^{1}H NMR (DMSO-d_6) δ 8.51 (1H, d, J = 5.3 Hz), 7.97 (1H, d, J = 7.8 Hz), 7.88 (1H, s), 7.74 (1H, d, J = 8.6 Hz), 7.65 (1H, d, J = 2.3 Hz), 7.40 (1H, s), 7.24 (1H, dd, J = 8.3, 2.0 Hz), 7.01 (1H, s), 6.85 (1H, d, J = 5.6 Hz), 4.12 (1H, m), 3.98 (3H, s), 2.60 (3H, s), 1.20 (6H,d, J = 6.6 Hz).

Anal. Calcd for $C_{24}H_{22}N_4O_3S$• 0.9 EtOAc: C, 63.04; H, 5.60; N, 10.66; S, 6.10. Found: C, 62.85; H, 5.52; N, 10.76; S, 6.24.

Example 84(a): 6-Methoxy-2-methyl-benzofuran-3-carboxylic acid isobutyl-amide

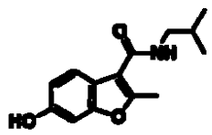


This material was prepared from 6-methoxy-2-methylbenzofuran 12a (500 mg, 3.1 mmole) by acylation with oxalyl chloride in the presence of $AlCl_3$, followed by treatment with isobutylamine in a manner as previously described for example 1c to give 585 mg (73%) of

an off-white solid. ^{1}H NMR (DMSO-d_6) δ 7.95 (1H, t, J = 5.8 Hz), 7.56 (1H, d, J = 8.8 Hz), 7.15(1H, d, J = 2.3 Hz), 6.91 (1H, dd, J = 8.6, 2.3 Hz), 3.76 (3H, s), 3.07 (2H, m), 2.57 (3H, s), 1.83 (1H, m), 0.88 (6H, d, J = 6.8 Hz).

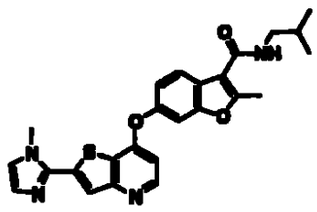
Anal. Calcd for $C_{15}H_{19}NO_3$: C, 68.94; H, 7.33; N, 5.36. Found: C, 68.75; H, 7.27; N, 5.38.

Example 84(b): 6-Hydroxy-2-methyl-benzofuran-3-carboxylic acid isobutyl amide



This material was prepared from 6-methoxy-2-methyl-benzofuran-3-carboxylic acid isobutyl amide 84a by treatment with BBr_3 in a manner as previously described for example 1d. ^{1}H *NMR* (DMSO-d_6) δ 9.53 (1H, s), 7.90 (1H, t, J = 6.1 Hz), 7.44 (1H, d, J = 8.3 Hz), 6.86 (1H, s), 6.74 (1H, dd, J = 8.6, 1.8 Hz), 3.07 (2H, t, J = 6.1 Hz), 2.52 (3H, s), 1.81 (1H, m). 0.90 (6H, d, J = 6.8 Hz).

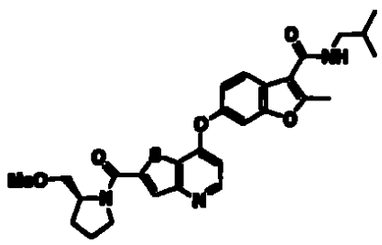
Example 84: 2-Methyl-6-[2-(1-methyl-1H-imidazol-2-yl)-thieno[3,2-b]pyridin-7-yloxy]-benzofuran-3-carboxylic acid isobutyl amide



This material was prepared by the reaction of 7-chloro-2-(1-methyl-1H-imidazol-2-yl)thieno[3,2-b]pyridine 1e with 6-hydroxy-2-methyl-benzofuran-3-carboxylic acid isobutyl amide 84b and Cs_2CO_3 in a manner as previously described for example 1. ^{1}H NMR (CD_3CN) δ 8.48 (1H ,d, J = 5.6 Hz), 7.81 (1H, d, J = 8.3 Hz), 7.74 (1H, s), 7.43 (1H, d, J = 2.0 Hz), 7.21 (1H, dd, J = 8.6, 2.3 Hz), 7.17 (1H, s), 7.04 (1H, s), 6.70 (1H, m), 6.67 (1H, d, J = 5.6 Hz), 3.97 (3H, s), 3.23 (2H, t, J = 6.6 Hz), 2.66 (3H, s), 1.78 (1H,m), 0.98 (6H, d, J = 6.6 Hz).

Anal. Calcd for $C_{25}H_{24}N_4O_3S \cdot 0.3\ H_2O$: C, 64.44; H, 5.32; N, 12.02; S, 6.88. Found: C, 64.40; H, 5.36; N, 11.76; S, 6.72.

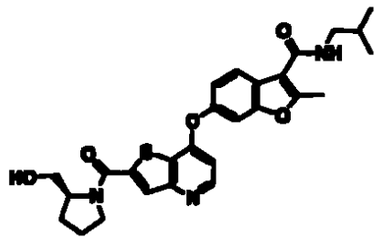
Example 85: 6-[2-(2-Methoxymethyl-pyrrolidine-1-carbonyl)-thieno[3,2-b]pyridin-7-yloxy]-3-methyl-benzofuran-3-carboxylic acid isobutyl amide



This material was prepared by the reaction of 7-chloro-2-[(R)-2-methoxymethylpyrrolidine-1-carbonyl]thieno[3,2-b]pyridine 2a with 6-hydroxy-2-methyl-benzofuran-3-carboxylic acid isobutyl amide 84b and Cs_2CO_3 in a manner as previously described for example 1. ^1H NMR (CD_3CN) δ 8.53 (1H,d, J = 5.3 Hz), 7.87 (1H, s), 7.82 (1H, d, J = 8.5 Hz), 7.41 (1H, d, J = 1.9 Hz), 7.20 (1H, dd, J = 8.5, 1.9 Hz), 6.70 (1H, d, J = 5.5 Hz), 4.38 (1H, m), 3.85 (2H, m), 3.65-3.41 (2H, m), 3.32 (3H, s), 3.23 (2H, t, J = 6.4 Hz), 2.85 (3H, s), 2.15-1.94 (4H,m, partially obscured by CD_3CN), 1.73 (1H, m),.

Anal. Calcd for $C_{29}H_{31}N_3O_5S$-0.2H_2O: C, 64.03; H, 6.03; N, 8.00; S, 6.10. Found: C, 64.02; H, 6.11; N, 7.79; S, 5.89.

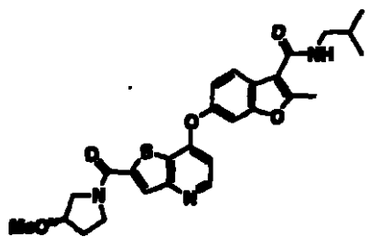
Example 86: 2-Methyl-6-[2-(2-hydroxymethyl-pyrrolidine-1-carbonyl)-thieno[3,2-b]pyridin-7-yloxy]-benzofuran-3-carboxylic acid isobutyl amide



This material was prepared from 2-methyl-6-[2-(2-methoxymethyl-pyrrolidine-1-carbonyl)-thieno[3,2-b]pyridin-7-yloxy]-benzofuran-3-carboxylic acid isobutyl amide 85 by treatment with BBr_3 in a manner as previously described for example 1d. ^1H NMR (CD_3CN) δ 8.52 (1H, d, J = 5.5 Hz), 7.89 (1H, s), 7.81 (1H, d, J = 8.5 Hz), 7.42 (1H, d, J = 2.1 Hz), 7.20 (1H, dd, J = 8.5, 2.1 Hz), 6.78 (1H, m), 6.71 (1H, d, J = 5.3 Hz), 4.29 (1H, m), 3.94 – 3.63 (4H, m), 3.22 (2H, t, J = 6.4 Hz), 2.65 (3H, s), 2.22-1.95 (4H, m), 0.96 (6H, d, J = 6.8 Hz).

Anal. Calcd for $C_{27}H_{29}N_3O_5S$: C, 63.89; H, 5.76; N, 8.28; S, 6.32. Found: C, 63.56; H, 5.95; N, 8.01; S, 6.07.

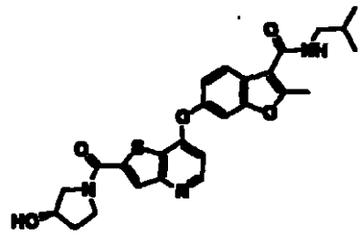
Example 87: 6-[2-(3-Methoxy-pyrrolidine-1-carbonyl)-thieno[3,2-b]pyridin-7-yloxy]-2-methyl-benzofuran-3-carboxylic acid isobutyl amide



This material was prepared by the reaction of 7-chloro-2-[(R)-3-methoxypyrrolidine-1-carbonyl]thieno[3,2-b]pyridine 4b with 6-hydroxy-2-methyl-benzofuran-3-carboxylic acid isobutyl amide 83b and Cs_2CO_3 in a manner as previously described for example 1. ^{1}H NMR (CD_3CN) δ 8.53 (1H,d, J = 5.5 Hz), 7.88 (1H, d, J = 3.0 Hz), 7.82 (1H, d, J = 8.5 Hz), 7.41 (1H, d, J = 2.3 Hz), 7.20 (1H, dd, J = 8.5, 2.3Hz), 6.70 (2H, d, J = 5.5 Hz), 4.10-3.83 (3H, m), 3.73-3.58 (2H, m), 3.33, 3.29 (3H, 2s), 3.23 (2H, t, J = 6.8 Hz), 2.65 (3H, s), 2.10-1.95 (2H,m), 0.98 (6H, d, J = 6.6 Hz).

Anal. Calcd for $C_{27}H_{33}N_3O_5S$: C, 63.89; H, 5.76; N, 8.28; S, 6.32. Found: C, 63.83; H, 5.85; N, 8.08; S, 6.10.

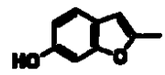
Example 88: 2-Methyl-6-[2-(3-hydroxy-pyrrolidine-1-carbonyl)-thieno[3,2-b]pyridin-7-yloxy]-benzofuran-3-carboxylic acid isobutyl amide



This material was prepared from 2-methyl-6-[2-(3-methoxy-pyrrolidine-1-carbonyl)-thieno[3,2-b]pyridin-7-yloxy]-benzofuran-3-carboxylic acid isobutyl amide 87 by treatment with BBr_3 in a manner as previously described for 1d. ^{1}H NMR (CD_3CN/DMSO-d_6) δ 8.55 (1H, d, J = 5.6 Hz), 7.94, 7.88 (1H, 2s), 7.81 (1H, d, J = 8.5 Hz), 7.46 (1H, d, J = 2.1 Hz), 7.38 (1H, m), 7.20 (1H, dd, J = 8.5, 2.1 Hz), 6.76 (1H, d, J = 5.7 Hz), 4.39 (1H, m), 3.94 (1H, m), 3.74 – 3.51 (3H, m), 3.16 (2H, t, J = 6.5 Hz), 2.63 (3H, s), 2.07-1.86 (2H, m, partially obscured by CD_3CN), 0.96 (6H, d, J = 6.6 Hz).

Anal. Calcd for $C_{26}H_{27}N_3O_5S \cdot 0.5\ CH_2Cl_2$: C, 59.37; H, 5.27; N, 7.84; S, 5.96. Found: C, 59.42; H, 5.44; N, 7.86; S, 5.99.

Example 89(a): 6-Hydroxy-2-methylbenzofuran

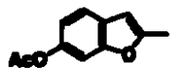


This material was prepared from 6-methoxy-2-methylbenzofuran (1.00 g, 6.17 mmole) by treatment with BBr_3 in a manner as previously described for 1d to give a colorless oil (890mg, 75%) which solidified on standing.

^{1}H NMR (DMSO-d_6) δ 9.32 (1H, s), 7.23 (1H, d, J = 8.3 Hz), 6.80 (1H, s), 6.64 (1H, d, J = 8.3 Hz), 6.37 (1H, s), 2.35 (3H, s).

Anal. Calcd for $C_9H_8O_2$: C, 72.96; H, 5.44. Found: C, 72.72; H, 5.43.

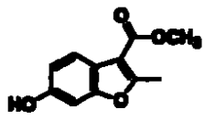
Example 89(b): 6-Acetoxy-2-methylbenzofuran



This material was prepared from 6-hydroxy-2-methylbenzofuran (654mg, 4.41mmole) by treatment with acetyl chloride (0.41ml, 5.74mmole) and triethylamine (0.74ml, 5.30mmole) in a manner as previously described for 8b to give the desired product as an oil (850mg, ~ quant). ^{1}H NMR ($CDCl_3$) δ 7.41 (1H, d, J = 8.3 Hz), 7.13 (1H, s), 6.89 (1H, dd, J = 8.3, 1.9 Hz), 6.32 (1H, s), 2.42 (3H, s), 2.30 (3H, s).

Anal. Calcd for $C_{11}H_{10}O_3$: C, 69.46; H, 5.30. Found: C, 69.02; H, 5.44.

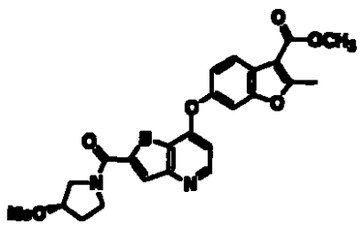
Example 89(c): Methyl 6-Hydroxy-2-methylbenzofuran-3-carboxylate



This material was prepared from 6-acetoxy-2-methylbenzofuran 89b (0.81g, 4.3mmole) by acylation with oxalyl chloride in the presence of $AlCl_3$, followed by treatment with methanol and K_2CO_3 in a manner as previously described for example 11a to give a beige solid (607mg, 69%). ^{1}H NMR (DMSO-d_6) δ 9.64 (1H, s), 7.62 (1H, d, J = 8.5 Hz), 6.93 (1H, d, J = 1.9 Hz), 6.78 (1H, dd, J = 8.5, 2.0 Hz), 3.79 (3H, s), 2.66 (3H, s).

Anal. Calcd for $C_{11}H_{10}O_4$: C, 64.07; H, 4.89. Found: C, 64.06; H, 4.89.

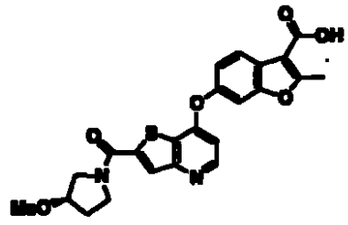
Example 89(d): Methyl 6-[2-(3-methoxypyrrolidine-1-carbonyl)-thieno[3,2-b]pyridin-7-yloxy]-2-methyl-benzofuran-3-carboxylate



This material was prepared by the reaction of 7-chloro-2-[(R)-3-methoxypyrrolidine-1-carbonyl]thieno[3,2-b]pyridine 4b (707mg, 2.38 mmole) with methyl 6-hydroxy-2-methyl-benzofuran-3-carboxylate 89c (565mg, 2.74 mmole) and Cs_2CO_3 (3.10g, 9.53mmole) in a manner as previously described for example to give 650mg (58%) of an off-white solid. ^{1}H NMR (DMSO-d_6) δ 8.57 (1H,d, J = 5.3 Hz), 8.07 (1H, s), 7.98 (1H, d, J = 8.6 Hz), 7.75 (1H, d, J = 2.0 Hz), 7.31 (1H, dd, J = 8.6, 2.0 Hz), 6.74 (1H, d, J = 5.6 Hz), 4.10-3.85 (3H, m), 3.90 (3H, s), 3.65-3.45 (2H, m), 3.25 (3H, d, J = 12.6 Hz), 2.77 (3H, s), 2.15-1.95 (2H,m).

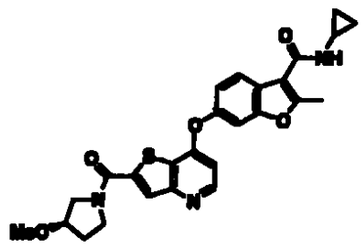
Anal. Calcd for $C_{24}H_{22}N_2O_5S$•0.2H_2O: C, 61.31; H, 4.80; N, 5.96; S, 6.82. Found: C, 61.21; H, 4.99; N, 5.90; S, 6.68.

Example 89(e): 6-[2-(3-Methoxypyrrolidine-1-carbonyl)-thieno[3,2-b]pyridin-7-yloxy]-2-methyl-benzofuran-3-carboxylic acid



To a stirred solution of methyl 6-[2-(3-methoxypyrrolidine-1-carbonyl)-thieno[3,2-b]pyridin-7-yloxy]-2-methyl-benzofuran-3-carboxylate 89d (540mg, 1.16mmole) in THF/MeOH/MeOH (6ml, 1:1:1) was added lithium hydroxide monohydrate (54mg, 1.29mmole). When the ester disappeared by thin layer chromatography (tlc), the organic solvents removed under reduced pressure, and the aqueous residue was neutralized with 2N HCl. The white solid which precipitated was collected by filtration and dried under vacuum to give the desired acid (411mg, 83%). ^{1}H NMR (DMSO-d_6) δ 13.02 (1H, bs), 8.57 (1H,d, J = 5.3 Hz), 8.05 (1H, s), 7.94 (1H, d, J = 8.5 Hz), 7.68 (1H, s), 7.25 (1H, d, J = 8.5 Hz), 6.75 (1H, d, J = 5.5 Hz), 4.10-3.85 (3H, m), 3.65-3.45 (2H, m), 3.25 (3H, d, J = 9.4 Hz), 2.74 (3H, s), 2.15-1.95 (2H,m).

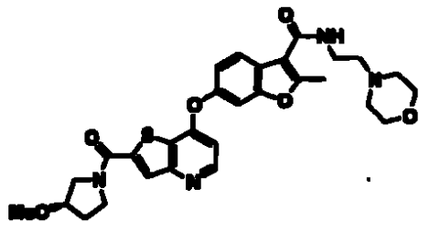
Example 89: 6-[2-(3-Methoxypyrrolidine-1-carbonyl)-thieno[3,2-b]pyridin-7-yloxy]-2-methyl-benzofuran-3- carboxylic acid cyclopropylamide



This material was prepared from 6-[2-(3-methoxypyrrolidine-1-carbonyl)-thieno[3,2-b]pyridin-7-yloxy]-2-methyl-benzofuran-3-carboxylic acid 89e (37mg, 0.09mmole) by treatment with oxalyl chloride (15 µl, 0.17mmole) and cyclopropylamine (56 µl, 0.81mmole) in a manner as previously described for example 16d to give a white solid (13mg, 33%). ^{1}H NMR (DMSO-d_6) δ 8.57 (1H, d, J = 5.1 Hz), 8.19 (1H,s), 8.06 (1H, bs), 7.74 (1H, d, J = 8.1 Hz), 7.65 (1H, s), 7.24 (1H, d, J = 8.1 Hz), 6.71 (1H, d, J = 1.8 Hz), 4.10 - 3.80 (3H, m), 3.70 – 3.35 (2H, m), 3.25 (3H, d, J = 13.1 Hz), 2.86 (1H, m), 2.59 (3H, s), 2.25 – 1.95 (2H, m), 0.71 (2H, m), 0.60 (2H, m).

Anal. Calcd for $C_{25}H_{25}N_3O_5S$•0.1 Hexanes: C, 63.87; H, 5.32; N, 8.40; S, 6.41. Found: C, 63.61; H, 5.51; N, 8.31; S, 6.23.

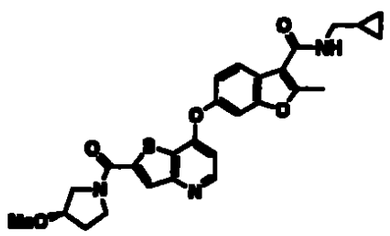
Example 90: 6-[2-(3-Methoxy-pyrrolidine-1-carbonyl)-thieno[3,2-b]pyridin-7-yloxy]-2-methyl-benzofuran-3-carboxylic acid (2-morpholin-4-yl-ethyl)-amide



This material was prepared from 6-[2-(3-methoxypyrrolidine-1-carbonyl)-thieno[3,2-b]pyridin-7-yloxy]-2-methyl-benzofuran-3-carboxylic acid 89e by treatment with oxalyl chloride and 2-(morpholin-4-yl)ethylamine in a manner as previously described for example 16d. ^{1}H NMR (DMSO-d_6) δ 8.57 (1H, d, J = 5.1 Hz), 8.06 (1H,s), 7.97 (1H, bs), 7.83 (1H, d, J = 8.6 Hz), 7.66 (1H, s), 7.27 (1H, d, J = 8.3 Hz), 6.71 (1H, d, J = 5.3 Hz), 4.20 - 3.95 (4H, m), 3.70 – 3.35 (10H, m), 3.25 (3H, d, J = 12.8 Hz), 2.64 (3H, s), 2.41 (3H, s), 2.08 (2H, m).

Anal. Calcd for $C_{28}H_{28}N_4O_6S \cdot 0.7\ H_2O$: C, 60.34; H, 5.83; N, 9.71; S, 5.55. Found: C, 60.67; H, 5.92; N, 9.71; S, 5.39.

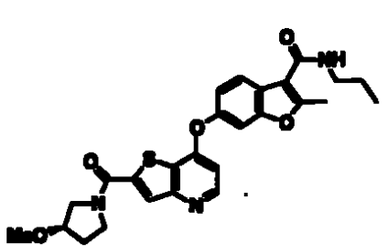
Example 91: 6-[2-(3-Methoxy-pyrrolidine-1-carbonyl)-thieno[3,2-b]pyridin-7-yloxy]-2-methyl-benzofuran-3-carboxylic acid cyclopropylmethyl-amide



This material was prepared from 6-[2-(3-methoxypyrrolidine-1-carbonyl)-thieno[3,2-b]pyridin-7-yloxy]-2-methyl-benzofuran-3-carboxylic acid 89e by treatment with oxalyl chloride and (aminomethyl)cyclopropane in a manner as previously described for example 16d. ^{1}H NMR (DMSO-d_6) δ 8.55 (1H, d, J = 5.1 Hz), 8.20 (1H,s), 8.05 (1H, s), 7.80 (1H, d, J = 8.6 Hz), 7.64 (1H, s), 7.22 (1H, d, J = 8.3 Hz), 6.69 (1H, d, J = 5.3 Hz), 4.10 - 3.80 (3H, m), 3.70 – 3.50 (2H, m), 3.26 (3H, d, J = 12.6 Hz), 3.15 (2H, m), 2.63 (3H, s), 2.20 – 1.95 (2H, m), 1.08 (1H,m), 0.45 (2H, d, J = 7.1Hz), 0.25 (2H, d, J = 4.3 Hz).

Anal. Calcd for $C_{27}H_{27}N_3O_5S \cdot 0.2$ Hexanes $\cdot 0.6H_2O$: C, 63.47; H, 5.86; N, 8.67; S, 6.01. Found: C, 63.54; H, 5.88; N, 7.74; S, 5.91.

Example 92: 6-[2-(3-Methoxy-pyrrolidine-1-carbonyl)-thieno[3,2-b]pyridin-7-yloxy]-2-methyl-benzofuran-3-carboxylic acid propyl amide

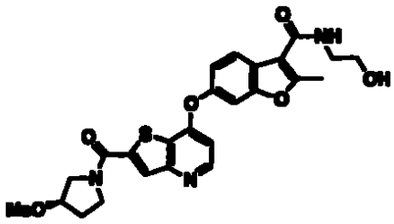


This material was prepared from 6-[2-(3-methoxypyrrolidine-1-carbonyl)-thieno[3,2-b]pyridin-7-yloxy]-2-methyl-benzofuran-3-carboxylic acid 89e by treatment with oxalyl chloride and 1-aminopropane in a manner as previously described for example

16d. ^{1}H NMR (DMSO-d_6) δ 8.57 (1H, dd, J = 5.6, 1.3 Hz), 8.09 (1H, m), 8.06 (1H,s), 7.79 (1H, d, J = 8.6 Hz), 7.66 (1H, d, J = 2.0 Hz), 7.26 (1H, dd, J = 8.6, 2.0 Hz), 6.72 (1H, d, J = 5.6 Hz), 4.06 - 3.82 (3H, m), 3.70 – 3.44 (2H, m), 3.27-3.22 (5H, m), 2.62 (3H, s), 2.15-1.92 (2H, m), 1.56-1.54 (2H, m), 0.92 (3H, t, J = 7.3 Hz).

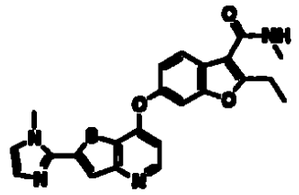
Anal. Calcd for $C_{28}H_{27}N_3O_6S$• 0.7 H_2O•0.3 MTBE: C, 62.01; H, 6.06; N, 7.89; S, 6.02. Found: C, 61.82; H, 6.07; N, 7.87; S, 5.97.

Example 93: 6-[2-(3-Methoxy-pyrrolidine-1-carbonyl)-thieno[3,2-b]pyridin-7-yloxy]-2-methyl-benzofuran-3-carboxylic acid 2-hydroxyethyl amide



This material was prepared from 6-[2-(3-methoxypyrrolidine-1-carbonyl)-thieno[3,2-b]pyridin-7-yloxy]-2-methyl-benzofuran-3-carboxylic acid 89e by treatment with oxalyl chloride and 2-aminoethanol in a manner as previously described for example 16d. ^{1}H NMR (DMSO-d_6) δ 8.57 (1H, d, J = 5.6Hz), 8.06 (1H,s), 8.00 (1H, t, J = 5.3 Hz), 7.82 (1H, d, J = 8.6 Hz), 7.66 (1H, d, J = 2.3 Hz), 7.26 (1H, dd, J = 8.3, 2.3 Hz), 6.72 (1H, d, J = 5.3 Hz), 4.76(1H, m), 4.10 - 3.82 (3H, m), 3.67 – 3.59 (2H, m), 3.55 (2H, t, J = 6.1 Hz), 3.37 (2H, t, J = 6.1 Hz), 3.27, 3.24 (3H, 2s), 2.63 (3H, s), 2.06 (2H, m).

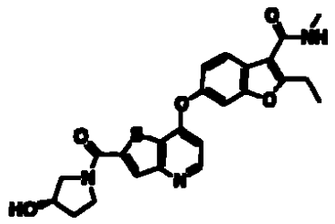
Example 94: 2-Ethyl-6-[2-(1-methyl-1H-imidazol-2-yl)-thieno[3,2-b]pyridin-7-yloxy]-benzofuran-3-carboxylic acid methylamide



This material was prepared by the reaction of 7-chloro-2-(1-methyl-1H-imidazol-2-yl)thieno[3,2-b]pyridine 1e (114 mg, 0.46 mmole) with 6-hydroxy-2-ethylbenzofuran-3-carboxylic acid methylamide 14c (120 mg, 0.55 mmole) and Cs_2CO_3 (594 mg, 1.82 mmole) in a manner as previously described for example 1 to give 60 mg (30%) of a tan solid. ^{1}H NMR (DMSO-d_6) δ 8.49 (1H ,d, J = 5.6 Hz), 8.00 (1H, d, J = 4.6 Hz), 7.89 (1H, s), 7.82 (1H, d, J = 8.6 Hz), 7.67 (1H, s), 7.41 (1H, s), 7.26 (1H, d, J = 8.6 Hz), 7.03 (1H, s), 6.66 (1H, d, J = 5.6 Hz), 3.99 (3H, s), 3.04 (2H, q, J = 7.6 Hz), 2.81 (3H, d, J = 4.6 Hz), 1.26 (3H, t, J = 7.3 Hz).

Anal. Calcd for $C_{22}H_{20}N_4O_3S \cdot 0.1$ Hexanes $\cdot 0.3$ H_2O: C, 63.48; H, 4.97; N, 12.55; S, 7.18. Found: C, 63.40; H, 5.07; N, 12.28; S, 7.15.

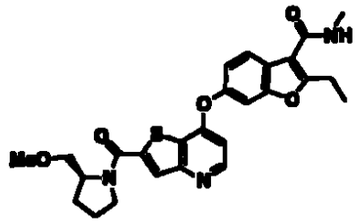
Example 95: 2-Ethyl-6-[2-(3-hydroxy-pyrrolidine-1-carbonyl)-thieno[3,2-b]pyridin-7-yloxy]-benzofuran-3-carboxylic acid methylamide



This material was prepared from 2-ethyl-6-[2-(3-methoxypyrrolidine-1-carbonyl)-thieno[3,2-b]pyridin-7-yloxy]benzofuran-3-carboxylic acid methylamide 14 by treatment with BBr_3 in a manner as previously described for 1d. ^{1}H NMR (DMSO-d_6) δ 8.56 (1H, d, J = 5.3 Hz), 8.07 (1H, s), 8.00 (1H, d, J = 4.1 Hz), 7.82 (1H, d, J = 8.6 Hz), 7.68 (1H, d, J = 2.0 Hz), 7.25 (1H, dd, J = 8.6, 2.0 Hz), 6.73 (1H, d, J = 5.3 Hz), 5.07 (1H, t, J = 3.5 Hz), 4.35 (1H, m), 3.97 (1H, m), 3.86 – 3.46 (3H, m), 3.03 (2H, q, J = 7.6 Hz), 2.80 (3H, d, J = 4.5 Hz), 2.10-1.80 (2H, m), 1.27 (3H, t, J = 7.6 Hz).

Anal. Calcd for $C_{24}H_{23}N_3O_5S \cdot 0.5$ H_2O: C, 60.74; H, 5.10; N, 8.86; S, 6.76. Found: C, 60.79; H, 5.24; N, 8.61; S, 6.69.

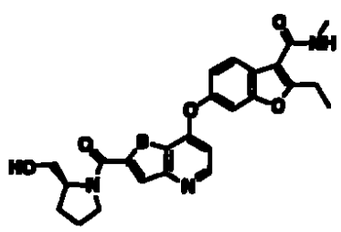
Example 96: 2-ethyl-6-[2-[(S)-3-(methoxymethyl)pyrrolidine-1-carbonyl]thieno[3,2-b]pyridin-7-yloxy]- benzofuran-3-carboxylic acid methyl amide



This material was prepared by the reaction of 7-chloro-2-[(R)-2-methoxymethylpyrrolidine-1-carbonyl]thieno[3,2-b]pyridine 2a with 6-hydroxy-2-ethylbenzofuran-3-carboxylic acid methyl amide 14c and Cs_2CO_3 in a manner as previously described. ^{1}H NMR (DMSO-d_6) δ 8.57 (1H,d, J = 5.5 Hz), 8.03 (1H, s), 8.01 (1H, m), 7.83 (1H, d, J = 8.6 Hz), 7.67 (1H, d, J = 2.1 Hz), 7.25 (1H, dd, J = 8.7, 2.1 Hz), 6.73 (1H, d, J = 5.5 Hz), 4.31 (1H, m), 3.92-3.77 (2H, m), 3.58-3.45 (2H, m), 3.27 (3H, s), 3.04 (2H, q, J = 7.5 Hz), 2.82 (3H, d, J = 4.5 Hz), 2.06-1.85 (4H,m), 1.26 (3H, t, J = 7.5 Hz).

Anal. Calcd for $C_{28}H_{27}N_3O_5S \cdot 0.5H_2O \cdot 0.2$ MTBE C, 62.34; H, 5.89; N, 8.08; S, 6.16. Found: C, 62.36; H, 5.86; N, 7.97; S, 6.15.

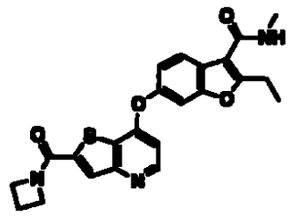
Example 97: 2-ethyl-6-[2-[(S)-2-(hydroxymethyl)pyrrolidine-1-carbonyl]thieno[3,2-b]pyridin-7-yloxy)- benzofuran-3-carboxylic acid methylamide



This material was prepared from 2-ethyl-6-[2-(2-methoxymethyl-pyrrolidine-1-carbonyl)-thieno[3,2-b]pyridin-7-yloxy]-benzofuran-3-carboxylic acid methylamide 95 by treatment with BBr_3 in a manner as previously described for 1d. ^{1}H NMR (DMSO-d_6) δ 8.56 (1H, d, J = 5.3 Hz), 8.01 (2H, m), 7.82 (1H, d, J = 8.6 Hz), 7.68 (1H, s), 7.25 (1H, dd, J = 8.3, 2.0 Hz), 6.73 (1H, d, J = 5.1 Hz), 4.82 (1H, m), 4.20 (1H, m), 3.92-3.47 (4H, m), 3.04 (2H, q, J = 7.6 Hz), 2.81 (3H, d, J = 4.5 Hz), 2.06-1.83 (4H, m), 1.26 (3H, t, J = 7.8 Hz).

Anal. Calcd for $C_{28}H_{29}N_3O_5S \cdot 1\ H_2O$: C, 60.35; H, 5.47; N, 8.45; S, 6.44. Found: C, 60.59; H, 5.47; N, 8.26; S, 6.20.

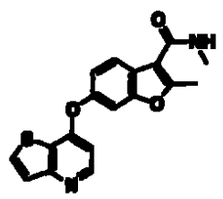
Example 98: 6-[2-(Azetidine-1-carbonyl)-thieno[3,2-b]pyridin-7-yloxy]-2-ethyl-benzofuran-3-carboxylic acid methylamide



This material was prepared by the reaction of 2-(azetidin-1-ylcarbonyl)-7-chlorothieno[3,2-*b*]pyridine 25a with 6-hydroxy-2-ethylbenzofuran-3-carboxylic acid methyl amide 14c and Cs_2CO_3 in a manner as previously described for example 1. ^{1}H NMR (DMSO-d_6) δ 8.56 (1H, d, J = 5.6 Hz), 7.99 (1H, m), 7.89 (1H, s), 7.82 (1H, d, J = 8.6 Hz), 7.67 (1H, d, J = 2.0 Hz), 7.25 (1H, dd, J = 8.6, 2.3 Hz), 6.72 (1H, d, J = 5.3 Hz), 4.82 (2H, t, J = 7.8 Hz), 4.11 (2H, t, J = 7.8 Hz), 3.04 (2H, q, J = 7.6 Hz), 2.81 (3H, d, J = 4.6Hz), 2.35 (2H, p, J = 7.7 Hz), 1.26 (3H, t, J = 7.6 Hz).

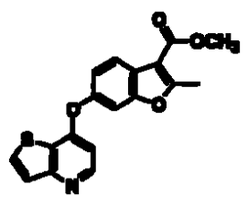
Anal. Calcd for $C_{28}H_{21}N_3O_4S \cdot 0.3\ H_2O$: C, 62.85; H, 4.94; N, 9.53; S, 7.27. Found: C, 62.88; H, 4.84; N, 9.47; S, 7.52.

Example 99: 6-[Thieno(3,2-b)pyridin-7-yloxy]-2-methyl-benzofuran-3-carboxylic acid methyl amide



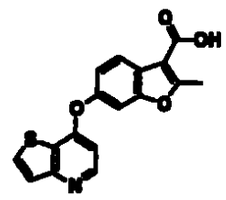
This material was prepared by the reaction of 7-chloro-thieno[3,2-b]pyridine with 6-hydroxy-2-methylbenzofuran-3-carboxylic acid methyl amide 12c and Cs_2CO_3 in a manner as previously described for example 1. ^1H NMR (CD_3CN) δ 8.48 (1H,d, J = 5.3 Hz), 7.91 (1H, d, J = 5.6 Hz), 7.84 (1H, d, J = 8.6 Hz), 7.53 (1H, d, J = 5.6 Hz), 7.41 (1H, d, J = 2.0 Hz), 7.20 (1H, dd, J = 8.6, 2.0 Hz), 6.62 (1H, d, J = 5.3 Hz), 6.60 (1H, bm), 2.91 (3H, d, J = 4.6 Hz) 2.66 (3H, s).

Example 100(a): Methyl 2-Methyl-6-[thieno[3,2-b]pyridin-7-yloxy]benzofuran-3-carboxylate



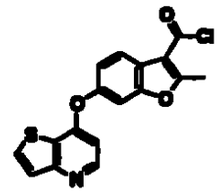
This material was prepared by the reaction of 7-chloro-thieno[3,2-b]pyridine with methyl 6-hydroxy-2-methylbenzofuran-3-carboxylate 89c and Cs_2CO_3 in a manner as previously described . ^1H NMR ($CDCl_3$) δ 8.48 (1H,d, J = 5.3 Hz), 7.99 (1H, d, J = 8.3 Hz), 7.74 (1H, d, J = 5.6 Hz), 7.56 (1H, d, J = 5.3 Hz), 7.29 (1H, d, J = 2.0 Hz), 7.16 (1H, dd, J = 8.6, 2.3 Hz), 6.53 (1H, d, J = 5.3 Hz), 3.96 (3H, s), 2.79 (3H, s).

Example 100: 2-Methyl-6-[thieno[3,2-b]pyridin-7-yloxy]benzofuran-3-carboxylic acid



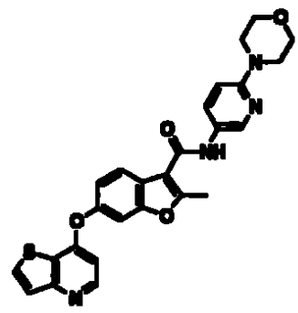
This material was prepared from methyl 2-methyl-6-[thieno[3,2-b]pyridin-7-yloxy]benzofuran-3-carboxylate 100a in a manner as previously described for example 99a. ^{1}H NMR (DMSO-d_6) δ 12.95 (1H, bs), 8.50 (1H, d, J = 5.3 Hz), 8.15 (1H, d, J = 5.5 Hz), 7.97 (1H, d, J = 8.3 Hz), 7.69 (1H, d, J = 2.1 Hz), 7.59 (1H, d, J = 5.5 Hz), 7.26 (1H, dd, J = 8.5, 2.1 Hz), 6.64 (1H, d, J = 5.5 Hz), 2.74 (3H, s).

Example 101: 2-Methyl-6-[thieno[3,2-b]pyridin-7-yloxy]benzofuran-3-carbonyl chloride



To a stirred suspension of 2-methyl-6-[thieno[3,2-b]pyridin-7-yloxy] benzofuran-3-carboxylic acid 100 (800mg, 2.33mmole) in $CHCl_3$ (20ml) was added thionyl chloride (850 µl, 11.6mmole) and a catalytic amount of DMF. The reaction was allowed to stir at 50°C for 3hr before the volatiles were removed under reduced pressure. The crude residue was triturated with MTBE to give the acid chloride as a pale yellow solid. ^{1}H NMR (DMSO-d_6) δ 8.81 (1H, d, J = 6.6 Hz), 8.57 (1H, d, J = 5.6 Hz), 8.03 (1H, d, J = 8.6 Hz), 7.86 (1H, d, J = 2.0 Hz), 7.82 (1H, d, J = 5.6 Hz), 7.39 (1H, dd, J = 8.6, 2.0 Hz), 7.06 (1H, d, J = 6.3 Hz), 2.76 (3H, s).

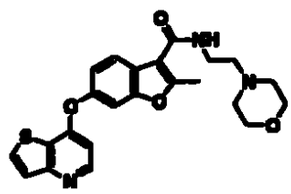
Example 102: 2-Methyl-6-(thieno[3,2-b]pyridin-7-yloxy)benzofuran-3-carboxylic acid (6-morpholin-4-yl-pyridin-3-yl)amide



A solution of 2-methyl-6-[thieno[3,2-b]pyridin-7-yloxy]benzofuran-3-carboxylic acid 100 (70mg, 0.215 mmole), 6-Morpholin-4-yl-pyridin-3-ylamine (77 mg, 0.43 mmole), HATU (163 mg, 0.43 mmole), and diisopropylethylamine (75 µl, 0.43 mmole) were stirred in DMF (2ml) at ambient temperature for 17 hr. The mixture was then added dropwise to a solution of cold aqueous $NaHCO_3$ resulting in a precipitate which was collected by filtration. This material was purified on silica gel using a gradient of 0 to 5% methanol in a 1:1 mixture of ethyl acetate and dichloromethane as eluent to give 77 mg (74%) of a lavender solid. ^1H NMR (CD_3CN) δ 8.50 (1H, d, J = 5.3 Hz), 8.37 (1H, d, J = 2.5 Hz), 8.29 (1H, s), 7.92-7.88 (3H, m), 7.54 (1H, d, J = 5.3 Hz), 7.45 (1H, d, J = 2.0 Hz), 7.23 (1H, dd, J = 8.8, 2.0 Hz), 6.76 (1H, d, J = 9.1 Hz), 6.64 (1H, d, J = 5.3 Hz), 3.76 (4H, t, J = 4.9 Hz), 3.44 (4H, t, J = 4.9 Hz), 2.72 (3H, s).

Anal. Calcd for $C_{28}H_{22}N_4O_4S$: C, 64.18; H, 4.56; N, 11.52; S, 6.59. Found: C, 64.42; H, 4.77; N, 11.32; S, 6.50.

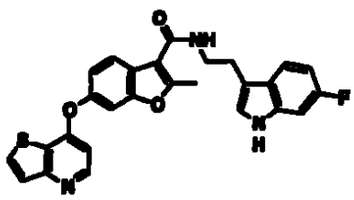
Example 103: 2-Methyl-6-[thieno[3,2-b]pyridin-7-yloxy]benzofuran-3-carboxylic acid [2-morpholin-4-yl-ethyl)-amide



This material was prepared from 2-methyl-6-[thieno[3,2-b]pyridin-7-yloxy]benzofuran-3-carboxylic acid 100 and 2-(morpholin-4-yl)ethylamine in a similar manner as that described for example 102. ^1H NMR (CD_3CN) δ 8.50 (1H, d, J = 5.3Hz), 7.92 (1H, d, J = 5.8 Hz), 7.89 (1H, d, J = 8.6 Hz), 7.54 (1H, d, J = 5.8 Hz), 7.42 (1H, d, J = 2.3 Hz), 7.23 (1H, dd, J = 8.6, 2.3 Hz), 6.83 (1H, bm), 6.63 (1H, d, J = 5.8 Hz), 3.65 (4H, t, J = 4.6 Hz), 3.51 (2H, q, J = 6.1 Hz), 2.69 (3H, s), 2.59 (2H, t, J = 6.1 Hz), 2.50 (4H, bm).

Anal. Calcd for $C_{23}H_{23}N_3O_4S \cdot 1.4\ H_2O \cdot 0.05\ CH_2Cl_2$: C, 59.28; H, 5.59; N, 9.00; S, 6.87. Found: C, 59.18; H, 5.23; N, 8.99; S, 6.74.

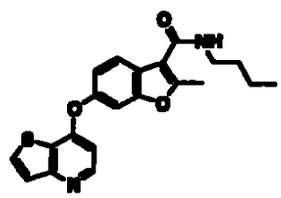
Example 104: 2-Methyl-6-(thieno[3,2-b]pyridin-7-yloxy)-benzofuran-3-carboxylic acid [2-(6-fluoro-1H-indol-3-yl)-ethyl]-amide



This material was prepared from 2-methyl-6-[thieno[3,2-b]pyridin-7-yloxy]benzofuran-3-carboxylic acid 100 and 2-(6-fluoro-1H-indol-3-yl)ethylamine in a similar manner as that described for example 102. ^{1}H NMR (CD_3CN) δ 8.48 (1H, d, J = 5.6Hz), 7.91 (1H, d, J = 5.6 Hz), 7.63-7.59 (2H, m), 7.54 (1H, d, J = 5.6 Hz), 7.38 (1H, d, J = 2.3 Hz), 7.17 (1H, d, J = 2.3 Hz), 7.14 (1H, t, J = 2.3 Hz), 7.11 (1H, d, J = 2.3 Hz), 6.85 (1H, m), 6.65 (1H, bm), 6.61 (1H, d, J = 5.6 Hz), 3.69 (2H, q, J = 7.1 Hz), 3.06 (2H, t, J = 7.1 Hz), 2.57 (3H, s).

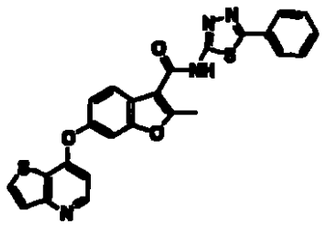
Anal. Calcd for $C_{27}H_{20}N_3O_3SF$•0.7 H_2O: C, 65.10; H, 4.33; N, 8.44; S, 6.44. Found: C, 65.04; H, 4.42; N, 8.34; S, 6.40.

Example 105: 2-Methyl-6-[Thieno(3,2-b)pyridin-7-yloxy]benzofuran-3-carboxylic acid butyl amide



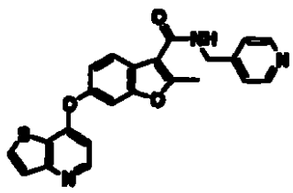
This material was prepared from 2-methyl-6-[thieno[3,2-b]pyridin-7-yloxy]benzofuran-3-carboxylic acid 100 and butylamine in a similar manner as that described for example 102. ^{1}H NMR (CD_3CN) δ 8.48 (1H,d, J = 5.3 Hz), 7.91 (1H, d, J = 5.6 Hz), 7.81 (1H, d, J = 8.6 Hz), 7.53 (1H, d, J = 5.6 Hz), 7.41 (1H, d, J = 2.3 Hz), 7.20 (1H, dd, J = 8.6, 2.3 Hz), 6.62 (1H, d, J = 5.3 Hz), 6.62 (1H, bm), 3.40 (2H, q, J = 6.9 Hz), 2.65 (3H, s), 1.60 (2H, m), 1.42 (2H, m), 0.97 (3H, t, J = 7.3 Hz).

Example 106: 2-Methyl-6-(thieno[3,2-b]pyridin-7-yloxy)-benzofuran-3-carboxylic acid (5-phenyl-[1,3,4]thiadiazol-2-yl)-amide



This material was prepared from 2-methyl-6-[thieno[3,2-b]pyridin-7-yloxy]benzofuran-3-carboxylic acid 100 and 5-phenyl-[1,3,4]thiadiazol-2-ylamine in a similar manner as that described for example 102. ^{1}H NMR (CD_3CN/CD_3OD) δ 8.45 (1H, d, J = 5.6 Hz), 8.00-7.95 (4H, m), 7.52-7.50 (4H, m), 7.48 (1H, d, J = 2.3 Hz), 7.25 (1H, dd, J = 8.6, 2.3 Hz), 6.66 (1H, d, J = 5.3 Hz), 2.76 (3H, s).

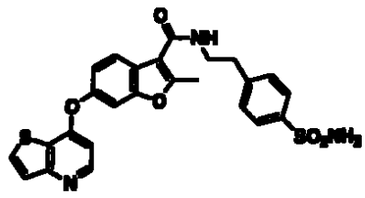
Example 107: 2-Methyl-6-[Thieno(3,2-b)pyridin-7-yloxy]benzofuran-3-carboxylic acid 2-[(4-pyridyl)-methyl] amide



This material was prepared from 2-methyl-6-[thieno[3,2-b]pyridin-7-yloxy]benzofuran-3-carboxylic acid 100 and 4-(aminomethyl)pyridine in a similar manner as that described for example 102. ^{1}H NMR (DMSO-d_6) δ 8.68 (1H, t, J = 5.6 Hz), 8.53 (2H, d, J = 5.3 Hz), 8.50 (1H, d, J =5.3 Hz), 8.15 (1H, d, J = 5.3 Hz), 7.86 (1H, d, J = 8.3 Hz), 7.68 (1H, d, J = 2.0 Hz), 7.60 (1H, d, J = 5.6 Hz), 7.36 (2H, d, J = 5.6 Hz), 7.27 (1H, dd, J = 8.6, 2.3 Hz), 6.62 (1H, d, J = 5.3 Hz), 4.53 (2H, d, J = 6.1 Hz), 2.67 (3H, s).

Anal. Calcd for $C_{23}H_{17}N_3O_3S$•0.4H_2O: C, 65.36; H, 4.25; N, 9.94; S, 7.59. Found: C, 65.33; H, 4.21; N, 9.92; S, 7.49.

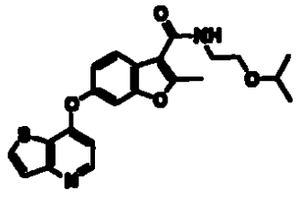
Example 108: 2-Methyl-6-(thieno[3,2-b]pyridin-7-yloxy)-benzofuran-3-carboxylic acid [2-(4-sulfamoyl-phenyl)-ethyl]-amide



A suspension of 2-methyl-6-[thieno[3,2-b]pyridin-7-yloxy]benzofuran-3-carbonyl chloride 101 (100mg, 0.29 mmol) in DMF (1 ml) was added dropwise to a solution of 2-(4-sulfamoyl-phenyl)-ethyl]-amine (116 mg, 0.58 mmol), triethylamine (80 µl, 0.58 mmol), and dimethylaminopyridine (5 mg) in DMF (2 ml) at 50C. The resulting yellow solution was stirred at 50C for 2 hr then added to an ice cold aqueous sodium bicarbonate solution. The resulting ppt was collected by filtration, washed with water and air dried. The filtrate was extracted with twice ethyl acetate. The extracts were washed with 1N NaOH, then combined with the earlier solid and dried over $MgSO_4$, and concentrated to dryness. The residue was triturated with MTBE then with EtOAc to obtain 49 mg (33%) of an off-white solid. ^1H NMR (CD_3CN) δ 8.48 (1H, d, J = 5.3Hz), 7.91 (1H, d, J = 5.6 Hz), 7.81 (1H, d, J = 8.3 Hz), 7.64 (1H, d, J = 8.6 Hz), 7.54 (1H, d, J = 5.3 Hz), 7.48 (1H, d, J = 8.3 Hz), 7.39 (1H, d, J = 2.0 Hz), 7.16 (1H, dd, J = 8.6, 2.0 Hz), 6.66 (1H, bm), 6.62 (1H, d, J = 5.6 Hz), 5.82 (2H, bs), 3.69 (2H, q, J = 6.8 Hz), 3.04 (2H, t, J = 6.8 Hz), 2.57 (3H, s).

Anal. Calcd for $C_{25}H_{21}N_3O_5S_2$•0.9 H_2O•0.4 EtOAc: C, 57.15; H, 4.69; N, 7.52; S, 11.47. Found: C, 57.15; H, 4.42; N, 7.80; S, 11.55.

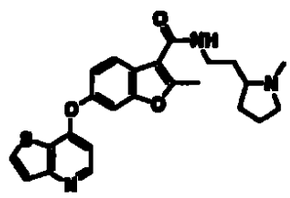
Example 109: 2-Methyl-6-(thieno[3,2-b]pyridin-7-yloxy)-benzofuran-3-carboxylic acid (2-isopropoxy-ethyl)-amide



This material was prepared from 2-methyl-6-[thieno[3,2-b]pyridin-7-yloxy]benzofuran-3-carbonyl chloride 101 and 2-(isopropoxy)ethylamine in a similar manner as that described for example 108. ^1H NMR (CD_3CN) δ 8.49 (1H, d, J = 5.6Hz), 7.91 (1H, d, J = 5.6 Hz), 7.82 (1H, d, J = 8.6 Hz), 7.54 (1H, d, J = 5.6 Hz), 7.41 (1H, d, J = 2.3 Hz), 7.20

(1H, dd, J = 8.6, 2.3 Hz), 6.67 (1H, bm), 6.63 (1H, d, J = 5.3 Hz), 3.8-3.51 (5H, m), 2.66 (3H, s), 1.15 (6H, d, J = 6.1 Hz). *Anal.* Calcd for $C_{22}H_{22}N_2O_4S$: C, 64.37; H, 5.40; N, 6.82; S, 7.81. Found: C, 64.35; H, 5.51; N, 6.78; S, 7.74.

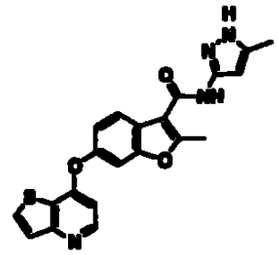
Example 110: 2-Methyl-6-(thieno[3,2-b]pyridin-7-yloxy)-benzofuran-3-carboxylic acid [2-(1-methyl-pyrrolidin-2-yl)-ethyl]-amide



This material was prepared from 2-methyl-6-[thieno[3,2-b]pyridin-7-yloxy]benzofuran-3-carbonyl chloride 101 and 2-(1-methylpyrrolidin-2-yl)ethylamine in a similar manner as that described for example 108. ^{1}H NMR (CD_3CN) δ 8.49 (1H, d, J = 5.6Hz), 7.91 (1H, d, J = 5.3 Hz), 7.85 (1H, d, J = 8.3 Hz), 7.61 (1H, bm), 7.53 (1H, d, J = 5.6 Hz), 7.40 (1H, d, J = 2.0 Hz), 7.20 (1H, dd, J = 8.6, 2.3 Hz), 6.63 (1H, d, J = 5.6 Hz), 3.61-3.53 (1H, m), 3.45-3.40 (1H, m), 3.05-3.00 (1H, m), 2.67 (3H, s), 2.42-2.36 (1H, m), 2.29 (3H, s), 2.18 (1H, q, J = 8.8 Hz), 2.05-1.95 (1H, m, partially obscured by CD_3CN), 1.87-1.66 (5H, m).

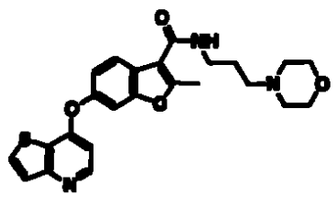
Anal. Calcd for $C_{24}H_{23}N_3O_3S$•0.5 H_2O: C, 64.84; H, 5.90; N, 9.45; S, 7.21. Found: C, 64.73; H, 5.94; N, 9.41; S, 6.98.

Example 111: 2-Methyl-6-(thieno[3,2-b]pyridin-7-yloxy)-benzofuran-3-carboxylic acid (5-methyl-1H-pyrazol-3-yl)-amide



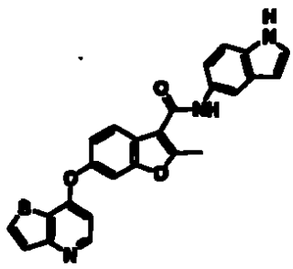
This material was prepared from 2-methyl-6-[thieno[3,2-b]pyridin-7-yloxy]benzofuran-3-carbonyl chloride 101 and (5-methyl-1H-pyrazol-3-yl)amine in a similar manner as that described for example 108. ^{1}H NMR (DMSO-d_6) δ 12.09 (1H, bs), 10.45 (1H, s), 8.50 (1H, d, J = 5.6 Hz), 8.14 (1H, d, J = 5.6 Hz), 7.77 (1H, d, J = 8.6 Hz), 7.65 (1H, d, J = 2.3 Hz), 7.59 (1H, d, J = 5.3 Hz), 7.24 (1H, dd, J = 8.3, 2.0 Hz), 6.64 (1H, d, J = 5.6 Hz), 6.39 (1H, bs), 2.64 (3H, s), 2.23 (3H, s).

Example 112: 2-Methyl-6-(thieno[3,2-b]pyridin-7-yloxy)benzofuran-3-carboxylic acid (3-morpholin-4-ylpropyl)-amide



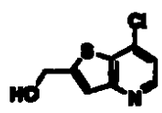
This material was prepared from 2-methyl-6-[thieno[3,2-b]pyridin-7-yloxy]benzofuran-3-carbonyl chloride 101 and 3-(morpholin-4-yl)propylamine in a similar manner as that described for example 108. ^{1}H NMR (DMSO-d_6) δ 8.50 (1H, d, J = 5.6 Hz), 8.14 (1H, d, J = 5.6 Hz), 8.07 (1H, bm), 7.80 (1H, d, J = 8.8 Hz), 7.84 (1H, d, J = 2.0 Hz), 7.59 (1H, d, J = 5.6 Hz), 7.24 (1H, dd, J = 8.3, 2.0 Hz), 6.61 (1H, d, J = 5.6 Hz), 3.56 (4H, bm), 3.35-3.27 (4H, m), 2.63 (3H, s), 2.36 (4H, bm), 1.73 (2H, bm).

Example 113: 2-Methyl-6-(thieno[3,2-b]pyridin-7-yloxy)-benzofuran-3-carboxylic acid (1H-indol-5-yl)-amide



This material was prepared from 2-methyl-6-[thieno[3,2-b]pyridin-7-yloxy]benzofuran-3-carbonyl chloride 101 and 5-aminoindole in a similar manner as that described for example 108. ^{1}H NMR (DMSO-d_6) δ 11.04 (1H, s), 9.96 (1H, s), 8.52 (1H, d, J = 5.6 Hz), 8.15 (1H, d, J = 5.3 Hz), 7.97 (1H, s), 7.83 (1H, d, J = 8.3 Hz), 7.69 (1H, d, J = 2.3 Hz), 7.60 (1H, d, J = 5.6 Hz), 7.36 (2H, s), 7.33 (1H, t, J = 2.8 Hz), 7.27 (1H, dd, J = 8.6, 2.3 Hz), 6.64 (1H, d, J = 5.3Hz), 6.41 (1H, t, J = 2.5 Hz), 2.69 (3H, s).

Example 114(a): 2-(Hydroxymethyl)-7-chlorothieno[3,2-b]pyridine



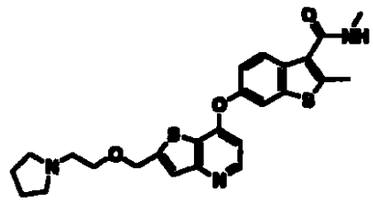
7-Chloro-thieno[3,2-b]pyridine-2-carboxylic acid lithium salt (2.0 g, 9.1 mmole) was dissolved in a solution of DMF (10 mL) and chloroform (50 mL). The carboxylate was treated with thionyl chloride (2.0 mL, 27.3 mmole) and refluxed for one hour. The resultant acid chloride was cooled to room temperature and added dropwise to a solution of sodium borohydride (0.7 g, 18.2 mmole) in DMF (10 mL) at 0 °C. The temperature was allowed to reach room temperature over 2 hours and the reaction was quenched with concentrated HCl. The reaction mixture was neutralized with NaOH and the workup was performed with MTBE, brine and $MgSO_4$. The crude product was triturated with MTBE, which provided the title compound as a beige solid (0.7 g, 40%): ^{1}H-NMR (DMSO-d_6, 400 MHz) δ 8.58 (1H, d, J = 5.1 Hz), 7.51 (1H, d, J = 5.1 Hz), 7.47 (1H, s), 5.84 (1H, t, J = 5.8 Hz), 4.84-4.82 (2H, m); MS m/z 200 (M + H)$^+$.

Example 114(b): 7-Chloro-2-[2-(pyrrolidin-1-yl]ethoxymethyl)thieno[3,2-b]pyridine



A mixture of 2-(hydroxymethyl)-7-chlorothieno[3,2-b]pyridine 114a (0.35 g, 1.8 mmole), 1-(2-chloro-ethyl)-pyrrolidine hydrochloride (31g, 18 mmole), benzyltriethylammonium bromide (0.2 g, 0.7 mmole) and 19 M sodium hydroxide (10 mL) in toluene was refluxed for three hours. The reaction mixture was buffered with 50% saturated sodium bicarbonate and the workup was performed with ethyl acetate, brine and magnesium sulfate. The crude product was purified over silica gel (100 g) using 2-7% methanol-chloroform with 0.1% ammonium hydroxide, which provided the title compound as an amber oil (0.38 g, 62%): ^{1}H-NMR (DMSO-d_6, 400 MHz) δ 8.62 (1H, d, J = 5.0 Hz), 7.58 (1H, s), 7.54 (1H, d, J = 5.1 Hz), 4.86 (2H, s), 3.62 (2H, t, J = 6.0 Hz), 2.64 (2H, t, J = 5.8 Hz), 2.49-2.47 (4H, m), 1.67-1.63 (4H, m); MS m/z 297 (M + H)$^+$.

Example 114: 2-Methyl-6-(2-[2-(pyrrolidin-1-yl)ethoxymethyl]thieno[3,2-b]pyridin-7-yloxy)benzo[b]thiophene-3-carboxylic acid methylamide

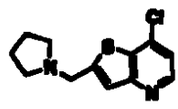


This material was prepared from 7-chloro-2-(2-pyrrolidin-1-yl-ethoxymethyl)-thieno[3,2-b]pyridine 114b (150 mg, 0.51 mmole), 6-hydroxy-2-methyl-benzo[b]thiophene-3-carboxylic acid methylamide 1d (123 mg, 0.56 mmole) and cesium carbonate (497 mg,

01.53 mmole) in a similar manner as described for example 1 to give a beige solid (0.1 g, 41%): ^{1}H-NMR (DMSO-d_6, 400 MHz) δ 8.48 (1H, d, J = 5.3 Hz), 8.28 (1H, q, J = 4.5 Hz), 7.92 (1H, d, J = 2.3 Hz), 7.84 (1H, d, J = 8.9 Hz), 7.51 (1H, s), 7.30 (1H, dd, J = 2.3, 8.9 Hz), 6.63 (1H, d, J = 5.6 Hz), 4.82 (2H, s), 3.60 (2H, t, J = 6.0 Hz), 2.82 (3H, d, J = 4.5 Hz), 2.64-2.60 (5H, m), 2.47 (4H, bs), 1.66-1.63 (4H, m); MS m/z 482 (M + H)$^+$;

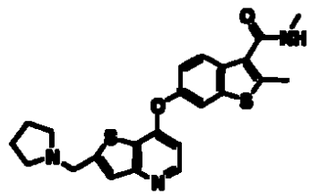
Anal. Calcd for $C_{25}H_{27}N_5O_2S_2$·0.3 H_2O: C, 61.65; H, 5.71; N, 8.63; S, 13.17: Found: C, 61.55; H, 5.71; N, 8.47; S, 12.97.

Example 115(a): 7-Chloro-2-(pyrrolidin-1-ylmethyl)thieno[3,2-b]pyridine



A solution of 2-(hydroxymethyl)-7-chlorothieno[3,2-b]pyridine 114a (100 mg, 0.5 mmole) in dichloroethane was treated with triethylamine (0.08 mL, 0.55 mmole) and mesyl chloride (0.04 mL, 0.55 mmole). The clear solution was stirred for 30 minutes and treated with pyrrolidine (0.12 mL, 1.5 mmole). After one hour, the reaction mixture was poured into 5% sodium bicarbonate and the workup was performed with dichloromethane, brine and magnesium sulfate. The crude product (167 mg greenish oil) was purified over silica gel (1 mm plate) using 2% methanol-chloroform with 0.1% ammonium hydroxide, which provided the title compound as a clear oil (71 mg, 56%): ^{1}H-NMR (DMSO-d_6, 400 MHz) δ 8.58 (1H, d, J = 5.1 Hz), 7.51-7.49 (2H, m), 3.96 (2H, s), 2.58 (4H, bs), 1.75-1.72 (4H, m); MS m/z 253 (M + H)$^+$.

Example 115: 2-Methyl-6-(2-[pyrrolidin-1-ylmethyl]thieno[3,2-b]pyridin-7-yloxy)benzo[b]thiophene-3-carboxylic acid methylamide

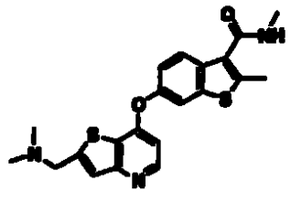


This material was prepared from 7-Chloro-2-(pyrrolidin-1-ylmethyl)thieno[3,2-b]pyridine 115a, 6-hydroxy-2-methyl-benzo[b]thiophene-3-carboxylic acid methylamide 1d and cesium carbonate in a similar manner as described in example 1. ^{1}H-NMR (DMSO-d_6, 400 MHz) δ 8.44 (1H, d, J = 5.3 Hz), 8.27 (1H, q, J = 4.6 Hz), 7.91 (1H, d, J = 2.3 Hz), 7.83 (1H, d, J = 8.6 Hz), 7.43 (1H, s), 7.28 (1H, dd, J = 2.3, 8.8 Hz), 6.60 (1H, d, J = 5.6

Hz), 3.93 (2H, s), 2.82 (3H, d, J = 4.8 Hz), 2.60 (3H, s), 2.54 (4H, bs), 1.72 (4H, s); MS m/z 438 $(M + H)^+$;

Anal. Calcd for $C_{22}H_{23}N_3O_2S_2$: C, 63.13; H, 5.30; N, 9.60; S, 14.66: Found: C, 62.75; H, 5.36; N, 9.35; S, 14.39.

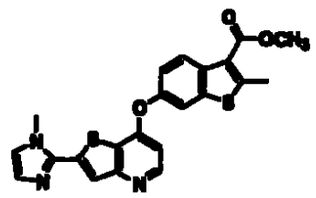
Example 116: 6-[2-[Dimethylaminomethyl]thieno[3,2-b]pyridin-7-yloxy)-2-methylbenzo[b]thiophene-3-carboxylic acid methylamide



This material was prepared from 7-chloro-2-(dimethylaminomethyl)thieno[3,2-b]pyridine, 6-hydroxy-2-methyl-benzo[b]thiophene-3-carboxylic acid methylamide 1d and cesium carbonate in a similar manner as described for example 1. ^{1}H-NMR (DMSO-d_6, 400 MHz) δ 8.45 (1H, d, J = 5.3 Hz), 8.27 (1H, q, J = 4.5 Hz), 7.92 (1H, d, J = 2.3 Hz), 7.83 (1H, d, J = 8.8 Hz), 7.44 (1H, s), 7.28 (1H, dd, J = 2.3, 8.9 Hz), 6.62 (1H, d, J = 5.3 Hz), 3.75 (2H, bs), 2.82 (3H, d, J = 4.5 Hz), 2.60 (3H, s), 2.24 (6H, s); MS m/z 412 $(M + H)^+$;

Anal. Calcd for $C_{21}H_{21}N_3O_2S_2$•0.3 H_2O: C, 60.49; H, 5.22; N, 10.08; S, 15.38: Found: C, 60.47; H, 5.01; N, 9.76; S, 15.09.

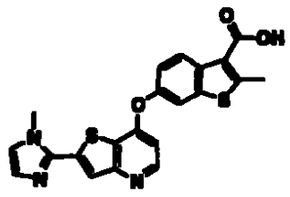
Example 117(a): Methyl 2-methyl-6-[[2-(1-methyl-1*H*-imidazol-2-yl)thieno[3,2-*b*]pyridin-7-yl]oxy]benzo[b]thiophene-3-carboxylate



This material was prepared from the reaction of methyl 6-hydroxy-2-methylbenzo[b]thiophene-3-carboxylate 11a (200 mg, 0.90 mmole) with 7-chloro-2-(1-methyl-1*H*-imidazol-2-yl)thieno[3,2-*b*]pyridine 1e (188 mg, 0.75 mmole) and Cs_2CO_3 (1.22 g, 3.75 mmole) in a manner as previously described for example 1 to give a yellow solid (200 mg, 51%). ^{1}H NMR (DMSO-d_6, 300 MHz) δ 8.52 (1H, d, *J* = 5.46 Hz), 8.38 (1H, d, *J* = 9.04 Hz),

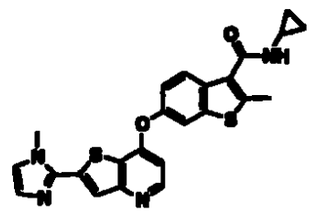
8.02 (1H, d, *J* = 2.26 Hz), 7.89 (1H, s), 7.40 (2H, s), 7.02 (1H, s), 6.73 (1H, d, *J* = 5.46 Hz), 3.98 (3H, s), 3.91 (3H, s), 2.82 (3H, s).

Example 117(b): 2-Methyl-6-{[2-(1-methyl-1*H*-imidazol-2-yl)thieno[3,2-*b*]pyridin-7-yl]oxy}benzo[b]thiophene-3-carboxylic acid



This material was prepared by the reaction of methyl 2-methyl-6-{[2-(1-methyl-1*H*-imidazol-2-yl)thieno[3,2-*b*]pyridin-7-yl]oxy}benzo[b]thiophene-3-carboxylate 117a (200 mg, 0.46 mmole) with $LiOH{\cdot}H_2O$ (192 mg, 4.6 mmole) in a manner as previously described for example 11c to give a yellow solid (185 mg, 85%). ^1H NMR (DMSO-d6, 300 MHz): δ 8.57 (1H, d, *J* = 5.46 Hz), 8.45 (1H, d, *J* = 8.85 Hz), 8.00 (2H, s), 7.53 (1H, s), 7.40 (1H, dd, *J* = 2.35, 8.95 Hz), 7.22 (1H, s), 6.79 (1H, d, *J* = 5.46 Hz), 4.00 (3H, s), 2.82 (3H, s).

Example 117: 2-Methyl-6-{[2-(1-methyl-1*H*-imidazol-2-yl)thieno[3,2-*b*]pyridin-7-yl]oxy}benzo[b]thiophene-3-carboxylic acid cyclopropylamide

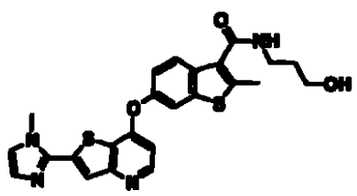


To a solution of 2-methyl-6-{[2-(1-methyl-1*H*-imidazol-2-yl)thieno[3,2-*b*]pyridin-7-yl]oxy}benzo[b]thiophene-3-carboxylic acid 117b (75 mg, 0.18 mmole) in DMF (1.5 mL) at 0 °C were added *N,N*-diisopropylethylamine (68 µL, 0.39 mmole) and HBTU (100 mg, 0.27 mmole). The reaction mixture was stirred 30 min at 0°C then warmed to room temperature and stirred 18 hr. The mixture was poured onto H_2O (25 mL) and the precipitate was collected by vacuum filtration. The filter paper was extracted with a mixture of CH_2Cl_2 (10 mL) and MeOH (10 mL). The solution was concentrated and the crude mixture was purified by silica gel chromatography (5% MeOH / EtOAc) to afford a pale yellow solid (58 mg, 71%). ^1H NMR (DMSO-d_6, 300 MHz) δ 8.52 (1H, d, *J* = 5.46 Hz), 8.48 (1H, d, *J* = 4.33 Hz), 7.95 (1H, d, *J* = 2.28 Hz), 7.88 (1H, s), 7.80 (1H, d, *J* = 8.67 Hz), 7.40 (1H, s), 7.32 (1H, dd, *J* = 2.26, 8.85

Hz), 7.02 (1H, s), 6.70 (1H, d, *J* = 5.46 Hz), 3.98 (3H, s), 2.90 (1H, m), 2.57 (3H, s); 0.73 (2H, m), 0.57 (2H, m).

Anal. Calcd. for $C_{24}H_{22}N_4O_2S_2$: C, 62.59; H, 4.38; N, 12.17; S, 13.92. Found: C, 62.04; H, 4.22; N, 11.91; S, 13.49.

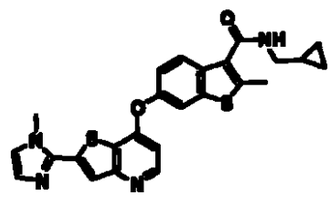
Example 116: 2-Methyl-6-[[2-(1-methyl-1*H*-imidazol-2-yl)thieno[3,2-*b*]pyridin-7-yl]oxy]benzo[b]thiophene-3-carboxylic acid 3-hydroxypropylamide



This material was prepared by the reaction of 2-methyl-6-[[2-(1-methyl-1*H*-imidazol-2-yl)thieno[3,2-*b*]pyridin-7-yl]oxy]benzo[b]thiophene-3-carboxylic acid 117b (65 mg, 0.20 mmole) with 3-amino-1-propanol (46 µL, 0.44 mmole), *N,N*-diisopropylethylamine (77 µL, 0.30 mmole), and HBTU (115 mg, 0.303 mmole) in a manner as previously described for example 117. The crude material was purified by silica gel chromatography (10:30:60% MeOH / CH_2Cl_2 / EtOAc) to give a yellow solid (57 mg, 59%). ^{1}H NMR (DMSO-d_6, 300 MHz) δ 8.52 (1H, d, *J* = 5.27 Hz), 8.37 (1H, t, *J* = 5.58 Hz), 7.95 (1H, d, *J* = 2.26 Hz), 7.88 (1H, s), 7.82 (1H, d, *J* = 8.85 Hz), 7.40 (1H, s), 7.33 (1H, dd, *J* = 2.35, 8.78 Hz), 7.02 (1H, d, *J* = 0.94 Hz), 6.70 (1H, d, *J* = 5.46 Hz), 4.51 (1H, t, *J* = 5.09 Hz), 3.98 (3H, s), 3.50 (2H, q, *J* = 6.22 Hz), 3.35 (2H, m), 2.60 (3H, s), 1.71 (2H, m).

Anal. Calcd. for $C_{24}H_{23}N_4O_3S_2$: C, 60.23; H, 4.63; N, 11.71; S, 13.40. Found: C, 59.01; H, 4.70; N, 11.13; S, 12.89.

Example 119: 2-Methyl-6-[[2-(1-methyl-1*H*-imidazol-2-yl)thieno[3,2-*b*]pyridin-7-yl]oxy]benzo[b]thiophene-3-carboxylic acid (cyclopropylmethyl)amide

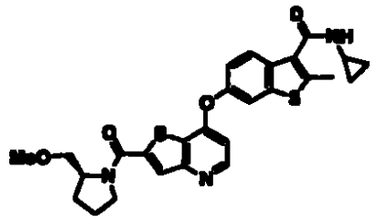


This material was prepared from the reaction of 2-methyl-6-[[2-(1-methyl-1*H*-imidazol-2-yl)thieno[3,2-*b*]pyridin-7-yl]oxy]benzo[b]thiophene-3-carboxylic acid 117b (70 mg, 0.188 mmole), (aminomethyl)cyclopropane (43 µL, 0.50 mmole) and diisopropylethylamine (58 µL,

0.33 mmole), and HBTU (94 mg, 0.25 mmole) in a manner similar to that previously described for example 117 to afford a pale yellow solid (64 mg, 53%). ^{1}H NMR (DMSO-d_6, 300 MHz) δ 8.61 (1H, d, J = 5.46 Hz), 8.49 (1H, t, J = 5.85 Hz), 8.07 (1H, s), 7.99 (1H, d, J = 2.26 Hz), 7.85 (1H, d, J = 8.67 Hz), 7.63 (1H, s), 7.37 (1H, s), 7.36 (1H, dd, J = 2.4, 8.67 Hz), 6.81 (1H, d, J = 5.85 Hz), 4.01 (3H, s), 3.20 (2H, t, J = 6.31 Hz), 2.62 (3H, s), 1.06 (1H, m), 0.47 (2H, m), 0.27 (2H, m).

Anal. Calcd. for $C_{29}H_{28}N_4O_5S_2 \cdot 2(CF_3CO_2H)$: C, 49.57; H, 3.44; N, 7.97; S, 9.13. Found: C, 48.25; H, 3.48; N, 7.64; S, 8.77.

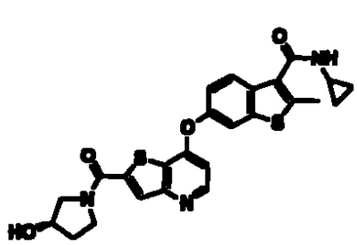
Example 120: 6-[(2-[[(2*S*)-2-(Methoxymethyl)pyrrolidin-1-yl]carbonyl]thieno[3,2-*b*]pyridin-7-yl)oxy]-2-methylbenzo[b]thiophene-3-carboxylic acid cyclopropylamide



This material was prepared by the reaction of 7-chloro-2-[[(2*S*)-2-(methoxymethyl)pyrrolidin-1-yl]carbonyl]thieno[3,2-*b*]pyridine 2a (124 mg, 0.40 mmole) with 6-hydroxy-2-methylbenzo[b]thiophene-3-carboxylic acid cyclopropylamide 8c (119 mg, 0.48 mmole) and Cs_2CO_3 (391 mg, 1.2 mmole) in a manner as previously described for example 1 to give a yellow solid (146 mg, 70%). ^{1}H NMR (DMSO-d_6, 300 MHz) δ 8.58 (1H, d, J = 5.27 Hz), 8.46 (1H, d, J = 4.33 Hz), 8.03 (1H, s), 7.96 (1H, d, J = 2.26 Hz), 7.80 (1H, d, J = 8.67 Hz), 7.32 (1H, dd, J = 2.17, 8.76 Hz), 6.75 (1H, d, J = 5.27 Hz), 4.30 (1H, m), 3.84 (2H, m), 3.53 (1H, m) 3.42 (1H, m), 3.27 (3H, s), 2.89 (1H, m), 2.57 (3H, s), 2.09-1.81 (4H, m) 0.72 (2H, *m*), 0.59 (2H, *m*).

Anal. Calcd. for $C_{27}H_{27}N_3O_4S_2$: C, 62.17; H, 5.22; N, 8.06; S, 12.19. Found: C, 60.94; H, 5.34; N, 7.71; S, 11.71.

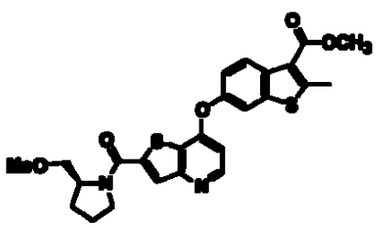
Example 121: 6-[(2-[[(3*R*)-3-Hydroxypyrrolidin-1-yl]carbonyl]thieno[3,2-*b*]pyridin-7-yl)oxy]-2-methylbenzo[b]thiophene-3-carboxylic acid cyclopropylamide



This material was prepared by the reaction of 7-chloro-2-[(R)-3-hydroxypyrrolidine-1-carbonyl]thieno[3,2-b]pyridine 4a (113 mg, 0.40 mmole) with 6-hydroxy-2-methylbenzo[b]thiophene-3-carboxylic acid cyclopropylamide 8c (119 mg, 0.48 mmole) and Cs_2CO_3 (391 mg, 1.2 mmole) in a manner as previously described for example 1 to give a yellow solid (130 mg, 66%). ^{1}H NMR (DMSO-d_6, 300 MHz) δ 8.58 (1H, d, J = 5.46 Hz), 8.46 (1H, d, J = 4.33 Hz), 8.06, 8.00 (1H, s), 7.96 (1H, d, J = 2.26 Hz), 7.80 (1H, d, J = 8.85 Hz), 7.33 (1H, dd, J = 2.35, 8.76 Hz), 6.75 (1H, d, J = 5.27 Hz), 5.07 (1H, m), 4.38, 4.33 (1H, br s), 4.02-3.92 (2H, m), 3.67-3.44 (2H, m), 2.93-2.87 (1H, m), 2.57 (3H, s), 2.08-1.79 (2H, m), 0.76-0.70 (2H, m), 0.60-0.55 (2H, m).

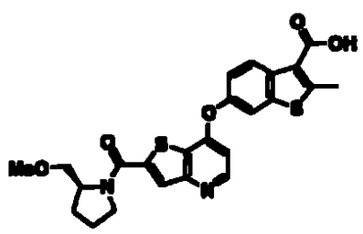
Anal. Calcd. for $C_{25}H_{23}N_3O_4S$: C, 60.83; H, 4.70; N, 8.51; S, 12.99. Found: C, 57.46; H, 4.80; N, 7.81; S, 13.85.

Example 122(a): Methyl 6-[(2-[[(2*S*)-2-(methoxymethyl)pyrrolidin-1-yl]carbonyl]thieno[3,2-*b*]pyridin-7-yl)oxy]-2-methylbenzo[b]thiophene-3-carboxylate



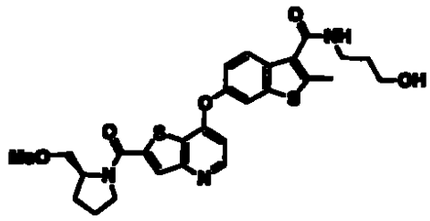
This material was prepared from the reaction of methyl 6-hydroxy-2-methylbenzo[b]thiophene-3-carboxylate 11a (85.8 mg, 0.386 mmole) with 7-chloro-2-[(2*S*)-2-(methoxymethyl)pyrrolidin-1-yl]carbonyl]thieno[3,2-*b*]pyridine 2a (100 mg, 0.322 mmole) and Cs_2CO_3 (524 mg, 1.61 mmole) in a manner similar to that previously described for example 1 to give a brown solid (84 mg, 40%). ^{1}H NMR (DMSO-d_6, 300 MHz) δ 8.70 (1H, d, J = 4.90 Hz), 8.51 (1H, d, J = 9.04 Hz), 8.15 (1H, s), 8.14 (1H, s), 7.54 (1H, dd, J = 2.17, 8.95 Hz), 6.91 (1H, d, J = 5.46 Hz), 4.47-4.38 (1H, m), 4.07-3.90 (2H, m), 4.03 (3H, s), 3.72-3.50 (2H, m), 3.42, 3.39 (3H, s), 2.94 (3H, s), 2.21-1.93 (4H, m).

Example 122(b): 6-[(2-[[(2*S*)-2-(Methoxymethyl)pyrrolidin-1-yl]carbonyl]thieno[3,2-*b*]pyridin-7-yl)oxy]-2-methylbenzo[b]thiophene-3-carboxylic acid



This material was prepared by the hydrolysis of methyl 6-[(2-[[(2*S*)-2-(methoxymethyl)pyrrolidin-1-yl]carbonyl]thieno[3,2-*b*]pyridin-7-yl)oxy]-2-methylbenzo[b]thiophene-3-carboxylate 122a (63 mg, 0.13 mmole) with LiOH-H_2O (54 mg, 13 mmole) in a manner as previously described for example 11c to give a white solid (46 mg, 75%). ^{1}H NMR (DMSO-d_6, 300 MHz) δ 8.58 (1H, d, *J* = 5.46 Hz), 8.44 (1H, d, *J* = 8.85 Hz), 8.03 (1H, s), 8.00 (1H, d, *J* = 2.26 Hz), 7.38 (1H, dd, *J* = 2.45, 9.04 Hz), 6.78 (1H, d, *J* = 5.84 Hz), 4.35-4.25 (1H, m), 3.93-3.76 (2 *H*, m), 3.59-3.50 (2H, m), 3.27, 3.15 (3H, s), 2.81 (3H, s), 2.11-1.83 (4H, m).

Example 122: 6-[(2-[[(2*S*)-2-(Methoxymethyl)pyrrolidin-1-yl]carbonyl]thieno[3,2-*b*]pyridin-7-yl)oxy]-2-methylbenzo[b]thiophene-3-carboxylic acid 3-hydroxypropylamide

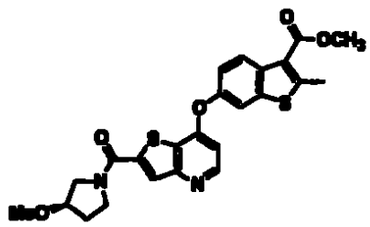


This material was prepared by the reaction of 6-[(2-[[(2*S*)-2-(methoxymethyl)-pyrrolidin-1-yl]carbonyl]thieno[3,2-*b*]pyridin-7-yl)oxy]-2-methylbenzo[b]thiophene-3-carboxylic acid 121b (45 mg, 0.093 mmole) with 3-amino-1-propanol (21 µL, 0.28 mmole), HBTU (53 mg, 0.14 mmole), and diisopropylethylamine (36 µL, 0.21 mmole) in a manner as previously described for example 117 to give a yellow solid (44 mg, 88%). ^{1}NMR (DMSO-d_6, 300 MHz) δ 8.58 (1H, d, *J* = 5.27 Hz), 8.36 (1H, t, *J* = 5.46 Hz), 8.03 (1H, s), 7.96 (1H, d, *J* = 2.26 Hz), 7.82 (1H, d, *J* = 8.85 Hz), 7.33 (1H, dd, *J* = 1.70, 8.67 Hz), 6.75 (1H, d, *J* = 5.27 Hz), 4.51 (1H, t, *J* = 5.18 Hz), 4.30 (1H, m), 3.85 (2H, m), 3.37 (2H, m), 3.27 (3H, s), 2.60 (3H, s), 2.09-1.83 (4H, m), 1.71 (2H, m).

Anal. Calcd. for $C_{27}H_{29}N_3O_3S_2$: C, 60.09; H, 5.42; N, 7.79; S, 11.88. Found: C, 57.22; H, 5.72; N, 7.22; S, 11.16.

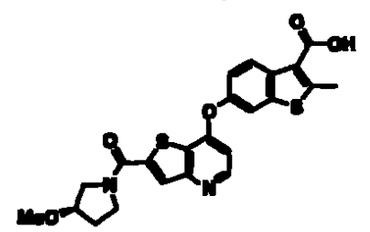
Example 123(a): Methyl 6-[(2-[[(3*R*)-3-methoxypyrrolidin-1-yl]carbonyl]thieno[3,2-*b*]pyridin-7-yl)oxy]-2-methylbenzo[b]thiophene-3-carboxylate

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This material was prepared from the reaction of 6-hydroxy-2-methylbenzo[b]thiophene-3-carboxylate 11a (257 mg, 1.20 mmole) with 7-chloro-2-[[(3*R*)-3-methoxypyrrolidin-1-yl]carbonyl]thieno[3,2-*b*]pyridine 4b (297 mg, 1.00 mmole) and Cs_2CO_3 (977 mg, 3.00 mmole) in a manner similar to that previously described for example 1 to give a brown solid (480 mg, 100%). ^{1}H NMR (DMSO-d_6, 300 MHz) δ 8.58 (1H, d, *J* = 5.46 Hz), 8.39 (1H, d, *J* = 8.85 Hz), 8.07 (1H, s), 8.02 (1H, d, *J* = 2.26 Hz), 7.42 (1H, dd, *J* = 2.35, 8.95 Hz), 6.79 (1H, d, *J* = 5.46 Hz), 4.12-3.80 (3H, m), 3.91 (3H, s), 3.66-3.46 (2H, m), 3.27, 3.24 (3H, s), 2.82 (3H, s), 2.17-1.92 (2H, m).

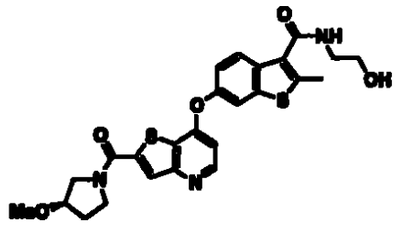
Example 123(b): 6-[[2-[[(3*R*)-3-Methoxypyrrolidin-1-yl]carbonyl]thieno[3,2-*b*]pyridin-7-yl]oxy]-2-methylbenzo[b]thiophene-3-carboxylic acid



This material was prepared by the reaction of methyl 6-[[2-[[(3*R*)-3-methoxypyrrolidin-1-yl]carbonyl]thieno[3,2-*b*]pyridin-7-yl]oxy]-2-methylbenzo[b]thiophene-3-carboxylate 122a (483 mg, 1.00 mmole) with LiOH·H_2O (420 mg, 10.0 mmole) in a manner analogous to that described for example 11c. The crude material was flushed through a silica gel plug with 10% MeOH / CH_2Cl_2 and the resulting mixture of products was used in subsequent reaction without further purification.

Example 123: 6-[[2-[[(3*R*)-3-Methoxypyrrolidin-1-yl]carbonyl]thieno[3,2-*b*]pyridin-7-yl]oxy]-2-methylbenzo[b]thiophene-3-carboxylic acid 2-hydroxyethylamide

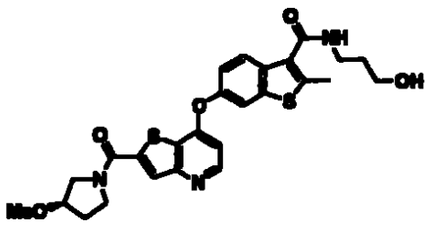
A61



This material was prepared from the reaction of 6-[(2-[[(3*R*)-3-methoxypyrrolidin-1-yl]carbonyl}thieno[3,2-*b*]pyridin-7-yl)oxy]-2-methylbenzo[b]thiophene-3-carboxylic acid 123b (130 mg, 0.278 mmole) with ethanolamine (84 µL, 1.39 mmole), *N,N*-diisopropylethylamine (0.15 mL, 0.83 mmole), and HBTU (263 mg, 0.694 mmole) in a manner similar to that previously described for example 117 to give a yellow solid (40 mg, 28%). ^{1}H NMR (DMSO-d_6, 300 MHz) δ 8.58 (1H, d, *J* = 5.27 Hz), 8.33 (1H, t, *J* = 5.56 Hz), 8.06 (1H, s), 7.98 (1H, d, *J* = 2.26 Hz), 7.86 (1H, d, *J* = 8.85 Hz), 7.32 (1H, dd, *J* = 2.26, 8.85 Hz), 6.75 (1H, d, *J* = 5.46 Hz), 4.76 (1H, br s), 4.13-3.81 (3H, m), 3.67-3.50 (4H, m), 3.43-3.32 (2H, m), 3.27, 3.24 (3H, s), 2.61 (3H, s), 2.18-1.94 (2H, m).

Anal. Calcd. for $C_{25}H_{25}N_3O_5S_2$: C, 58.69; H, 4.93; N, 8.21; S, 12.54. Found: C, 58.58; H, 5.01; N, 7.82; S, 11.67.

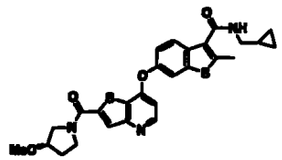
Example 124: 6-[(2-[[(3*R*)-3-Methoxypyrrolidin-1-yl]carbonyl}thieno[3,2-*b*]pyridin-7-yl)oxy]-2-methylbenzo[b]thiophene-3-carboxylic acid 3-hydroxypropylamide



This material was prepared from the reaction of 6-[(2-[[(3*R*)-3-methoxypyrrolidin-1-yl]carbonyl}thieno[3,2-*b*]pyridin-7-yl)oxy]-2-methylbenzo[b]thiophene-3-carboxylic acid 123b (130 mg, 0.278 mmole) with 3-amino-1-propanol (106 µL, 1.39 mmole), *N,N*-diisopropylethylamine (0.15 mL, 0.83 mmole), and HBTU (263 mg, 0.694 mmole) in a manner similar to that previously described for example 117 to give a yellow solid (34 mg, 23%). ^{1}H NMR (DMSO-d_6, 300 MHz) δ 8.58 (1H, d, *J* = 5.27 Hz), 8.36 (1H, t, *J* = 5.65 Hz), 8.08 (1H, s), 7.98 (1H, d, *J* = 2.07 Hz), 7.83 (1H, d, *J* = 8.85 Hz), 7.33 (1H, dd, *J* = 2.07, 8.85 Hz), 6.75 (1H, d, *J* = 5.27 Hz), 4.51 (1H, t, *J* = 5.18 Hz), 4.13-3.82 (3H, m), 3.62 (2H, m), 3.50 (2H, m), 3.39-3.30 (2H, m), 3.27, 3.24 (3H, s), 2.60 (3H, s), 2.18-1.93 (2H, m), 1.71 (2H, quintet, *J* = 6.6 Hz).

Anal. Calcd for $C_{28}H_{27}N_3O_4S_2$•HCl C 55.56 H, 5.02 N, 7 48 S, 11.41 Found C 53.38, H, 4 96; N 7 09 S 10.83.

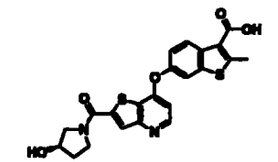
Example 125. 6-[(2-{[(3*R*)-3-Methoxypyrrolidin-1-yl]carbonyl}thieno[3,2-*b*]pyridin-7-yl)oxy]-2-methylbenzo[b]thiophene-3-carboxylic acid (cyclopropylmethyl)amide



This material was prepared by the reaction of 6-[(2-{[(3*R*)-3-methoxypyrrolidin-1-yl]carbonyl}thieno[3,2-*b*]pyridin-7-yl)oxy]-2-methylbenzo[b]thiophene-3-carboxylic acid 122b (130 mg 0.276 mmole) with (aminomethyl)cyclopropane (120 µL, 1.39 mmole) diisopropylethylamine (0.15 mL, 0.83 mmole) and HBTU (263 mg 0.694 mmole) in a manner similar to that previously described for example 117 to afford a pale yellow solid (42 mg 24%) ^{1}H NMR (DMSO-d_6, 300 MHz) δ 8.61 (1H d, *J* = 5.56 Hz) 8.49 (1H t, *J* = 5.56 Hz) 8.08 (1H s) 7 97 (1H s), 7.84 (1H d *J* = 8.59 Hz) 7.34 (1H dd, *J* = 2.27 8.84 Hz) 6.79 (1H d, *J* = 5.56 Hz), 4.11-3.80 (3H, m) 3.70-3.46 (2H m) 3.27 3.24 (3H, s), 3.20 (2H, t, *J* = 6.19 Hz) 2.62 (3H s)2.18-1.91 (2H, m) 1.08 (1H, m) 0.47 (2H m) 0.26 (2H, m)

Anal. Calcd. for $C_{27}H_{27}N_3O_4S_2$•2(CF_3CO_2H) C, 49 66; H, 3.90; N 5.60; S, 8.55. Found: C 49.29 H, 4.03; N 5.64 S 8 59

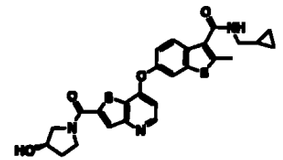
Example 126(a). 6-[(2-{[(3*R*)-3-Hydroxypyrrolidin-1-yl]carbonyl}thieno[3,2-*b*]pyridin-7-yl)oxy]-2-methylbenzo[b]thiophene-3-carboxylic acid



This material was prepared from the reaction of methyl 6-hydroxy-2-methylbenzo[b]thiophene-3-carboxylate 11a (263 mg 1.00 mmole) with 7-chloro-2-[(R)-3-hydroxypyrrolidine-1-carbonyl]thieno[3,2-b]pyridine 4a and Cs_2CO_3 (977 mg 3.00 mmole) in a manner as previously described for example 1 The crude product was then reacted with LiOH-H_2O (227 mg 5.4 mmole) in a manner similar to that described for example 11c to give

a yellow solid (202 mg, 45%) ^{1}H NMR (DMSO-d_6, 300 MHz) δ 8.58 (1H d, *J* = 5.31 Hz) 8.44 (1H d *J* = 8.84 Hz) 8.14 8 07 (1H s) 8.00 (1H s) 7.39 (1H dd *J* = 2.40, 8 97 Hz) 6.78 (1H d, *J* = 5.56 Hz) 4.38 4.33 (1H br s), 4.01-3.91 (1 H, m) 3.68-3.56 (2H, m), 3.49-3.22 (2H, m) 2.81 (3H, s), 2.07 1 79 (2H m)

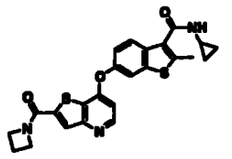
Example 126: 6-[(2-[[(3*R*)-3-Hydroxypyrrolidin-1-yl]carbonyl]thieno[3,2-*b*]pyridin-7-yl)oxy]-2-methylbenzo[b]thiophene-3-carboxylic acid (cyclopropylmethyl)amide



This material was prepared from the reaction of 6-{(2-[[(3*R*)-3-hydroxypyrrolidin-1-yl]carbonyl]thieno[3,2-*b*]pyridin-7-yl)oxy}-2-methylbenzo[b]thiophene-3-carboxylic acid 126a (65 mg 0.14 mmole) with (aminomethyl)cyclopropane (37 µL, 0.43 mmole) diisopropylethylamine (50 µL, 0.29 mmole) and HBTU (81 mg 0.22 mmole) in a similar manner previously described for example 117 to give a pale yellow solid (47 mg, 48%) ^{1}H NMR (DMSO-d_6, 300 MHz) δ 8.60 (1H, d, *J* = 5 56 Hz) 8.49 (1H, t, *J* = 5.68 Hz), 8.07 8.01 (1H, s), 7.97 (1H, d, *J* = 2.27 Hz) 7.84 (1H d *J* = 8.59 Hz) 7 34 (1H, dd, *J* = 2.27 8.84 Hz) 6.78 (1H d, *J* = 5.31 Hz), 4.38, 4.33 (0.5H, br s) 4.01-3.93 (3H m) 3 67-3.47 (2H m), 3.20 (2H, t, *J* = 6.19 Hz) 2.62 (3H, s) 2 07 1.81 (2H m) 1.08 (1H, m) 0.46 (2H m), 0.26 (2H, m)

Anal. Calcd. for $C_{25}H_{25}N_3O_4S_2 \cdot 2(CF_3CO_2H)$ C, 49 72; H 3.77; N 5.86; S 6.95. Found: C, 49.52; H, 3.71 N 5.83 S 6.92.

Example 127: 6-[[2-(Azetidin-1-ylcarbonyl)thieno[3,2-*b*]pyridin-7-yl]oxy]2-methylbenzo[b]thiophene-3-carboxylic acid cyclopropylamide

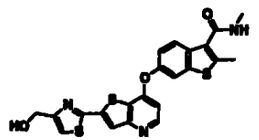


This material was prepared by reacting 2-(azetidin-1-ylcarbonyl)-7-chlorothieno[3,2-*b*]pyridine 25e (80 mg, 0.36 mmole) with 6-hydroxy-2-methylbenzo[b]thiophene-3-carboxylic acid cyclopropyl amide 6c (106 mg 0.43 mmole) and Cs_2CO_3 (349 mg 1.07 mmole) in a manner analogous to that described for example 1 to give a yellow solid (106 mg 47%) ^{1}H

NMR (DMSO-d_6, 300 MHz) δ 8.58 (1H d *J* = 5.27) 8.45 (1H d *J* = 3.77 Hz) 7.95 (1H, d *J* = 2.07 Hz) 7.89 (1H, s) 7.80 (1H, d, *J* = 8 67 Hz) 7.32 (1H, dd *J* = 2.17 8.95 Hz) 6.75 (1H, d *J* = 5 46 Hz) 4.62 (2H t, *J* = 7 35 Hz) 4 10 (2H, t, *J* = 7 72 Hz) 2.90 (1H, m) 2.57 (3H, s) 2.34 (2H m) 0.73 (2H m) 0.58 (2H m)

Anal. Calcd. for $C_{24}H_{21}N_3O_3S_2$•1.5 (CF_3CO_2H). C 51 10; H, 3.57· N 6.62; S, 10.11 Found: C 51.40· H, 3.95, N 6.85, S, 10.29

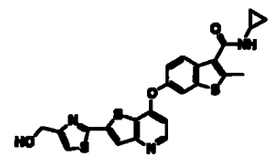
Example 128: (5-{[2-[4-(hydroxymethyl)-1,3-thiazol-2-yl]thieno[3,2-*b*]pyridin-7-yl]oxy}-2-methylbenzo[b]thiophene-3-carboxylic acid methyylamide



This material was prepared by reacting 7-chloro-2-[4-(hydroxymethyl)-1,3-thiazol-2-yl]thieno[3,2-*b*]pyridine (113 mg, 0.4 mmole) with 6-hydroxy-2-methylbenzo[b]thiophene-3-carboxylic acid methylamide 1d (111 mg, 0.5 mmole) and Cs_2CO_3 (6511 mg, 2 mmole) in a manner similar to that previously described for example 1 to give a yellow solid (89 mg 53%). ^1H *NMR* (DMSO-d_6, 300 MHz) δ 8.56 (1H, d, *J* = 5.4 Hz) 8.29 (1H, q, *J* = 4.5 Hz) 8.17 (1H, s) 7.96 (1H, d, *J* = 2.2 Hz) 7.85 (1H d *J* = 8.7 Hz) 7 83 (1H s) 7.33 (1H, dd, *J* = 2.2, 8.7 Hz) 6.75 (1H d, *J* = 5.4 Hz) 5.45 (1H, bs) 4.60 (2H, s) 2.83 (3H, d, *J* = 4.5 Hz) 2.60 (3H s)

Anal. Calcd for $C_{22}H_{17}N_3O_2S_3$•0.3 CH_3OH•0.2 EtOAc: C, 56.07· H 4.03; N 8.49· S 19.44. Found C, 56.05· H 4.08; N 8.43, S 19.47

Example 129. (5-{[2-[4-(Hydroxymethyl)-1,3-thiazol-2-yl]thieno[3,2-*b*]pyridin-7-yl]oxy}-2-methylbenzo[b]thiophene-3-carboxylic acid cyclopropylamide

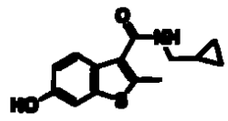


This material was prepared by reacting [2-(7-chlorothieno[3,2-*b*]pyridin-2-yl) 1,3-thiazol-4-yl]methanol (124 mg 0.5 mmole) with 6-hydroxy-2-methylbenzo[b]thiophene-3-carboxylic acid cyclopropylamide 8c (113 mg, 0.4 mmole) and Cs_2CO_3 (391 mg 1.2 mmole) in a manner similar to that previously described for example 1 to give a yellow solid (86 mg,

44%). ^{1}H NMR (DMSO-d_6, 300 MHz) δ 8.56 (1H, d, *J* = 5.4 Hz), 8.46 (1H, d, *J* = 4.3 Hz), 8.17 (1H, s), 7.96 (1H, d, *J* = 2.2 Hz), 7.81 (1H, d, *J* = 8.8 Hz), 7.63 (1H, s), 7.34 (1H, dd, *J* = 2.2, 8.8 Hz), 6.75 (1H, d, *J* = 5.4 Hz), 4.60 (2H, d, *J* = 4.9 Hz), 2.86-2.85 (1H, m), 2.57 (3H, s), 0.78-0.67 (2H, m), 0.62-0.53 (2H, m).

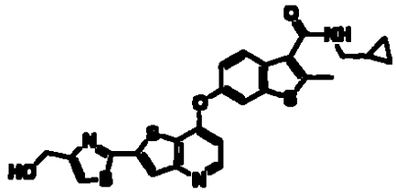
Anal. Calcd. for $C_{24}H_{19}N_3O_3S_2 \cdot 1.2\ H_2O$: C, 55.94; H, 4.19; N, 8.16; S, 18.67. Found: C, 55.85; H, 4.19; N, 7.95; S, 19.01.

Example 130(a): 6-Hydroxy-2-methyl-1-benzo[b]thiophene-3-carboxylic acid (cyclopropylmethyl)amide



This material was prepared by the reaction of crude 3-(chlorocarbonyl)-2-methyl-1-benzothien-6-yl acetate (650 mg, 2.42 mmole (theoretical)) with (aminomethyl)cyclopropane (1.2 mL, 13.8 mmole) and *N,N*-diisopropylethylamine (0.5 mL, 2.9 mmole) in a manner similar to that previously described for example 8c. The crude product was purified by silica gel chromatography (25-50% EtOAc / hexanes) to afford a yellow glass (457 mg, 72%). ^{1}H NMR δ 9.56 (1H, s), 8.31 (1H, t, *J* = 5.56 Hz), 7.52 (1H, d, *J* = 8.67 Hz), 7.18 (1H, d, *J* = 2.07 Hz), 6.84 (1H, dd, *J* = 2.26, 8.67 Hz), 3.16 (2H, m), 2.51 (3H, s), 1.05 (1H, m), 0.44 (2H, m), 0.24 (2H, m).

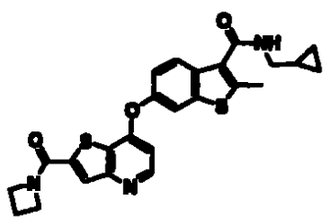
Example 130: (6-{[2-[4-(Hydroxymethyl)-1,3-thiazol-2-yl]thieno[3,2-*b*]pyridin-7-yl]oxy}-2-methylbenzo[b]thiophene-3-carboxylic acid (cyclopropylmethyl)amide



This material was prepared by reacting [2-(7-chlorothieno[3,2-*b*]pyridin-2-yl)-1,3-thiazol-4-yl]methanol (85 mg, 0.30 mmole) with 6-hydroxy-2-methylbenzo[b]thiophene-3-carboxylic acid (cyclopropylmethyl)amide 130a (94 mg, 0.36 mmole) and Cs_2CO_3 (195 mg, 0.60 mmole) in a manner similar to that previously described for example 1b to give a yellow solid (57 mg, 25%). ^{1}H NMR (DMSO-d_6, 300 MHz) δ 8.56 (1H, d, *J* = 5.46 Hz), 8.49 (1H, t, *J* = 5.75 Hz), 8.17 (1H, s), 7.96 (1H, d, *J* = 2.26 Hz), 7.84 (1H, d, *J* = 8.67 Hz), 7.65 (1H, s), 7.36 (1H, dd, *J* = 2.35, 8.76 Hz), 6.80 (1H, d, *J* = 5.46 Hz), 4.60 (2H, s), 3.20 (2H, t, *J* = 6.22 Hz), 2.62 (3H, s), 1.07 (1H, m), 0.47 (2H, m), 0.26 (2H, m).

Anal. Calcd. for $C_{28}H_{21}N_3O_3S_2$•2(CF_3CO_2H): C, 47.34; H, 3.15; N, 5.71; S, 13.08. Found: C, 46.72; H, 3.15; N, 5.71; S, 12.82.

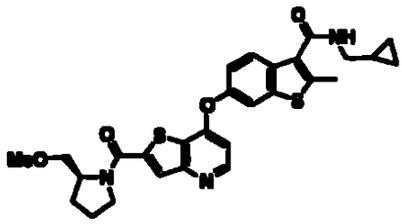
Example 131: 6-[[2-(Azetidin-1-ylcarbonyl)thieno[3,2-*b*]pyridin-7-yl]oxy]-2-methylbenzo[b]thiophene-3-carboxylic acid (cyclopropylmethyl)amide



This material was prepared by reacting 2-(azetidin-1-ylcarbonyl)-7-chlorothieno[3,2-*b*]pyridine 25a (88 mg, 0.35 mmole) with 6-hydroxy-2-methyl-1-benzo[b]thiophene-3-carboxylic acid (cyclopropylmethyl)amide 130a (110 mg, 0.42 mmole) and Cs_2CO_3 (228 mg, 0.70 mmole) in a manner similar to that previously described for example 1 to give a yellow solid (90 mg, 54%). ^{1}H NMR (DMSO-d_6, 300 MHz) δ 8.58 (1H, d, *J* = 5.46 Hz), 8.49 (1H, t, *J* = 5.46 Hz), 7.96 (1H, d, *J* = 2.26 Hz), 7.89 (1H, s), 7.83 (1H, d, *J* = 8.85 Hz), 7.33 (1H, dd, *J* = 2.35, 8.76 Hz), 6.75 (1H, d, *J* = 5.46 Hz), 4.62 (2H, t, *J* = 7.72 Hz), 4.10 (2H, t, *J* = 7.82 Hz), 3.20 (2H, t, *J* = 6.91 Hz), 2.62 (3H, s), 2.35 (2H, m), 1.07 (1H, m), 0.46 (2H, m), 0.26 (2H, m).

Anal. Calcd. for $C_{28}H_{25}N_3O_3S_2$: C, 62.87; H, 4.85; N, 8.80; S, 13.43. Found: C, 62.58; H, 4.90; N, 8.66; S, 13.33.

Example 132: 6-[[2-[[(2*S*)-2-(Methoxymethyl)pyrrolidin-1-yl]carbonyl]thieno[3,2-*b*]pyridin-7-yl]oxy]-2-methylbenzo[b]thiophene-3-carboxylic acid (cyclopropylmethyl)amide

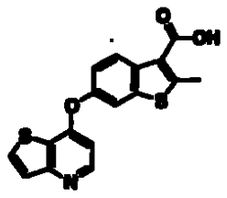


This material was prepared from 7-chloro-2-[[(3*R*)-3-methoxypyrrolidin-1-yl]carbonyl]thieno[3,2-*b*]pyridine 2a (93 mg, 0.30 mmole), 6-hydroxy-2-methylbenzo[b]thiophene-3-carboxylic acid (cyclopropylmethyl)amide 130a (94 mg, 0.36 mmole) and Cs_2CO_3 (195 mg, 0.60 mmole) in a manner similar to that previously described for example 1 to give a yellow solid (33 mg, 18%). ^{1}H NMR (DMSO-d_6, 300 MHz) δ 8.64 (1H, d, *J* = 5.46 Hz), 8.51 (1H, t, *J* = 5.65 Hz), 8.05 (1H, s), 7.99 (1H, d, *J* = 2.26 Hz), 7.85 (1H, d,

J = 8.85 Hz), 7.36 (1H, dd, *J* = 2.26, 8.85 Hz), 6.83 (1H, d, *J* = 5.46 Hz), 4.30 (1H, m), 3.85 (2H, m), 3.53 (1H, m), 3.42 (1H, m), 3.27 (3H, s), 3.20 (2H, m), 2.63 (3H, s), 1.97 (2H, m), 1.90 (2H, m), 1.07 (1H, m), 0.46 (2H, m), 0.26 (2H, m).

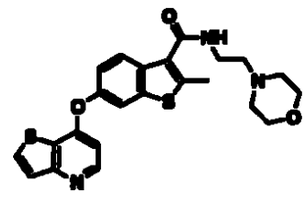
Anal. Calcd. for $C_{28}H_{29}N_3O_4S_2$•1.5(HCl): C, 56.96; H, 5.21; N, 7.12; S, 10.86. Found: C, 56.05; H, 5.44; N, 709; S, 10.66.

Example 133(a): 2-Methyl-6-(thieno[3,2-*b*]pyridin-7-yloxy)benzo[b]thiophene-3-carboxylic acid



This material was prepared by reacting 7-chlorothieno[3,2-*b*]pyridine (170 mg, 1.0 mmole) with methyl 6-hydroxy-2-methylbenzo[b]thiophene-3-carboxylate 11a (267 mg, 1.2 mmole) and Cs_2CO_3 (488 mg, 1.5 mmole) in a manner similar to that previously described for example 1. Silica gel chromatography (10% MeOH / $CHCl_3$) provided the title compound as a brown viscous oil (93 mg, 27%) of. ^{1}H NMR (DMSO-d_6, 300 MHz) δ 8.47 (1H, d, *J* = 5.27 Hz), 8.41 (1H, d, *J* = 8.85 Hz), 8.11 (1H, d, *J* = 5.46 Hz), 7.93 (1H, d, *J* = 2.07 Hz), 7.55 (1H, d, *J* = 7.55 Hz), 7.32 (1H, dd, *J* = 2.26, 8.85 Hz), 6.84 (1H, d, *J* = 5.27 Hz), 2.77 (3H, s).

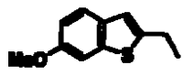
Example 133: 2-Methyl 6-(thieno[3,2-*b*]pyridin-7-yloxy)benzo[b]thiophene-3-carboxylic acid (2-morpholin-4-yl)ethylamide



This material was prepared from the reaction of 2-methyl-6-(thieno[3,2-*b*]pyridin-7-yloxy)benzo[b]thiophene-3-carboxylic acid 133a (93 mg, 0.27 mmole) with 4-(2-aminoethyl)morpholine (0.12 mL, 0.82 mmole), diisopropylethylamine (0.10 mL, 0.55 mmole), and HBTU (155 mg, 0.41 mmole) in a manner similar to that previously described for example 117 to give a white crystalline solid (35 mg, 28%). ^{1}H NMR (DMSO-d_6, 300 MHz) δ 8.51 (1H, d, *J* = 5.27 Hz), 8.28 (1H, t, *J* = 5.37 Hz), 8.15 (1H, d, *J* = 5.46 Hz), 7.94 (1H, dd, *J* = 2.26 Hz), 7.94 (1H, d, *J* = 8.48 Hz), 7.59 (1H, d, *J* = 5.46 Hz), 7.33 (1H, dd, *J* = 2.26, 8.85 Hz), 6.84 (1H, d, *J* = 5.27 Hz), 3.58 (4H, t, *J* = 4.33 Hz), 3.43 (2H, q, *J* = 6.09 Hz), 3.32 (2H, m), 2.63 (3H, s), 2.52-2.39 (4H, m).

Anal. Calcd. for $C_{22}H_{22}N_2O_3S_2$: C, 60.90; H, 5.11; N, 9.26; S, 14.4 Found: C, 61.12; H, 5.16; N, 9.16; S, 14.02.

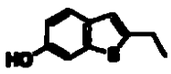
Example 134(a): 2-Ethyl 6-hydroxybenzo[b]thiophene



This material was prepared from 6-methoxybenzo[b]thiophene 1a (2.63 g, 16 mmole) by treatment with n-BuLi and ethyl iodide (7.80 g, 50 mmole) in a manner as previously described for example 1b to give a white solid (2.78 g, 90%). ^{1}H NMR (DMSO-d_6) δ 7.56 (1H, d, J = 8.7 Hz), 7.44 (1H, d, J = 2.3 Hz), 7.02 (1H, s), 6.92 (1H, dd, J = 2.3, 8.7 Hz), 2.84 (2H, q, J = 7.5 Hz), 1.27 (3H, t, J = 7.5 Hz).

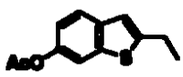
Anal. Calcd. for $C_{11}H_{12}OS$: C, 68.71; H, 6.29; S, 16.68. Found: C, 69.50; H, 6.21; S, 16.93.

Example 134(b): 2-Ethyl-6-hydroxybenzo[b]thiophene



This material was prepared from 2-ethyl-6-methoxybenzo[b]thiophene 134a (2.30 g, 12 mmole) by treatment with BBr_3 in a manner as previously described for example 1d to give a white solid (1.75 g, 82%). ^{1}H NMR (DMSO-d_6) δ 9.43 (1H, s), 7.48 (1H, d, J = 8.5 Hz), 7.16 (1H, d, J = 2.2 Hz), 6.95 (1H, s), 6.78 (1H, dd, J = 2.2, 8.5 Hz), 2. 61 (2H, q, J = 7.5 Hz), 1.26 (3H, t, J = 7.5 Hz).

Example 134(c): 6-Acetoxy-2-ethylbenzo[b]thiophene

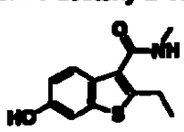


This material was prepared by treatment of 2-ethyl-6-hydroxybenzo[b]thiophene 134b (1.60 g, 9 mmole) with acetyl chloride (1 ml, 1.10 g, 14 mmole) and Et_3N (2 ml, 1.45 g, 14 mmole) in a manner as previously described for example 8b to give a white solid (2.03 g, 93%). ^{1}H NMR (DMSO-d_6) δ 7.72 (1H, d, J = 8.5 Hz), 7.69 (1H, d, J = 2.2 Hz), 7.15 (1H, s), 7.08 (1H, dd, J = 2.2, 8.5 Hz), 2. 69 (2H, q, J = 7.5 Hz), 2.28 (3H, s), 1.29 (3H, t, J = 7.5 Hz).

Anal. Calcd. for $C_{12}H_{12}O_2S$: C, 65.43; H, 5.49; S, 14.56. Found: C, 65.64; H, 5.61; S, 14.49.

Example 134(d): 2-Ethyl-6-hydroxybenzo[b]thiophene-3-carboxylic acid methylamide

This material was prepared from 6-acetoxy-2-ethylbenzo[b]thiophene 134c (1.77 g,

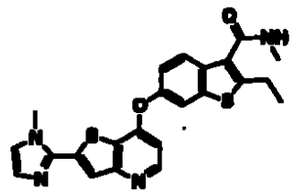


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8 mmole) by acylation with oxalyl chloride in the presence of $AlCl_3$, followed by treatment with methylamine in a manner as previously described for example 1d to give a pale yellow solid (1.55 g, 82%). ^{1}H NMR (DMSO-d_6) δ 9.57 (1H, s), 8.15 (1H, q, J = 4.5Hz), 7.48 (1H, d, J = 8.6 Hz), 7.19 (1H, d, J = 2.3 Hz), 6.84 (1H, dd, J = 2.3, 8.6 Hz), 2. 90 (2H, q, J = 7.5 Hz), 2.78 (3H, d, J = 4.5 Hz), 1.22 (3H, t, J = 7.5 Hz).

Anal. Calcd for $C_{15}H_{15}NO_2S$: C, 61.25; H, 5.57; N, 5.95; S, 13.63. Found: C, 61.11; H, 5.68; N, 5.88; S, 13.41.

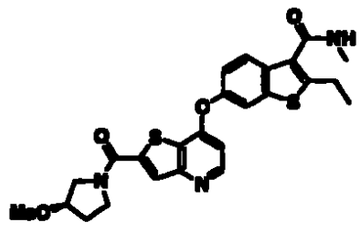
Example 134: 2-Ethyl 6-[[2-(1-methyl-1*H*-imidazol-2-yl)thieno[3,2-*b*]pyridin-7-yl]oxy]benzo[b]thiophene-3-carboxylic acid methylamide



This material was prepared by reacting 7-chloro-2-(1-methyl-1*H*-imidazol-2-yl)thieno[3,2-*b*]pyridine 1e (87 mg, 0.35 mmole) with 2-ethyl-6-hydroxybenzo[b]thiophene-3-carboxylic acid methylamide 134d (99 mg, 0.42 mmole) and Cs_2CO_3 (342 mg, 1.05 mmole) in a manner analogous to that described for example 1 to give a yellow solid (89 mg, 37%). ^{1}H NMR (DMSO-d_6, 300 MHz), δ 8.52 (1H, d, *J* = 5.56 Hz), 8.33 (1H, m), 7.98 (1H, d, *J* = 2.27 Hz), 7.89 (1H, s), 7.81 (1H, d, *J* = 8.59 Hz), 7.40 (1H, s), 7.33 (1H, dd, *J* = 2.27, 8.84 Hz), 7.02 (1H, s), 6.97 (1H, d, *J* = 5.31 Hz), 3.96 (3H, s), 3.00 (2H, q, *J* = 7.58 Hz), 2.83 (3H, d, *J* = 4.80 Hz), 1.28 (3H, t, *J* = 7.58 Hz).

Anal. Calcd. for $C_{20}H_{20}N_4O_2S_2$•2(CF_3CO_2H): C, 47.93; H, 3.28; N, 8.28; S, 9.48. Found: C, 47.63; H, 3.24; N, 8.14; S, 9.29.

Example 135: 2-Ethyl-6-[[2-[[(3*R*)-3-methoxypyrrolidin-1-yl]carbonyl]thieno[3,2-*b*]pyridin-7-yl]oxy]benzo[b]thiophene-3-carboxylic acid methylamide

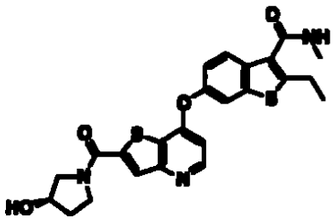


This material was prepared by reacting 7-chloro-2-[[(3*R*)-3-methoxypyrrolidin-1-yl]carbonyl]thieno[3,2-*b*]pyridine 4b (74 mg, 0.25 mmole) with 2-ethyl-6-hydroxybenzo[b]thiophene-3-carboxylic acid methylamide 134d (71 mg, 0.30 mmole) and

Cs_2CO_3 (244 mg, 0.75 mmole) in a manner analogous to that described for example 1 to give a yellow solid (34 mg, 19%). ^1H NMR (DMSO-d_6, 300 MHz), δ 8.59 (1H, d, J = 5.31 Hz), 8.33 (1H, q, J = 4.46 Hz), 8.06 (1H, s), 7.99 (1H, d, J = 2.27 Hz), 7.81 (1H, d, J = 8.84 Hz), 7.34 (1H, dd, J = 2.27, 8.84 Hz), 6.76 (1H, d, J = 5.56 Hz), 4.06-3.83 (3H, m), 3.67-3.48 (2H, m), 3.27, 3.24 (3H, s), 3.00 (2H, t, J = 7.49 Hz), 2.83 (3H, d, J = 4.55 Hz), 2.16-1.95 (2H, m), 1.28 (3H, t, J = 7.58 Hz).

Anal. Calcd. for $C_{25}H_{25}N_3O_4S_2$•1.25(CH_3CO_2H): C, 51.76; H, 4.15; N, 6.58; S, 10.05. Found: C, 51.24; H, 4.23; N, 6.55; S, 10.05.

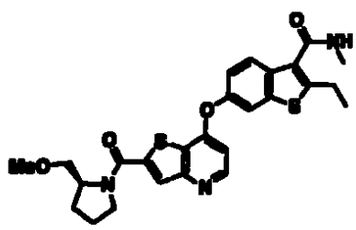
Example 136: 2-Ethyl-6-[(2-[[(3*R*)-3-hydroxypyrrolidin-1-yl]carbonyl]thieno[3,2-*b*]pyridin-7-yl)oxy]benzo[b]thiophene-3-carboxylic acid methylamide



This material was prepared by reacting 7-chloro-2-[[(3*R*)-3-hydroxypyrrolidin-1-yl]carbonyl]thieno[3,2-*b*]pyridine 4a (71 mg, 0.25 mmole) with 2-ethyl-6-hydroxybenzo[b]thiophene-3-carboxylic acid methylamide 134d (71 mg, 0.30 mmole) and Cs_2CO_3 (244 mg, 0.75 mmole) in a manner analogous to that described for example 1 to give a light brown solid (76 mg, 63%). ^1H NMR (DMSO-d_6, 300 MHz), δ 8.58 (1H, d, J = 5.56 Hz), 8.32 (1H, q, J = 4.36 Hz), 8.07, 8.00 (1H, s), 7.98 (1H, d, J = 2.27 Hz), 7.80 (1H, d, J = 8.84 Hz), 7.33 (1H, dd, J = 2.27, 8.59 Hz), 6.75 (1H, d, J = 5.31 Hz), 4.38, 4.33 (1H, br s), 4.01-3.93 (2H, m), 3.67-3.45 (3H, m), 3.00 (2H, t, J = 7.49 Hz), 2.83 (3H, d, J = 4.55 Hz), 2.06-1.80 (2H, m), 1.28 (3H, t, J = 7.58 Hz).

Anal. Calcd. for $C_{24}H_{23}N_3O_4S_2$: C, 59.86; H, 4.81; N, 8.73; S, 13.32. Found: C, 58.63; H, 4.78; N, 8.46; S, 13.33.

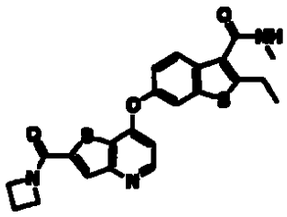
Example 137: 2-Ethyl-6-[(2-[[(2*S*)-2-(methoxymethyl)pyrrolidin-1-yl]carbonyl]thieno[3,2-*b*]pyridin-7-yl)oxy]benzo[b]thiophene-3-carboxylic acid methylamide



This material was prepared by reacting 7-chloro-2-[[(3*R*)-3-methoxypyrrolidin-1-yl]carbonyl]thieno[3,2-*b*]pyridine 2a (155 mg, 0.5 mmole) with 2-ethyl-6-hydroxybenzo[b]thiophene-3-carboxylic acid methylamide 134d (141 mg, 0.60 mmole) and Cs_2CO_3 (488 mg, 1.5 mmole) in a manner analogous to that described for example 1 to give a yellow solid (25 mg, 10%). ^{1}H NMR (DMSO-d_6, 300 MHz), δ 8.59 (1H, d, *J* = 5.56 Hz), 8.33 (1H, d, *J* = 4.55 Hz), 8.03 (1H, s), 7.99 (1H, d, *J* = 2.02 Hz), 7.81 (1H, d, *J* = 8.59 Hz), 7.33 (1H, dd, *J* = 2.27, 8.84 Hz), 6.77 (1H, d, *J* = 5.56 Hz), 4.31 (1H, br s), 3.90-3.81 (2H, m), 3.37-3.15 (2H, m), 3.37 (3H, s), 3.00 (2H, q, *J* = 7.41 Hz), 2.83 (3H, d, *J* = 4.55 Hz), 2.09-1.84 (4H, m), 1.28 (3H, t, *J* = 7.58 Hz).

Anal. Calcd. for $C_{25}H_{27}N_3O_4S_2$•1.75(HCl): C, 54.46; H, 5.05; N, 7.33; S, 11.18. Found: C, 54.50; H, 5.19; N, 7.30; S, 11.22.

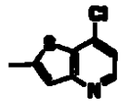
Example 138: 6-[[2-(Azetidin-1-ylcarbonyl)thieno[3,2-*b*]pyridin-7-yl]oxy]-2-ethylbenzo[b]thiophene-3-carboxylic acid methylamide



This material was prepared by reacting 2-(azetidin-1-ylcarbonyl)-7-chlorothieno[3,2-*b*]pyridine 25a (97 mg, 0.40 mmole) with 2-ethyl-6-hydroxybenzo[b]thiophene-3-carboxylic acid methylamide 134d (113 mg, 0.48 mmole) and Cs_2CO_3 (391 mg, 1.2 mmole) in a manner similar to that previously described for example 1 to give a yellow solid (120 mg, 52%). ^{1}H NMR (DMSO-d_6, 300 MHz) δ 8.59 (1H, d, *J* = 5.67 Hz), 8.31 (1H, m), 7.98 (1H, d, *J* = 2.27 Hz), 7.89 (1H, s), 7.81 (1H, d, *J* = 8.69 Hz), 7.33 (1H, dd, *J* = 1.51, 8.69 Hz), 6.76 (1H, d, *J* = 5.29 Hz), 4.62 (2H, t, *J* = 7.37 Hz), 4.11 (2H, t, *J* = 7.37 Hz), 3.00 (2H, q, *J* = 7.55 Hz), 2.83 (3H, d, *J* = 4.53 Hz), 2.35 (2H, m), 1.28 (3H, t, *J* = 7.56 Hz).

Anal. Calcd. for $C_{24}H_{21}N_3O_3S_2$•CF_3CO_2H: C, 53.09; H, 3.92; N, 7.43; S, 11.34. Found: C, 52.58; H, 3.80; N, 7.28; S, 11.12.

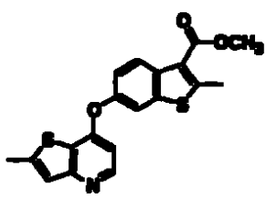
Example 139(a): 7-Chloro-2-methylthieno[3,2-b]pyridine



This material was prepared from 7-chlorothieno[3,2-b]pyridine (1.69 g, 10 mmole) by treatment with *n*-BuLi and iodomethane (2 ml, 4.56 g, 32 mmole) in a manner as previously described for example 1b to give a pale yellow, low-melting solid (1.48 g, 81%). ^{1}H NMR (DMSO-d_6): δ 8.56 (1H, d, J = 5.1 Hz), 7.48 (1H, d, J = 5.1 Hz), 7.38 (1H, s), 2.65 (3H, s).

Anal. Calcd. for C_8H_6NSCl: C, 52.32; H, 3.29; N, 7.63; S, 17.46; Cl, 19.30. Found: C, 52.13; H, 3.36; N, 7.86; S, 17.44; Cl, 19.20.

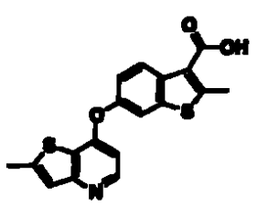
Example 139(b): Methyl 2-methyl-6-(2-methylthieno[3,2-b]pyridin-7-yloxy)-benzo[b]thiophene-3-carboxylate



This material was prepared by the reaction of 7-chloro-2-methylthieno[3,2-b]pyridine 139a (1.29 g, 7 mmole) with methyl 6-hydroxy-2-methylbenzo[b]thiophene-3-carboxylate 11a (2.18 g, 9.8 mmole) and Cs_2CO_3 (6.51 g, 20 mmole) in a manner as previously described for example 1 to give a yellow solid (1.91 g, 74%). ^{1}H NMR ($CDCl_3$) δ 8.43 (1H,d, J = 5.4 Hz), 8.37 (1H, d, J = 9.0 Hz), 7.97 (1H, d, J = 2.2 Hz), 7.37 (1H, dd, J = 2.2, 9.0 Hz), 7.30 (1H, s), 6.63 (1H, d, J = 5.4 Hz), 3.91 (3H, s), 2.81 (3H, s), 2.61 (3H, s).

Anal. Calcd for $C_{19}H_{15}N_3O_3S \cdot 0.1\ CH_2Cl_2$: C, 60.70; H, 4.05; N, 3.71; S, 16.97. Found: C, 60.71; H, 4.17; N, 3.60; S, 17.11.

Example 139(c): 2-Methyl-6-(2-methylthieno[3,2-b]pyridin-7-yloxy)benzo[b]thiophene-3-carboxylic acid

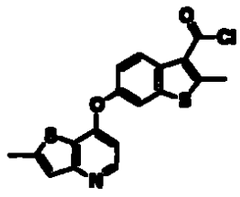


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This material was prepared from methyl 2-methyl-6-(2-methylthieno[3,2-b]pyridin-7-yloxy)benzo[b]thiophene-3-carboxylate 139b (1.50 g, 4.8 mmole) in a manner as previously described for example 11c to give a yellow solid (1.41 g, 82%). ^{1}H NMR (DMSO-d_6) δ 13.08 (1H, bs), 8.45 (1H, d, J = 5.5 Hz), 8.43 (1H, d, J = 8.8 Hz), 7.96 (1H, d, J = 2.4 Hz), 7.35 (1H, dd, J = 2.4, 8.8 Hz), 7.32 (1H, s), 6.66 (1H, d, J = 5.5 Hz), 2.81 (3H, s), 2.62 (3H, s).

Anal. Calcd for $C_{18}H_{13}NO_3S_2$•0.5 H_2O: C, 59.32; H, 3.87; N, 3.84; S, 17.60. Found: C, 59.31; H, 3.74; N, 3.79; S, 17.49.

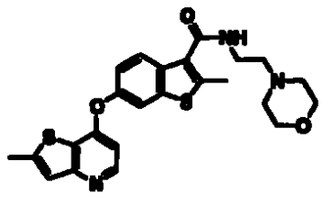
Example 139(d): 2-Methyl-6-(2-methylthieno[3,2-b]pyridin-7-yloxy)benzo[b]thiophene-3-carbonyl chloride



This material was prepared from 2-methyl-6(2-methylthieno[3,2-b]pyridin-7-yloxy)benzo[b]thiophene-3-carboxylic acid 139c (1.34 g, 3.8 mmole) by treatment with thionyl chloride (1 ml, 1.63 g, 13.7 mmole) in a manner as previously described for example 11 to give an orange solid (1.37 g, 97%). ^{1}H NMR (DMSO-d_6): δ 8.74 (1H, d, J = 6.8 Hz), 8.50 (1H, d, J = 9.0 Hz), 8.12 (1H, d, J = 2.4 Hz), 7.80 (1H, s), 7.48 (1H, dd, J = 2.4, 9.0 Hz), 7.05 (1H, d, J = 6.6 Hz), 2.83 (3H, s), 2.75 (3H, s).

Anal. Calcd for $C_{18}H_{12}NOS_2Cl$•0.9 HCl: C, 50.69; H, 3.57; N, 3.28; S, 15.04; Cl, 15.79. Found: C, 50.64; H, 3.56; N, 3.22; S, 14.98; Cl, 15.65.

Example 139: 2-Methyl-6-(2-methylthieno[3,2-b]pyridin-7-yloxy)benzo[b]thiophene-3-carboxylic acid (2-morpholin-4-yl-ethyl)-amide

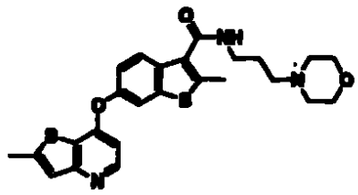


This material was prepared from 2-methyl-6-(2-methylthieno[3,2-b]pyridin-7-yloxy)benzo[b]thiophene-3-carbonyl chloride 139d (112 mg, 0.3 mmole) and 2-(morpholin-4-yl)ethylamine (157 mg, 1.2 mmole) in a similar manner as that described for example 108 to

give a yellow solid (105 mg, 75%). ^{1}H NMR (DMSO-d_6) δ 8.44 (1H, d, J = 5.5 Hz), 8.29 (1H, t, J = 4.8 Hz), 7.94 (1H, d, J = 8.7 Hz), 7.92 (1H, d, J = 2.3 Hz), 7.31 (1H, s), 7.30 (1H, dd, J = 2.3, 8.7 Hz), 6.60 (1H, d, J = 5.5 Hz), 3.60 (4H, t, J = 4.2 Hz), 3.45 (2H, dt, J = 4.8, 6.2 Hz), 2.64 (3H, s), 2.62 (3H, s), 2.55-2.41 (6H, m).

Anal. Calcd for $C_{24}H_{25}N_3O_3S_2$: C, 61.64; H, 5.39; N, 8.99; S, 13.71. Found: C, 61.34; H, 5.49; N, 8.90; S, 13.68.

Example 140: 2-Methyl-6-(2-methylthieno[3,2-b]pyridin-7-yloxy)benzo[b]thiophene-3-carboxylic acid (3-morpholin-4-ylpropyl)-amide



This material was prepared from 2-methyl-6-(2-methylthieno[3,2-b]pyridin-7-yloxy)benzo[b]thiophene-3-carbonyl chloride 139d (112 mg, 0.3 mmole) and 3-(morpholin-4-yl)propylamine (175 mg, 1.2 mmole) in a similar manner as that described for example 108 to give a yellow solid (84 mg, 44%). ^{1}H NMR (DMSO-d_6) δ 8.43 (1H, d, J = 5.5 Hz), 8.38 (1H, t, J = 5.3 Hz), 7.91 (1H, d, J = 2.3 Hz), 7.81 (1H, d, J = 8.6 Hz), 7.30 (1H, s), 7.28 (1H, dd, J = 2.3, 8.6 Hz), 6.59 (1H, d, J = 5.5 Hz), 3.56 (4H, t, J = 4.3 Hz), 3.33 (2H, dt, J = 5.3, 6.8 Hz), 2.61 (3H, s), 2.60 (3H, s), 2.42-2.31 (6H, m), 1.72 (2H, tt, J = 6.8, 7.0 Hz).

Anal. Calcd for $C_{24}H_{27}N_3O_3S_2 \cdot 0.1\ CH_2Cl_2$: C, 61.51; H, 5.59; N, 8.57; S, 13.06. Found: C, 61.53; H, 5.55; N, 8.25; S, 13.06.

The exemplary compounds described above may be tested for their activity using the tests described below.

BIOLOGICAL TESTING; ENZYME ASSAYS

The stimulation of cell proliferation by growth factors such as VEFG, FGF, and others is dependent upon their induction of autophosphorylation of each of their respective receptor's tyrosine kinases. Therefore, the ability of a protein kinase inhibitor to block cellular proliferation induced by these growth factors is directly correlated with its ability to block receptor autophosphorylation. To measure the protein kinase inhibition activity of the compounds, the following constructs were devised.

<u>VEGF-R2 Construct for Assay:</u>

This construct determines the ability of a test compound to inhibit tyrosine kinase activity. A construct (VEGF-R2Δ50) of the cytosolic domain of human vascular endothelial growth factor receptor 2 (VEGF-R2) lacking the 50 central residues of the 68 residues of the kinase insert domain was expressed in a baculovirus/insect cell system. Of the 1356

residues of full-length VEGF-R2, VEGF-R2Δ50 contains residues 806-839 and 990-1171, and also one point mutation (E990V) within the kinase insert domain relative to wild-type VEGF-R2. Autophosphorylation of the purified construct was performed by incubation of the enzyme at a concentration of 4 μM in the presence of 3 mM ATP and 40 mM $MgCl_2$ in 100 mM HEPES, pH 7.5, containing 5% glycerol and 5 mM DTT, at 4 °C for 2 h. After autophosphorylation, this construct has been shown to possess catalytic activity essentially equivalent to the wild-type autophosphorylated kinase domain construct. See Parast et al., *Biochemistry*, 37, 16788-16801 (1998).

FGF-R1 Construct for Assay:

The intracellular kinase domain of human FGF-R1 was expressed using the baculovirus vector expression system starting from the endogenous methionine residue 458 to glutamate 766, according to the residue numbering system of Mohammadi et al., *Mol. Cell. Biol.*, 16, 977-989 (1996). In addition, the construct also has the following 3 amino acid substitutions: L457V, C488A, and C584S.

VEGF-R2 Assay

Coupled Spectrophotometric (FLVK-P) Assay

The production of ADP from ATP that accompanies phosphoryl transfer was coupled to oxidation of NADH using phosphoenolpyruvate (PEP) and a system having pyruvate kinase (PK) and lactic dehydrogenase (LDH). The oxidation of NADH was monitored by following the decrease of absorbance at 340 nm (ε_{340} = 6.22 cm^{-1} mM^{-1}) using a Beckman DU 650 spectrophotometer. Assay conditions for phosphorylated VEGF-R2Δ50 (indicated as FLVK-P in the tables below) were the following: 1 mM PEP; 250 μM NADH; 50 units of LDH/mL; 20 units of PK/mL; 5 mM DTT; 5.1 mM poly(E_4Y_1); 1 mM ATP; and 25 mM $MgCl_2$ in 200 mM HEPES, pH 7.5. Assay conditions for unphosphorylated VEGF-R2Δ50 (indicated as FLVK in the tables) were the following: 1 mM PEP; 250 μM NADH; 50 units of LDH/mL; 20 units of PK/mL; 5 mM DTT; 20 mM poly(E_4Y_1); 3 mM ATP; and 60 mM $MgCl_2$ and 2 mM $MnCl_2$ in 200 mM HEPES, pH 7.5. Assays were initiated with 5 to 40 nM of enzyme. K_i values were determined by measuring enzyme activity in the presence of varying concentrations of test compounds. The percent inhibition at 50 nm (% Inhibition @ 50 nm) was determined by linear least-squares regression analysis of absorbance as a function of time. The binding inhibitions were fitted to equation as described by Morrison. The data were analyzed using Enzyme Kinetic and Kaleidagraph software.

FGF-R Assay

The spectrophotometric assay was carried out as described above for VEGF-R2, except for the following changes in concentration: FGF-R = 50 nM, ATP = 2 mM, and poly(E4Y1) = 15 mM.

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HUVEC + VEGF Proliferation Assay

This assay determines the ability of a test compound to inhibit the growth factor-stimulated proliferation of human umbilical vein endothelial cells ("HUVEC"). HUVEC cells (passage 3-4, Clonetics, Corp.) were thawed into EGM2 culture medium (Clonetics Corp) in T75 flasks. Fresh EGM2 medium was added to the flasks 24 hours later. Four or five days later, cells were exposed to another culture medium (F12K medium supplemented with 10% fetal bovine serum (FBS), 60 µg/mL endothelial cell growth supplement (ECGS), and 0.1 mg/mL heparin). Exponentially-growing HUVEC cells were used in experiments thereafter. Ten to twelve thousand HUVEC cells were plated in 96-well dishes in 100 µl of rich, culture medium (described above). The cells were allowed to attach for 24 hours in this medium. The medium was then removed by aspiration and 105 µl of starvation media (F12K+1% FBS) was added to each well. After 24 hours, 15 µl of test agent dissolved in 1% DMSO in starvation medium or this vehicle alone was added into each treatment well; the final DMSO concentration was 0.1%. One hour later, 30 µl of VEGF (30 ng/mL) in starvation media was added to all wells except those containing untreated controls; the final VEGF concentration was 6 ng/mL. Cellular proliferation was quantified 72 hours later by MTT dye reduction, at which time cells were exposed for 4 hours MTT (Promega Corp.). Dye reduction was stopped by addition of a stop solution (Promega Corp.) and absorbance at 595 nm was determined on a 96-well spectrophotometer plate reader.

Mouse PK Assay

The pharmacokinetics (e.g., absorption and elimination) of drugs in mice were analyzed using the following experiment. Test compounds were formulated as a suspension in a 30:70 (PEG 400: acidified H_2O) vehicle. This solution was administered orally (p.o.) and intraperitoneally (i.p.) at 50 mg/kg to two distinct groups (n=4) of B6 female mice. Blood samples were collected via an orbital bleed at time points: 0 hour (pre-dose), 0.5 hr, 1.0 hr, 2.0 hr, and 4.0 hr post dose. Plasma was obtained from each sample by centrifugation at 2500 rpm for 5 min. Test compound was extracted from the plasma by an organic protein precipitation method. For each time bleed, 50 µL of plasma was combined with 1.0 mL of acetonitrile, vortexed for 2 min. and then spun at 4000 rpm for 15 min. to precipitate the protein and extract out the test compound. Next, the acetonitrile supernatant (the extract containing test compound) was poured into new test tubes and evaporated on a hot plate (25°C) under a steam of N_2 gas. To each tube containing the dried test compound extract, 125 µL of mobile phase (60:40, 0.025 M $NH_4H_2PO_4$ + 2.5 mL/L TEA:acetonitrile) was added. The test compound was resuspended in the mobile phase by vortexing and more protein was removed by centrifugation at 4000 rpm for 5 min. Each sample was poured into an HPLC vial for test compound analysis on an Hewlett Packard 1100 series HPLC with UV detection.

From each sample, 95 µL was injected onto a Phenomenex-Prodigy reverse phase C-18, 150 x 3.2 mm column and eluted with a 45-50% acetonitrile gradient run over 10 min. Test-compound plasma concentrations (µg/mL) were determined by a comparison to standard curve (peak area vs. conc. µg/mL) using known concentrations of test compound extracted from plasma samples in the manner described above. Along with the standards and unknowns, three groups (n=4) of quality controls (0.25 µg/mL, 1.5 µg/mL, and 7.5 µg/mL) were run to insure the consistency of the analysis. The standard curve had an $R_s > 0.99$ and the quality controls were all within 10% of their expected values. The quantitated test samples were plotted for visual display using Kaldagraph software and their pharmacokinetic parameters were determined using WIN NONLIN software.

Human Liver Microsome (HLM) Assay

Compound metabolism in human liver microsomes was measured by LC-MS analytical assay procedures as follows. First, human liver microsomes (HLM) were thawed and diluted to 5 mg/mL with cold 100 mM potassium phosphate (KPO_4) buffer. Appropriate amounts of KPO_4 buffer, NADPH-regenerating solution (containing B-NADP, glucose-6-phosphate, glucose-6-phosphate dehydrogenase, and $MgCl_2$), and HLM were preincubated in 13 x 100 mm glass tubes at 37°C for 10 min. (3 tubes per test compound--triplicate). Test compound (5 µM final) was added to each tube to initiate reaction and was mixed by gentle vortexing, followed by incubation at 37°C. At t=0, and 2 h, a 250-uL sample was removed from each incubation tube to separate 12 x 75 mm glass tubes containing 1 mL ice-cold acetonitrile with 0.05 µM reserpine. Samples were centrifuged at 4000 rpm for 20 min. to precipitate proteins and salt (Beckman Allegra 6KR, S/N ALK98D06, #634). Supernatant was transferred to new 12 x 75 mm glass tubes and evaporated by Speed-Vac centrifugal vacuum evaporator. Samples were reconstituted in 200 µL 0.1% formic acid/acetonitrile (90/10) and vortexed vigorously to dissolve. The samples were then transferred to separate polypropylene microcentrifuge tubes and centrifuged at 14000x g for 10 min. (Fisher Micro 14, S/N M0017580). For each replicate (#1-3) at each timepoint (0 and 2 h), an aliquot sample of each test compound was combined into a single HPLC vial insert (6 total samples) for LC-MS analysis, which is described below.

The combined compound samples were injected into the LC-MS system, composed of a Hewlett-Packard HP1100 diode array HPLC and a Micromass Quattro II triple quadruple mass spectrometer operating in positive electrospray SIR mode (programmed to scan specifically for the molecular ion of each test compound). Each test compound peak was integrated at each timepoint. For each compound, peak area at each timepoint (n=3) was averaged, and this mean peak area at 2 h was divided by the average peak area at time 0 hour to obtain the percent test compound remaining at 2 h.

KDR (VEGFR2) phosphorylation in PAE-KDR cells assay

This assay determines the ability of a test compound to inhibit the autophosphorylation of KDR in porcine aorta endothelial (PAE)-KDR cells. PAE cells that overexpress human KDR were used in this assay. The cells were cultured in Ham's F12 media supplemented with 10% fetal bovine serum (FBS) and 400ug/mL G418. Thirty thousands cells were seeded into each well of a 96-well plate in 75 µL of growth media and allowed to attach for 6 hours at 37°C. Cells were then exposed to the starvation media (Ham's F12 media supplemented with 0.1% FBS) for 16 hours. After the starvation period was over, 10 µL of test agent in 5% DMSO in starvation media were added to the test wells and 10 µL of the vehicle (5% DMSO in starvation media) were added into the control wells. The final DMSO concentration in each well was 0.5%. Plates were incubated at 37°C for 1 hour and the cells were then stimulated with 500 ng/ml VEGF (commercially available from R & D System) in the presence of 2mM Na_3VO_4 for 8 minutes. The cells were washed once with 1 mm Na_3VO_4 in HBSS and lysed by adding 50 µL per well of lysis buffer. One hundred µL of dilution buffer were then added to each well and the diluted cell lysate was transferred to a 96-well goat anti-rabbit coated plate (commercially available from Pierce) which was pre-coated with Rabbit anti Human Anti-flk-1 C-20 antibody (commercially available from Santa Cruz). The plates were incubated at room temperature for 2 hours and washed seven times with 1% Tween 20 in PBS. HRP-PY20 (commercially available from Santa Cruz) was diluted and added to the plate for a 30-minute incubation. Plates were then washed again and TMB peroxidase substrate (commercially available from Kirkegaard & Perry) was added for a 10-minute incubation. One hundred µL of 0.09 N H_2SO_4 was added to each well of the 96-well plates to stop the reaction. Phosphorylation status was assessed by spectrophotometer reading at 450 nm. IC_{50} values were calculated by curve fitting using a four-parameter analysis.

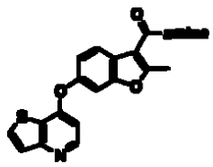
PAE-PDGFRβ phosphorylation in PAE-PDGFRβ cells assay

This assay determines the ability of a test compound to inhibit the autophosphorylation of PDGFRβ in porcine aorta endothelial (PAE)- PDGFRβ cells. PAE cells that overexpress human PDGFRβ were used in this assay. The cells were cultured in Ham's F12 media supplemented with 10% fetal bovine serum (FBS) and 400ug/ml G418. Twenty thousands cells were seeded in each well of a 96-well plate in 50 µL of growth media and allowed to attach for 6 hours at 37°C. Cells were then exposed to the starvation media (Ham's F12 media supplemented with 0.1% FBS) for 16 hours. After the starvation period was over, 10 µL of test agent in 5% DMSO in starvation media were added to the test wells and 10 µL of the vehicle (5% DMSO in starvation media) were added into the control wells. The final DMSO concentration in each well was 0.5%. Plates were incubated at 37°C for 1

hour and the cells were then stimulated with 1μg/mL PDGF-BB (R & D System) in the presence of 2mM Na_3VO_4 for 8 minutes. The cells were washed once with 1 mm Na_3VO_4 in HBSS and lysed by adding 50 μL per well of lysis buffer. One hundred μL of dilution buffer were then added to each well and the diluted cell lysate was transferred to a 96-well goat anti-rabbit coated plate (Pierce), which was pre-coated with Rabbit anti Human PDGFRβ antibody (Santa Cruz). The plates were incubated at room temperature for 2 hours and washed seven times with 1% Tween 20 in PBS. HRP-PY20 (Santa Cruz) was diluted and added to the plate for a 30-minute incubation. Plates were then washed again and TMB peroxidase substrate (Kirkegaard & Perry) was added for a 10-minute incubation. One hundred μL of 0.09 N H_2SO_4 was added into each well of the 96-well plate to stop the reaction. Phosphorylation status was assessed by spectrophotometer reading at 450 nm. IC_{50} values were calculated by curve fitting using a four-parameter analysis.

The results of the testing of the compounds using various assays are summarized in Tables 1 and 2 below, where a notation of "% @" indicates the percent inhibition at the stated concentration.

All of the amines listed in Table 3 were reacted with Example 101and are denoted as R_{101} in Table 3 having the following structure:



The library plates for Table 3 were prepared in the following general manner:

General Procedure for amide bond formation:

0.13 M solution of each amine in Table 3 in a 1:1 mixture of anhydrous pyridine and DMF were prepared and placed into the appropriate wells of a 1 mL deepwell plate. 0.10 M solution of Example 101 in a DMF solution was prepared and added to each well. The reactions were agitated at 50°C for 4 h. The volatiles were removed using the Speedvac™ apparatus, and the crude mixtures were reconstituted in DMSO to afford solutions with a final theoretical concentration of 0.01M.

TABLE 1

Compound	FLVK (% Inh @ 50 nM)	FLVK Ki (nM)	HUVEC + VEGF IC50 (nM) AVG	PAE KDR autophos IC50 (nM) AVG	PAE PDGFR autophos IC50 (nM) AVG	bFGF Huvec IC50 (nM) Avg.
1	92%	1.02	0.68	0.31	164	122
2	75%	4.14	2.3	1.8	912	3333
3	59%	0.811	0.442	0.9	756	942
4	88%	2.58	0.404	0.47	284	NT
5	73%	1.91	1.55	NT	1000	295
6	94%	0.721	1.2	NT	255	145
7	95%	1.04	1.21	1.95	1000	2474
8	94%	0.403	1.37	NT	1000	504
9	83%	1.57	13	NT	313	135
10	74%	2.31	10	NT	451	99
11	93%	0.492	0.56	NT	103.5	40
12	100%	0.314	0.26	0.14	14.4	20
13	97%	0.322	0.082	0.21	41	27
14	81%	1.46	9.4	NT	NT	287
15	13%	48.3	NT	NT	NT	NT
16	46%	8.14	10	NT	NT	1000
17	77%	2.77	1.2	0.47	20	847
18	78%	2.373	0.64	0.62	32	1000
19	75%	2.63	2.7	1.7	172	10000
20	99%	0.082	0.19	0.217	43	1902
21	43%	13.11	NT	NT	NT	NT
22	38%	25.8	NT	NT	NT	NT
23	19%	78	NT	NT	NT	NT
24	69%	4.2	32	NT	NT	10000
25	70%	4.08	0.45	NT	12	7460
26	63%	3.66	0.74	NT	13	2233
27	13%	96	NT	NT	205	NT
28	78%	2.8	0.272	NT	15	462
29	6%	88.77	NT	NT	NT	NT
30	63%	6	33.6	NT	74	10000
31	25%	30.2	NT	NT	NT	NT

TABLE 1

Compound	FLVK (% inh @ 50 nM)	FLVK KI (nM)	HUVEC + VEGF IC50 (nM) AVG	PAE KDR autophos IC50 (nM) AVG	PAE PDGFR autophos IC50 (nM) AVG	bFGF Huvec IC50 (nM) Avg.
32	22%	39.4	NT	NT	29.2	NT
33	61%	11.5	10	NT	63	10000
34	45%	11.4	NT	NT	31.3	NT
35	23%	35.166	NT	NT	70	NT
36	41%	11.513	NT	NT	NT	NT
37	66%	4.3	10	NT	1000	NT
38	60%	6.12	27	NT	12.3	10000
39	12%	47	8.7	NT	61	NT
40	77%	2.95	1.12	NT	24.2	7798
41	71%	3.3	3.7	NT	22.1	1224
42	76%	2.8	4.34	NT	8.9	NT
43	67%	3.21	10	NT	1000	NT
44	87%	1.2	1.78	NT	21.28	6036
45	64%	4.65	10	NT	26.9	NT
46	69%	6.49	3.13	NT	NT	NT
47	41%	19.7	NT	NT	NT	NT
48	91%	NT	0.94	NT	21	239
49	67%	16	7	NT	NT	NT
50	36%	36.5	NT	NT	NT	NT
51	34%	27.7	82	NT	NT	NT
52	41%	24.9	NT	NT	NT	NT
53	93%	1.07	1.8	NT	229	7233
54	89%	1.71	1.8	NT	133	10000
55	62%	4.86	5.8	NT	31	NT
56	60%	3.8	22	NT	109	10000
57	63%	9.8	NT	87	NT	
58	55%	7.59	3.65	NT	124	7830
59	81%	1.378	0.045	NT	115	1164
60	81%	2.17	1.34	NT	38.3	1703
61	89%	NT	0.605	0.4	17.8	3995
62	91%	0.57	2.15	0.24	18.7	619
63	67%	9.33	10	NT	84	10000
64	64%	11.8	10	NT	1000	10000

TABLE 1

Compound	FLVK (% Inh @ 50 nM)	FLVK KI (nM)	HUVEC + VEGF IC50 (nM) AVG	PAE KDR autophos IC50 (nM) AVG	PAE PDGFR autophos IC50 (nM) AVG	bFGF Huvec IC50 (nM) Avg.
65	65%	7.97	10	NT	59	10000
66	75%	5.2	5.8	NT	90.7	NT
67	58%	12.51	NT	NT	NT	NT
68	37%	NT	NT	NT	NT	NT
69	95%	0.3	0.57	NT	6.52	4314
70	95%	0.43	0.537	NT	47.1	3975
71	5%	NT	NT	NT	NT	NT
72	2%	NT	NT	NT	NT	NT
73	48%	10.286	NT	NT	NT	NT
74	43%	12.721	NT	NT	312.5	NT
75	84%	2.62	1.4	NT	16.6	10000
76	36%	6.26	NT	NT	NT	NT
77	99%	0.2	0.2	NT	7.4	8
78	93%	0.221	0.507	NT	14.8	30
79	90%	0.276	0.223	NT	15.5	130
80	95%	0.436	0.239	NT	31	60
81	100%	0.2	0.09	NT	7	25.06
82	89%	0.884	2.26	NT	53.1	2058
83	98%	0.2	0.77	NT	28.8	142
84	94%	0.58	0.322	NT	12.4	429
85	83%	1.71	3.82	NT	27.3	6987
86	81%	1.44	3.07	NT	17.9	
87	98%	0.615	1.25	NT	17.8	6044
88	94%	0.574	0.46	NT	15.1	363
89	95%	0.419	NT	NT	250	5.2
90	93%	0.739	2.14	NT	33	745
91	94%	0.356	0.168	NT	16.5	250
92	100%	0.2	0.18	NT	4.4	13
93	84%	2.72	NT	NT	44	NT
94	81%	1.453	0.7	NT	112	251
95	89%	0.848	10	NT	235	96
96	51%	9.81	NT	NT	NT	NT
97	70%	4.84	10	NT	293	223

TABLE 1

Compound	FLVK (% Inh @ 50 nM)	FLVK KI (nM)	HUVEC + VEGF IC50 (nM) AVG	PAE KDR autophos IC50 (nM) AVG	PAE PDGFR autophos IC50 (nM) AVG	bFGF Huvec IC50 (nM) Avg.
98	86%	0.36	9.4	NT	126.6	NT
99	66%	4.66	NT	NT	562.6	NT
100	0%	NT	NT	NT	NT	NT
102	96%	0.91	0.186	NT	49	1718
103	52%	7	NT	NT	203.4	NT
104	100%	NT	8.4	NT	163.9	227
105	61%	8.37	NT	NT	127	NT
106	98%	NT	10	NT	1000	638
107	17%	36.69	NT	NT	NT	NT
108	61%	NT	NT	NT	NT	NT
109	82%	NT	NT	NT	NT	NT
110	21%	NT	NT	NT	NT	NT
111	96%	NT	NT	NT	NT	NT
112	91%	NT	NT	NT	NT	NT
113	99%	NT	NT	NT	NT	NT
114	16%	118.85	NT	NT	1000	NT
115	4%	NT	NT	NT	1000	NT
116	4%	NT	NT	NT	NT	NT
117	87%	0.2	0.07	NT	189	86
118	84%	1.2	0.9	NT	1000	736
119	95%	0.375	1.46	NT	90.6	1827
120	93%	0.6	0.491	NT	405	489
121	94%	0.2	0.24	NT	220	100
122	58%	5.14	NT	NT	351	NT
123	74%	2.63	10	NT	229	NT
124	82%	2.19	1.6	NT	376	8243
125	95%	0.219	2	NT	179	969
126	96%	0.5896	10	NT	336	5656
127	100%	0.2	1	NT	102	41
128	91%	0.57	0.13	NT	148	100
129	86%	0.2	0.219	NT	168	100
130	95%	0.39	0.49	NT	335	100
131	96%	0.2	1.89	NT	97	280

TABLE 1

Compound	FLVK (% Inh @ 50 nM)	FLVK Ki (nM)	HUVEC + VEGF IC50 (nM) AVG	PAE KDR autophos IC50 (nM) AVG	PAE PDGFR autophos IC50 (nM) AVG	bFGF Huvec IC50 (nM) Avg.
132	80%	1.78	5.8	NT	467	NT
133	40%	5.9	NT	NT	467.9	NT
134	94%	1.44	0.856	NT	176.9	1070
135	87%	1.5411	1.02	NT	212	559
136	88%	1.1704	10	NT	609	NT
137	84%	5.1	2.1	NT	213	294
138	85%	0.78	9.9	NT	110	NT
139	40%	NT	NT	NT	NT	NT
140	90%	NT	NT	NT	NT	NT

TABLE 2

Compound	mouse PK AUC, po ng-h/mL**	mouse Cmax, po (ng/mL)	mouse Cmin, po (ng/mL)	% remain (HLM-UDPGA, 0.5 h)	% remain (HLM-NADPH, 0.5 h)
1	182808	124745	2793	NT	NT
2	NT	NT	NT	NT	NT
3	2450	956	88	NT	NT
4	7674	2340	200	NT	NT
5	12254	6743	256	NT	NT
6	586	355	20	NT	NT
7	NT	NT	NT	NT	NT
8	2348	666	105	NT	NT
9	NT	NT	NT	NT	NT
10	NT	NT	NT	NT	NT
11	NT	NT	NT	NT	NT
12	11970	5423	270	NT	NT
13	63000	24760	1700	NT	NT
14	NT	NT	NT	NT	NT
15	NT	NT	NT	NT	NT
16	NT	NT	NT	NT	NT
17	71580	28817	2334	NT	NT
18	8724	4120	342	NT	NT
19	120	51	4	NT	NT

TABLE 3

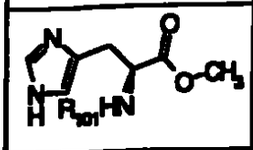
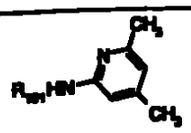
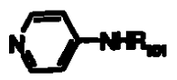
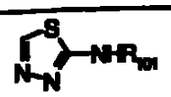
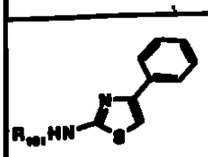
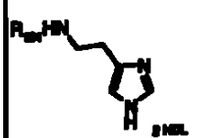
Amine	% TIC	FLVK (% @ 100 nM)	FGF (%@100nM)	PAE PDGFR autophos IC50 (nM)
	56.552	52	NT	49
	53.7991	103	2	53
	0	28	NT	NT
	51.8111	79	20	50
	5.4277	20	NT	NT
	88.1771	75	35	>100
	0	16	NT	NT
	55.2161	17	NT	NT

TABLE 3

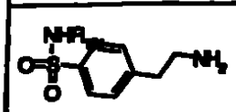
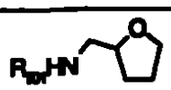
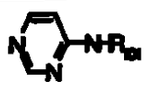
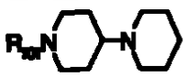
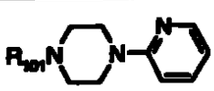
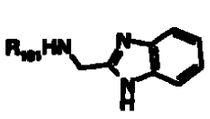
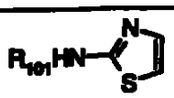
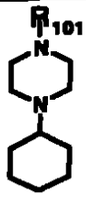
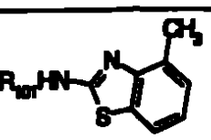
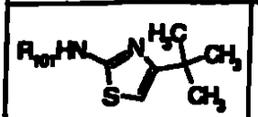
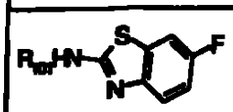
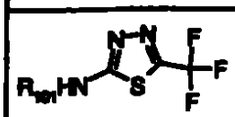
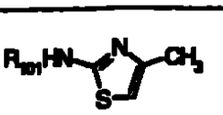
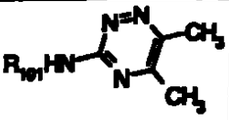
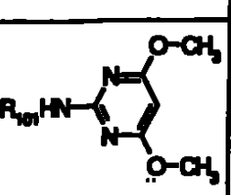
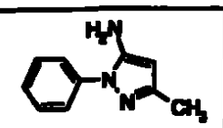
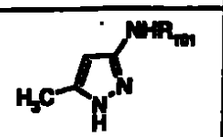
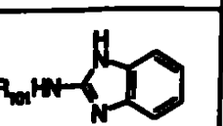
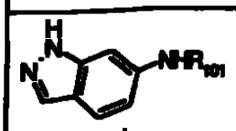
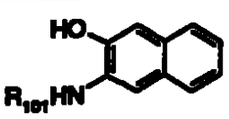
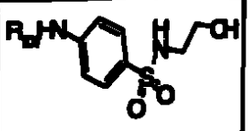
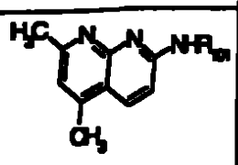
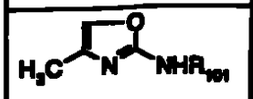
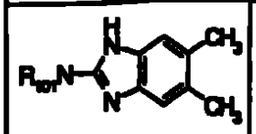
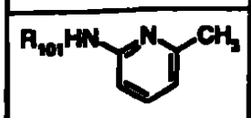
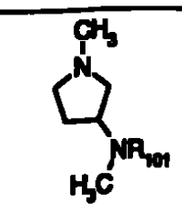
Amine	% TIC	FLVK (% @ 100 nM)	FGF (%@100nM)	PAE PDGFR autophos IC50 (nM)
	65.4679	68	0	>100
	95.752	38	NT	NT
	97.7442	24	NT	NT
	65.2303	20	NT	NT
	48.8673	22	NT	NT
	45.8972	24	NT	NT
	12.783	90	20	>100
	55.6	14	NT	NT
	0	20	NT	NT

TABLE 3

Amine	% TIC	FLVK (% @ 100 nM)	FGF (%@100nM)	PAE PDGFR autophos IC50 (nM)
	0	27	NT	NT
	0	26	NT	NT
	0	14	NT	NT
	5.35845	62	7	>100
	0	14	NT	NT
	0	16	NT	NT
	0	30	NT	NT
	19.2675	100	4	46
	58.6779	16	NT	NT

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TABLE 3

Amine	% TIC	FLVK (% @ 100 nM)	FGF (%@100nM)	PAE PDGFR autophos IC50 (nM)
	29.8321	87	0	57
	10.8303	29	NT	NT
	77.1177	16	NT	NT
	0	20	NT	NT
	0	13	NT	NT
	55.2355	14	NT	NT
	0	14	NT	NT
	49.6134	25	NT	NT
	43.8419	25	NT	NT

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TABLE 3

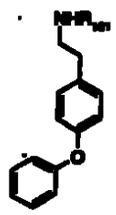
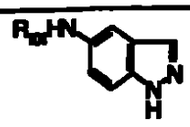
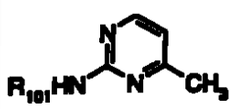
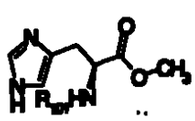
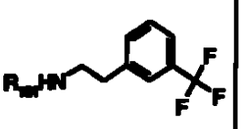
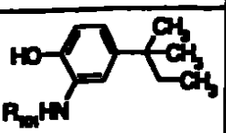
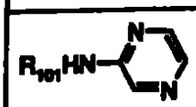
Amine	% TIC	FLVK (% @ 100 nM)	FGF (%@100nM)	PAE PDGFR autophos IC50 (nM)
	11.5047	21	NT	NT
	75.9893	98	0	~100
	0	10	NT	NT
	28.1067	13	NT	NT
	28.1967	97	0	>100
	24.8781	28	NT	NT
	0	10	NT	NT

TABLE 3

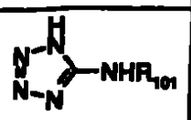
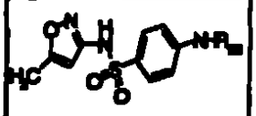
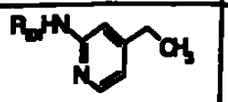
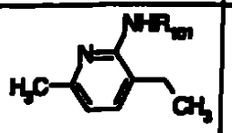
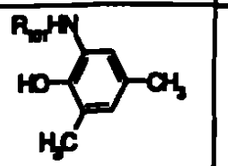
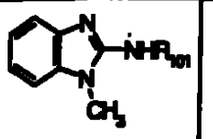
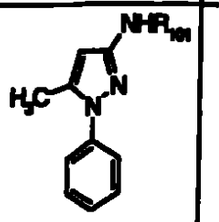
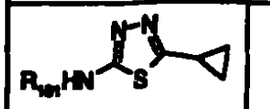
Amine	% TIC	FLVK (% @ 100 nM)	FGF (%@100nM)	PAE PDGFR autophos IC50 (nM)
	22.1224	8	NT	NT
	1.78077	7	NT	NT
	0	18	NT	NT
	0	22	NT	NT
	28.8916	67	13	~100
	50.8697	12	NT	NT
	1.10495	13	NT	NT
	38.7228	100	4	>100

TABLE 3

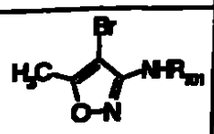
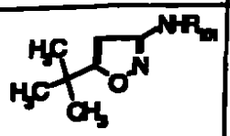
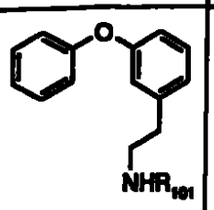
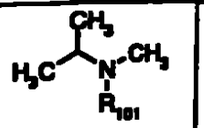
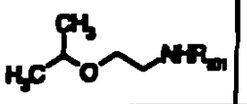
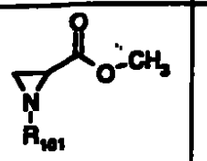
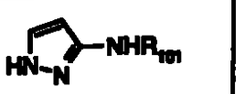
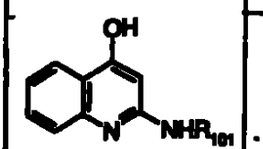
Amine	% TIC	FLVK (% @ 100 nM)	FGF (%@100nM)	PAE PDGFR autophos IC50 (nM)
	0	4	NT	NT
	0	15	NT	NT
	24.5486	36	NT	NT
	22.7289	17	NT	NT
	55.7071	94	0	61
	25.3022	51	NT	>100
	74.3184	91	NT	>100
	0	23	8	NT

TABLE 3

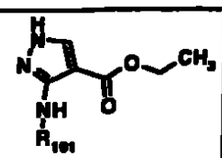
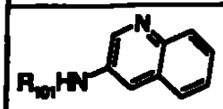
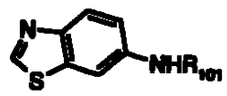
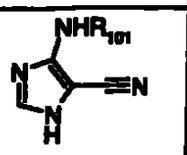
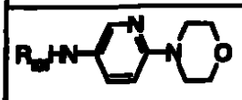
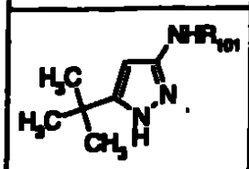
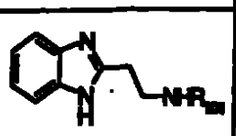
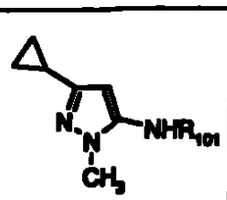
Amine	% TIC	FLVK (% @ 100 nM)	FGF (%@100nM)	PAE PDGFR autophos IC50 (nM)
	4.01691	13	NT	NT
	43.6451	85	7	>100
	15.585	98	0	>100
	0	5	NT	NT
	58.6541	101	0	57
	20.5224	100	56	>100
	29.3082	22	NT	NT
	3.03715	56	3	>100

TABLE 3

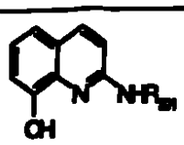
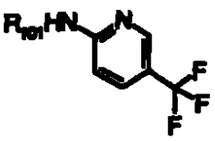
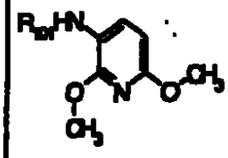
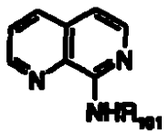
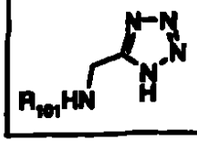
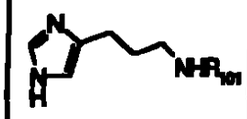
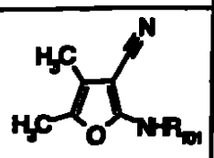
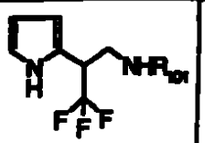
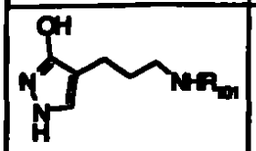
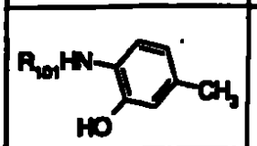
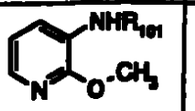
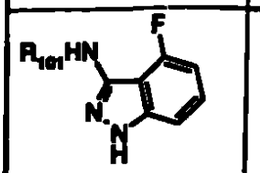
Amine	% TIC	FLVK (% @ 100 nM)	FGF (%@100nM)	PAE PDGFR autophos IC50 (nM)
	54.7208	24	NT	NT
	0	27	NT	NT
	0	24	NT	NT
	27.931	94	0	>100
	16.4145	92	1	>100
	0	10	NT	NT
	49.5375	10	NT	NT

TABLE 3				
Amine	% TIC	FLVK (% @ 100 nM)	FGF (%@100nM)	PAE PDGFR autophos IC50 (nM)
	41.0058	25	NT	NT
	0	13	NT	NT
	45.0518	85	3	>100
	38.7067	12	NT	NT
	33.1065	85	0	~100
	1.9193	35	NT	NT
	0	61	0	>100

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TABLE 3

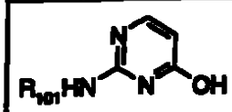
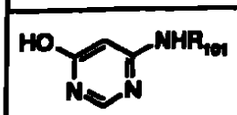
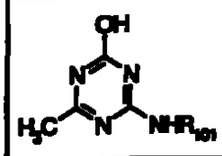
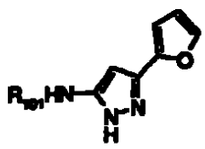
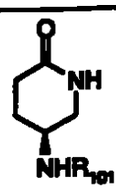
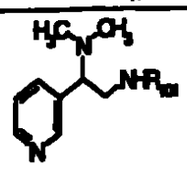
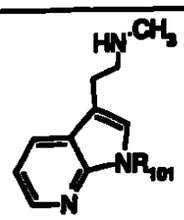
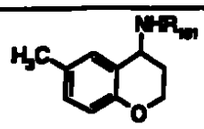
Amine	% TIC	FLVK (% @ 100 nM)	FGF (%@100nM)	PAE PDGFR autophos IC50 (nM)
	0	19	NT	NT
	0	17	NT	NT
	0	15	NT	NT
	15.0813	101	1	>100
	19.6253	19	NT	NT
	64.8885	18	NT	NT
	20.3244	9	NT	NT

TABLE 3

Amine	% TIC	FLVK (% @ 100 nM)	FGF (%@100nM)	PAE PDGFR autophos IC50 (nM)
	24.2001	46	NT	NT

The exemplary compounds described above may be formulated into pharmaceutical compositions according to the following general examples.

Example 1: Parenteral Composition

To prepare a parenteral pharmaceutical composition suitable for administration by injection, 100 mg of a water-soluble salt of a compound of Formula I is dissolved in DMSO and then mixed with 10 mL of 0.9% sterile saline. The mixture is incorporated into a dosage unit form suitable for administration by injection.

Example 2: Oral Composition

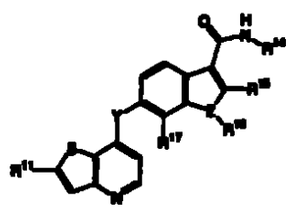
To prepare a pharmaceutical composition for oral delivery, 100 mg of a compound of Formula I is mixed with 750 mg of lactose. The mixture is incorporated into an oral dosage unit for, such as a hard gelatin capsule, which is suitable for oral administration.

It is to be understood that the foregoing description is exemplary and explanatory in nature, and is intended to illustrate the invention and its preferred embodiments. Through routine experimentation, the artisan will recognize apparent modifications and variations that may be made without departing from the spirit of the invention. Thus, the invention is intended to be defined not by the above description, but by the following claims and their equivalents.

CLAIMS

We claim:

1. A compound represented by the formula I:



I

wherein:

Y is –NH-, -O-, -S-, or $–CH_2–$;

Z is -O-, -S-, or -N-;

R^{14} is a C_1-C_6 alkyl, C_1-C_6 alkylamino, C_1-C_6 alkylhydroxy, C_3-C_{10} cycloalkylamino, or methylureido group;

R^{15} and R^{17} are independently H, halo, or a C_1-C_6 alkyl group unsubstituted or substituted by one or more R^5 groups;

R^{16} is H or a C_1-C_6 alkyl group when Z is N, and R^{16} is absent when Z is –O- or –S-;

R^{11} is H, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, $-C(O)NR^{12}R^{13}$, $-C(O)(C_6$-C_{10} aryl), $-(CH_2)_r(C_6$-C_{10} aryl), $-(CH_2)_r$(5 to 10 membered heterocyclic), $-(CH_2)_rNR^{12}R^{13}$, $-SO_2NR^{12}R^{13}$ or $-CO_2R^{12}$, wherein said C_1-C_6 alkyl, $-C(O)(C_6$-C_{10} aryl), $-(CH_2)_r(C_6$-C_{10} aryl), and $-(CH_2)_r$(5 to 10 membered heterocyclic) moieties of the said R^{11} groups are unsubstituted or substituted by one or more R^5 groups;

each R^5 is independently selected from halo, cyano, nitro, trifluoromethoxy, trifluoromethyl, azido, $-C(O)R^6$, $-C(O)OR^6$, $-OC(O)R^6$, $-OC(O)OR^6$, $-NR^6C(O)R^7$, $-C(O)NR^6R^7$, $-NR^6R^7$, $-OR^6$, $-SO_2NR^6R^7$, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, C_1-C_6 alkylamino, $-(CH_2)_rO(CH_2)_qNR^6R^7$, $-(CH_2)_rO(CH_2)_qOR^6$, $-(CH_2)_rOR^6$, $-S(O)_t(C_1$-C_6 alkyl), $-(CH_2)_r(C_6$-C_{10} aryl), $-(CH_2)_r$(5 to 10 membered heterocyclic), $-C(O)(CH_2)_r(C_6$-C_{10} aryl), $-(CH_2)_rO(CH_2)_r(C_6$-C_{10} aryl), $-(CH_2)_rO(CH_2)_r$(5 to 10 membered heterocyclic), $-C(O)(CH_2)_r$(5 to 10 membered heterocyclic), $-(CH_2)_rNR^7(CH_2)_qNR^6R^7$, $-(CH_2)_rNR^7CH_2C(O)NR^6R^7$, $-(CH_2)_rNR^7(CH_2)_qNR^6C(O)R^6$, $(CH_2)_rNR^7(CH_2)_rO(CH_2)_qOR^6$, $-(CH_2)_rNR^7(CH_2)_qS(O)_t(C_1$-$C_6$ alkyl), $-(CH_2)_rNR^7(CH_2)_qR^6$, $-SO_2(CH_2)_r(C_6$-C_{10} aryl), and $-SO_2(CH_2)_r$(5 to 10 membered heterocyclic), the $-(CH_2)_q$- and $-(CH_2)_r$- moieties of the said R^5 groups optionally include a carbon-carbon double or triple bond, and the alkyl, aryl and heterocyclic moieties of the said R^5 groups are unsubstituted or substituted with one or more substituents independently selected from halo, cyano, nitro, trifluoromethyl, azido, -OH, $-C(O)R^6$, $-C(O)OR^6$, $-OC(O)R^6$, $-OC(O)OR^6$, $-NR^6C(O)R^7$, $-C(O)NR^6R^7$, $-(CH_2)_rNR^6R^7$, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl,

-$(CH_2)_t(C_6$-C_{10} aryl), -$(CH_2)_t$(5 to 10 membered heterocyclic), -$(CH_2)_tO(CH_2)_qOR^9$, and -$(CH_2)_tOR^9$;

each R^6 and R^7 is independently selected from H, OH, C_1-C_8 alkyl, C_3-C_{10} cycloalkyl, -$(CH_2)_t(C_6$-C_{10} aryl), -$(CH_2)_t$(5 to 10 membered heterocyclic), -$(CH_2)_tO(CH_2)_qOR^9$, -$(CH_2)_tCN(CH_2)_qOR^9$, -$(CH_2)_tCN(CH_2)_tR^9$ and -$(CH_2)_tOR^9$, and the alkyl, aryl and heterocyclic moieties of the said R^6 and R^7 groups are unsubstituted or substituted with one or more substituents independently selected from hydroxy, halo, cyano, nitro, trifluoromethyl, azido, -$C(O)R^9$, -$C(O)OR^9$, -$CO(O)R^9$, -$OC(O)OR^9$, -$NR^9C(O)R^{10}$, -$C(O)NR^9R^{10}$, -NR^9R^{10}, C_1-C_8 alkyl, -$(CH_2)_t(C_6$-C_{10} aryl), -$(CH_2)_t$(5 to 10 membered heterocyclic), -$(CH_2)_tO(CH_2)_qOR^9$, and -$(CH_2)_tOR^9$, where when R^6 and R^7 are both attached to the same nitrogen, then R^6 and R^7 are not both bonded to the nitrogen directly through an oxygen;

each R^8 is independently selected from H, C_1-C_{10} alkyl, C_3-C_{10} cycloalkyl, -$(CH_2)_t(C_6$-C_{10} aryl), and -$(CH_2)_t$(5 to 10 membered heterocyclic);

t is an integer from 0 to 6; j is an integer from 0 to 2; q is an integer from 2 to 6;

each R^9 and R^{10} is independently selected from H, -OR^8, C_1-C_8 alkyl, and C_3-C_{10} cycloalkyl; and

each R^{12} and R^{13} is independently selected from H, C_1-C_8 alkyl, C_3-C_{10} cycloalkyl, -$(CH_2)_t(C_3$-C_{10} cycloalkyl), -$(CH_2)_t(C_6$-C_{10} aryl), -$(CH_2)_t$(5 to 10 membered heterocyclic), -$(CH_2)_tO(CH_2)_qOR^9$, and -$(CH_2)_tOR^9$, and the alkyl, aryl and heterocyclic moieties of the said R^{12} and R^{13} groups are unsubstituted or substituted with one or more substituents independently selected from R^5, or R^{12} and R^{13} are taken together with the nitrogen to which they are attached to form a C_3-C_9 azabicyclic, aziridinyl, azetidinyl, pyrrolidinyl, piperidyl, piperazinyl, morpholinyl, thiomorpholinyl, isoquinolinyl, or dihydroisoquinolinyl ring, wherein said C_3-C_9 azabicyclic, aziridinyl, azetidinyl, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, thiomorpholinyl, isoquinolinyl, or dihydroisoquinolinyl rings are unsubstituted or substituted with one or more R^5 substituents, where R^{12} and R^{13} are not both bonded to the nitrogen directly through an oxygen;

or prodrugs or metabolites thereof, or pharmaceutically acceptable salts or solvates of said compounds and said prodrugs and said metabolites.

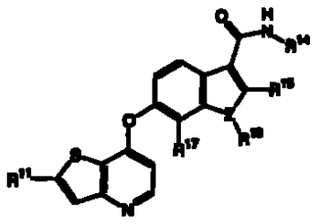
2. A compound of claim 1, wherein R^{11} is a thiazolyl, unsubstituted or substituted by 1 to 5 R^5 groups.

3. A compound of claim 1, wherein R^{11} is an imidazolyl, unsubstituted or substituted by 1 to 5 R^5 groups.

4. A compound of claim 1, wherein R^{10} is methyl.

5. A compound of claim 1, wherein R^{14} is methyl.

6. A compound represented by the formula II:



II.

wherein:

Z is -O-, -S-, or -N- ;

R^{14} is a C_1-C_6 alkyl, C_1-C_6 alkylamino, C_1-C_6 alkylhydroxy, C_3-C_{10} cycloalkylamino, or methylureido group;

R^{15} and R^{17} are independently H, halo, or a C_1-C_6 alkyl group;

R^{16} is H or a C_1-C_6 alkyl group when Z is –N- and R^{16} is absent when Z is –O- or –S-;

R^{11} is a heteroaryl group unsubstituted or substituted by one or more halo, cyano, nitro, trifluoromethoxy, trifluoromethyl, azido, $-C(O)R^6$, $-C(O)OR^6$, $-OC(O)R^6$, $-OC(O)OR^6$, $-NR^6C(O)R^7$, $-C(O)NR^6R^7$, $-NR^6R^7$, $-OR^6$, $-SO_2NR^6R^7$, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, $-(CH_2)_tO(CH_2)_qNR^6R^7$, $-(CH_2)_tO(CH_2)_qOR^6$, $-(CH_2)_tOR^6$, $-S(O)_t(C_1$-C_6 alkyl), $-(CH_2)_t(C_6$-C_{10} aryl), $-(CH_2)_t$(5 to 10 membered heterocyclic), $-C(O)(CH_2)_t(C_6$-C_{10} aryl), $-(CH_2)_tO(CH_2)_t(C_6$-C_{10} aryl), $-(CH_2)_tO(CH_2)_q$(5 to 10 membered heterocyclic), $-C(O)(CH_2)_t$(5 to 10 membered heterocyclic), $-(CH_2)_tNR^7(CH_2)_qNR^6R^7$, $-(CH_2)_tNR^7CH_2C(O)NR^6R^7$, $-(CH_2)_tNR^7(CH_2)_qNR^6C(O)R^6$, $-(CH_2)_tNR^7(CH_2)_tO(CH_2)_qOR^6$, $-(CH_2)_tNR^7(CH_2)_qS(O)_t(C_1$-$C_6$ alkyl), $-(CH_2)_tNR^7$ $-(CH_2)_tR^6$, $-SO_2(CH_2)_t(C_6$-C_{10} aryl), and $-SO_2(CH_2)_t$(5 to 10 membered heterocyclic), the $-(CH_2)_q$- and $-(CH_2)_t$- moieties of the said R^6 groups optionally include a carbon-carbon double or triple bond, and the alkyl, aryl and heterocyclic moieties of the said R^6 groups are unsubstituted or substituted with one or more substituents independently selected from halo, cyano, nitro, trifluoromethyl, azido, -OH, $-C(O)R^8$, $-C(O)OR^8$, $-OC(O)R^8$, $-OC(O)OR^8$, $-NR^8C(O)R^7$, $-C(O)NR^8R^7$, $-(CH_2)_tNR^8R^7$, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, $-(CH_2)_t(C_6$-C_{10} aryl), $-(CH_2)_t$(5 to 10 membered heterocyclic), $-(CH_2)_tO(CH_2)_qOR^8$, and $-(CH_2)_tOR^8$;

each R^6 and R^7 is independently selected from H, OH, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, $-(CH_2)_t(C_6$-C_{10} aryl), $-(CH_2)_t$(5 to 10 membered heterocyclic), $-(CH_2)_tO(CH_2)_qOR^8$, $-(CH_2)_tCN(CH_2)_tOR^8$, $-(CH_2)_tCN(CH_2)_tR^8$ and $-(CH_2)_tOR^8$, and the alkyl, aryl and heterocyclic moieties of the said R^6 and R^7 groups are unsubstituted or substituted with one or more substituents independently selected from hydroxy, halo, cyano, nitro, trifluoromethyl, azido, $-C(O)R^8$, $-C(O)OR^8$, $-CO(O)R^8$, $-OC(O)OR^8$, $-NR^8C(O)R^{10}$, $-C(O)NR^8R^{10}$, $-NR^8R^{10}$, C_1-C_6 alkyl, $-(CH_2)_t(C_6$-C_{10} aryl), $-(CH_2)_t$(5 to 10 membered heterocyclic), $-(CH_2)_tO(CH_2)_qOR^8$, and $-(CH_2)_tOR^8$, where when R^6 and R^7 are both attached to the same nitrogen, then R^6 and R^7 are not both bonded to the nitrogen directly through an oxygen;

each R^8 is independently selected from H, C_1-C_{10} alkyl, C_3-C_{10} cycloalkyl,

$-(CH_2)_t(C_6-C_{10}$ aryl), and $-(CH_2)_t$(5 to 10 membered heterocyclic);

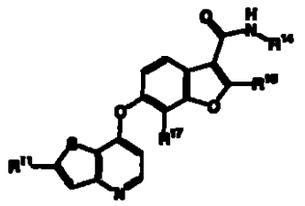
each R^9 and R^{10} is independently selected from H, C_1-C_8 alkyl, and C_3-C_{10} cycloalkyl;

t is an integer from 0 to 6; j is an integer from 0 to 2; q is an integer from 2 to 6;

or prodrugs or metabolites thereof, pharmaceutically acceptable salts or solvates of said compounds, said prodrugs, or said metabolites.

7. A compound of claim 6, R^{14} is methyl.

8. A compound represented by the formula IV:



IV

wherein:

R^{14} is a C_1-C_8 alkyl, C_1-C_8 alkylamino, C_1-C_8 alkylhydroxy, C_3-C_{10} cycloalkylamino, or methylureido group;

R^{16} and R^{17} are independently H, halo, or a C_1-C_8 alkyl group;

R^{11} is a heterocyclic or a heteroaryl group unsubstituted or substituted by one or more groups selected from $-C(O)OR^9$, C_1-C_8 alkyl, and $-(CH_2)_tOR^9$;

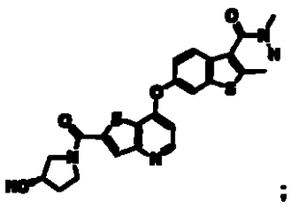
each R^9 is independently selected from H, C_1-C_{10} alkyl, C_3-C_{10} cycloalkyl, $-(CH_2)_t(C_6-C_{10}$ aryl), and $-(CH_2)_t$(5 to 10 membered heterocyclic);

each R^9 is independently selected from H, C_1-C_8 alkyl, and C_3-C_{10} cycloalkyl; and

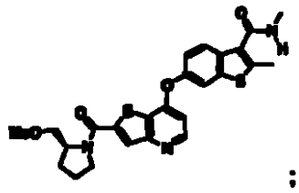
t is an integer from 0 to 6; j is an integer from 0 to 2; q is an integer from 2 to 6;

or prodrugs or metabolites thereof, pharmaceutically acceptable salts or solvates of said compounds, said prodrugs, and said metabolites.

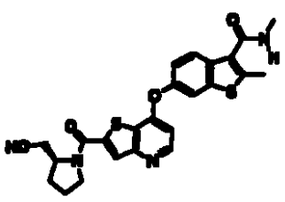
9. A compound of claim 1 wherein said compound is selected from the group consisting of:



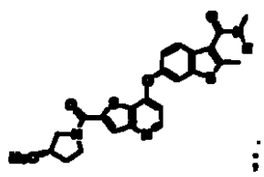
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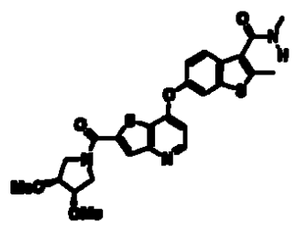
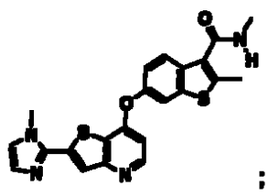
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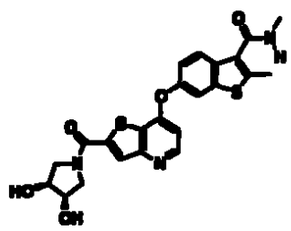
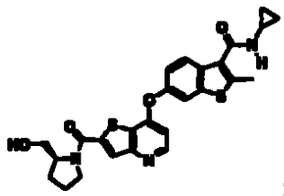


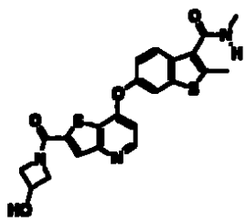
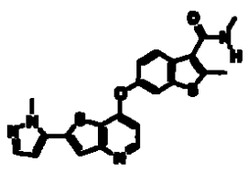
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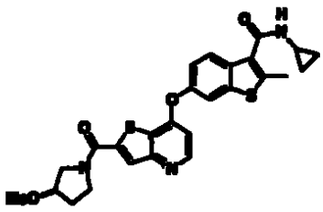
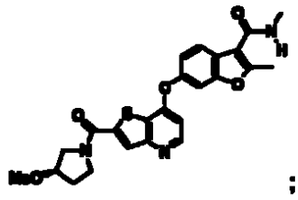


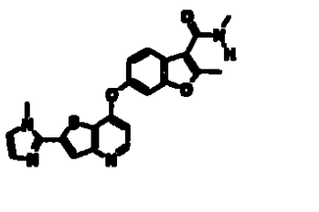
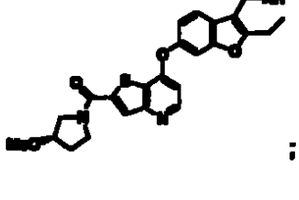
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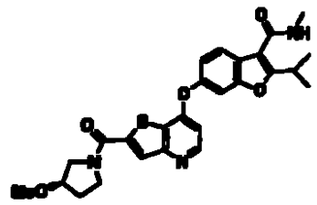
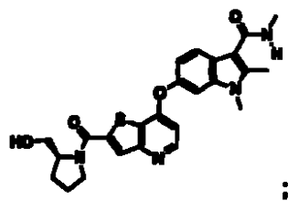
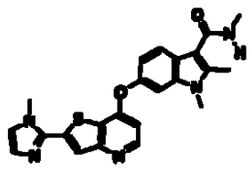
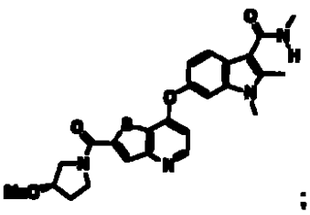
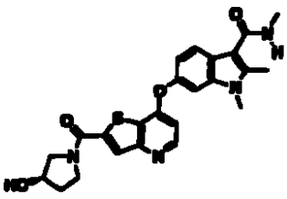
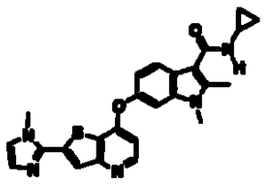
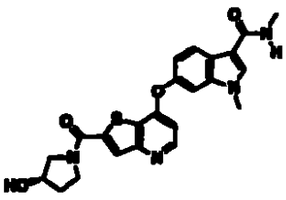
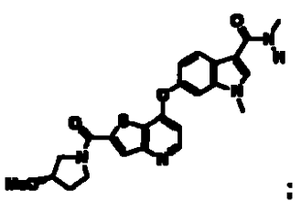
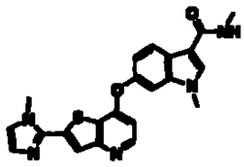
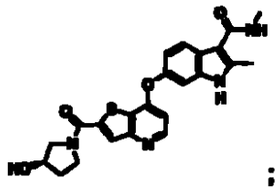

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or prodrugs or metabolites thereof, or pharmaceutically acceptable salts or solvates of said compounds, said prodrugs, and said metabolites.

10. A pharmaceutical composition for the treatment of a hyperproliferative disorder in a mammal comprising a therapeutically effective amount of a compound, prodrug, metabolite, salt or solvate of claim 1 and a pharmaceutically acceptable carrier.

11. The pharmaceutical composition of claim 10, wherein said hyperproliferative disorder is cancer or noncancerous.

12. A pharmaceutical composition for treating a disease related to vasculogenesis or angiogenesis in a mammal comprising a therapeutically effective amount of a compound, prodrug, metabolite, salt or solvate of claim 1 and a pharmaceutically acceptable carrier.

13. The pharmaceutical composition of claim 12 wherein said disease is selected from the group consisting of tumor angiogenesis, chronic inflammatory disease, atherosclerosis, skin diseases, diabetes, diabetic retinopathy, retinopathy of prematurity, age-related macular degeneration, hemangioma, glioma, melanoma, Kaposi's sarcoma and ovarian, breast, lung, pancreatic, prostate, colon and epidermoid cancer.

14. A pharmaceutical composition for treating a disease related to vasculogenesis or angiogenesis in a mammal comprising a therapeutically effective amount of a compound, prodrug, metabolite, salt or solvate of claim 1, a therapeutically effective amount of a compound, prodrug, metabolite, salt or solvate of an antihypertensive agent, and a pharmaceutically acceptable carrier.

15. A pharmaceutical composition for treating a disease related to vasculogenesis or angiogenesis in a mammal comprising administering to said mammal a therapeutically effective amount of a compound, prodrug, metabolite, salt or solvate of claim 1 in conjunction with a therapeutically effective amount of an anti-hypertensive agent.

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DERIVADOS DE HETEROARILAMIDA BENZOCONDENSADA DE TIEN PIRIDINAS UTILES COMO AGENTES TERAPEUTICOS, COMPOSICIONES FARMACEUTICAS QUE INCLUYEN A LOS MISMOS, Y METODOS PARA SU USO.

La presente solicitud de patente reivindica prioridad al documento de Estados Unidos No. de Serie 60/389.110, presentado el 14 de junio de 2002, que se incorpora aquí como referencia en su totalidad para todos los propósitos.

Campo de la Invención

Esta invención se refiere a nueva tienopiridina y derivados de tienopiridina que son útiles en el tratamiento de enfermedades hiperproliferativas, tales como cánceres, en mamíferos. Esta invención se refiere también a un método de usar tales compuestos en el tratamiento de enfermedades hiperproliferativas en mamíferos, especialmente seres humanos, y a composiciones farmacéuticas que contienen tales compuestos.

Antecedentes de la Invención

Se sabe que una célula se puede convertir en cancerígena en virtud de la transformación de una porción de su ADN en un oncogen (es decir, un gen que con la activación conduce a la formación de células tumorales malignas). Muchos oncogenes codifican proteínas que son tirosina quinasas aberrantes capaces de provocar la transformación celular. Alternativamente, la sobreexpresión de una tirosina quinasa protooncogénica normal puede también dar como resultado trastornos proliferativos, dando como resultado a veces un fenotipo maligno.

Las tirosina quinasas del receptor son grandes enzimas que abarcan la membrana celular y poseen un dominio de unión extracelular para factores de crecimiento tales como factor de crecimiento epidérmico, un dominio transmembrana, y una porción intracelular que funciona como una quinasa para fosforilar un resto de tirosina específico en proteínas y por tanto influir en la proliferación celular. Las tirosina quinasas precedentes se pueden clasificar como quinasas del receptor (por ejemplo, EGFR; PDGFR, FGFR y erbB2) o no del receptor (por ejemplo, c-src- y bcr-abl) del factor de crecimiento. Se sabe que tales quinasas se expresan a menudo aberrantemente en cánceres humanos comunes tales como cáncer de pecho, cáncer gastrointestinal tal como cáncer de colon, de recto o de estómago, leucemia, y cáncer de ovarios, de bronquios o de páncreas. La actividad de erbB2 aberrante ha sido implicada en los cánceres de pecho, de ovarios, de pulmón de células no pequeñas, de páncreas, gástrico y de colon. También se ha mostrado que el receptor del factor de crecimiento epidérmico (EGFR) está mutado o sobreexpresado en muchos

cánceres humanos tales como cánceres de cerebro, pulmones, células escamosas, vejiga, gástrico, de pecho, cabeza y cuello, esofágico, ginecológico y de tiroides. De este modo, se cree que los inhibidores de tirosina quinasas del receptor, tales como los compuestos de la presente invención, son útiles como inhibidores selectivos del crecimiento de células cancerosas de mamíferos.

También se ha mostrado que los inhibidores de EGFR pueden ser útiles en el tratamiento de pancreatitis y enfermedades del riñón (tales como glomerulonefritis proliferativa y enfermedad renal inducida por la diabetes), y pueden reducir la implantación de blastocitos con éxito y por lo tanto pueden ser útiles como anticonceptivos. Véase la publicación de la solicitud internacional PCT número WO 95/19970 (publicada el 27 de julio, 1995), incorporada por eso como referencia en su totalidad.

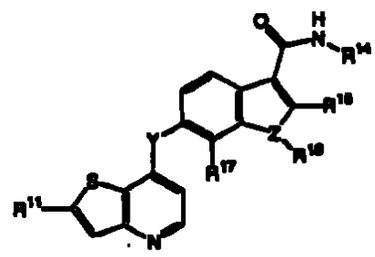
Se sabe que los factores de crecimiento de polipéptido tales como el factor de crecimiento endotelial vascular (VEGF) que tienen una alta afinidad por el receptor que contiene el dominio de inserción de la quinasa humana (KDR) o el receptor de quinasa de hígado fetal de ratón (FLK-1) han sido asociados con la proliferación de células endoteliales y más particularmente, vasculogénesis y angiogénesis. Véase la publicación de solicitud internacional PCT número WO 95/21613 (publicada el 17 de agosto, 1995), incorporada por eso como referencia en su totalidad. Los agentes, tales como los compuestos de la presente invención, que son capaces de unirse a o modular el receptor KDR/FLK-1 se pueden usar para tratar trastornos relacionados con la vasculogénesis o angiogénesis tales como diabetes, retinopatía diabética, degeneración macular relacionada con la edad, hemangioma, glioma, melanoma, sarcoma de Kaposi y cáncer de ovario, pecho, pulmón, páncreas, próstata, colon y epidermoide.

Los compuestos que son útiles en el tratamiento de enfermedades hiperproliferativas se describen también en las siguientes patentes y solicitudes: publicación de solicitud de patente internacional PCT número WO 00/38665 (publicada el 6 de julio de 2001), publicación de solicitud de patente internacional PCT número WO 97/49688 (publicada el 31 de diciembre de 1997), publicación de solicitud de patente internacional PCT número WO 98/23613 (publicada 4 de junio de 1998), solicitud de patente de EE.UU. número 60/360.952 (presentada el 1 de marzo de 2002), solicitud de patente de EE.UU. número 60/299.879 (presentada el 21 de junio de 2001), solicitud de patente de EE.UU. número 09/502.129 (presentada el 10 de febrero de 2000), solicitud de patente de EE.UU. número 60/209.686 (presentada el 6

de junio de 2000), solicitud de patente de EE.UU. número 60/214.373 (presentada el 28 de junio de 2000), solicitud de patente de EE.UU. número 08/953.078 (presentada el 17 de octubre de 1997), patente de EE.UU. número 6.071.935 (otorgada el 6 de junio de 2000), publicación de solicitud de patente internacional PCT número WO 96/30347 (publicada el 3 de octubre de 1996), publicación de solicitud de patente internacional PCT número WO 96/40142 (publicada el 19 de diciembre de 1996), publicación de solicitud de patente internacional PCT número WO 97/13771 (publicada el 17 de abril de 1997), y publicación de solicitud de patente internacional PCT número WO 95/23141 (publicada el 31 de agosto de 1995). Las patentes y solicitudes precedentes se incorporan cada una aquí como referencia en su totalidad.

Sumario de la Invención

En uno de los aspectos, la presente invención se refiere a un compuesto representado por la fórmula I:



I

en la que:

Y es -NH-, -O-, -S-, o -CH_2-;

Z es -O-, -S-, o -N-;

R^{14} es un alquilo de C_1-C_6, alquil de C_1-C_6-amino, alquil de C_1-C_6-hidroxi, cicloalquil de C_3-C_{10}-amino, o grupo metilureido;

R^{15} y R^{17} son independientemente H, halo, o un grupo alquilo de C_1-C_6 sin substituir o substituido con uno o más grupos R^5;

R^{16} es H o un grupo alquilo de C_1-C_6, preferentemente metilo, cuando Z es N, y R^{16} está ausente cuando Z es -O- o -S-;

R^{11} es H, alquilo de C_1-C_6, cicloalquilo de C_3-C_{10}, -C(O)$NR^{12}R^{13}$, -C(O)(arilo de C_1-C_6), -$(CH_2)_k$(arilo de C_6-C_{10}), -$(CH_2)_k$(heterociclo de 5 a 10 miembros), -$(CH_2)_kNR^{12}R^{13}$, -$SO_2NR^{12}R^{13}$ o -CO_2R^{12}, en la que dicho alquilo de C_1-C_6, -C(O)(arilo de C_6-C_{10}) y restos -$(CH_2)_k$(heterociclo de 5 a 10 miembros) de dichos grupos R^{11} están sin substituir o substituidos con uno o más grupos R^5;

cada R^5 se selecciona independientemente de halo, ciano, nitro, trifluorometoxi, trifluorometilo, azido, $-C(O)R^8$, $-C(O)OR^8$, $-OC(O)R^8$, $-OC(O)OR^8$, $-NR^6C(O)R^7$, $-CONR^6R^7$, $-NR^6R^7$, $-OR^9$, $-SO_2NR^6R^7$, alquilo de C_1-C_6, cicloalquilo de C_3-C_{10}, alquil de C_1-C_6-amino, $-(CH_2)_jO(CH_2)_qNR^6R^7$, $-(CH_2)_tO(CH_2)_qOR^9$, $-(CH_2)_tOR^9$, $-S(O)_j$(alquilo de C_1-C_6), $-(CH_2)_t$(arilo de C_6-C_{10}), $-(CH_2)_t$(heterociclo de 5 a 10 miembros), $-C(O)(CH_2)_t$(arilo de C_6-C_{10}), $-(CH_2)_tO(CH_2)_j$(arilo de C_6-C_{10}), $-(CH_2)_tO(CH_2)_q$(heterociclo de 5 a 10 miembros), $-C(O)(CH_2)_t$(heterociclo de 5 a 10 miembros), $-(CH_2)_jNR^7(CH_2)_qNR^6R^7$, $-(CH_2)_jNR^7CH_2C(O)NR^6R^7$, $-(CH_2)_jNR^7(CH_2)_qNR^6C(O)R^6$, $-(CH_2)_jNR^7(CH_2)_tO(CH_2)_qOR^9$, $-(CH_2)_jNR^7(CH_2)_qS(O)_j$(alquilo de C_1-C_6), $-(CH_2)_jNR^7(CH_2)_tNR^6$, $-SO_2(CH_2)_t$(arilo de C_6-C_{10}), y $-SO_2(CH_2)_t$(heterociclo de 5 a 10 miembros), los restos $-(CH_2)_q$- y $-(CH_2)_t$- de dichos grupos R^5 opcionalmente incluyen un doble o triple enlace carbono-carbono en los que t es un número entero entre 2 y 6, y el alquilo, arilo y restos heterocíclicos de dichos grupos R^6 están sin substituir o substituidos con uno o más substituyentes independientemente seleccionados de halo, ciano, nitro, trifluorometilo, azido, -OH, $-C(O)R^8$, $-C(O)OR^8$, $-OC(O)R^8$, $-OC(O)OR^8$, $-NR^6C(O)R^7$, $-C(O)NR^6R^7$, $-(CH_2)_tNR^6R^7$, alquilo de C_1-C_6, cicloalquilo de C_3-C_{10}, $-(CH_2)_t$(arilo de C_6-C_{10}), $-(CH_2)_t$(heterociclo de 5 a 10 miembros), $-(CH_2)_tO(CH_2)_qOR^9$, y $-(CH_2)_tOR^9$;

cada R^6 y R^7 se selecciona independientemente de H, OH, alquilo de C_1-C_6, cicloalquilo de C_3-C_{10}, $-(CH_2)_t$(arilo de C_6-C_{10}), $-(CH_2)_t$(heterociclo de 5 a 10 miembros), $-(CH_2)_tO(CH_2)_qOR^9$, $(CH_2)_tCN(CH_2)_tOR^9$, $(CH_2)_tCN(CH_2)_tR^9$ y $–(CH_2)_tOR^9$, y el alquilo, arilo y restos heterocíclicos de dichos grupos R^6 y R^7 están sin substituir o substituidos con uno o más substituyentes independientemente seleccionados de hidroxi, halo, ciano, nitro, trifluorometilo, azido, $-C(O)R^8$, $-C(O)OR^8$, $-CO(O)R^8$, $-OC(O)OR^8$, $-NR^8C(O)R^{10}$, $-C(O)NR^8R^{10}$, $-NR^8R^{10}$, alquilo de C_1-C_6, $-(CH_2)_t$(arilo de C_6-C_{10}), $-(CH_2)_t$(heterociclo de 5 a 10 miembros), $-(CH_2)_tO(CH_2)_qOR^8$, y $-(CH_2)_tOR^8$, en los que R^6 y R^7 están ambos unidos al mismo nitrógeno, luego R^6 y R^7 no están ambos unidos al nitrógeno directamente por medio de un oxígeno;

cada R^8 se selecciona independientemente de H, alquilo de C_1-C_{10}, cicloalquilo de C_3-C_{10}, $-(CH_2)_t$(arilo de C_6-C_{10}), y $-(CH_2)_t$(heterociclo de 5 a 10 miembros);

cada R^9 y R^{10} se selecciona independientemente de H, $-OR^8$, alquilo de C_1-C_6 y cicloalquilo de C_3-C_{10};

en los que j es un número entero de 0 a 2, t es un número entero de 0 a 6, q es un número entero de 2 a 6; y

cada R^{12} y R^{13} se selecciona independientemente de H, alquilo de C_1-C_6, cicloalquilo de C_3-C_{10}, -$(CH_2)_t$(cicloalquilo de C_3-C_{10}), -$(CH_2)_t$(arilo de C_6-C_{10}), -$(CH_2)_t$(heterociclo de 5 a 10 miembros), -$(CH_2)_tO(CH_2)_sOR^9$, y -$(CH_2)_tOR^9$, y el alquilo, arilo y restos heterocíclicos de dichos grupos R^{12} y R^{13} están sin substituir o substituidos con uno o más substituyentes independientemente seleccionados de R^5, o R^{12} y R^{13} se toman conjuntamente con el nitrógeno al que están unidos para formar un anillo azabiciclo de C_5-C_9, aziridinilo, azetidinilo, pirrolidinilo, piperidinilo, piperazinilo, morfolinilo, tiomorfolinilo, isoquinolinilo o dihidroisoquinolinilo, en los que dichos anillos azabiciclo de C_5-C_9, aziridinilo, azetidinilo, pirrolidinilo, piperidinilo, piperazinilo, morfolinilo, tiomorfolinilo, isoquinolinilo o dihidroisoquinolinilo están substituidos o sin substituir con uno o más substituyentes, en los que R^{12} y R^{13} no están ambos unidos al nitrógeno directamente por medio de un oxígeno;

o sus profármacos, o sales o solvatos farmacéuticamente aceptables de dichos compuestos y dichos profármacos.

En una realización del compuesto de fórmula I, R^{11} es -$(CH_2)_t$(heterociclo de 5 a 10 miembros), -$C(O)NR^{12}R^{13}$, -$SO_2NR^{12}R^{13}$ y -CO_2R^{12}, en los que dicho grupo R^{11} -$(CH_2)_t$(heterociclo de 5 a 10 miembros) está sin substituir o substituido con uno o más grupos R^5 y en los que cada R^{12} y R^{13} se selecciona independientemente de H, alquilo de C_1-C_6, cicloalquilo de C_3-C_{10}, -$(CH_2)_t$(cicloalquilo de C_3-C_{10}), -$(CH_2)_t$(arilo de C_6-C_{10}), -$(CH_2)_t$(heterociclo de 5 a 10 miembros), -$(CH_2)_tO(CH_2)_sOR^9$, -$(CH_2)_tOR^9$, y el alquilo, arilo y restos heterocíclicos de dichos grupos R^{12} y R^{13} están sin substituir o substituidos con uno o más substituyentes independientemente seleccionados de R^5, o R^{12} y R^{13} se toman conjuntamente con el nitrógeno al que están unidos para formar un anillo azabiciclo de C_5-C_9, aziridinilo, azetidinilo, pirrolidinilo, piperidinilo, piperazinilo, morfolinilo, tiomorfolinilo, isoquinolinilo o dihidroisoquinolinilo, en los que dicho anillo azabiciclo de C_5-C_9, aziridinilo, azetidinilo, pirrolidinilo, piperidinilo, piperazinilo, morfolinilo, tiomorfolinilo, isoquinolinilo o dihidroisoquinolinilo está sin substituir o substituido con uno o más substituyentes R^5, en los que R^{12} y R^{13} no están ambos unidos al nitrógeno directamente por medio de un oxígeno;

En otra realización del compuesto de formula I, R^{11} es -$(CH_2)_t$(heterociclo de 5 a 10 miembros), y -$C(O)NR^{12}R^{13}$.

En otra realización más del compuesto de fórmula I, R^{11} es -$C(O)NR^{12}R^{13}$, en la que R^{12} y R^{13} se seleccionan independientemente de H, alquilo de C_1-C_6, cicloalquilo de C_3-C_{10}, -$(CH_2)_t$(cicloalquilo de C_3-C_{10}), -$(CH_2)_t$(arilo de C_6-C_{10}), -$(CH_2)_t$(heterociclo de 5 a 10 miembros), -$(CH_2)_tO(CH_2)_sOR^9$, -$(CH_2)_tOR^9$, en las que t es un número entero

de 0 a 6, q es un número entero de 2 a 6, y el alquilo, arilo y restos heterocíclicos de dichos grupos R^{12} y R^{13} están sin substituir o substituidos con uno o más substituyentes independientemente seleccionados de R^5, o R^{12} y R^{13} se toman conjuntamente con el nitrógeno al que están unidos para formar un anillo azabiciclo de C_5-C_9, aziridinilo, azetidinilo, pirrolidinilo, piperidinilo, piperazinilo, morfolinilo, tiomorfolinilo, isoquinolinilo o dihidroisoquinolinilo, en el que dicho anillo azabiciclo de C_5-C_9, aziridinilo, azetidinilo, pirrolidinilo, piperidinilo, piperazinilo, morfolinilo, tiomorfolinilo, isoquinolinilo o dihidroisoquinolinilo está sin substituir o substituido con 1 a 5 substituyentes R^5, en los que R^{12} y R^{13} no están ambos unidos al nitrógeno directamente por medio de un oxígeno;

En otra realización del compuesto de la fórmula I, R^{11} es $-C(O)NR^{12}R^{13}$, en la que R^{12} y R^{13} se toman conjuntamente con el nitrógeno al que están unidos para formar un anillo azabiciclo de C_5-C_9, aziridinilo, azetidinilo, pirrolidinilo, piperidinilo, piperazinilo, morfolinilo, tiomorfolinilo, isoquinolinilo o dihidroisoquinolinilo, en el que dicho anillo azabiciclo de C_5-C_9, aziridinilo, azetidinilo, pirrolidinilo, piperidinilo, piperazinilo, morfolinilo, tiomorfolinilo, isoquinolinilo o dihidroisoquinolinilo está sin substituir o substituido con 1 a 5 substituyentes R^6.

En otra realización más del compuesto de fórmula I, R^{11} es $-C(O)NR^{12}R^{13}$, en la que R^{12} y R^{13} se toman conjuntamente con el nitrógeno al que están unidos para formar un anillo pirrolidinilo, piperidinilo, piperazinilo, morfolinilo, tiomorfolinilo, isoquinolinilo o dihidroisoquinolinilo, en el que dicho anillo pirrolidinilo, piperidinilo, piperazinilo, morfolinilo, tiomorfolinilo, isoquinolinilo o dihidroisoquinolinilo está sin substituir o substituido con 1 a 5 substituyentes R^6.

En otra realización más del compuesto de fórmula I, R^{11} es $-C(O)NR^{12}R^{13}$, en la que R^{12} y R^{13} se toman conjuntamente con el nitrógeno al que están unidos para formar un anillo pirrolidinilo, piperidinilo, piperazinilo, morfolinilo o tiomorfolinilo, en el que dicho anillo pirrolidinilo, piperidinilo, piperazinilo, morfolinilo o tiomorfolinilo está sin substituir o substituido con 1 a 5 substituyentes R^6.

En otra realización más del compuesto de fórmula I, R^{11} es $-C(O)NR^{12}R^{13}$, en la que R^{12} y R^{13} se toman conjuntamente con el nitrógeno al que están unidos para formar un anillo pirrolidinilo o piperidinilo, en el que dicho anillo pirrolidinilo o piperidinilo, está sin substituir o substituido con 1 a 5 substituyentes R^6.

En otra realización más del compuesto de fórmula I, R^{11} es $-C(O)NR^{12}R^{13}$, en la que R^{12} y R^{13} se toman conjuntamente con el nitrógeno al que están unidos para

formar un anillo pirrolidinilo, en el que dicho anillo pirrolidinilo está sin substituir o substituido con 1 a 5 substituyentes R^5.

En otra realización más del compuesto de fórmula I, R^{11} es $-C(O)NR^{12}R^{13}$, en la que R^{12} y R^{13} se toman conjuntamente con el nitrógeno al que están unidos para formar un anillo pirrolidin-1-ilo, en el que dicho anillo pirrolidin-1-ilo está sin substituir o substituido con 1 a 5 substituyentes R^5.

En otra realización más del compuesto de fórmula I, R^{11} es un grupo $-(CH_2)_t$(heterociclo de 5 a 10 miembros), en el que dicho grupo $-(CH_2)_t$(heterociclo de 5 a 10 miembros) está sin substituir o substituido con 1 a 5 grupos R^5

En otra realización más del compuesto de fórmula I, R^{11} es un grupo $-(CH_2)_t$(heterociclo de 5 a 8 miembros), en el que dicho grupo $-(CH_2)_t$(heterociclo de 5 a 8 miembros) está sin substituir o substituido con 1 a 5 grupos R^5.

En otra realización más del compuesto de fórmula I, R^{11} es un grupo $-(CH_2)_t$(heterociclo de 5 o 6 miembros), en el que dicho grupo $-(CH_2)_t$(heterociclo de 5 o 6 miembros) está sin substituir o substituido con 1 a 5 grupos R^5.

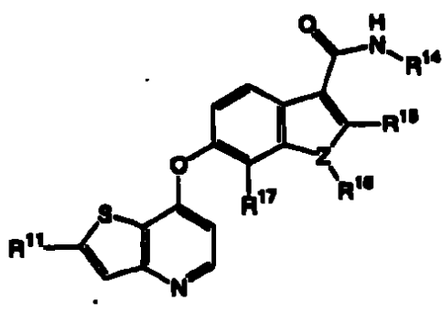
En otra realización más del compuesto de fórmula I, R^{11} es un grupo $-(CH_2)_t$(heterociclo de 5 miembros), en el que dicho grupo $-(CH_2)_t$(heterociclo de 5 miembros) está sin substituir o substituido con 1 a 5 grupos R^5.

En otra realización más del compuesto de la fórmula I, R^{11} es $-(CH_2)_t$tiazolilo, en el que t es un número entero de 0 a 6, dicho $-(CH_2)_t$tiazolilo está sin substituir o substituido con 1 a 5 grupos R^5.

En otra realización más del compuesto de fórmula I, R^{11} es un tiazolilo, dicho tiazolilo está sin substituir o substituido con 1 a 5 grupos R^5.

En otra realización más del compuesto de fórmula I, R^{11} es un imidazolilo, dicho imidazolilo está sin substituir o substituido con 1 a 5 grupos R^5.

La presente invención se refiere también a los compuestos representados por la fórmula II:



II

en la que:

Z es -O-, -S-, o -N-;

R^{14} es un alquilo de C_1-C_6, alquil de C_1-C_6-amino, alquil de C_1-C_6-hidroxi, cicloalquil de C_3-C_{10}-amino, o grupo metilureido;

R^{15} y R^{17} son independientemente H, halo, o un grupo alquilo de C_1-C_6;

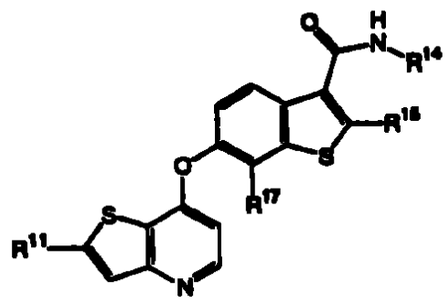
R^{16} es H o un grupo alquilo de C_1-C_6 cuando Z es N; y R^{16} está ausente cuando Z es -O- o -S-; y

en la que R^{11} es como se define para dichos compuestos, profármaco, metabolito, sal o solvato de fórmula I o sus profármacos o metabolitos, sales o solvatos farmacéuticamente aceptables de dichos compuestos, dichos profármacos y dichos metabolitos.

En una realización R^{16} es metilo.

En otra realización R^{14} es metilo.

La presente invención se refiere adicionalmente a compuestos representados por la fórmula III:



III

en la que:

R^{14} es un alquilo de C_1-C_6, alquil de C_1-C_6-amino, alquil de C_1-C_6-hidroxi, cicloalquil de C_3-C_{10}-amino, o grupo metilureido;

R^{15} y R^{17} son independientemente H, o un grupo alquilo de C_1-C_6, y

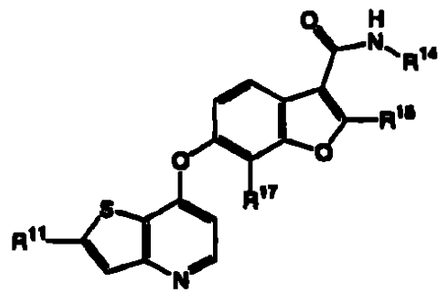
R^{11} es un heterocicio o un grupo heteroarilo sin substituir o substituido con uno o más grupos seleccionados de -C(O)OR^8, alquilo de C_1-C_6, y -$(CH_2)_t$$OR^8$, en el que t es un número entero de 0 a 6;

cada R^8 se selecciona independientemente de H, alquilo de C_1-C_{10}, cicloalquilo de C_3-C_{10}, -$(CH_2)_t$(arilo de C_6-C_{10}), y -$(CH_2)_t$(heterocicio de 5 a 10 miembros), en los que t es un número entero de 0 a 6;

cada R^9 se selecciona independientemente de H, alquilo de C_1-C_6, y cicloalquilo de C_3-C_{10};

o sus profármacos, sales o solvatos farmacéuticamente aceptables de dichos compuestos y dichos profármacos.

En otra realización, la presente invención es un compuesto representado por la fórmula IV:



IV

en la que:

R^{14} es un alquilo de C_1-C_6, alquil de C_1-C_6-amino, alquil de C_1-C_6-hidroxi, cicloalquil de C_3-C_{10}-amino, o grupo metilureido;

R^{15} y R^{17} son independientemente H, o un grupo alquilo de C_1-C_6, y

R^{11} es un heterociclo o un grupo heteroarilo sin substituir o substituido con uno o más grupos seleccionados de -C(O)OR^8, alquilo de C_1-C_6, y -$(CH_2)_t$$OR^8$, en el que t es un número entero de 0 a 6;

cada R^8 se selecciona independientemente de H, alquilo de C_1-C_{10}, cicloalquilo de C_3-C_{10}, -$(CH_2)_t$(arilo de C_6-C_{10}), y -$(CH_2)_t$(heterociclo de 5 a 10 miembros), en los que t es un número entero de 0 a 6;

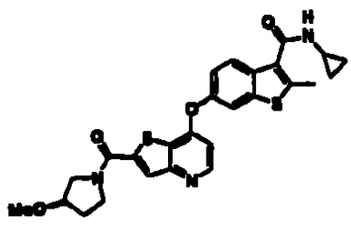
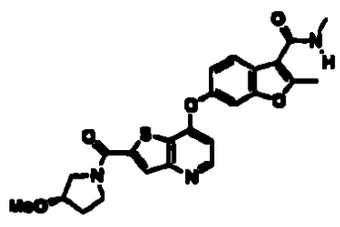
cada R^9 se selecciona independientemente de H, alquilo de C_1-C_6, y cicloalquilo de C_3-C_{10};

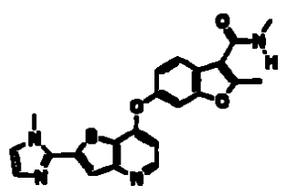
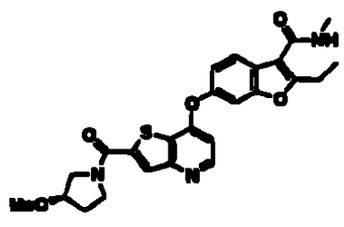
o sus profármacos o metabolitos, sales o solvatos farmacéuticamente aceptables de dichos compuestos, dichos profármacos, y dichos metabolitos.

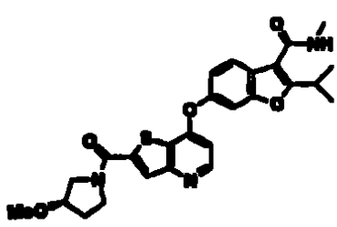
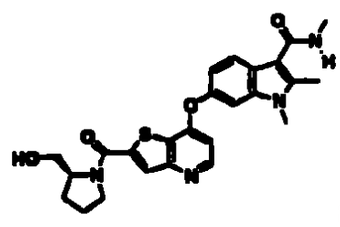
Los compuestos anteriores de fórmulas II, III y IV se pueden usar para preparar los anteriores compuestos representados por la fórmula I.

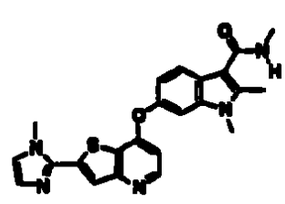
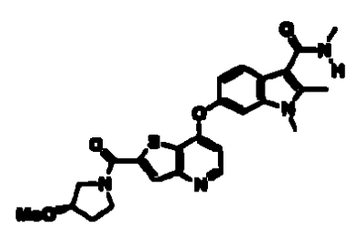
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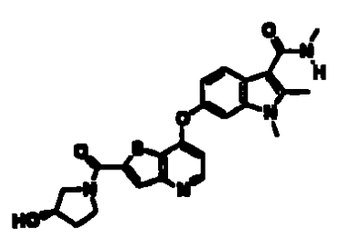
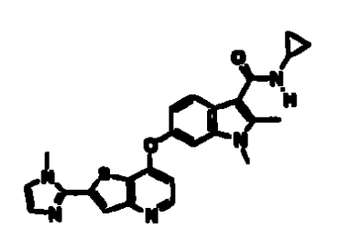
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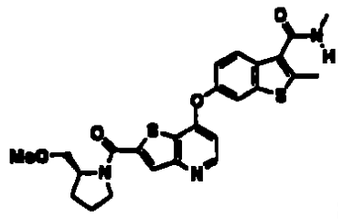
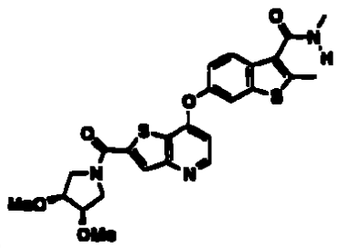

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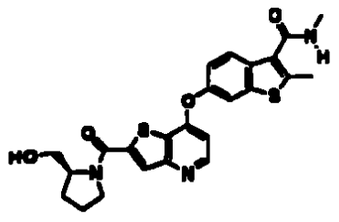
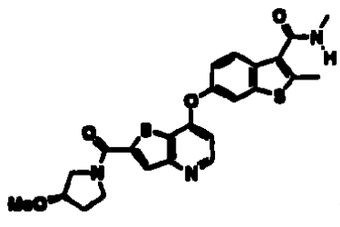

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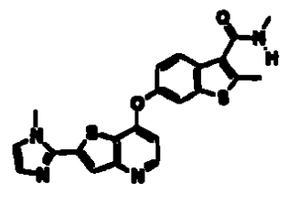
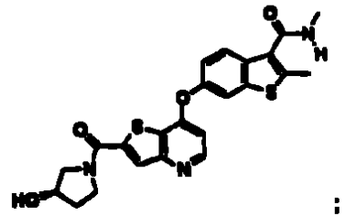

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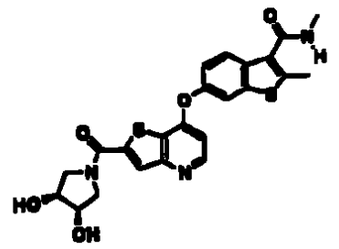
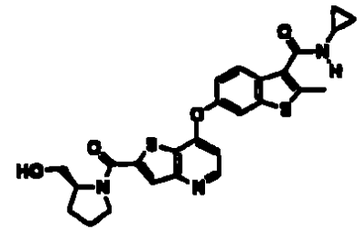
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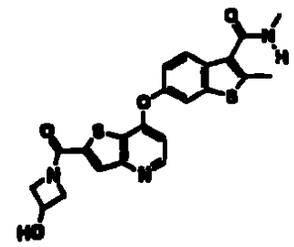
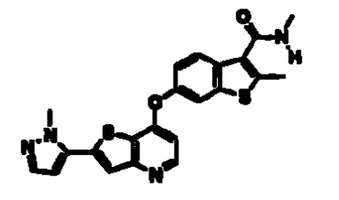
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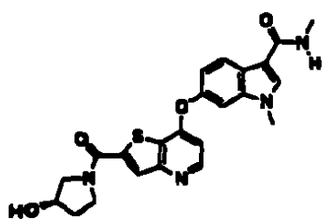

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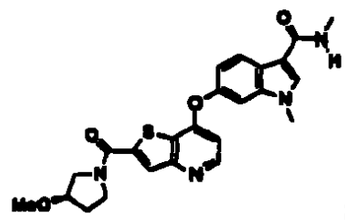

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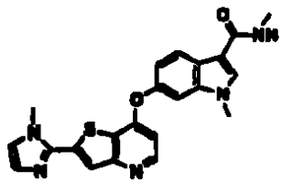

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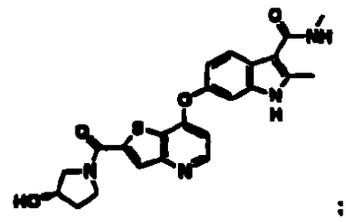
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o sus profármacos o metabolitos, o sales o solvatos farmacéuticamente aceptables de dichos compuestos, dichos profármacos, y dichos metabolitos.

Los pacientes que pueden ser tratados con los compuestos de fórmula I, y sus profármacos, sales o solvatos farmacéuticamente aceptables de dichos compuestos y dichos profármacos, según los métodos de esta invención, incluyen, por ejemplo, pacientes que se ha sido diagnosticado que tienen psoriaris, BPH, cáncer de pulmón, cáncer de ojos, cáncer de huesos, cáncer pancreático, cáncer de piel, cáncer de cabeza y cuello, melanoma cutáneo o intraocular, cáncer de útero, cáncer de ovarios, cáncer de recto, cáncer de la región anal, cáncer de estómago, cáncer de colon, cáncer de pecho, tumores ginecológicos (por ejemplo, sarcomas uterinos, carcinoma de las trompas de falopio, carcinoma del endometrio, carcinoma del cervix, carcinoma de la vagina o carcinoma de la vulva), enfermedad de Hodkin, cáncer de esófago, cáncer del intestino delgado, cáncer del sistema endocrino (por ejemplo, cáncer de tiroides, paratiroides o glándulas adrenales), sarcomas de tejidos blandos, cáncer de uretra, cáncer del pene, cáncer de próstata, leucemia crónica o aguda, tumores sólidos de la niñez, linfomas linfocíticos, cáncer de la vejiga, cáncer de riñón o uréter (por ejemplo, carcinoma de células renales, carcinoma de pelvis renal), o neoplasmas del sistema nervioso central (por ejemplo, linfoma del SNC primario, tumores de la médula espinal, gliomas del tronco cerebral o adenomas pituitarios).

Esta invención se refiere también a composiciones farmacéuticas que los contienen y a métodos para tratar el crecimiento celular anormal administrando profármacos de los compuestos de la fórmula I. Compuestos de fórmula I que tienen

grupos amino, amido, hidroxi o carboxílico libres que se pueden convertir en profármacos.

La invención se refiere también a una composición farmacéutica para el tratamiento de un trastorno hiperproliferativo en un mamífero que comprende una cantidad terapéuticamente efectiva de un compuesto de fórmula I, o sus profármacos, sales o solvatos farmacéuticamente aceptables de dichos compuestos y dichos profármacos, y un vehículo farmacéuticamente aceptable. En una realización, dicha composición farmacéutica es para el tratamiento del cáncer, tal como cáncer de cerebro, pulmón, oftálmico, de células escamosas, vejiga, gástrico, pancreático, de pecho, cabeza, cuello, renal, de riñón, ovario, próstata, colorectal, esofágico, ginecológico o de tiroides. En otra realización, dicha composición farmacéutica es para el tratamiento de un trastorno hiperproliferativo no canceroso tal como hiperplasia benigna de la piel (por ejemplo, psoriasis) o de próstata (por ejemplo, hipertropia prostática benigna (BPH)).

La invención se refiere también a una composición farmacéutica para el tratamiento de pancreatitis o enfermedad del riñón (que incluye glomerulonefritis proliferativa y enfermedad renal inducida por la diabetes) en un mamífero, que comprende una cantidad terapéuticamente efectiva de un compuesto de fórmula I, o sus profármacos, sales o solvatos farmacéuticamente aceptables de dichos compuestos y dichos profármacos, y un vehículo farmacéuticamente aceptable.

La invención se refiere también a una composición farmacéutica para la prevención de la implantación de blastocitos en un mamífero, que comprende una cantidad terapéuticamente efectiva de un compuesto de fórmula I, o sus profármacos, sales o solvatos farmacéuticamente aceptables de dichos compuestos y dichos profármacos, y un vehículo farmacéuticamente aceptable.

La invención se refiere también a una composición farmacéutica para tratar una enfermedad relacionada con vasculogénesis o angiogénesis en un mamífero, que comprende una cantidad terapéuticamente efectiva de un compuesto de fórmula I, o sus profármacos, sales o solvatos farmacéuticamente aceptables de dichos compuestos y dichos profármacos y un vehículo farmacéuticamente aceptable. En una realización, dicha composición farmacéutica es para tratar una enfermedad seleccionada del grupo que consiste en angiogénesis tumoral, enfermedad inflamatoria crónica tal como artritis reumatoide, aterosclerosis, enfermedades de la piel tales como psoriasis, eczema, y escleroderma, diabetes, retinopatía diabética, retinopatía del prematuro, degeneración macular relacionada con la edad,

hemangioma, glioma, melanoma, sarcoma de Kaposi y cáncer de ovario, pecho, pulmón, pancreático, de próstata, colon y epidermoide.

La invención se refiere también a un método de tratar un trastorno hiperproliferativo en un mamífero, que comprende administrar a dicho mamífero una cantidad terapéuticamente efectiva del compuesto de fórmula I, o sus profármacos, sales o solvatos farmacéuticamente aceptables de dichos compuestos y dichos profármacos. En una realización, dicho método se refiere al tratamiento de cáncer tal como cáncer cerebral, oftálmico, de células escamosas, de vejiga, gástrico, pancreático, de pecho, cabeza, cuello, esofágico, de próstata, colorectal, de pulmón, renal, de riñón, de ovario, ginecológico o de tiroides. En otra realización, dicho método se refiere al tratamiento de un trastorno hiperproliferativo no canceroso tal como hiperplasia benigna de la piel (por ejemplo, psoriasis) o próstata (por, ejemplo, hipertropia prostática benigna (BPH)).

La invención se refiere también a un método para el tratamiento de un trastorno hiperproliferativo en un mamífero, que comprende administrar a dicho mamífero una cantidad terapéuticamente efectiva de un compuesto de fórmula I, o sus profármacos, sales o solvatos farmacéuticamente aceptables de dichos compuestos y dichos profármacos, en combinación con un agente anti-tumor seleccionado del grupo que consiste en inhibidores mitóticos, agentes alquilantes, anti-metabolitos, antibióticos intercalantes, inhibidores del factor de crecimiento, inhibidores del ciclo celular, enzimas, inhibidores de la topoisomerasa, modificadores de la respuesta biológica, anti-hormonas, y anti-andrógenos.

El tratamiento de un trastorno hiperproliferativo en un mamífero, que comprende administrar a dicho mamífero una cantidad terapéuticamente efectiva de un inhibidor de la tirosina quinasa del receptor de VEGF puede conducir a un incremento sostenido de la presión sanguínea. Los compuestos de la presente invención se pueden usar en conjunción con un anti-hipertensivo, tal como NORVASC o PROCARDIA XL, comercialmente disponible de Pfizer, para uso en el tratamiento de un trastorno hiperproliferativo en un mamífero.

Esta invención se refiere también a una composición farmacéutica para tratar una enfermedad relacionada con vasculogénesis o angiogénesis en un mamífero, que comprende una cantidad terapéuticamente efectiva de un compuesto, profármaco, metabolito, sal o solvato de la reivindicación 1, una cantidad terapéuticamente efectiva de un compuesto, profármaco, metabolito, sal o solvato de un agente anti-hipertensivo, y un vehículo farmacéuticamente aceptable.

Esta invención se refiere también a una composición farmacéutica para inhibir el crecimiento celular anormal en un mamífero, incluyendo a un ser humano, que comprende una cantidad de un compuesto de la fórmula I como se define anteriormente, o su profármaco, sal farmacéuticamente aceptable o solvato de dicho compuesto y dicho profármaco, que es efectivo para inhibir la farnesil-protein-transferasa, y un vehículo farmacéuticamente aceptable.

Esta invención se refiere también a una composición farmacéutica para inhibir el crecimiento celular anormal en un mamífero, que comprende una cantidad de un compuesto de fórmula I, o su profármaco, sal farmacéuticamente aceptable o solvato de dicho compuesto y dicho profármaco, en combinación con una cantidad de un compuesto quimioterapéutico, en el que las cantidades del compuesto, sal, solvato, o profármaco, y del compuesto quimioterapéutico son conjuntamente efectivas para inhibir el crecimiento celular anormal. Se conocen actualmente en la técnica muchos compuestos quimioterapéuticos. En una realización, el compuesto quimioterapéutico se selecciona del grupo que consiste en inhibidores mitóticos, agentes de alquilación, anti-metabolitos, antibióticos intercalantes, inhibidores del factor de crecimiento, inhibidores del ciclo celular, enzimas, inhibidores de la topoisomerasa, modificadores de la respuesta biológica, anti-hormonas, por ejemplo, anti-andrógenos.

La invención se refiere adicionalmente a un método para inhibir el crecimiento celular anormal en un mamífero, método que comprende administrar al mamífero una cantidad de un compuesto de fórmula I, o su profármaco, sal farmacéuticamente aceptable o solvato de dicho compuesto y dicho profármaco, en combinación con terapia de radiación, en la que la cantidad del compuesto, sal, solvato o profármaco está en combinación con la terapia de radiación efectiva para inhibir el crecimiento celular anormal en el mamífero. Se conocen en la técnica técnicas para administrar terapia de radiación, y estas técnicas se pueden usar en la terapia de combinación descrita aquí. La administración del compuesto de la invención en esta terapia de combinación se puede determinar como se describe aquí.

Se cree que los compuestos de fórmula I pueden convertir las células anormales en más sensibles al tratamiento con radiación con el propósito de matar y/o inhibir el crecimiento de tales células. Por consiguiente, esta invención se refiere adicionalmente a un método para sensibilizar células anormales en un mamífero para el tratamiento con radiación, que comprende administrar al mamífero una cantidad de un compuesto de fórmula I o su profármaco, sal farmacéuticamente aceptable o solvato de dicho compuesto y dicho profármaco, tal cantidad es efectiva para

sensibilizar células anormales para el tratamiento con radiación. La cantidad del compuesto, sal, solvato o profármaco en este método se puede determinar según los medios para verificar las cantidades efectivas de tales compuestos descritos aquí.

Esta invención se refiere también a un método y a una composición farmacéutica para inhibir el crecimiento celular anormal en un mamífero, que comprende una cantidad de un compuesto de fórmula I, su profármaco, sal farmacéuticamente aceptable o solvato de dicho compuesto y dicho profármaco, o uno de sus derivados marcado isotópicamente, y una cantidad de una o más substancias seleccionadas de agentes anti-angiogénesis, inhibidores de la transducción de la señal, y agentes antiproliferativos.

Los agentes anti-angiogénesis, tales como los inhibidores de MMP-2 (matriz-metaloproteinasa 2), inhibidores de MMP-9 (matriz-metaloproteinasa 9), e inhibidores de COX-II (ciclooxigenasa II) se pueden usar en conjunción con un compuesto de fórmula 1 y las composiciones farmacéuticas descritas aquí.

Los ejemplos de inhibidores de COX-II útiles incluyen CELEBREX™ (alecoxib), valdecoxib, y rofecoxib. Los ejemplos de inhibidores de metaloproteinasa de matriz útiles se describen en los documentos WO 96/33172 (publicado el 24 de octubre de 1996), WO 96/27583 (publicado el 7 de marzo de 1996), Solicitud de Patente Europea No. 97304971.1 (presentada el 8 de julio de 1997), Solicitud de Patente Europea No. 99308617.2 (presentada el 29 de octubre de 1999), documentos WO 98/07697 (publicado el 26 de febrero de 1998), WO 98/03516 (publicado el 29 de enero de 1998), WO 98/34918 (publicado el 13 de agosto de 1998), WO 98/34915 (publicado el 13 de agosto de 1998), WO 98/33768 (publicado el 6 de agosto de 1998), WO 98/30566 (publicado el 16 de julio de 1998), Publicación de Patente Europea 606.046 (publicada el 13 de julio de 1994), Publicación de Patente Europea 931.788 (publicada el 28 de julio de 1999), documentos WO 90/05719 (publicado el 31 de mayo de 1990), WO 99/52910 (publicado el 21 de octubre de 1999), WO 99/52889 (publicado el 21 de octubre de 1999), WO 99/29667 (publicado el 17 de junio de 1999), Solicitud internacional PCT No. PCT/IB98/01113 (presentada el 21 de julio de 1998), Solicitud de Patente Europea No. 99302232.1 (presentada el 25 de marzo de 1999), solicitud de patente de Gran Bretaña número 9912961.1 (presentada el 3 de junio de 1999), Solicitud Provisional de EE.UU. No. 60/148.464 (presentada el 12 de agosto de 1999), Patente de EE:UU. 5.863.949 (otorgada el 26 de enero de 1999), Patente de EE.UU. 5.861.510 (otorgada el 19 de enero de 1999), y Publicación de Patente Europea 780.386 (publicada el 25 de junio de 1997), todas las cuales se incorporan aquí en su

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totalidad como referencia. Los inhibidores de MMP-2 y MMP-9 preferidos son aquellos que tienen poca o ninguna actividad de inhibir MMP-1. Más preferidos son aquellos que inhiben selectivamente MMP-2 y/o MMP-9 en relación a las otras matriz-metaloproteinasas (es decir, MMP-1, MMP-3, MMP-4, MMP-5, MMP-6, MMP-7, MMP-8, MMP-10, MMP-11, MMP-12 y MMP-13).

Algunos ejemplos específicos de inhibidores de MMP útiles en la presente invención son Prinomastat, RO 32-3555, RS 13-0830, y los compuestos citados en la siguiente lista:

ácido 3-[[4-(4-fluoro-fenoxi)-bencenosulfonil]-(1-hidroxicarbamoil-ciclopentil)-amino]-propionico; hidroxiamida del ácido 3-exo-3-[4-(4-fluoro-fenoxi)-bencenosulfonilamino]-8-oxa-biciclo[3.2.1]octano-3-carboxílico; hidroxiamida del ácido (2R, 3R) 1-[4-(2-cloro-4-fluoro-benciloxi)-bencenosulfonil]-3-hidroxi-3-metil-piperidina-2-carboxílico; hidroxiamida del ácido 4-[4-(4-fluoro-fenoxi)-bencenosulfonilamino]-tetrahidro-piran-4-carboxílico; ácido 3-[[4-(4-fluoro-fenoxi)-bencenosulfonil]-(1-hidroxicarbamoil-ciclobutil)-amino]-propiónico; hidroxiamida del ácido 4-[4-(4-cloro-fenoxi)-bencenosulfonilamino]-tetrahidro-piran-4-carboxílico; hidroxiamida del ácido (R) 3-[4-(4-cloro-fenoxi)-bencenosulfonilamino]-tetrahidro-piran-3-carboxílico; hidroxiamida del ácido (2R, 3R) 1-[4-(4-fluoro-2-metil-benciloxi)-bencenosulfonil]-3-hidroxi-3-metil-piperidina-2-carboxílico; ácido 3-[[4-(4-fluoro-fenoxi)-bencenosulfonil]-(1-hidroxicarbamoil-1-metil-etil)-amino]-propiónico; ácido 3-[[4-(4-fluoro-fenoxi)-bencenosulfonil]-(4-hidroxicarbamoil-tetrahidro-piran-4-il)-amino]-propiónico; hidroxiamida del ácido 3-exo-3-[4-(4-cloro-fenoxi)-bencenosulfonilamino]-8-oxa-biciclo[3.2.1]octano-3-carboxílico; hidroxiamida del ácido 3-endo-3-[4-(4-cloro-fenoxi)-bencenosulfonilamino]-8-oxa-biciclo[3.2.1]octano-3-carboxílico; e hidroxiamida del ácido (R) 3-[4-(4-fluoro-fenoxi)-bencenosulfonilamino]-tetrahidro-furan-3-carboxílico; y sales y solvatos farmacéuticamente aceptables de dichos compuestos. También se pueden usar en la presente invención otros agentes anti-angiogenésis, incluyendo otros inhibidores de COX-II y otros inhibidores de MMP.

Esta invención se refiere adicionalmente a un método para tratar una enfermedad relacionada con vasculogénesis o angiogénesis en un mamífero, que comprende administrar a dicho mamífero una cantidad terapéuticamente efectiva de un compuesto, profármaco, metabolito, sal o solvato de la reivindicación 1 en conjunción con una cantidad terapéuticamente efectiva de un agente anti-hipertensivo.

Un compuesto de fórmula I, se puede usar también con inhibidores de transducción de la señal, tales como agentes que pueden inhibir las respuestas del

EGFR (receptor del factor de crecimiento epidérmico), tales como anticuerpos de EGFR, anticuerpos de EGF, y moléculas que son inhibidores del EGFR; inhibidores del VEGF (factor de crecimiento endotelial vascular), tales como receptores de VEGF y moléculas que pueden inhibir el VEGF; e inhibidores del receptor ergB2, tales como moléculas orgánicas o anticuerpos que se unen al receptor erbB2, por ejemplo, HERCEPTIN™ (Genetech, Inc. de South San Francisco, California, USA).

Se describen inhibidores de EGFR, por ejemplo, en los documentos WO 95/19970 (publicado el 27 de julio de 1995), WO 98/14451 (publicado el 9 de abril de 1998), WO 98/02434 (publicado el 22 de enero de 1998), y patente de EE.UU. 5.747.498 (otorgada el 5 de mayo de 1998), y tales substancias se pueden usar en la presente invención tal como se describe aquí. Los agentes que inhiben EGFR incluyen, pero no están limitados a, los anticuerpos monoclonales C225 y 22Mab anti-EGFR (ImClone Systems Incorporated of New York, New York, USA), los compuestos ZD-1839 (AstraZeneca), BIBX-1382 (Boehringer Ingelheim), MDX-447 (Medarex Inc. de Annadale, New Jersey, USA), y OLX-103 (Merck & Co. de Whitehouse Station, New Yersey USA), VRCTC-310 (Ventech Research y la tosina de fusión de EGF (Seragen Inc. de Hopkinton, Massachusetts. Este y otros agentes inhibidores de EGFR se pueden usar en la presente invención.

Los inhibidores del VEGF, por ejemplo SU-5416 y SU-6668 (Sugen Inc. de South San Francisco, California, USA), se pueden combinar también con el compuesto de la presente invención. Los inhibidores del VEGF se describen, por ejemplo, en el documento WO 99/24440 (publicado el 20 de mayo de 1999), Solicitud Internacional PCT PCT/IB99/00797 (presentada el 3 de mayo de 1999), en los documentos 95/21613 (publicado el 17 de agosto de 1995), WO 99/61442 (publicado el 2 de diciembre de 1999), Patente de EE.UU. 5.834.504 (otorgada el 10 de noviembre de 1998), documento WO 98/50356 (publicado el 12 de noviembre de 1998), Patente de EE.UU. 5.883.113 (otorgada el 16 de marzo de 1999), Patente de EE.UU. 5.886.020 (otorgada el 23 de marzo de 1999), Patente de EE.UU. 5.792.783 (otorgada el 11 de agosto de 1998), documentos WO 99/10349 (publicado el 4 de marzo de 1999), WO 97/32856 (publicado el 12 de septiembre de 1999), WO 97/22596 (publicado el 26 de junio de 1997), WO 98/54093 (publicado el 3 de diciembre de 1998), WO 98/02438 (publicado el 22 de enero de 1998), WO 99/16755 (publicado el 8 de abril de 1999) y WO 98/02437 (publicado el 22 de enero de 1998), todos los cuales se incorporan aquí en su totalidad como referencia. Otros ejemplos de algunos inhibidores específicos del VEGF útiles en la presente invención son IM862 (Cytran Inc. de Kirkland, Washinton,

USA); anticuerpo monoclonal anti-VEGF de Genetech Inc. de South San Francisco, California; y angiozima, una ribozima sintética de Ribozyme (Boulder, Colorado y Chiron (Emeryville, California). Estos y otros inhibidores del VEGF se pueden usar en la presente invención como se describe aquí.

Los inhibidores del receptor ErbB2, tales como GW-282974 (Glaxo Wellcome plc.) y los anticuerpos monoclonales Ar-209 (Aronex Pharmaceuticals Inc. de The Woodlands, Texas, USA) y 2B-1 (Chiron), se pueden combinar además con el compuesto de la invención, por ejemplo, aquellos indicados en los documentos WO 98/02243 (publicado el 22 de enero de 1998), WO 99/35146 (publicado el 15 de julio de 1999), WO 99/35132 (publicado el 15 de julio de 1999), WO 99/02437 (publicado el 22 de enero de 1999), WO 97/13760 (publicado el 17 de abril de 1997), WO 95/19970 (publicado el 27 de julio de 1995), Patente de EE.UU: 5.587.458 (otorgada el 24 de diciembre de 1996), y patente de EE.UU. 5,877.305 (otorgada el 2 de marzo de 1999), que se incorporan todos aquí por eso en su totalidad como referencia. Los inhibidores del receptor de ErbB2 útiles en la presente invención se describen también en la Solicitud Provisional de EE.UU. No 60/117.341, presentada el 27 de enero de 1999, y en la Solicitud Provisional de EE.UU: No. 60/117.346, presentada el 27 de enero de 1999, ambas se incorporan aquí en su totalidad como referencia. Los compuestos del inhibidor del receptor de erbB2 y la substancia descrita en las anteriormente mencionadas solicitudes PCT, patentes de EE.UU., solicitudes provisionales, así como otros compuestos y substancias que inhiben el receptor de erbB2, se pueden usar con los compuestos de la presente invención.

Los compuestos de la invención se pueden usar también con otros agentes útiles para tratar el crecimiento celular anormal o cáncer, que incluyen, pero no están limitados a, agentes capaces de mejorar las respuestas inmunes antitumor, tales como los anticuerpos de CTLA4 (antígeno de linfocito citotóxico 4), y otros agentes capaces de bloquear el CTLA4; y agentes antiproliferativos tales como otros inhibidores de la farnesil-protein-transferasa, y similares. Los anticuerpos de CTLA4 específicos que se pueden usar en la presente invención incluyen aquellos descritos en la Solicitud Provisional de EE.UU. 60/113.647 (presentada el 23 de diciembre de 1998) que se incorpora como referencia en su totalidad, sin embargo se pueden usar otros anticuerpos de CTLA4 en la presente invención.

La presente invención también incluye compuestos isotópicamente marcados, que son idénticos a los citados en la fórmula I, excepto por el hecho de que uno o más átomos están reemplazados por un átomo que tiene una masa atómica o número de

masa diferente de la masa atómica o número de masa usualmente encontrada en la naturaleza. Los ejemplos de isótopos que se pueden incorporar en los compuestos de la invención incluyen isótopos de hidrógeno, carbono, nitrógeno, oxígeno, fósforo, flúor y cloro, tales como ^{2}H, ^{3}H, ^{13}C, ^{14}C, ^{15}N, ^{18}O, ^{17}O, ^{31}P, ^{32}P, ^{35}S, ^{18}F y ^{36}Cl, respectivamente. Los compuestos de la presente invención, sus profármacos, y sales farmacéuticamente aceptables de dichos compuestos o de dichos profármacos que contienen los anteriormente mencionados isótopos y/u otros isótopos de otros átomos están dentro del alcance de la invención. Ciertos compuestos isotópicamente marcados de la presente invención, por ejemplo, aquellos en los que se incorporan isótopos radiactivos tales como ^{3}H y ^{14}C, son útiles en ensayos de distribución en el tejido del substrato y/o fármaco. Los isótopos tritiados, es decir con ^{3}H, y los de Carbono-14, es decir, ^{14}C , son particularmente preferidos por su facilidad de preparación y detectabilidad. Además, la substitución con isótopos más pesados tales como deuterio, es decir, ^{2}H, puede dar ciertas ventajas terapéuticas que son el resultado de mayor estabilidad metabólica, por ejemplo, media vida incrementada in vivo o requerimientos de dosificación reducidos y, por consiguiente, se pueden preferir en algunas circunstancias. Los compuestos isotópicamente marcados de fórmula I, II, III, o IV de esta invención y sus profármacos se pueden preparar generalmente llevando a cabo los procedimientos descritos en los Esquemas y/o en los Ejemplos a continuación, substituyendo un reactivo no isotópicamente marcado por un reactivo isotópicamente marcado fácilmente disponible. Los compuestos de fórmula I y sus sales y solvatos farmacéuticamente aceptables se puede usar también cada uno independientemente en una terapia paliativa neoadyuvante/adyuvante para aliviar los síntomas asociados a las enfermedades citadas aquí además de los síntomas asociados al crecimiento celular anormal. Tal terapia puede ser una monoterapia o puede ser en una combinación con quimioterapia y/o inmunoterapia.

Las expresiones "crecimiento celular anormal" y "trastorno hiperproliferativo" se usan intercambiablemente en esta solicitud.

"Crecimiento celular anormal", tal como se usa aquí, ser refiere al crecimiento celular que es independiente de los mecanismos reguladores normales (por ejemplo, pérdida de inhibición por contacto), que incluyen el crecimiento anormal de células normales y el crecimiento de células anormales. Este incluye, pero no está limitado, al crecimiento anormal de: (1) células tumorales (tumores), tanto benignos como malignos, que expresan un oncogén Ras activado; (2) células tumorales, tanto benignas como malignas, en las que la proteína de Ras se activa como resultado de

mutación oncogénica en otro gen; (3) células benignas y malignas de otras enfermedades proliferativas en las que ocurre la activación de Ras aberrante. Los ejemplos de tales enfermedades proliferativas benignas son psoriasis, hipertropia prostática benigna, virus de papiloma humano (HPV), y restinosis. El "crecimiento celular anormal" se refiere también e incluye el crecimiento anormal de células, tanto benignas como malignas. que es el resultado de la actividad de la enzima famesil-protein-transferasa.

El término "tratar", tal como se usa aquí, a menos que se indique lo contrario, quiere decir invertir, aliviar, inhibir el progreso de, o prevenir el trastorno o el estado al que se aplica tal término, o uno o más síntomas de tal trastorno o estado. El término "tratamiento" tal como se usa aquí, se refiere al acto de tratar, tal como se define "tratar" inmediatamente antes.

El término "halo" tal como se usa aquí, a menos que se indique lo contrario, quiere decir fluoro, cloro, bromo o yodo. Los grupos halo preferidos son fluoro, cloro y bromo.

El término "alquilo", tal como se usa aquí, a menos que se indique lo contrario, quiere decir radicales hidrocarbonados monovalentes saturados que tienen restos lineales, cíclicos o ramificados. Dicho grupo "alquilo" puede incluir un doble o triple enlace carbono-carbono opcional en el que dicho grupo alquilo comprende por lo menos dos átomos de carbono. Se entiende que para los restos cíclicos se requieren por lo menos tres átomos de carbono en dicho grupo alquilo.

El término "alcoxi", tal como se usa aquí, a menos que se indique lo contrario, quiere decir grupos O-alquilo en los que el "alquilo" es como se define anteriormente.

El término "arilo", tal como se usa aquí, a menos que se indique lo contrario, quiere decir un radical orgánico derivado de un hidrocarburo aromático por retirada de un hidrógeno, tal como fenilo o naftilo.

La expresión "grupo heterocíclico", tal como se usa aquí, incluye grupos heterocíclicos aromáticos y no aromáticos. A menos que se indique lo contrario, los grupos heterocíclicos preferidos incluyen grupos que tienen de 3 a 13 átomos en el anillo, más preferentemente de 5 a 10 átomos en el anillo, y aún más preferentemente de 5 a 6 átomos en el anillo. Además, los grupos heterocíclicos preferidos incluyen grupos que contienen de uno a cuatro heteroátomos cada uno seleccionado de O, S y N. Los grupos heterocíclicos incluyen sistemas de anillo benzocondensados y sistemas de anillo substituido con uno o dos restos oxo (=O) tales como pirrolidin-2-ona. Un ejemplo de un grupo heterocíclico de 5 miembros es tiazolilo, un ejemplo de

un grupo heterocíclico de 10 miembros es quinolinilo, y un ejemplo de un grupo heterocíclico de 13 miembros es un grupo carbazol. Los ejemplos de grupos heterocíclicos no aromáticos incluyen pirrolidinilo, piperidino, morfolino, tiomorfolino y piperazinilo. Los ejemplos de grupos heterocíclicos aromáticos incluyen piridinilo, imidazolilo, pirimidinilo, pirazolilo, triazolilo, pirazinilo, tetrazolilo, furilo, tienilo, isoxazolilo y tiazolilo. Los grupos heterocíclicos que tienen un anillo de benceno condensado incluyen benzimidazolilo, benzofuranilo y benzo[1,3]dioxolilo.

La frase "sal(es) farmacéutica(s) aceptable(s)", tal como se usa aquí, a menos que se indique lo contrario, quiere decir sales de grupos ácidos o básicos que pueden estar presentes en los compuestos o profármacos de fórmula I. Los compuestos y profármacos de fórmula I que son de naturaleza básica son capaces de formar una amplia variedad de sales con varios ácidos inorgánicos y orgánicos. Los ácidos que se pueden usar para preparar sales de adición de ácido farmacéuticamente aceptable de tales compuestos y profármacos básicos de fórmula I son aquellos que forman sales de adición de ácido no tóxico, es decir, sales que contienen aniones farmacológicamente aceptables, tales como las sales de hidrocloruro, hidrobromuro, hidroyoduro, nitrato, sulfato, bisulfato, fostato, fosfato ácido, isonicotinato, acetato, lactato, salicilato, citrato, citrato ácido, tartrato, pantotenato, bitartrato, ascorbato, succinato, maleato, gentisinato, fumarato, gluconato, glucaronato, sacarato, formiato, benzoato, glutamato, metanosulfonato, etanosulfonato, bencenosulfonato, p-toluenosulfonato y pamoato [es decir, 1,1'-metileno-bis(2-hidroxi-3-naftoato)].

Aquellos compuestos y profármacos de las fórmulas I que son de naturaleza ácida, son capaces de formar sales básicas con varios cationes farmacológicamente aceptables. Los ejemplos de tales sales incluyen las sales de metal alcalino o metal alcalinotérreo y particularmente, las sales de sodio y potasio.

Los compuestos de la presente invención pueden tener átomos de carbono asimétrico. Tales mezclas diastereoisómeras se pueden separar en sus diastereoisómeros individuales en base a sus diferencias químicofísicas por métodos conocidos por los expertos en la técnica, por ejemplo, por cromatografía o cristalización fraccionada. Los enantiómeros se pueden separar convirtiendo las mezclas enantiómeras en una mezcla diastereoisómera por reacción con un compuesto ópticamente activo apropiado (por ejemplo, alcohol), separando los diastereoisómeros y convirtiendo (por ejemplo, hidrolizando) los diastereoisómeros individuales en los enantiómeros puros correspondientes. Todos de tales isómeros,

que incluyen las mezclas diastereoisómeras y los enantiómeros puros se consideran parte de la invención.

Los compuestos de la presente invención pueden en ciertos casos existir como tautómeros. Esta invención se refiere al uso de todos de tales tautómeros y sus mezclas.

El término "profármaco", tal como se usa aquí, a menos que se indique lo contrario, quiere decir los compuestos que son precursores del fármaco, que a continuación de su administración, desprenden el fármaco in vivo vía algún proceso químico o fisiológico (por ejemplo, un profármaco al ser llevado al pH fisiológico se convierte en la forma de fármaco deseada).

Los profármacos incluyen compuestos en los que un resto aminoácido, o una cadena de polipéptido, de dos o más (por ejemplo, dos, tres o cuatro) restos aminoácido se unen covalentemente por medio de un enlace amida o éster a un grupo amino, hidroxi o carboxílico libre de los compuestos de fórmula I. Los restos aminoácido incluyen, pero no están limitados a, los 20 aminoácidos naturales comúnmente designados por símbolos de tres letras y también incluyen 4-hidroxiprolina, hidroxilisina, demosina, isodemosina, 3-metilhistidina, norvalina, beta-alanina, ácido gamma-aminobutírico, citrulina, homocisteína, homoserina, ornitina y metioninasulfona. También se incluyen tipos adicionales de profármacos. Por ejemplo, se pueden derivar grupos carboxilo libre como amidas o ésteres de alquilo. Los grupos hidroxi libres se pueden derivar usando grupos que incluyen, pero no están limitados a, hemisuccinatos, ésteres de fosfato, dimetilaminoacetatos, y fosforiloximetiloxicarbonilos, como se describen en Advanced Drug Delivery Reviews, 1996, 19, 115. Los profármacos de carbamato de grupos hidroxi y amino son también incluidos, como lo son los profármacos de carbonato, ésteres de sulfonato y ésteres de sulfato de grupos hidroxi. La derivación de grupos hidroxi como ésteres de (aciloxi)metilo y (aciloxi)etilo en los que el grupo acilo puede ser un éster alquílico, opcionalmente substituido con grupos que incluyen, pero no están limitados a funcionalidades éter, amina y ácido carboxílico, o en los que el grupo acilo es un aminoácido-éster tal como se describe anteriormente, también están incluidos. Los profármacos de este tipo se describen en J. Med. Chem, 1996, 39, 10. Las aminas libres se pueden derivar también como amidas, sulfonamidas o fosfonamidas. Todos estos restos de profármaco pueden incorporar grupos que incluyen, pero no están limitados a, funcionalidades éter, amina y ácido carboxílico.

Se apreciará que cualquier forma de solvato (por ejemplo, hidrato) de los compuestos de fórmula I y sus profármacos se puede usar para los propósitos de la presente invención.

Las expresiones "que comprende" y "que incluye" se usan aquí en su sentido abierto, no limitante.

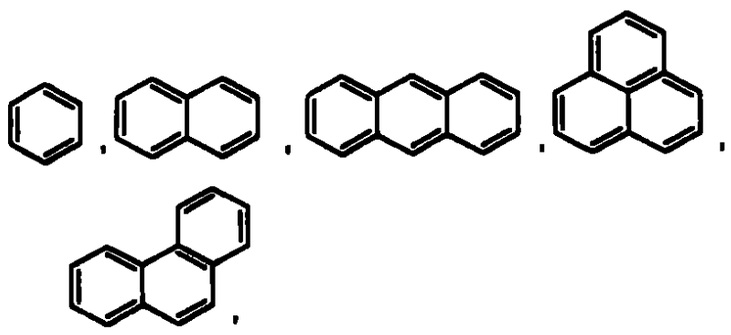
El término "alquilo" tal como se usa aquí se refiere a grupos alquilo de cadena lineal y ramificada que tienen de uno a doce átomos de carbono, preferentemente de 1 a 6 carbonos, y más preferentemente de 1 a 3 carbonos. Los grupos alquilo ejemplares incluyen metilo (Me), etilo, n-propilo, isopropilo, butilo, isobutilo, sec-butilo, terc-butilo (tBu), pentilo, isopentilo, terc-pentilo, hexilo, isohexilo y similares.

El término "heteroalquilo" tal como se usa aquí se refiere a grupos alquilo de cadena lineal y ramificada que contienen uno o más heteroátomos seleccionados de S, O y N.

El término "alquenilo" se refiere a grupos alquenilo de cadena lineal y ramificada que tienen de dos a doce átomos de carbono, preferentemente de 2 a 6 carbonos, y más preferentemente de 2 a 4 carbonos. Los grupos alquenilo ilustrativos incluyen prop-2-enilo, but-2-enilo, but-3-enilo, 2-metilprop-2-enilo, hex-2-enilo, y similares.

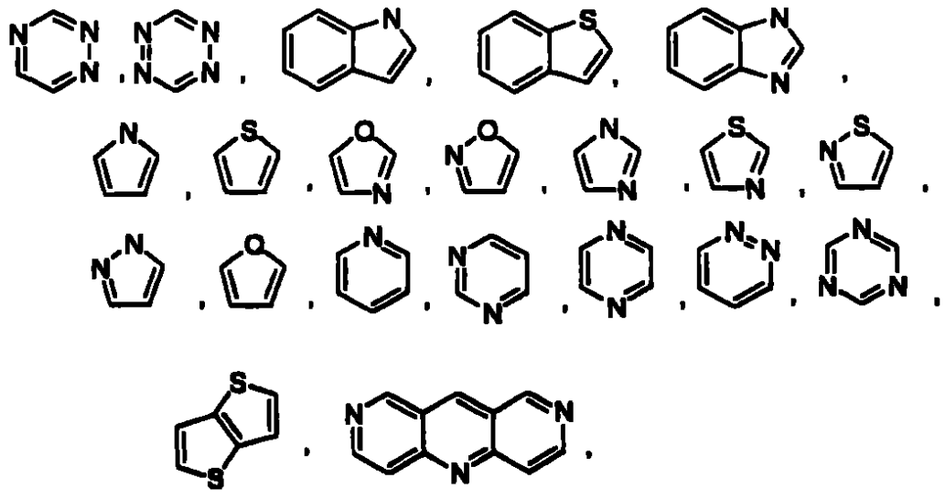
El término "alquinilo" se refiere a grupos alquinilo de cadena lineal y ramificada que tienen de dos a doce átomos de carbono, preferentemente de 2 a 6 carbonos, y más preferentemente de 2 a 4 carbonos. Los grupos alquinilo ilustrativos incluyen prop-2-inilo, but-2-inilo, but-3-inilo, 2-metilbut-2-inilo, hex-2-inilo, y similares.

El término "arilo" (Ar) se refiere a estructuras de anillo aromático monocíclico y policíclico que contienen solo carbono e hidrógeno. Los grupos arilo preferidos tienen de 4 a 20 átomos en el anillo, y más preferentemente de 6 a 14 átomos en el anillo. Los ejemplos ilustrativos de grupos arilo incluyen los siguientes restos:



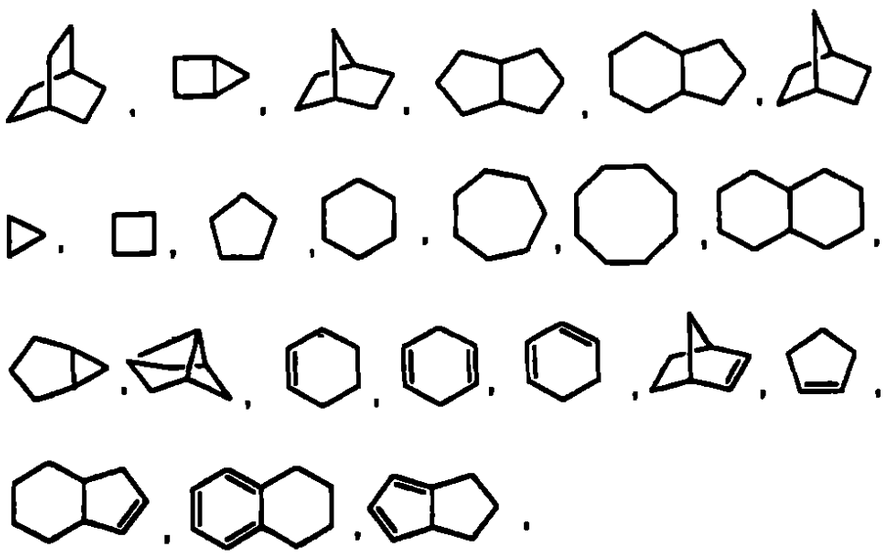
y similares.

El término "heteroarilo" (heteroAr) se refiere a un grupo arilo que incluye uno o más heteroátomos en el anillo seleccionados de nitrógeno, oxígeno y azufre. El grupo heteroarilo policíclico puede ser condensado o no condensado. Los ejemplos ilustrativos de grupos heteroarilo incluyen los siguientes restos:



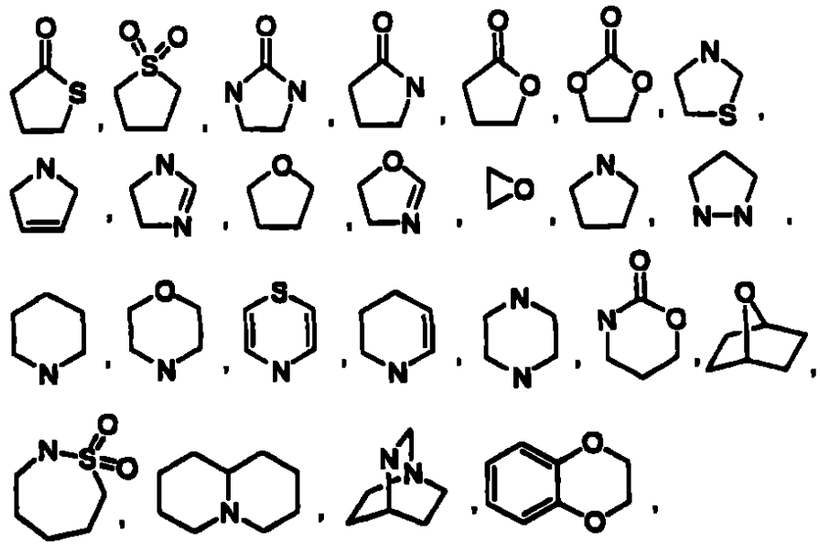
y similares.

El término "cicloalquilo" se refiere a un radical monocíclico o policíclico que contiene solo carbono e hidrógeno, y puede ser saturado, parcialmente insaturado, o totalmente insaturado. Los grupos cicloalquilo preferidos incluyen grupos que tienen de tres a doce átomos en el anillo, más preferentemente de 5 a 10 átomos en el anillo, y aún más preferentemente de 5 a 6 átomos en el anillo. Los ejemplos ilustrativos de grupos cicloalquilo incluyen los siguientes ejemplos:



y compuestos similares.

Un grupo "heterocicloalquilo" se refiere a un grupo cicloalquilo que incluye por lo menos un heteroátomo seleccionado de nitrógeno, oxígeno y azufre. Los radicales se pueden condensar con un arilo o heteroarilo. Los ejemplos ilustrativos o grupos heterocicloalquilo incluyen:



y similares

El término "heterocíclico" comprende tanto los grupos heterocicloalquilo como heteroarilo.

El término "alcoxi" se refiere al radical -O-R en el que R es un alquilo como se define anteriormente. Los ejemplos de grupos alcoxi incluyen metoxi, etoxi, propoxi y similares.

El término "halógeno" representa cloro, flúor, bromo o yodo. El término "halo" representa cloro, fluoro, bromo o yodo.

El término "alcohol" se refiere al radical -R-OH en el que R es alquilo, alquenilo, alquinilo, Ar, heteroarilo, heterocicloalquilo, o cicloalquilo como se define anteriormente. Los ejemplos de alcoholes incluyen metanol, etanol, propanol, fenol, y similares.

El término "acilo" representa -C(O)R, -C(O)OR, -OC(O)R o -OC(O)OR en los que R es alquilo, alquenilo, alquinilo, Ar, heteroarilo, heterocicloalquilo, o cicloalquilo como se define anteriormente.

El término "amida" se refiere al radical -C(O)N(R')(R") en el que R' y R" se seleccionan cada uno independientemente de hidrógeno, alquilo, alquenilo, alquinilo, -OH, alcoxi, cicloalquilo, heterocicloalquilo, heteroarilo, arilo como se define

anteriormente; o R' y R" se ciclan conjuntamente con el nitrógeno para formar un heterocicloalquilo o heteroarilo como se define anteriormente.

El término "substituido" tal como se usa aquí quiere decir que el grupo en cuestión, por ejemplo, grupo alquilo, etc., puede llevar uno o más substituyentes.

Los grupos alquilo, cicloalquilo, arilo, heterocicloalquilo y heteroarilo y los substituyentes que contienen estos grupos, como se define aquí anteriormente, pueden estar opcionalmente substituidos por lo menos con otro substituyente. La expresión "opcionalmente substituido" se desea que indique expresamente que el grupo específico está sin substituir o substituido con uno o más substituyentes como se define anteriormente. Varios grupos pueden estar sin substituir o substituidos (es decir, están opcionalmente substituidos) como se indica.

Si los substituyentes mismos no son compatibles con los métodos sintéticos de esta invención, el substituyente se puede proteger con un grupo protector apropiado que es estable en las condiciones de reacción usadas en estos métodos. El grupo protector se puede retirar en un momento apropiado de la secuencia de reacción del método para proporcionar un intermedio deseado o el compuesto objetivo. Los grupos protectores apropiados y los métodos para proteger y desproteger diferentes substituyentes usando tales grupos protectores apropiados son bien conocidos para los expertos en la técnica, ejemplos de los cuales se pueden encontrar en T. Greene and P. Wuts, Protecting Groups in Chemical Synthesis (3rd de.), John Wiley & Sons, NY (1999), que se incorpora aquí como referencia en su totalidad. En algunos casos, se puede seleccionar que un substituyente sea reactivo en las condiciones de reacción usadas en los métodos de esta invención. En estas circunstancias, las condiciones de reacción convierten el substituyente seleccionado en otro substituyente que es útil como compuesto intermedio en los métodos de esta invención o es un substituyente deseado en un compuesto objetivo.

Algunos de los compuestos de la invención pueden existir en varias formas estereoisómeras o tautómeras. La presente invención incluye todos de tales compuestos inhibidores de la proliferación celular, que incluyen compuestos activos en forma de enantiómeros puros individuales (es decir, esencialmente libres de otros estereoisómeros), racematos, mezclas de enantiómeros, y/o diastereoisómeros, y/o tautómeros. Preferentemente, los compuestos de la invención que son ópticamente activos se usan en forma ópticamente pura.

Como se entiende generalmente por los expertos en la técnica, un compuesto ópticamente puro que tiene un centro quiral (es decir, un átomo de carbono asimétrico)

es uno que consiste esencialmente en uno de los dos posibles enantiómeros (es decir, enantiómeramente puro), y un compuesto ópticamente puro que tiene más de un centro quiral es uno que es tanto diastereoisoméricamente puro como enantioméricamente puro.

Preferentemente, los compuestos de la presente invención se usan en una forma que es por lo menos 90% ópticamente pura, esto es, una forma que contiene por lo menos 90% de un isómero individual (80% de exceso enantiomérico ("e.e") o exceso diastereoisomérico ("d.e"), más preferentemente por lo menos 95% (90% e.e o d.e), incluso más preferentemente por lo menos 97,5% (95% e.e o d.e), y lo más preferentemente por lo menos 99% (98% e.e. o d.e.).

Adicionalmente, se pretende que las fórmulas abarquen las formas solvatadas además de las no solvatadas de las estructuras identificadas. Por ejemplo, la fórmula I incluye compuestos de la estructura indicada tanto en las formas hidratadas como en las no hidratadas. Los ejemplos adicionales de solvatos incluyen las estructuras en combinación con isopropanol, etanol, metanol, DMSO, acetato de etilo, ácido acético o etanolamina.

Además de los compuestos de fórmula I, la invención incluye profármacos farmacéuticamente aceptables, metabolitos farmacéuticamente activos y sales farmacéuticamente aceptables de tales compuestos y metabolitos.

La expresión "farmacéuticamente aceptable" quiere decir farmacológicamente aceptable y sustancialmente no tóxico para el sujeto al que se está administrando el agente.

"Un profármaco farmacéuticamente aceptable" es un compuesto que se puede convertir en condiciones fisiológicas o por solvolisis en el compuesto especificado o en una sal farmacéuticamente aceptable de tal compuesto. "Un metabolito farmacéuticamente activo" se pretende que signifique un producto farmacológicamente activo producido por el metabolismo en el cuerpo de un compuesto especificado o su sal. Los profármacos y los metabolitos activos de un compuesto se pueden identificar usando técnicas rutinarias conocidas en la técnica. Véase, por ejemplo, Bertolini et al., J. Med. Chem. 40, 2011-2016 (1997); Shan et al., J. Pharm. Sci., 86 (7), 765-767; Bagshawe, Drug Dev. Res., 34, 220-230 (1995); Bodor, Advances in Drug Res., 13, 224-331 (1984); Bundgaard, Design of Prodrugs (Elsevier Press 1985); y Larsen, Design and Application of Prodrugs, Drug Design and Development (Krogsgaard-Larsen et al., eds., Harwood Academic Publishers, 1991).

"Una sal farmacéuticamente aceptable" se pretende que signifique una sal que retiene la efectividad biológica de los ácidos y bases libres del compuesto especificado y que no es indeseable biológicamente o de otro modo. Un compuesto de la invención puede poseer un grupo funcional suficientemente ácido, uno suficientemente básico o ambos, y por consiguiente puede reaccionar con cualquiera de varias bases orgánicas o inorgánicas, y ácidos orgánicos o inorgánicos, para formar una sal farmacéuticamente aceptable. Las sales farmacéuticamente aceptables ejemplares incluyen aquellas sales preparadas por reacción de los compuestos de la presente invención con un ácido orgánico o mineral, o una base inorgánica, tales como las sales que incluyen sulfatos, pirosulfatos, bisulfatos, sulfitos, bisulfitos, fosfatos, monohidrogenofosfatos, dihidrogenofosfatos, metafosfatos, pirofosfatos, cloruros, bromuros, yoduros, acetatos, propionatos, decanoatos, caprilatos, acrilatos, formiatos, isobutiratos, caproatos, heptanoatos, propiolatos, oxalatos, malonatos, succinatos, suberatos, sebacatos, fumaratos, maleatos, butino-1,4-dioatos, hexino-1,6-dioatos, benzoatos, clorobenzoatos, metilbenzoatos, dinitrobenzoatos, hidroxibenzoatos, metoxibenzoatos, ftalatos, sulfonatos, xilenosulfonatos, fenilacetatos, fenilpropionatos, fenilbutiratos, citratos, lactatos, γ-hidroxibutiratos, glicolatos, tartratos, metanosulfonatos, propanosulfonatos, naftaleno-1-sulfonatos, naftaleno-2-sulfonatos y mandelatos.

Si el compuesto de la invención es una base, la sal farmacéuticamente aceptable deseada se puede preparar por cualquier método apropiado disponible en la técnica, por ejemplo, tratamiento de la base libre con un ácido inorgánico, tal como ácido clorhídrico, ácido bromhídrico, ácido sulfúrico, ácido sulfámico, ácido nítrico, ácido fosfórico y similares, o con un ácido orgánico, tal como ácido acético, ácido fenilacético, ácido propiónico, ácido esteárico, ácido láctico, ácido ascórbico, ácido maleico, ácido hidroximaleico, ácido isetiónico, ácido succínico, ácido mandélico, ácido fumárico, ácido maiónico, ácido pirúvico, ácido oxálico, ácido glicólico, ácido salicílico, un ácido piranosidílico tal como ácido glucurónico o ácido galacturónico, un alfa-hidroxi-ácido, tal como ácido cítrico o tartárico, un aminoácido, tal como ácido aspártico o ácido glutámico, un ácido aromático tal como ácido benzoico, ácido 2-acetoxibenzoico o ácido cinámico, un ácido sulfónico, tal como ácido p-toluenosulfónico, ácido metanosulfónico o ácido etanosulfónico, o similares.

Si el compuesto de la invención es un ácido, la sal farmacéuticamente aceptable deseada se puede preparar por cualquier método apropiado, por ejemplo, tratamiento del ácido libre con una base orgánica o inorgánica, tal como una amina

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(primaria, secundaria o terciaria), un hidróxido de metal alcalino o un hidróxido de metal alcalinotérreo, o similares. Los ejemplos ilustrativos de sales apropiadas incluyen sales orgánicas derivadas de aminoácidos, tales como glicina y arginina, amoniaco, carbonatos, bicarbonatos, aminas primarias, secundarias y terciarias, y aminas cíclicas, tales como benzilaminas, pirrolidinas, piperidina, morfolina y piperazina, y sales inorgánicas derivadas de sodio, calcio, potasio, magnesio, manganeso, hierro, cobre, cinc, aluminio y litio.

Las composiciones farmacéuticas según la invención pueden, alternativamente o además de un compuesto de Fórmula I, comprender como ingrediente activo profármacos farmacéuticamente activos, metabolitos farmacéuticamente activos, y sales farmacéuticamente aceptables de tales compuestos y metabolitos. Tales compuestos, profármacos, multímeros, sales, y metabolitos se denominan a veces aquí colectivamente "agentes activos" o "agentes".

En el caso de agentes que son sólidos, se entiende por los expertos en la técnica que los compuestos y sales de la invención pueden existir en diferentes formas cristalinas o polimórficas, todas las cuales se pretende que estén dentro del alcance de la presente invención y fórmulas especificadas.

Se pueden usar cantidades terapéuticamente efectivas de los agentes activos de la invención para tratar enfermedades mediadas por la modulación o regulación de proteína quinasas. Una "cantidad efectiva" se pretende que signifique esa cantidad de un agente que inhibe significativamente la proliferación y/o previene la des-diferenciación de una célula eucariota, por ejemplo, una célula de un mamífero, insecto, planta u hongo, y es efectiva para la utilidad indicada, por ejemplo, el tratamiento terapéutico específico.

La cantidad de un agente dado que corresponderá a tal cantidad variará dependiendo de factores tales como el compuesto particular, estado de la enfermedad y su severidad, la identidad (por ejemplo, peso) del sujeto u hospedante que necesita el tratamiento, pero sin embargo se puede determinar rutinariamente de una manera conocida en la técnica según las circunstancias particulares que rodean el caso, que incluyen, por ejemplo, el agente específico que se está administrando, la ruta de administración, el estado que se está tratando, y el sujeto u hospedante que se está tratando. "Tratar" se pretende que signifique por lo menos la mitigación de un estado de enfermedad en un sujeto tal como un mamífero (por ejemplo, un ser humano), que está afectado, por lo menos en parte, por la actividad de una o más quinasas, por ejemplo proteína quinasas, tales como tirosina quinasas, e incluye: prevenir que ocurra

el estado de enfermedad en un mamífero, particularmente cuando se encuentra que el mamífero está predispuesto a tener el estado de enfermedad pero aún no se ha diagnosticado que la tenga; modular y/o inhibir el estado de enfermedad; y/o aliviar el estado de enfermedad.

Son preferidos los agentes que regulan, modulan o inhiben potentemente la proliferación celular. Para ciertos mecanismos se prefiere la inhibición de la actividad de la proteína quinasa asociada a los complejos CDK, entre otras, y los que inhiben la angiogénesis y/o la inflamación. La presente invención se refiere adicionalmente a métodos de modular o inhibir la actividad de la proteína quinasa, por ejemplo, en tejido de mamífero, administrando un compuesto de la invención. La actividad de los agentes como antiproliferativos se mide fácilmente por métodos conocidos, por ejemplo, usando cultivos de células enteras en un ensayo MTT. La actividad de los agentes de la invención como moduladores de la actividad de la proteína quinasa, tal como la actividad de las quinasas, se puede medir por cualquiera de los métodos disponibles para los expertos en la técnica, que incluyen ensayos in vivo y/o in vitro. Los ejemplos de ensayos apropiados para las medidas de actividad incluyen los descritos en International Publication No. WO 99/21845; Parast et al., Biochemistry, 37 16788-16801 (1988); Connell-Crowley and Harpes, Cell Cycle: Materials and Methods, (Michele Pagano, de. Springer, Berlin, Germany) (1995); International Publication No. WO 97/34876; e International Publication No. WO 96/14843. Estas propiedades se pueden verificar, por ejemplo, usando uno o más de los procedimientos de ensayo biológico descritos en los ejemplos a continuación.

Los agentes activos de la invención se pueden formular en composiciones farmacéuticas como se describe a continuación. Las composiciones farmacéuticas de esta invención comprenden una cantidad inhibidora, reguladora o moduladora efectiva de un compuesto de Fórmula I o Fórmula II y un vehículo o diluyente inerte farmacéuticamente aceptable. En una realización de las composiciones farmacéuticas, se proporcionan concentraciones eficaces de los agentes de la invención para proporcionar beneficios terapéuticos que implican capacidad antiproliferativa. Por "concentraciones eficaces" se entiende concentraciones en las que se inhibe o controla la proliferación. Estas composiciones se preparan en forma de dosificación unitaria apropiada para el modo de administración, por ejemplo, administración parenteral u oral.

Un agente de la invención se puede administrar en forma de dosificación convencional preparada combinando una cantidad terapéuticamente efectiva de un

agente (por ejemplo, un compuesto de Fórmula I) como ingrediente activo con vehículos o diluyentes farmacéuticamente apropiados según procedimientos convencionales. Estos procedimientos pueden implicar mezclar, granular y comprimir o disolver los ingredientes según sea apropiado para la preparación deseada.

El vehículo farmacéutico apropiado puede ser un sólido o líquido. Los vehículos sólidos ejemplares son lactosa, sacarosa, talco, gelatina, agar, pectina, acacia, estearato de magnesio, ácido esteárico y similares. Los vehículos líquidos ejemplares son jarabe, aceite de cacahuete, aceite de oliva, agua y similares. Similarmente, el vehículo o diluyente puede incluir material de retardo o de desprendimiento en el tiempo conocido en la técnica, tal como monoestearato de glicerilo o diestearato de glicerilo solos o con una cera, etilcelulosa, hidroxipropilcelulosa, metacrilato de metilo y similares.

Se pueden emplear varias formas farmacéuticas. De este modo, si se usa un vehículo sólido, la preparación se puede comprimir, colocar en una cápsula de gelatina dura en forma de polvo o pelet o en forma de un trocisco o pastilla romboédrica. La cantidad de vehículo sólido puede variar, pero generalmente será de alrededor de 25 mg a alrededor de 1 g. Si se usa un vehículo líquido, la preparación será en forma de jarabe, emulsión, cápsula de gelatina blanda, disolución o suspensión inyectable estéril en una ampolla o vial o suspensión líquida no acuosa.

Para obtener una forma estable de dosis soluble en agua, una sal farmacéuticamente aceptable de un agente de la invención se puede disolver en una disolución acuosa de un ácido orgánico o inorgánico, tal como disolución 0,3 M de ácido succínico o ácido cítrico. Si no está disponible una forma de sal soluble, el agente se puede disolver en un codisolvente apropiado o en combinaciones de codisolventes. Los ejemplos de codisolventes apropiados incluyen, pero no están limitados a, alcohol, propilenglicol, polietilenglicol 300, polisorbato 80, glicerina y similares en concentraciones que varían de 0-60% del volumen total. En una realización ejemplar, se disuelve un compuesto de Fórmula I en DMSO y se diluye con agua. La composición puede estar también en la forma de una disolución de una forma de sal del ingrediente activo en un vehículo acuoso apropiado tal como agua o disolución salina isotónica o disolución de dextrosa.

Se apreciará que las dosificaciones reales de los agentes usados en las composiciones de esta invención variarán según el complejo particular que se va a usar, la composición particular formulada, el modo de administración, y el sitio, hospedante y enfermedad particular que se va a tratar. Las dosificaciones óptimas

para un conjunto dado de estados se pueden verificar por los expertos en la técnica usando ensayos convencionales de determinación de la dosificación en vista de los datos experimentales para un agente. Para la administración oral, una dosis diaria ejemplar empleada es de alrededor de 0,001 a alrededor de 1000 mg/kg de peso corporal, con secuencias de tratamiento repetido a intervalos apropiados. La administración de profármacos está típicamente dosificada a concentraciones en peso que son químicamente equivalentes a las concentraciones en peso de la forma activa completa.

Las composiciones de la invención se pueden fabricar de maneras generalmente conocidas para preparar composiciones farmacéuticas, por ejemplo, usando técnicas convencionales tales como mezclar, disolver, granular, fabricar grageas, levigar, emulsionar, encapsular, inmovilizar o liofilizar. Las composiciones farmacéuticas se pueden formular de una manera convencional usando uno o más vehículos fisiológicamente aceptables, que se pueden seleccionar de excipientes y compuestos auxiliares que facilitan el procesado de los compuestos activos en forma de preparaciones que se pueden usar farmacéuticamente.

La formulación apropiada depende de la ruta de administración escogida. Para inyección, los agentes de la invención se pueden formular en disoluciones acuosas, preferentemente en tampones fisiológicamente compatibles tales como la disolución de Hank, disolución de Ringer, o tampón salino fisiológico. Para la administración transmucosa, se usan en la formulación penetrantes apropiados para la barrera que se va a permear. Tales penetrantes son generalmente conocidos en la técnica.

Para la administración oral, los compuestos se pueden formular fácilmente combinando los compuestos con vehículos farmacéuticamente aceptables conocidos en la técnica. Tales vehículos permiten que los compuestos de la invención se formulen en forma de comprimidos, píldoras, grageas, cápsulas, líquidos, geles, jarabes, suspensiones y similares, para la ingestión por parte de un paciente que se va tratar. Las preparaciones farmacéuticas para uso oral se pueden obtener usando un excipiente sólido mezclado con el ingrediente activo (agente), moliendo opcionalmente la mezcla resultante, y procesando la mezcla de gránulos después de añadir compuestos auxiliares apropiados, si se desea, para obtener comprimidos o núcleos de grageas. Los excipientes apropiados incluyen: cargas tales como azúcares, que incluyen lactosa, sacarosa, manitol, o sorbitol; y preparaciones de celulosa, por ejemplo, almidón de maíz, almidón de trigo, almidón de arroz, almidón de patata, gelatina, goma, metilcelulosa, hidroxipropilmetilcelulosa, carboximetilcelulosa de sodio,

o polivinilpirrolidona (PVP). Si se desea, se pueden añadir agentes desintegrantes, tales como polivinilpirrolidona reticulada, agar, o ácido algínico o una de sus sales tales como alginato de sodio.

Se proporcionan revestimientos apropiados a los núcleos de grageа. Para este propósito, se pueden usar disoluciones concentradas de azúcar, que pueden opcionalmente contener goma arábiga, polivinilpirrolidona, gel Carbopol, polietilenglicol, y/o dióxido de titanio, disoluciones de laca, y disolventes orgánicos apropiados o mezclas disolventes. Se pueden añadir colorantes o pigmentos a los comprimidos o revestimientos de grageas para su identificación o para caracterizar diferentes combinaciones de agentes.

Las preparaciones farmacéuticas que se pueden usar oralmente incluyen cápsulas push-fit de gelatina, además de cápsulas selladas blandas hechas de gelatina y un plastificante, tal como glicerol o sorbitol. Las cápsulas push-fit pueden contener los agentes mezclados con cargas tales como lactosa, aglomerantes tales como almidones, y/o lubricantes tales como talco o estearato de magnesio, y, opcionalmente, estabilizantes. En las cápsulas blandas, los agentes pueden estar disueltos o suspendidos en líquidos apropiados, tales como aceites grasos, parafina líquida, o polietilenglicoles líquidos. Además, se pueden añadir estabilizantes. Todas las formulaciones para la administración oral deben estar en dosis apropiadas para tal administración. Para la administración bucal, las composiciones toman la forma de comprimidos o pastillas romboédricas formuladas de maneras convencionales.

Para la administración intranasal o para inhalación, los compuestos para su uso según la presente invención se suministran convenientemente en forma de una presentación de pulverización de aerosol en envases presurizados o en un nebulizador, con el uso de un propulsor apropiado, por ejemplo, diclorodifluorometano, triclorofluorometano, diclorotetrafluoroetano, dióxido de carbono u otro gas apropiado. En el caso de un aerosol presurizado la unidad de dosificación se puede determinar proporcionando una válvula para suministrar una cantidad medida. Se pueden formular cápsulas y cartuchos de gelatina para su uso en un inhalador o insuflador y similares que contienen una mezcla de polvo del compuesto y una base de polvo apropiada tal como lactosa o almidón.

Los compuestos se pueden formular para la administración parenteral por inyección, por ejemplo, por inyección de bolus o infusión continua. Las formulaciones para inyección se pueden presentar en forma de dosificación unitaria, por ejemplo, en ampollas o en recipientes multidosis, con un conservante añadido. Las composiciones

pueden tener tales formas como suspensiones, disoluciones o emulsiones en vehículos acuosos o aceitosos, y pueden contener agentes de formulación tales como agentes suspensores, estabilizantes y/o dispersantes.

Las formulaciones farmacéuticas para administración la parenteral incluyen disoluciones acuosas de los agentes en forma soluble en agua. Adicionalmente, se pueden preparar suspensiones de los agentes tales como suspensiones para inyección aceitosas apropiadas. Los disolventes o vehículos lipófilos apropiados incluyen aceites grasos tales como aceite de sésamo, o ésteres de ácidos grasos sintéticos, tales como oleato de etilo o triglicéridos, o liposomas. Las suspensiones acuosas para inyección pueden contener substancias que incrementan la viscosidad de la suspensión, tales como carboximetilcelulosa de sodio, sorbitol o dextran. Opcionalmente, la suspensión puede contener también estabilizantes apropiados o agentes que incrementan la solubilidad de los compuestos para permitir la preparación de disoluciones altamente concentradas.

Para la administración en los ojos, el agente se suministra en un vehículo oftálmico farmacéuticamente aceptable de tal modo que el compuesto se mantiene en contacto con la superficie ocular durante un periodo de tiempo suficiente para permitir que el compuesto penetre en la córnea y regiones internas del ojo, por ejemplo, la cámara anterior, cámara posterior, cuerpo vítreo, humor acuoso, humor vítreo, córnea, iris/ciliar, cristalino, coroides/retina y esclerótica. El vehículo oftálmico farmacéuticamente aceptable puede ser una pomada, aceite vegetal, o un material de encapsulación. Un compuesto de la invención se puede inyectar también directamente dentro del humor vítreo y acuoso.

Alternativamente, los agentes pueden estar en forma de polvo para su constitución con un vehículo apropiado, por ejemplo, agua estéril libre de pirógenos, antes de su uso. Los compuestos también se pueden formular en composiciones rectales tales como supositorios o enemas de retención, por ejemplo, que contienen bases de supositorio convencionales tales como manteca de cacao u otros glicéridos.

Además de las formulaciones descritas anteriormente, los agentes se pueden formular también como una preparación de almacenamiento. Tales formulaciones de larga duración se pueden administrar por implantación (por ejemplo, subcutáneamente o intramuscularmente) o por inyección intramuscular. De este modo, por ejemplo, los compuestos se pueden formular con materiales hidrófobos o poliméricos apropiados (por ejemplo, en forma de emulsión en un aceite aceptable) o resinas de intercambio

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iónico, o como derivados escasamente solubles, por ejemplo, en forma de sal escasamente soluble.

Un vehículo farmacéutico ejemplar para compuestos hidrófobos es un sistema codisolvente que comprende alcohol bencílico, un tensioactivo no polar, un polímero orgánico miscible en agua, y una fase acuosa. El sistema codisolvente puede ser un sistema codisolvente VPD. El VPD es una disolución de 3% peso/v de alcohol bencílico, 8% peso/v del tensioactivo no polar polisorbato 80, y 65% peso/v de polietilenglicol 300, completado hasta el volumen total con etanol absoluto. El sistema codisolvente VPD (VPD:5W) contiene VPD diluido 1:1 con dextrosa al 5% en disolución acuosa. Este sistema codisolvente disuelve bien los compuestos hidrófobos, y él mismo produce baja toxicidad en la administración sistémica. Naturalmente, las proporciones del sistema codisolvente se pueden variar considerablemente sin destruir sus características de solubilidad y toxicidad. Además, la identidad de los componentes codisolventes se puede variar: por ejemplo, se pueden usar en lugar de polisorbato 80 otros tensioactivos no polares de baja toxicidad; se puede variar el tamaño de la fracción del polietilenglicol; otros polímeros biocompatibles pueden reemplazar al polietilenglicol, por ejemplo, polivinilpirrolidona; y otros azúcares o polisacáridos pueden substituir a la dextrosa.

Alternativamente, se pueden emplear otros sistemas de suministro para los compuestos farmacéuticos hidrófobos. Los liposomas y emulsiones son ejemplos conocidos de vehículos de suministro o portadores para fármacos hidrófobos. También se pueden emplear ciertos disolventes orgánicos tales como dimetilsulfóxido, aunque usualmente con el coste de mayor toxicidad. Adicionalmente, los compuestos se pueden suministrar usando un sistema de desprendimiento sostenido, tales como matrices semipermeables de polímeros hidrófobos sólidos que contienen el agente terapéutico. Se han establecido varios materiales de desprendimiento sostenido y son conocidos por los expertos en la técnica. Las cápsulas de desprendimiento sostenido pueden, dependiendo de su naturaleza química, desprender los productos desde durante unas pocas semanas hasta alrededor de 100 días. Dependiendo de la naturaleza química y la estabilidad biológica del reactivo terapéutico, se pueden emplear estrategias adicionales para la estabilización de proteínas.

Las composiciones farmacéuticas pueden comprender también vehículos o excipientes apropiados en fase sólido o gel. Los ejemplos de tales vehículos o excipientes incluyen carbonato de calcio, fosfato de calcio, azúcares, almidones, derivados de celulosa, gelatina, y polímeros tales como polietilenglicoles.

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Algunos de los compuestos de la invención se pueden proporcionar en forma de sales con contraiones farmacéuticamente compatibles. Se puede formar sales farmacéuticamente compatibles con muchos ácidos, que incluyen clorhídrico, sulfúrico, acético, láctico, tartárico, málico, succínico, etc. Las sales tienden a ser más solubles en disolventes acuosos u otros disolventes protónicos de lo que lo son las formas de base libre correspondientes.

Los agentes de la invención pueden ser útiles en combinación con conocidos tratamientos anticáncer tales como: agentes interactivos con el ADN tales como cisplatina o doxorubicina; inhibidores de la topoisomerasa II tales como etopóxido; inhibidores de la topoisomerasa I tales como CPT-11 o topotecan; agentes que interaccionan con la tubulina tales como paclitaxel, docetaxel o las epotilonas; agentes hormonales tales como tamoxifen; inhibidores de la timidilato sintasa tales como 5-fluoracilo; y antimetabolitos tales como metotrexato. Se pueden administrar conjuntamente o secuencialmente, y cuando se administran secuencialmente, los agentes se pueden administrar previamente o después de la administración del agente anticáncer o citotóxico conocido.

Los agentes se pueden preparar usando las rutas de reacción y esquemas de síntesis tal como se describe a continuación, empleando las técnicas generales conocidas en la técnica usando materiales de partida que están fácilmente disponibles. La preparación de los compuestos preferidos de la presente invención se describe con detalle en los siguientes ejemplos, pero el experto reconocerá que las reacciones químicas descritas se pueden adaptar fácilmente para preparar varios otros antiproliferativos o inhibidores de la proteína quinasa de la invención. Por ejemplo, la síntesis de compuestos no ejemplificados según la invención se puede realizar con éxito por modificaciones evidentes para los expertos en la técnica, por ejemplo, protegiendo apropiadamente los grupos que interfieren, cambiando a otros reactivos apropiados conocidos en la técnica, o haciendo modificaciones rutinarias de las condiciones de reacción. Alternativamente, se reconocerá que otras reacciones descritas aquí o generalmente conocidas en la técnica tienen aplicabilidad para preparar otros compuestos de la invención.

DESCRIPCION DETALLADA DE LA INVENCION

EJEMPLOS

En los ejemplos descritos a continuación, a menos que se indique lo contrario, todas las temperaturas se dan en grados Celsius y todas las partes y porcentajes están en peso. Los reactivos se compraron de suministradores tales como Aldrich

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Chemical Company o Lancaster Synthesis Ltd. y se usaron sin purificación adicional a menos que se indique lo contrario. Tetrahidrofurano (THF), N,N-dimetilformamida (DMF), diclorometano, tolueno y dioxano se compraron de Aldrich en botellas Sure Seal y se usaron tal como se recibieron. Todos los disolventes se purificaron usando métodos estándar fácilmente conocidos por los expertos en la técnica, a menos que se indique lo contrario.

Las reacciones descritas a continuación se realizaron generalmente bajo presión positiva de argón o nitrógeno o con un tubo de secado, a temperatura ambiente (a menos que se afirme lo contrario), en disolventes anhidros, y los matraces de reacción estaban provistos de septos de caucho para la introducción de substratos y reactivos vía una jeringa. El material de vidrio se secó en el horno y/o se secó con calor. Se realizó cromatografía analítica en capa fina (TLC) en placas de gel de sílice con refuerzo de vidrio Analtech 60 F 254 (0,25 mm) y se eluyó con las relaciones de disolventes apropiadas (v/v), y se citan cuando es apropiado. Las reacciones se verificaron por TLC y terminaron tal como se juzgó por el consumo de material de partida.

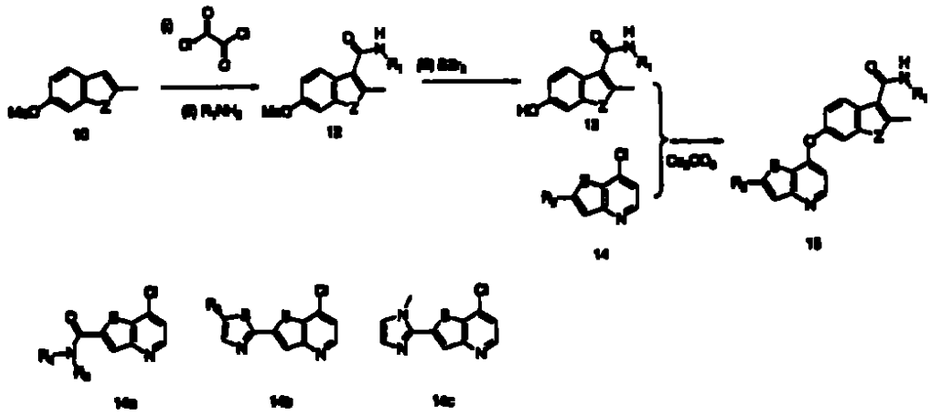
La visualización de las placas de TLC se realizó con un agente de pulverización de p-anisaldehído o reactivo de ácido fosfomolíbdico (Aldrich Chemical, al 20% en peso en etanol) y se activó con calor. Los tratamientos se realizaron típicamente doblando el volumen de reacción con el disolvente de reacción o disolvente de extracción y a continuación lavando con las disoluciones acuosas indicadas usando el 25% en volumen del volumen de extracción a menos que se indique lo contrario. Las disoluciones del producto se secaron sobre Na_2SO_4 previamente a la filtración y evaporación de los disolventes a presión reducida o en evaporador rotatorio y se citan como disolventes retirados a vacío. Se realizó cromatografía flash en columna (Still et al., J. Org. Chem. 43, 2923 (1978)) usando gel de sílice de flash de grado Baker (47-61 μm) y una relación gel de sílice/material en bruto de alrededor de 20:1 a 50:1, a menos que se afirme lo contrario. La hidrogenolisis se realizó a la presión indicada en los ejemplos o a presión atmosférica.

Los espectros ^1H RMN se registraron en un instrumento Bruker funcionando a 300 MHz y los espectros ^{13}C RMN se registraron funcionando a 75 MHz. Los espectros de RMN se obtuvieron en forma de disoluciones de $CDCl_3$ (dadas en ppm), usando cloroformo como estándar de referencia (7,25 ppm y 77,00 ppm) o CD_3OD (3,4 y 4,8 ppm y 49,3 ppm), o internamente tetrametilsilano (0,00 ppm) cuando era apropiado. Se usaron otros disolventes para RMN cuando fue necesario. Cuando se

dan multiplicidades de los picos, se usan las siguientes abreviaturas: s (singlete), d (doblete), t (triplete), m (multiplete), br (ensanchado), dd (doblete de dobletes), dt (doblete de tripletes). Las constantes de acoplamiento, cuando se dan, se dan en Hercios (Hz).

Se registraron espectros de infrarrojo (IR) en un espectrofotómetro de infrarrojos Perkin-Elmer FT-IR en forma de aceites puros, en forma de pelets en KBR, o en forma de disoluciones de $CDCl_3$, y cuando se dan, se dan en números de onda (cm^{-1}). Los espectros de masas se obtuvieron usando LSIMS o electroespray. Todos los puntos de fusión (p.f.) están sin corregir.

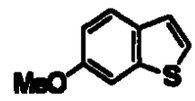
En un procedimiento sintético general, se preparan compuestos de Fórmula I según el siguiente esquema de reacción:



El 6-metoxi-2-metilbenzo[2]tiofeno o el correspondiente benzofurano (compuesto 10), que son conocidos en la bibliografía, se acilan con cloruro de oxalilo en presencia de tricloruro de aluminio. El tratamiento del cloruro de ácido resultante con un exceso de la amina apropiada, por ejemplo, metilamina, proporciona el derivado de amida requerido de fórmula 12. La desmetilación con un reactivo apropiado, tal como tribromuro de boro, da compuestos de fórmula 13. Los compuestos de fórmula 13 y 14 se combinan calentándolos con una base, preferentemente Cs_2CO_3, en un disolvente tal como DMSO, DMF o acetonitrilo para formar los compuestos de Formula 15. Alternativamente a usar los compuestos de fórmulas 14 a, 14b y 14 c, se pueden usar los compuestos de fórmula 14 en la que R_2 es un ácido carboxílico en la reacción de copulación que genera los compuestos de fórmula 15. La formación de la amida sería entonces la etapa final.

Los análogos de indol se pueden fabricar de un modo similar como se describe anteriormente para los benzofuranos y benzotiofenos.

Ejemplo 1(a): 6-metoxibenzo[b]tiofeno



Una mezcla de 3-metoxibencenotiol (10 ml, 11,30 g, 80 mmol), K_2CO_3 (11,5 g, 80 mmol) y acetal dietílico de bromoacetaldehido (12 ml, 15,72 g, 80 mmol) en acetona (100 ml) se agitó a temperatura ambiente durante 16 horas, a continuación se filtró. El filtrado se concentró subsecuentemente a vacío. El residuo obtenido se repartió entre H_2O (150 ml) y Et_2O (150 ml). Las capas se separaron y se extrajo la capa acuosa con Et_2O (150 ml). Los extractos orgánicos combinados se lavaron con KOH acuoso 0,5 M, H_2O y salmuera, a continuación se secaron sobre Na_2SO_4 y se concentraron a vacío, para dar 20,4 g de un aceite ámbar que se usó directamente en la ciclación subsecuente sin ninguna purificación adicional.

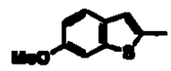
Método A: Una disolución de este 1-(2,2-dietoxietilsulfanil)-3-metoxibenceno (6,41 g, 25 mmol) en bruto en CH_2Cl_2 (50 ml) se añadió gota a gota a una disolución de eterato de trifluoruro de boro (3,4 ml, 3,81 g, 27 mmol) en CH_2Cl_2 (500 ml). La disolución resultante se agitó a temperatura ambiente durante unos 30 minutos adicionales. Se añadió $NaHCO_3$ (200 ml) acuoso saturado y la mezcla de dos fases se agitó durante otra hora. Las capas se separaron y la fase acuosa se extrajo con CH_2Cl_2 (150 ml). Los extractos orgánicos combinados se secaron sobre Na_2SO_4 y se concentraron a vacío para dar 4,3 g de un aceite rojo que se purificó por cromatografía en gel de sílice. La elución con hexano:Et_2O (98:2) y la evaporación de las fracciones apropiadas dio 1,62 g (39%) de un aceite incoloro.

Método B: Una disolución de 1-(2,2-dietoxietisulfanil)-3-metoxibenceno (8,27 g, 32,3 mmol) en bruto en hexano (100 ml) se añadió gota a gota a una disolución de ácido metanosulfónico (1,05 ml, 1,55 g, 16,1 mmol) en hexano (1000 ml) que contiene 16,5 g de celite (2 eq. en peso). La disolución resultante se calentó a reflujo durante una hora. Después de enfriar hasta temperatura ambiente, la reacción se enfrió rápidamente por adición de Et_3N (4,5 ml, 3,26 g, 32,3 mmol). La mezcla de reacción en bruto se filtró y el filtrado se concentró a vacío para dar un aceite rojo que se purificó por cromatografía en gel de sílice. La elución con hexano:Et_2O (98:2) y la evaporación

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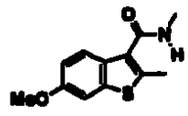
de las fracciones apropiadas dio 3,35 g (63%) de un aceite incoloro. ^{1}H RMN (DMSO-d_6) δ 7,74 (1H, d, J=8,7 Hz), 7,56 (1H, d, J=2,3 Hz), 7,52 (1H, d, J=5,3 Hz), 7,33 (1H, d, J=5,3 Hz), 6,99 (1H, dd, J=2,3, 8,7 Hz), 3,81 (3H, s), Análisis. Calculado para C_9H_8OS: C, 65, 82,; H, 4,91; S, 19,53. Encontrado: C, 66,01; H, 5,00; S, 19,40.

Ejemplo 1(b): 6-metoxi-2-metilbenzo[b]tiofeno



Una disolución 2,5 M de n-butillitio en hexanos (20 ml, 50 mmol) se añadió en argón a una disolución de 6-metoxibenzo[b]tiofeno 1 a (3,68 g, 22,4 mmol) en THF (150 ml) a -75°C. Después de agitar a -75°C durante unos 30 minutos adicionales, se cambió el baño de refrigeración y se calentó la reacción hasta -10°C previamente a la adición de CH_3I (4,2 ml, 9,58 g, 67 mmol). La mezcla resultante se agitó a 0°C durante unos 30 minutos adicionales, a continuación se dejó calentar gradualmente hasta temperatura ambiente antes de diluir con $NaHCO_3$ saturado (150 ml). Las capas se separaron y la fase acuosa se extrajo con EtOAc (2 x 100 ml). Los extractos orgánicos combinados se secaron sobre Na_2SO_4 y se concentraron a vacío para dar 4,2 g de un aceite ámbar que se purificó por cromatografía en gel de sílice. La elución con hexano:Et_2O (98:2) y la evaporación de las fracciones apropiadas dio 3,63 g (91%) de un aceite incoloro. ^{1}H RMN (DMSO-d_6) δ 7,57 (1H, d, J=8,7 Hz), 7,43 (1H, d, J=2,4 Hz), 6,99 (1H, s), 6,92 (1H, dd, J=2,4, 8,7 Hz), 3,78 (3H, s), 2,50 (3H, s), Análisis. Calculado para $C_{10}H_{10}OS$: C, 67,38; H, 5,66; S, 17,99. Encontrado: C, 67,42; H, 5,74; S, 17,87.

Ejemplo 1(c): metilamida del ácido 6-metoxi-2-metilbenzo[b]tiofeno-3-carboxílico.

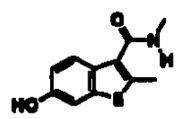


Una disolución 2,0 M de cloruro de oxalilo en CH_2Cl_2 (10 ml, 20 mmol) se añadió a una suspensión de $AlCl_3$ (2,69 g, 20 mmol) en CH_2Cl_2 (20 ml) a 0°C. Después de agitar a 0°C durante unos 30 minutos adicionales, se añadió una disolución de 6-metoxi-2-metilbenzo[b]tiofeno 1 b (725 mg, 4,1 mmol) en CH_2Cl_2 (40 ml) en un intervalo de 10 minutos. Se retiró el baño de enfriamiento y la reacción se agitó a temperatura ambiente durante 3 horas previamente a la adición de hielo picado (50

ml). Las capas se separaron y la fase acuosa se extrajo con CH_2Cl_2 (3 x 50 ml). Los extractos orgánicos combinados se secaron sobre Na_2SO_4 y se concentraron a vacío para dar 950 mg de una resina ámbar que se empleó sin purificación adicional.

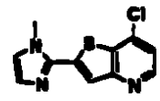
Una disolución de este cloruro de 6-metoxi-2-metilbenzo[b]tiofeno-3-carbonilo en bruto en THF (50 ml) se combinó con una disolución 2,0 M de CH_3NH_2 en THF (20 ml, 40 mmol). La mezcla de reacción resultante se agitó a temperatura ambiente durante 3 horas. El disolvente se retiró por concentración a vacío y el residuo obtenido se repartió entre H_2O (50 ml) y CH_2Cl_2 (50 ml). Las capas se separaron y la fase acuosa se extrajo con CH_2Cl_2 (2 x 30 ml). Los extractos orgánicos combinados se secaron sobre Na_2SO_4 y se concentraron a vacío para dar 0,8 g de un sólido ámbar que se purificó por cromatografía en gel de sílice. La elución con CH_2Cl_2:EtOAc (80:20) y la evaporación de las fracciones apropiadas dio 693 mg (72%) de un sólido blancuzco. ^{1}H RMN (DMSO-d_6) δ 8,15 (1H, q, J=4,6 Hz), 7,62 (1H, d, J=8,9 Hz), 7,47 (1H, d, J=2,4 Hz), 6,97 (1H, dd, J=2,4, 8,9 Hz), 3,79 (3H, s), 2,80 (3H, d, J=4,6 Hz), 2,53 (3H, s). Análisis. Calculado para $C_{12}H_{13}NO_2S$: C, 61,25; H, 5,57; N, 5,95; S, 13,63. Encontrado: C, 60,97; H, 5,56; N, 5,85; S, 13, 44.

Ejemplo 1(d): metilamida del ácido 6-hidroxi-2-metilbenzo[b]tiofeno-3-carboxílico.



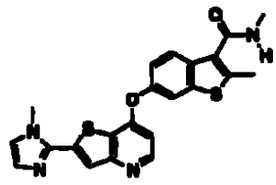
Una disolución 1,0 M de BBr_3 en CH_2Cl_2 (6 ml, 6 mmol) se añadió a una disolución de metilamida del ácido 6-metoxi-2-metilbenzo[b]tiofeno-3-carboxílico 1 c (683 mg, 2,9 mmol) en CH_2Cl_2 (60 ml) a 0°C. La reacción se dejó agitando durante 14 horas, calentando gradualmente hasta temperatura ambiente, a continuación se vertió sobre hielo triturado (~70 g). Las capas se separaron y la fase acuosa se extrajo con EtOAc (2 x 50 ml). Los extractos orgánicos combinados se secaron sobre Na_2SO_4 y se concentraron a vacío para dar 623 mg (97%) de un sólido beis que se empleó sin purificación adicional. ^{1}H RMN (DMSO-d_6) δ 9,56 (1H, s), 8,11 (1H, q, J=4,4 Hz), 7,53 (1H, d, J=8,7 Hz), 7,18 (1H, d, J=2,3 Hz), 6,83 (1H, dd, J=2,3, 8,7 Hz), 2,79 (3H, d, J=4,4 Hz), 2,50 (3H, s).

Ejemplo 1(e): 7-cloro-2-(1-metil-1H-imidazol-2-il)tieno[2,3-b]piridina.



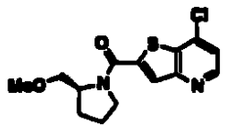
El compuesto del título se preparó por el método descrito en la solicitud PCT WO-99/24440, Ejemplo 149; incorporada aquí como referencia.

Ejemplo 1: metilamida del ácido 2-metil-6-[2-(1-metil-1H-imidazol-2-il]tieno[3,2-b]piridin-7-iloxi)benzo[b]tiofeno-3-carboxílico.



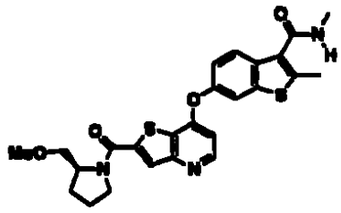
Una disolución de 7-cloro-2-(1-metil-1H-imidazol-2-il)tieno[3,2-b]piridina 1 e (100 mg, 0,4 mmol) y metilamida del ácido 6-hidroxi-2-metilbenzo[b]tiofeno-3-carboxílico 1 d (133 mg, 0,6 mmol) en DMSO (10 ml) se purgó con argón durante minutos a temperatura ambiente previamente a la adición de Cs_2CO_3 recientemente molido (651 mg, 2 mmol). La mezcla de reacción resultante se calentó a 110°C durante 2 horas. Después de enfriar hasta temperatura ambiente, la mezcla de reacción en bruto se vertió en agua fría (60 ml). El precipitado que se formó se recogió por filtración y se purificó por cromatografía en gel de sílice. La elución con CH_2Cl_2:CH_3OH (95:5) y la evaporación de las fracciones apropiadas dio 69 mg (40%) de un sólido blancuzco. ^{1}H RMN (DMSO-d_6): δ 8,52 (1H, d, J=5,4 Hz), 8,29 (1H, q, J=4,6 Hz), 7,95 (1H, d, J=2,3 Hz), 7,88 (1H, s), 7,85 (1H, d, J=8,8 Hz), 7,40 (1H, d, J=0,8 Hz), 7,32 (1H, dd, J=2,3, 8,8 Hz), 7,02 (1H, d, J=0,8 Hz), 6,70 (1H, d, J=5,4 Hz), 3,98 (3H, s), 2,83 (3H, d, J=4,6 Hz), 2,60 (3H, s). Análisis. Calculado para $C_{22}H_{18}N_4O_2S_2$. 0,3 CH_2Cl_2.0,2 CH_3OH: C, 57,94; H, 4,19; N, 12,01. Encontrado: C, 57,67; H, 4,13; N, 12,04.

Ejemplo 2(a): 7-cloro-2-[(S)-2-(metoximetil)pirrolidina-1-carbonil]tieno[3,2-b]piridina.



A una mezcla de 7-clorotieno[3,2-b]piridina-2-carboxilato de litio (6,59 g, 30 mmol) en DMF (100 ml) se añadieron diisopropiletilamina (6 ml, 4,45 g, 34,4 mmol), hexafluorofosfato de benzotriazol-1-iloxitris(pirrolidino)fosfonio (16,6 g, 31 mmol) y S-(+)-2-(metoximetil)pirrolidina (3,73 g, 32,4 mmol). La mezcla de reacción resultante se agitó a temperatura ambiente durante 16 horas. La mezcla de reacción en bruto se vertió en agua (600 ml) y se extrajo con EtOAc (3 x 200 ml). Los extractos orgánicos combinados se lavaron con agua (4 x 200 ml), se secaron sobre Na_2SO_4 y se concentraron a vacío para dar 8,8 g de un aceite ámbar, que se purificó por cromatografía en gel de sílice. La elución con Et_2O:EtOAc (67:33) y la evaporación del las fracciones apropiadas dio 6,89 g (74%) de un jarabe naranja. ^{1}H RMN (DMSO-d_6): δ 8,62 (1H, d, J=5,0 Hz), 7,88 (1H, s), 7,35 (1H, d, J=5,0 Hz), 4,54-4,47(1H, m), 3,93-3,75 (2H, m), 3,71-3,55 (2H, m), 3,37 (3H, s), 2,15-1,92 (4H, m). Análisis. Calculado para $C_{14}H_{15}N_2O_2SCl$: C, 54,10; H, 4,87; N, 9,01; S, 10,32; Cl, 11,41. Encontrado: C, 53,96.

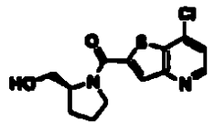
Ejemplo 2: metilamida del ácido 6-(2-[(S)-2-metoximetil)pirrolidina-1-carbonil]tieno[3,2-b]piridin-7-iloxi)-2-metilbenzo[b]tiofeno-3-carboxílico.



Este material se preparó por la reacción de 7-cloro-2-[(S)-1-(metoximetil)pirrolidina-1-carbonil]tieno[3,2-b]piridina 2 a (153 mg, 0,5 mmol) con metilamida del ácido 6-hidroxi-2-metilbenzo[b]tiofeno-3-carboxílico 1 d (164 mg, 0,7 mmol) y Cs_2CO_3 (868 mg, 2,7 mmol) de una manera como se describe previamente para el ejemplo 1 para dar 178 mg (73%) de un sólido amarillo. ^{1}H RMN (DMSO-d_6): δ 8,57 (1H, d, J=5,4 Hz), 8,29 (1H, q, J=4,5 Hz), 8,02 (1H, s), 7,95 (1H, d, J=2,2 Hz),

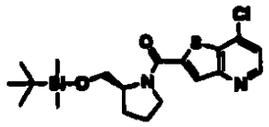
7,85 (1H, d, J=8,8 Hz); 7,32 (1H, dd, J=2,2, 8,8 Hz), 6,75 (1H, d, J=5,4 Hz), 4,37-4,23 (1H, m), 3,95-3,74 (2H, m), 3,60-3,48 (2H, m), 3,27 (3H, s), 2,83 (3H, d, J=4,5 Hz), 2,60 (3H, s), 2,08-1,81 (4H, m). Análisis. Calculado para $C_{25}H_{25}N_3O_4S_2$: C, 60,58; H, 5,08; N, 8,48; S, 12,94. Encontrado: C, 60,55; H, 5,33; N, 8,27; S, 12,68.

Ejemplo 3(a): 7-cloro-2-[(S)-2-(hidroximetil)pirrolidina-1-carbonil]tieno[3,2-b]piridina.



Este material se preparó por la copulación de 7-clorotieno[3,2-b]piridina-2-carboxilato de litio y S-(+)-2-(hidroximetil)pirrolidina de una manera como se describe previamente para el ejemplo 2 a para dar 4,95 g (55%) de un sólido blancuzco. ^{1}H RMN (DMSO-d_6) δ 8,72 (1H, d, J=5,1 Hz), 8,08 (1H, s), 7,68 (1H, d, J=5,1 Hz), 4,27-4,13 (1H, m), 3,94-3,73 (2H, m), 3,67-3,44 (2H, m), 2.09-1,79 (4H, m).
Análisis. Calculado para $C_{13}H_{13}N_2O_2SCl$: C, 52,61; H, 4,42; N, 9,44; S, 10,80; Cl, 11,95: Encontrado: C, 52, 61; H, 4,52; N, 9,62; S, 10,59; Cl, 11,96.

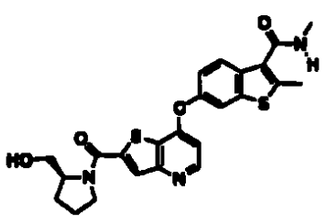
Ejemplo 3(b): 7-cloro-2-[(S)-2-([t-butildimetilsililoxi]metil)pirrolidina-1-carbonil]tieno[3,2-b]piridina



A una disolución agitada de 7-cloro-2-[(S)-2-(hidroximetil)pirrolidina-1-carbonil]tieno[3,2-b]piridina 3 a (4,50 g, 15 mmol) se añadieron t-butildimetilclorosilano (3,18 g, 21 mmol) y trietilamina (3,4 ml, 2,47 g, 24 mmol). La mezcla de reacción resultante se agitó a temperatura ambiente durante 16 horas. La mezcla de reacción en bruto se vertió en agua (150 ml) y se extrajo con CH_2Cl_2 (150 ml). Los extractos orgánicos combinados se lavaron con salmuera (150 ml), se secaron sobre Na_2SO_4 y se concentraron a vacío para dar 7,8 g de un jarabe naranja, que se purificó por cromatografía en gel de sílice. La elución con Et_2O:hexano (67:33) y la evaporación de las fracciones apropiadas dio 5,73 g (92%) de un sólido blancuzco. ^{1}H RMN (DMSO-d_6) δ 8,72 (1H, d, J=5,0 Hz), 8,07 (1H, s), 7,68 (1H, d, J=5,0 Hz), 4,30-4,15 (1H, m), 3,94-3,67 (4H, m), 2,12-1,81 (4H, m), 0,85 (9H, s), 0,03 (3H, s), 0,00 (3H, s). Análisis

Calculado para $C_{19}H_{27}N_2O_2SClSi$: C, 55,52; H, 6,62; N, 6,82; S, 7,80; Cl, 8,63. Encontrado: C, 55,49; H, 6,46; N, 6,92; S, 7,80; Cl, 8,88.

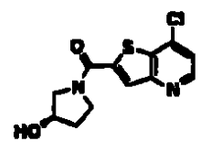
Ejemplo 3: metilamida 6-(2-[(S)-2-(hidroximetil)pirrolidina-1-carbonil]tieno[3,2-b]piridin-7-iloxi)-2-metilbenzo[b]tiofeno-3-carboxílico.



El ejemplo 3 se preparó por la reacción de 7-cloro-2-[(S)-2-([t-butildimetilsililoxi]metil)-pirrolidina-1-carbonil]tieno[3,2-b]piridina 3 b (812 mg, 2 mmol) con metilamida del ácido 6-hidroxi-2-metilbenzo[b]tiofeno-3-carboxílico 1 d (656 mg, 3 mmol) y Cs_2CO_3 (3,47 g, 11 mmol) de una manera como se describe previamente para el ejemplo 1 para dar 302 mg (32%) de un sólido amarillo. ^{1}H RMN (DMSO-d_6) δ 8,57 (1H, d, J=5,3 Hz), 8,29 (1H, q, J=4,5 Hz), 8,01 (1H, s), 7,96 (1H, d, J=2,2 Hz), 7,85 (1H, d, J=8,8 Hz), 7,32 (1H, dd, J=2,2, 8,8 Hz), 6,75 (1H, d, J=5,3 Hz), 4,81 (1H, t, J=5,9 Hz), 4,24-4,12 (1H, m), 3,92-3,74 (2H, m), 3,63-3,44 (2H, m), 2,83 (3H, d, J=4,5 Hz), 2,60 (3H, s), 2,08-1,81 (4H, m).

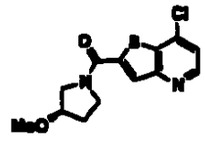
Análisis Calculado para $C_{24}H_{23}N_3O_4S_2$. 0,4 CH_2Cl_2: C, 56,84; H, 4,65; N, 8,15; S, 12,44. Encontrado: C, 56,81; H, 4,78; N, 7,99; S, 12,49.

Ejemplo 4(a): 7-cloro-2-[(R)-3-hidroxipirrolidina-1-carbonil]tieno[3,2-b]piridina.



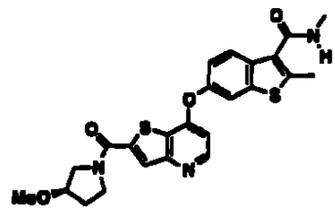
Este material se preparó por la copulación de 7-clorotieno[3,2-b]piridina-2-carboxilato de litio y (R)-3-hidroxipirrolidina de una manera como se describe previamente para el ejemplo 2 a para dar 3,06 g (36%) de un sólido blancuzco. ^{1}H RMN (DMSO-d_6) δ 8,73 (1H, d, J=5,1 Hz), 8,15, 8,09 (1H, s), 7,69 (1H, d, J=5,1 Hz), 5,10-5,06 (1H, m), 4,43-4,29 (1H, m), 4,05-3,89 (2H, m), 3,72-3,43 (2H, m), 2,08-1,79 (2H, m).

Ejemplo 4(b): 7-cloro-2-[(R)-3-metoxipirrolidina-1-carbonil]tieno[3,2-b]piridina.



Una disolución de 7-cloro-2-[(R)-3-hidroxipirrolidina-1-carbonil]tieno[3,2-b]piridina 4 a (1,86 g, 6,6 mmol) en THF (150 ml) se enfrió hasta -10°C previamente a la adición de NaH (920 mg, 23 mmol en forma de dispersión en aceite mineral al 60% en peso). La mezcla resultante se agitó a 0°C durante 40 minutos. Se añadió a continuación yodometano (4 ml, 9,12 g, 64 mmol) a la reacción que se agitó durante otras 3 horas, calentando gradualmente hasta temperatura ambiente. La mezcla de reacción en bruto se enfrió rápidamente con $NaHCO_3$ saturado (150 ml), a continuación se extrajo con EtOAc (2 x 100 ml). Los extractos orgánicos combinados se secaron sobre Na_2SO_4 y se concentraron a vacío para dar 2,4 g de una pasta ámbar que se purificó por cromatografía en gel de sílice. La elución con CH_2Cl_2:CH_3OH (98:2) y la evaporación de las fracciones apropiadas dio 1,64 g (84%) de un sólido amarillo. ^1H RMN (DMSO-d_6): δ 8,73 (1H, d, J=5,1 Hz), 8,15 (1H, s), 7,69 (1H, d, J=5,1 Hz), 4,11-3,83 (3H, m), 3,69-3,47 (2H, m), 3,27, 3,24 (3H, s), 2,18-1,93 (2H, m). Análisis Calculado para $C_{13}H_{13}N_2O_2SCl$: C, 52,61; H, 4,42; N, 9,44; S, 10,80; Cl, 11,95. Encontrado: C, 52,76; H, 4,47; N, 9,38; S, 10,84; Cl, 12,01.

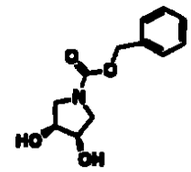
Ejemplo 4: metilamida 6-(2-[(R)-3-metoxipirrolidina-1-carbonil]tieno[3,2-b]piridin-7-iloxi)-2-metilbenzo[b]tiofeno-3-carboxílico.



Este material se preparó por la reacción de 7-cloro-2-[(R)-3-metoxipirrolidina-1-carbonil]tieno[3,2-b]piridina 4 b (267 mg, 0,9 mmol) con metilamida del ácido 6-hidroxi-2-metilbenzo[b]tiofeno-3-carboxílico 1 d (299 mg, 1,4 mmol) y Cs_2CO_3 (1,47 g, 4,5 mmol) de una manera como se describe previamente para el ejemplo 1 para dar 356 mg (82%) de un sólido amarillo. ^1H RMN (DMSO-d_6) δ 8,58 (1H, d, J=5,4 Hz), 8,29

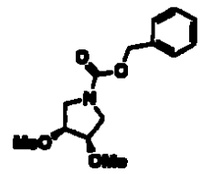
(1H, q, J=4,6 Hz), 8,06 (1H, s), 7,96 (1H, d, J=2,3 Hz), 7,85 (1H, d, J=8,7 Hz), 7,32 (1H, dd, J=2,3, 8,7 Hz), 6,75 (1H, d, J=5,4 Hz), 4,11-3,82 (3H, m), 3,68-3,45 (2H, m), 3,27, 3,24 (3H, s), 2,83 (3H, d, J=4,6 Hz), 2,60 (3H, s), 2,17-1,93 (2H, m). Análisis Calculado para $C_{24}H_{23}N_3O_4S_2$. 0,4 H_2O: C, 58,97; H, 4,91; N, 8,60; S, 13,12. Encontrado: C, 58,98; H, 4,98; N, 8,40; S, 13,37.

Ejemplo 5(a): éster bencílico del ácido 3,4-cis-dihidroxi-pirrolidina-1-carboxílico.



A una disolución de 3-pirrolina-1-carboxilato de bencilo (15 g, 90%, 66,4 mmol) en THF (100 ml) y agua (25 ml) se añadió tetróxido de osmio (10 ml, disolución al 2,5% en peso en 2-metil-2-propanol, 0,8 mmol) y N-óxido de 4-metilmorfolina (8,56 g, 73 mmol) en forma de sólido. La mezcla se agitó a temperatura ambiente durante la noche y se concentró a vacío. El residuo se redisolvió en EtOAc (300 ml) y se lavó con disolución acuosa de Na_2SO_3 (1,5 g en 100 ml de agua), disolución acuosa de $NaHCO_3$ y salmuera. La capa acuosa combinada se extrajo una vez con EtOAc (100 ml). Los extractos orgánicos combinados se secaron sobre Na_2SO_4 y se concentraron a vacío. El producto en bruto se purificó adicionalmente por cromatografía flash en columna eluyendo con MeOH al 4-5% en CH_2Cl_2 para dar 15,26 g (97%) de un sólido blanco. ^1H RMN (300 MHz, $CDCl_3$) δ 7,34 (5H, m), 5,11 (2H, s ancho), 4,26 (2H, m), 3,66 (2H, m), 3,41 (2H, m), 1,56 (2H, s ancho).

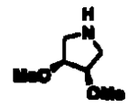
Ejemplo 5(b): éster bencílico del ácido 3,4-cis-dimetoxi-pirrolidina-1-carboxílico.



A una disolución agitada de éster bencílico del ácido 3,4-cis-dihidroxi-pirrolidina-1-carboxílico 5 a (15,2 g, 64,3 mmol) en THF anhidro (130 ml) se añadió yodometano (36 g, 257 mmol) a 0°C; se añadió lentamente a continuación hidruro de sodio (6,4 g, al 60% en aceite mineral, 160 mmol) a 0°C. La mezcla se dejó calentar

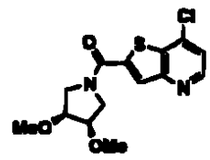
hasta temperatura ambiente y se agitó a temperatura ambiente durante 3 horas. Se añadió a continuación HCl acuoso 1 N (30 ml) a la mezcla que se concentró a vacío para retirar THF. El residuo se redisolvió en EtOAc (300 ml) y se lavó con agua y salmuera. La capa orgánica se secó sobre Na_2SO_4, se filtró y concentró a vació. El producto en bruto se purificó adicionalmente por cromatografía flash en columna eluyendo con EtOAc al 5-25% en CH_2Cl_2 para dar 17 g (99%) de un aceite amarillo. ^1H RMN (300 MHz, $CDCl_3$) δ 7,35 (5H, m), 5,12 (2H, m), 3,87 (2H, m), 3,55 (2H, m), 3,42 (6H, s ancho), 1,58 (2H, s)

Ejemplo 5(c): 3,4-cis-dimetoxi-pirrolidina



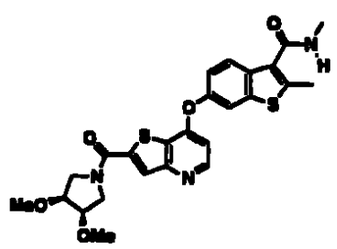
A una disolución agitada de éster bencílico del ácido 3,4-cis-dimetoxi-pirrolidina-1-carboxílico 5 b (16,95 g, 63,9 mmol) en MeOH (150 ml) se añadió 10% de Pd sobre C (1,3 g). La mezcla se agitó en un globo de H_2 a temperatura ambiente durante 3 horas y se filtró a través de celite. El filtrado se concentró a vacio, se redisolvió en CH_2Cl_2 y se secó sobre Na_2SO_4. La disolución se concentró para dar 8,3 g (99%) de un aceite amarillo. ^1H RMN (300 MHz, $CDCl_3$) δ 3,80 (2H, m), 3,47 (2H, s ancho), 3,41 (6H, s), 3,01 (2H, s ancho).

Ejemplo 5(d): 7-cloro-2-[meso-3,4-dimetoxipirrolidina-1-carbonil]tieno[3,2-b]piridina.



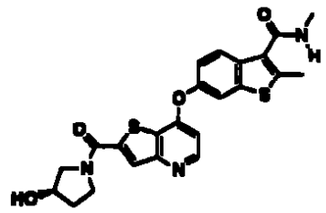
Este material se preparó por la copulación de 7-clorotieno[3,2-b]piridina-2-carboxilato de litio y 3,4-cis-dimetoxipirrolidina 5 c de una manera como se describe previamente para el ejemplo 2 a para dar un jarabe amarillo pálido. ^1H RMN (CD_3OD): δ 8,70 (1H, d, J=5,1 Hz), 8,03 (1H, s), 7,61 (1H, d, J=5,1 Hz), 4,20-4,07 (2H, m), 3,97-3,75 (2H, m), 3,52 (3H, s), 3,48 (3H, s), 3,35-3,29 (2H, m).

Ejemplo 5: metilamida del ácido 6-(2-[meso-3,4-dimetoxipirrolidina-1-carbonil]tieno[3,2-b]piridin-7-iloxi)-2-metilbenzo[b]tiofeno-3-carboxílico.



Este material se preparó por la reacción de 7-cloro-2-[meso-3,4-dimetoxipirrolidina-1-carbonil]tieno[3,2-b]piridina 5 d (164 mg, 0,5 mmol) con metilamida del ácido 6-hidroxi-2-metilbenzo[b]tiofeno-3-carboxílico 1 d (164 mg, 0,7 mmol) y Cs_2CO_3 (868 mg, 2,7 mmol) de una manera como se describe previamente para el ejemplo 1 para dar 123 mg (48%) de un sólido blancuzco. ^{1}H RMN (DMSO-d_6): δ 8,59 (1H, d, J=5,4 Hz), 8,29 (1H, q, J=4,7 Hz), 8,07 (1H, s), 7,96 (1H, d, J=2,3 Hz), 7,85 (1H, d, J=8,8 Hz), 7,32 (1H, dd, J=2,3, 8,8 Hz), 6,76 (1H, d, J=5,4 Hz), 4,12-3,98 (3H, m), 3,83 (1H, dd, J=3,6, 9,1 Hz), 3,66 (1H, dd, J=4,8, 12,9 Hz), 3,51 (1H, dd, J=4,2, 12,9 Hz), 3,36 (6H, s), 2,83 (3H, d, J=4,7 Hz), 2,60 (3H, s). Análisis Calculado para $C_{25}H_{25}N_3O_5S_2$. 0,6 H_2O: C, 57,47; H, 5,06; N, 8,04; S, 12,28: Encontrado: C, 57,35; H, 5,02; N, 7,89; S, 12,37.

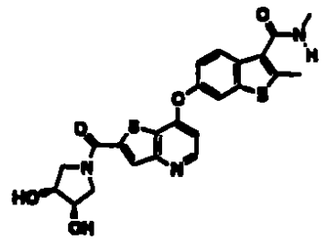
Ejemplo 6: metilamida del ácido 6-(2-[(R)-3-hidroxipirrolidina-1-carbonil]tieno[3,2-b]piridin-7-iloxi)-2-metilbenzo[b]tiofeno-3-carboxílico.



Este material se preparó a partir de metilamida del ácido 6-(2-[(R)-3-metoxipirrolidina-1-carbonil]tieno[3,2-b]piridin-7-iloxi)-2-metilbenzo[b]tiofeno-3-carboxílico 4 (172 mg, 0,4 mmol) por tratamiento con BBr_3 de una manera como se describe previamente para el ejemplo 1 d para dar 108 mg (65%) de un sólido blancuzco. ^{1}H RMN (DMSO-d_6): δ 8,58 (1H, d, J=5,3 Hz), 8,29 (1H, q, J=4,4 Hz), 8,06 (1H, s), 7,96 (1H, d, J=1,2 Hz), 7,85 (1H, d, J=8,7 Hz), 7,33 (1H, dd, J=1,2, 8,7 Hz), 6,75 (1H, d, J=5,3 Hz), 4,44-4,27 (1H, m), 4,05-3,88 (1H, m), 3,71-3,42 (3H, m), 2,83 (3H, d, J=4,4 Hz), 2,60 (3H, s), 2,10-1,77 (2H, m). Análisis Calculado para

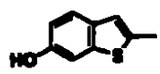
$C_{23}H_{21}N_3O_4S_2$. 1,0 CH_3OH: C, 57,70; H, 5,04; N, 8,41; S, 12,84. Encontrado: C, 57,41; H, 4,98; N, 8,42; S, 12,63.

Ejemplo 7: metilamida del ácido 6-(2-[meso-3,4-dihidroxipirrolidina-1-carbonil]tieno[3,2-b]piridin-7-iloxi)-2-metilbenzo[b]tiofeno-3-carboxílico.



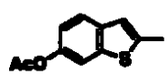
El ejemplo 7 se preparó a partir de metilamida del ácido 6-(2-[meso-3,4-dimetoxipirrolidina-1-carbonil]tieno[3,2-b]piridin-7-iloxi)-2-metilbenzo[b]tiofeno-3-carboxílico 5 (74 mg, 0,1 mmol) por tratamiento con BBr_3 de una manera como se describe previamente para el ejemplo 1 d para dar 51 mg (73%) de un sólido blancuzco. ^1H RMN (DMSO-d_6): δ 8,58 (1H, d, J=5,4 Hz), 8,29 (1H, q, J=4,6 Hz), 7,99 (1H, s), 7,96 (1H, d, J=2,3 Hz), 7,85 (1H, d, J=8,8 Hz), 7,32 (1H, dd, J=2,3, 8,8 Hz), 6,75 (1H, d, J=5,4 Hz), 5,1 (2H, d, J=5,3 Hz), 4,18-4,07 (2H, m), 4,02 (1H, dd, J=5,6, 10,2 Hz), 3,66 (1H, dd, J=4,9 Hz, 10,2 Hz), 3,62 (1H, dd, J=5,1, 12,8 Hz), 3,40 (1H, dd, J=4,4, 12,8 Hz), 2,83 (3H, d, J=4,7 Hz), 2,60 (3H, s). Análisis Calculado para $C_{25}H_{25}N_3O_5S_2$. 0,5 NaBr. H_2O: C, 49,95; H, 4,19; N, 7,60; S, 11,60. Encontrado: C, 49,93; H, 4,15; N, 7,44; S, 11,44.

Ejemplo 8a: 6-hidróxido-2-metilbenzo[b]tiofeno.



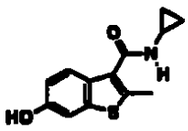
Este material se preparó a partir de 6-metoxi-2-metilbenzo[b]tiofeno 1 b (2,92 g, 16,4 mmol) por tratamiento con BBr_3 de una manera como se describe previamente para el ejemplo 1 d para dar 2,51 g (93%) de un sólido blanco. ^1H RMN (DMSO-d_6) δ 9,43 (1H, s), 7,47 (1H, d, J=8,5 Hz), 7,14 (1H, d, J=2,2 Hz), 6,92 (1H, s), 6,78 (1H, dd, J=2,2, 8,5 Hz), 2,46 (3H, s). Análisis Calculado para C_9H_8OS: C, 65,82; H, 4,91; S, 19,53. Encontrado: C, 65,96; H, 5,11; S, 19,69.

Ejemplo 8(b): 6-acetoxi-2-metilbenzo[b]tiofeno



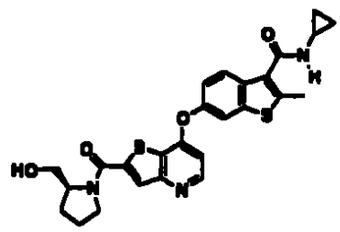
Se añadieron cloruro de acetilo (1,5 ml, 1,66 g, 21 mmol) y Et_3N (3 ml, 2,18 g, 21,5 mmol) secuencialmente a una disolución de 6-hidroxi-2-metilbenzo[b]tiofeno **8 a** (2,51 g, 15 mmol) en THF (120 ml) a 0°C. La reacción se dejó agitando durante 14 horas, calentando gradualmente hasta temperatura ambiente, se diluyó a continuación con EtOAc (100 ml) y se lavó con H_2O (100 ml). Los extractos orgánicos combinados se secaron subsecuentemente sobre $NaSO_4$ y se concentraron a vacio para dar 3,9 g de un sólido amarillo que se purificó por cromatografía en gel de sílice. La elución con hexano:Et_2O (90:10) y la evaporación de las fracciones apropiadas dio 2,93 g (93%) de un sólido blanco. ^1H RMN (DMSO-d_6) δ 7,70 (1H, d, J=8,6 Hz), 7,66 (1H, d, J=2,2 Hz), 7,12 (1H, s), 7,07 (1H, dd, J=2,2, 8,6 Hz), 2,54 (3H, s), 2,27 (3H, s), Análisis Calculado para $C_{11}H_{10}O_2S$: C, 64,05; H, 4,89; S, 15,55. Encontrado: C, 63,84; H, 4,93; S, 15,57.

Ejemplo 8(c): ciclopropilamida del ácido 6-hidroxi-2-metilbenzo[b]tiofeno-3-carboxílico.



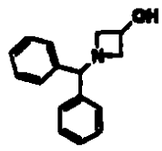
Este material se preparó a partir de 6-acetoxi-2-metilbenzo[b]tiofeno **8 b** (413 mg, 2 mmol) por acilación con cloruro de oxalilo en presencia de $AlCl_3$ seguido de tratamiento con ciclopropilamina de una manera como se describe previamente para el ejemplo **1 c** para dar 384 mg (78%) de un sólido amarillo pálido. ^1H RMN (DMSO-d_6) δ 9,56 (1H, s), 8,29 (1H, d, J=4,3 Hz), 7,48 (1H, d, J=8,7 Hz), 7,17 (1H, d, J=2,2 Hz), 6,83 (1H, dd, J=2,2, 8,7 Hz), 2,92-2,81 (1H, m), 2,46 (3H, s), 0,74-0,66 (2H, m), 0,58-0,51 (2H, m). Análisis Calculado para $C_{13}H_{13}NO_2S$. 0,2 H_2O: C, 62,23; H, 5,38; N, 5,60. Encontrado: C, 62,22; H, 5,36; N, 5,60.

Ejemplo 8: ciclopropilamida del ácido 6-(2-[(S)-2-(hidroximetil)pirrolidina-1-carbonil]tieno[3,2-b]piridin-7-iloxi)-2-metilbenzo[b]tiofeno-3-carboxílico.



Este material se preparó por la reacción de 7-cloro-2-[(S)-2-([t-butildimetilsililoxi]metil)-pirrolidina-1-carbonil]tieno[3,2-b]piridina **3 b** (206 mg, 0,5 mmol) con ciclopropilamida del ácido 6-hidroxi-2-metilbenzo[b]tiofeno-3-carboxílico **8 c** (186 mg, 0,75 mmol) y Cs_2CO_3 (868 mg, 2,7 mmol) de una manera como se describe previamente para el ejemplo 1 para dar 132 mg (52%) de un sólido amarillo. ^{1}H RMN (DMSO-d_6): δ 8,58 (1H, d, J=5,4 Hz), 8,46 (1H, d, J=4,3 Hz), 8,00 (1H, s), 7,95 (1H, d, J=2,3 Hz), 7,80 (1H, d, J=8,8 Hz), 7,32 (1H, dd, J=2,3, 8,8 Hz), 6,75 (1H, d, J=5,4 Hz), 4,90-4,72 (1H, m), 4,24-4,11 (1H, m), 3,92-3,74 (2H, m), 3,64-3,43 (2H, m), 2,95-2,84 (1H, m), 2,57 (3H, s), 2,09-1,80 (4H, m), 0,77-0,67 (2H, m), 0,60-0,52 (2H, m). Análisis Calculado para $C_{24}H_{23}N_3O_4S_2$. 0,4 CH_2Cl_2. 0,4 CH_3OH: C, 58,06; H, 4,98; N, 7,58. Encontrado: C, 58,03; H, 4,98; N, 7,52.

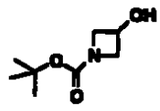
Ejemplo 9(a): 1-benzhidrilazetidin-3-ol.



Una mezcla de (difenilmetil)amina (2,2 ml, 12,8 mmol), 2-clorometiloxirano (2,0 ml, 25,6 mmol) en DMF (25 ml) se calentó a 95°C durante 72 horas. La disolución amarilla resultante se enfrió hasta 0°C y se trató con HCl 0,5 M (250 ml). La capa acuosa se lavó con metil-(t-butil)-éter (3 x 150 ml) y se descartaron las capas orgánicas. La capa acuosa se hizo básica con NaOH y la suspensión blanca lechosa resultante se extrajo con metil-(t-butil)-éter (3 x 150 ml). Las capas orgánicas combinadas se lavaron con salmuera, se secaron sobre $MgSO_4$ y se concentraron a vacío para dar un aceite transparente (3,1 g). El aceite se trituró con ciclohexano y metil-(terc-butil)-éter y proporcionó un sólido blanco (2,3 g; 74%): TLC (4% metanol-

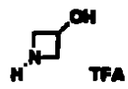
cloroformo con 0,1% hidróxido de amonio) R_f 0,3: ^{1}H RMN (DMSO-d_6, 400 MHz) δ 7,40-7,38 (4H, m), 7,27-7,23 (4H, m), 7,17-7,13 (2H, m), 5,28 (1H, d, J=6,3 Hz), 4,34 (1H, s), 4,22-4,18 (1H, m), 3,36-3,34 (2H, m), 2,69-2,66 (2H, m).

Ejemplo 9(b): éster terc-butílico del ácido 3-hidroxiazetidina-1-carboxílico.



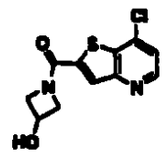
Se añadieron 1-benzhidril-azetidin-3-ol **9 a** (4,0 g, 16,7 mmol), EtOAc (150 ml), dicarbonato de di-terc-butilo (4,4 g, 20,1 mmol) y 20% de $Pd(OH)_2$ sobre carbono (0,8 g, 20% en peso) secuencialmente a un matraz de fondo redondo. La mezcla se desgasificó y purgó con hidrógeno. La hidrogenolisis fue completa después de 24 horas a una atmósfera. La mezcla de reacción se filtró a través de celite y se concentró a vacío hasta dar un aceite transparente (7,0 g). El producto en bruto se disolvió en CH_2Cl_2 (10 ml) y se purificó sobre un relleno de gel de sílice (35 g), que se eluyó con CH_2Cl_2 (150 ml) seguido de EtOAc (150 ml). Las fracciones de EtOAc se concentraron a vacío hasta dar un aceite transparente (3,1 g, >100%): TLC (50% acetato de etilo-ciclohexano) R_f 0,4 (mancha de I_2); ^{1}H RMN (DMSO-d_6, 300 MHz) δ 5,62 (1H, d, J=6,4 Hz), 4,39-4,32 (1H, m), 3,97 (2H, t, J=7,8 Hz), 3,57 (2H, t, J=4,4 Hz), 1,35 (9H, s).

Ejemplo 9(c): sal del ácido trifluoroacético y azetidin-3-ol



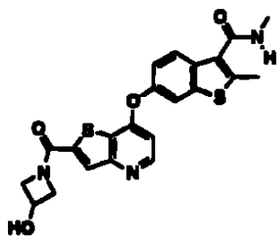
Se disolvió éster terc-butílico del ácido 3-hidroxi-azetidina-1-carboxílico **9 b** (0,73 g, 4.2 mmol) en CH_2Cl_2 (2 ml) y ácido trifluoroacético. PRECAUCION: La desprotección generó un rápido desprendimiento de gas. La disolución transparente se agitó durante 75 minutos y se retiró el disolvente a vacío hasta dar un aceite transparente (1,4 g, >100%): ^{1}H RMN (DMSO-d_6, 400 MHz),δ 8,63 (2H, s ancho), 4,55-4,48 (1H, m), 4,09-4,02 (2H, m), 3,76-3,68 (2H, m).

Ejemplo 9(d): 7-cloro-2-[3-hidroxiazetidin-1-carbonil]tieno[3,2-b]piridina



Una mezcla de la sal de litio del ácido 7-clorotieno[3,2-b]piridina-2-carboxílico (0,92 g, 4,2 mmol), CH_2Cl_2 (40 ml) y cloruro de tionilo (0,92 ml, 12,6 mmol) se calentó a reflujo. La suspensión blanca resultante dio lugar a una disolución ámbar con la adición del DMF (5 ml). Después de 60 minutos la mezcla de reacción se concentró a vacío hasta dar una suspensión blanca. El cloruro de ácido se suspendió en CH_2Cl_2 (40 ml) y se trató con una disolución de sal del ácido trifluoroacético y azetidin-3-ol **9 c** (0,78 g, 4,2 mmol) y Et_3N (0,58 ml, 4,2 mmol) en DMF (2 ml). Después de 60 minutos se retiró la capa de CH_2Cl_2 a vacío y el residuo beis resultante se vertió en $NaHCO_3$ saturado (100 ml). La capa acuosa se extrajo con EtOAc (3 x 100 ml). Las capas orgánicas combinadas se lavaron con salmuera, se secaron sobre $MgSO_4$ y se concentraron a vacío hasta dar una suspensión beis (1,7 g). La suspensión se trituró con metil-(terc-butil)-éter y proporcionó un sólido beis (0,23 g, 21%): TLC (5% metanol-diclorometano) R_f 0,4; ^1H RMN (DMSO-d_6, 400 MHz) δ 8,74 (1H, d, J=5,1 Hz), 7,99 (1H, s), 7,70 (1H, d, J=4,8 Hz), 5,88 (1H, d, J=6,3 Hz), 4,80-4,78 (1H, m), 4,60-4,56 (1H, m), 4,37-4,34 (2H, m), 3,86-3,84 (1H, m); ESIMS m/z 269 $(M+H)^+$.

Ejemplo 9: metilamida del ácido 6-(2-[3-hidroxiazetidina-1-carbonil]tieno[3,2-b]piridin-7-iloxi)-2-metilbenzo[b]tiofeno-3-carboxílico.



Una suspensión de 7-cloro-2-[3-hidroxiazetidin-1-carbonil]tieno[3,2-b]piridina **9 d** (120 mg, 0,45 mmol), metilamida del ácido 6-hidroxi-2-metilbenzo[b]tiofeno-3-carboxílico **1 d** (100 mg, 0,45 mmol) y Cs_2CO_3 (0,73 g, 2,2 mmol) en acetonitrilo (15 ml) se calentó hasta 70°C. Después de 30 horas quedaban ambos materiales de partida, pero la reacción se paró. La mezcla de reacción se vertió en una disolución al 50% de $NaHCO_3$ saturado (150 ml). La capa acuosa se extrajo con 10% isopropanol-

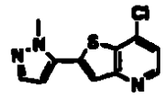
cloroformo (3 x 50 ml). Las capas orgánicas combinadas se secaron con salmuera, sulfato de magnesio, se filtraron y concentraron a vacío hasta dar un sólido blanco (0,18 g). El producto en bruto se purificó por cromatografía radial en gel de sílice y el gradiente de la fase móvil era 5-10% CH_3OH-CH_2Cl_2 con NH_4OH al 0,1%. El producto se trituró con acetato de etilo-ciclohexano y se aisló en forma de sólido blanco (40 mg, 20%): TLC (5% CH_3OH-CH_2Cl_2) R_f 0,2; ^1H RMN (DMSO-d_6, 400 MHz) δ 8,58 (1H, d, J=5,3 Hz), 8,30-8,27 (1H, m), 7,96-7,84 (3H, m), 7,32 (1H, d, J=8,9 Hz), 6,75 (1H, d, J=5,3 Hz), 5,88 (1H, d, J=6,6 Hz), 4,80-4,78 (1H, m), 4,58-4,55 (1H, m), 4,35-4,30 (2H, m), 3,87-3,82 (1H, m), 2,84 (3H, d, J=4,3 Hz), 2,60 (3H, s). ESIMS m/z 454 $(M+H)^+$. p.f. 237-239°C. Análisis Calculado para $C_{22}H_{19}N_3O_4S_2$. 0,9 H_2O: C, 56,25; H, 4,46; N, 8,95; S, 13,65. Encontrado: C, 56,36; H, 4,22; N, 9,00; S, 13,51.

Ejemplo 10(a): 1-metil-5-trimetilestannil-1H-pirazol



Una disolución de 1-metil-1H-pirazol (1,6 g, 20,0 mmol) en Et_2O se trató con n-butillitio (12,5 ml, 1,6 M en hexanos, 20,0 mmol) durante un periodo de 10 minutos a temperatura ambiente. La suspensión amarilla se agitó durante unos 90 minutos adicionales. Subsecuentemente, se añadió en una porción cloruro de trimetilestaño (4,0 g, 20,0 mmol). La suspensión marrón se agitó durante 30 minutos, se filtró y el filtrado se concentró a vacío hasta dar un aceite negro (5,0 g). El producto se aisló por destilación a 1,5 torr (67-72°C) en forma de aceite transparente (2,1 g, 42%): ^1H RMN (DMSO-d_6, 400 MHz) δ 7,40 (1H, d, J=1,5 Hz), 6,27 (1H, d, J=1,7 Hz), 3,84 (3H, s), 0,34 (9H, s), ESIMS m/z 243-247 conglomerado iónico $(M+H)^+$.

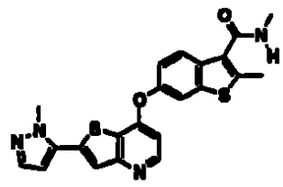
Ejemplo 10(b): 7-cloro-2-(2-metil-2H-pirazol-3-il)tieno[3,2-b]piridina



Una mezcla de 1-metil-5-trimetilestannil-1H-pirazol **10 a** (2,1 g, 8,5 mmol), 7-cloro-2-yodo-tieno[3,2-b]piridina (2,5 g, 8,5 mmol), tetraquis(trifenilfosfina)paladio(0) (0,5 g, 0,4 mmol, 5% mol) en o-xileno (85 ml) se desgasificó, se purgó con nitrógeno y se calentó a 120°C, lo que dio una disolución naranja. Después de 14 horas la mezcla de reacción negra se diluyó con tolueno (100 ml) y se extrajo con HCl 1,2 M (3 x 60 ml). Las fases acuosas combinadas se lavaron con tolueno (100 ml). Las capas

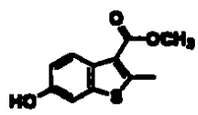
orgánicas se desecharon y la capa acuosa se trató con NaOH hasta pH 14. Se recogió el sólido blanco resultante (1,1 g, 52%): TLC (6% metanol-diclorometano) R_f 0,8; ^{1}H RMN (DMSO-d_6, 400 MHz) δ 8,70 (1H, d, J=5,3 Hz), 8,00 (1H, s), 7,63 (1H, d, J=5,3 Hz), 7,56 (1H, d, J=2,0 Hz), 6,79 (1H, d, J=2,0 Hz), 4,09 (3H, s), ESIMS 250 m/z 250 $(M+H)^+$.

Ejemplo 10: metilamida del ácido 2-metil-6-(2-[2-metil-2H-pirazol-3-il]tieno[3,2-b]piridin-7-iloxi)benzo[b]tiofeno-3-carboxílico.



El ejemplo 10 se preparó por la reacción de 7-cloro-2-(2-metil-2H-pirazol-3-il)tieno[3,2-b]piridina **10 b** con metilamida del ácido 6-hidroxi-2-metilbenzo[b]tiofeno-3-carboxílico **1 d** y Cs_2CO_3 de una manera como se describe previamente para el ejemplo 1 para dar 115 mg de un sólido beis (60%): TLC (6% metanol-diclorometano) R_f 0,6; ^{1}H RMN (DMSO-d_6, 400 MHz) δ 8,54 (1H, d, J=5,5 Hz), 8,28 (1H, q, J=4,5 Hz), 7,96 (1H, d, J=2,3 Hz), 7,92 (1H, s), 7,86 (1H, d, J=8,8 Hz), 7,54 (1H, d, J=2,0 Hz), 7,33 (1H, dd, J=2,3, 8,8 Hz), 6,72 (1H, d, J=2,0 Hz), 6,68 (1H, d, J=5,5 Hz), 4,08 (3H, s), 2,84 (1H, d, J=4,5 Hz), 2,60 (3H, s). ESIMS m/z 435 $(M+H)^+$, p.f. 210-212°C. Análisis Calculado para $C_{22}H_{18}N_4O_2S_2$. 1,3 H_2O: C, 57,70; H, 4,53; N, 12,23; S, 14,00. Encontrado: C, 57,75; H, 4,55; N, 12,21; S, 14,13.

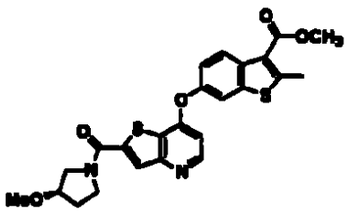
Ejemplo 11(a): 6-hidroxi-2-metilbenzo[b]tiofeno-3-carboxilato de metilo.



Este material se preparó a partir de 6-acetoxi-2-metilbenzo[b]tiofeno **8 b** (500 mg, 2,42 mmol) por acilación con cloruro de oxalilo en presencia de $AlCl_3$ como se describe previamente para el ejemplo 1 c. Una disolución de cloruro de 6-metoxi-2-metilbenzo[b]tiofeno-3-carbonilo en bruto en MeOH (24 ml) se enfrió a 0°C previamente a la adición de K_2CO_3 (351 mg, 2,66 mmol). La reacción se calentó hasta temperatura ambiente y se agitó 3 horas. El disolvente se retiró a vacio y el residuo resultante se diluyó con CH_2Cl_2 (75 ml) y H_2O (25 ml). La capa orgánica se separó y la

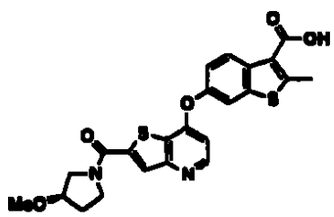
capa acuosa se extrajo con CH_2Cl_2 (50 ml). Las capas orgánicas combinadas se lavaron con salmuera (25 ml), se secaron (Na_2SO_4), se filtraron y se concentraron a vacío para dar 468 mg (87%) de un sólido marrón pálido. ^1H RMN (300 MHz, DMSO-d_6) δ 9,68 (1H, s), 8,06 (1H, d, J=8,9 Hz), 7,23 (1H, d, J=2,3 Hz), 6,91 (1H, dd, J=2,3, 8,9 Hz).

Ejemplo 11(b): 6-[(2-{[(3R)-3-metoxipirrolidin-1-il]carbonil}tieno[3,2-b]piridin-7-il)oxi]-2-metilbenzo[b]tiofeno-3-carboxilato de metilo.



El ejemplo 11(b) se preparó por la reacción de 7-cloro-2-[(R)-3-metoxipirrolidina-1-carbonil]tieno[3,2-b]piridina **4 b** (417 mg, 1,40 mmol) con 6-hidroxi-2-metilbenzo[b]tiofeno-3-carboxilato de metilo **11 a** (417 mg, 2,11 mmol) y Cs_2CO_3 (2,29 g, 7.02 mmol) de una manera como se describe previamente para el ejemplo 1 para dar 290 mg (43%) de un sólido amarillo. ^1H RMN (DMSO-d_6): δ 8,58 (1H, d, J=5,4 Hz), 8,39 (1H, d, J=9,0 Hz), 8,07 (1H, s), 8,02 (1H, d, J=2,3 Hz), 7,42 (1H, dd, J=2,3, 9,0 Hz), 6,79 (1H, d, J=5,4 Hz), 4,08-3,99 (3H, m), 3,87-3,86 (2H, m), 3,91 (3H, s), 3,64-3,59 (2H, m), 3,27, 3,24 (3H, s), 2,82 (3H, s).

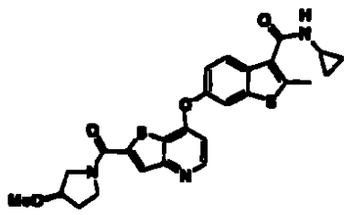
Ejemplo 11(c): ácido 6-[(2-{[(3R)-3-metoxipirrolidin-1-il]carbonil}tieno[3,2-b]piridin-7-il)oxi]-2-metilbenzo[b]tiofeno-3-carboxílico



A una disolución de 6-[(2-{[(3R)-3-metoxipirrolidin-1-il]carbonil}tieno[3,2-b]piridin-7-il)oxi]-2-metilbenzo[b]tiofeno-3-carboxilato de metilo **11 b** (258 mg, 0,535 mmol) en una mezcla de THF/MeOH/H_2O (3:2:1,6 ml) se añadió LiOH. H_2O (224 mg, 5,35 mmol). La reacción se agitó 24 horas a temperatura ambiente. La mezcla se

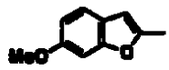
diluyó con H_2O (10 ml) y se acidificó a pH 1 con HCl 1 M. El precipitado se recogió por filtración a vacío, se lavó con MeOH, y se secó a 50°C a vacío para dar 116 mg (45%) de un sólido marrón pálido. ^{1}H RMN (DMSO-d_6) δ 8,58 (1H, d, J=5,4 Hz), 8,44 (1H, d, J=8,9 Hz), 8,07 (1H, s), 8,00 (1H, d, J=24 Hz), 7,39 (1H, dd, J=2,4, 8,9 Hz), 6,78 (1H, d, J=5,4 Hz), 4,10-3,81 (3H, m), 3,69-3,54 (4H, m), 3,27, 3,24 (3H, s), 2,81 (3H, s).

Ejemplo 11: ciclopropilamida del ácido 6-[(2-{[(3R)-3-metoxipirrolidin-1-il]carbonil}tieno[3,2-b]piridin-7-il)oxi]-2-metilbenzo[b]tiofeno-3-carboxílico.



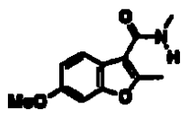
Se añadió cloruro de tionilo (31 µl, 0,427 mmol) a una suspensión de ácido 6-[(2-{[(3R)-3-metoxipirrolidin-1-il]carbonil}tieno[3,2-b]piridin-7-il)oxi]-2-metilbenzo[b]tiofeno-3-carboxílico **11 c** (40 mg, 0,085 mmol) en dicloroetano (1 ml). La mezcla de reacción se calentó a reflujo durante 90 minutos, se enfrió hasta temperatura ambiente y se concentró a vacío. El residuo amarillo se disolvió en CH_2Cl_2 (1 ml) y se añadió ciclopropilamina (30 µl, 0,427 mmol). La mezcla resultante se agitó a temperatura ambiente durante 16 horas, se diluyó con CH_2Cl_2 (10 ml) y se lavó con H_2O (5 ml). La capa acuosa se extrajo con CH_2Cl_2 (2 x 5 ml) y las capas orgánicas combinadas se secaron (Na_2SO_4), se filtraron y se concentraron a vacío. La mezcla en bruto se purificó por cromatografía en gel de sílice (5% MeOH/EtOAc) para dar 20 mg (46%) de un sólido amarillo pálido. ^{1}H RMN (DMSO-d_6, 300 MHz) δ 8,58 (1H, d, J=5,3 Hz), 8,46 (1H, d, J=4,5 Hz), 8,06 (1H, s), 7,96 (1H, d, J=2,3 Hz), 7,81 (1H, J=8,7 Hz), 7,32 (1H, dd, J=2,3, 8,7 Hz), 6,75 (1H, d, J=5,3 Hz), 4,10-3,82 (4H, m), 3,61 (2H, m), 3,27, 3,24 (3H, s), 2,91 (1H, m), 2,72 (1H, m), 2,57 (3H, s), 0,76-0,70 (2H, m), 0,50-0,55 (2H, m). Análisis Calculado para $C_{28}H_{25}N_3O_4S_2$: C, 61,52; H, 4,96; N, 8,28; S, 12,63. Encontrado: C, 59,30; H, 4,78; N, 7,95; S, 12,23.

Ejemplo 12(a): 6-metoxi-2-metilbenzofurano.



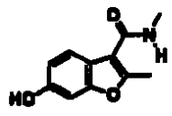
Un tubo a presión se cargó con una barra agitadora, 2-yodo-5-metoxifenol (500 mg, 2,0 mmol) (preparado según Heterocycles 45, (6), 1997, 1137), $Cl_2Pd(PPh_3)_2$ (70 mg, 0,1 mmol), CuI (19 mg, 0,1 mmol), 1,1,3,3-tetrametilguanidina (2,5 ml, 20,0 mmol) y DMF (10 ml), a continuación se enfrió a –78°C mientras se condensó propino gaseoso. El tubo se selló y se dejó calentar hasta temperatura ambiente. Después de 18 horas, los contenidos del tubo se vertieron en disolución saturada de NaCl y se extrajeron con EtOAc (2 x). Las capas orgánicas combinadas se lavaron con salmuera (3 x), se secaron ($MgSO_4$) y se concentraron a presión reducida. El residuo se sometió a cromatografía flash en gel de sílice eluyendo con 3:1 (hexanos/acetato de etilo) para dar 239 mg (74%) de un líquido ámbar. ^{1}H RMN (DMSO-d_6) δ 7,31 (1H, d, J=8,3 Hz), 6,95 (1H, d, J=2,2 Hz), 6,80 (1H, dd, J=2,2, 8,3 Hz), 6,27 (1H, s), 3,85 (3H, s), 2,40 (3H, s). Análisis Calculado para $C_{10}H_{10}O_2$. 0,05 hexanos: C, 74,30; H, 6,48. Encontrado: C, 74,63; H, 6,48.

Ejemplo 12(b): metilamida del ácido 6-metoxi-2-metilbenzofuran-3-carboxílico.



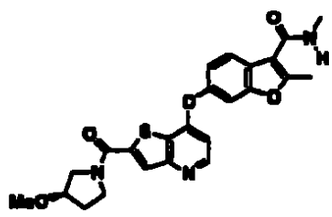
Este material se preparó a partir de 6-metoxi-2-metilbenzofuran 11 a (500 mg, 3,1 mmol) por acilación con cloruro de oxalilo en presencia de $AlCl_3$, seguido de tratamiento con metilamina de una manera como se describe previamente para el ejemplo 1 c para dar 541 mg (80%) de un sólido blancuzco. ^{1}H RMN ($CDCl_3$) δ (como un par de rotámeros) 7,48, 7,41 (1H, d, J=8,6 Hz), 6,98, 6,65 (1H, s), 6,89, 6,71 (1H, dd, J=2,3, 8,6 Hz), 6,22, 5,83 (1H, s ancho), 3,84, 3,82 (3H, s), 3,03, 2,93 (3H, d, J=4,8 Hz), 2,69, 2,38 (3H, s). Análisis Calculado para $C_{12}H_{13}NO_3$: C, 65,74; H, 5,98; N, 6,39. Encontrado: C, 65,86; H, 5,96; N, 6,35.

Ejemplo 12 (c): metilamida del ácido 6-hidroxi-2-metilbenzofuran-3-carboxílico.



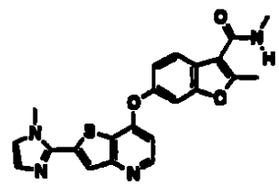
Este material se preparó a partir de metilamida del ácido 6-metoxi-2-metilbenzo[b]furan-3-carboxílico **11 b** (516 mg, 2,35 mmol) por tratamiento con BBr_3 de una manera como se describe previamente para el ejemplo 1 d para dar 429 mg (89%) de un sólido blancuzco. ^{1}H RMN (DMSO-d_6) δ 9,54 (1H, s), 7,80 (1H, d, J=4,5 Hz), 7,50 (1H, d, J=8,3 Hz), 6,88 (1H, s), 6,72 (1H, d, J=8,3 Hz), 2,79 (3H, d, J=4,5 Hz), 2,57 (3H, s). Análisis Calculado para $C_{11}H_{11}NO_3$. 0,1 EtOAc: C, 63,97; H, 5,56; N, 6,54. Encontrado: C, 63,87; H, 5,68; N, 6,45.

Ejemplo 12: metilamida del ácido 6-(2-[3-metoxipirrolidina-1-carbonil]tieno[3,2-b]piridin-7-iloxi)-2-metilbenzofuran-3-carboxílico.



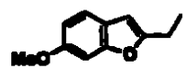
Este material se preparó por la reacción de 7-cloro-2-[(R)-3-metoxipirrolidina-1-carbonil]tieno[3,2-b]piridina **4 b** (144 mg, 0,5 mmol) con metilamida del ácido 6-hidroxi-2-metilbenzo[b]furan-3-carboxílico **11 c** (120 mg, 0,6 mmol) y Cs_2CO_3 (794 mg, 2,4 mmol) de una manera como se describe previamente para el ejemplo 1 para dar 134 mg (59%) de un sólido blancuzco. ^{1}H RMN (DMSO-d_6) δ 8,58 (1H, d, J=5,3 Hz), 8,07 (1H, s), 7,97 (1H, d, J=4,5 Hz), 7,83 (1H, d, J=8,6 Hz), 7,65 (1H, d, J=2,0 Hz), 7,24 (1H, dd, J=2,0, 8,6 Hz), 6,72 (1H, d, J=5,3 Hz), 4,25-3,75 (3H, m), 3,65-3,45 (2H, m), 3,27, 3,24 (3H, s), 2,82 (3H, d, J=4,3 Hz), 2,62 (3H, s), 2,15-1,95 (2H, m). Análisis Calculado para $C_{24}H_{23}N_3O_5S$. 0,5 H_2O: C, 60,74; H, 5,10; N, 8,86; S, 6,76. Encontrado: C, 60,89; H, 5,16; N, 8,69; S, 6,58.

Ejemplo 13: metilamida del ácido 2-metil-6-[2-(1-metil-1H-imidazol-2-il)tieno[3,2-b]piridin-7-iloxi]-benzofuran-3-carboxílico.



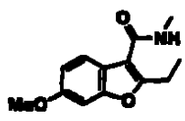
Este material se preparó por la reacción de 7-cloro-2-(1-metil-1H-imidazol-2-il)tieno[3,2-b]piridina 1 e con mietilamida del ácido 6-hidroxi-2-metilbenzo[b]furan-3-carboxílico 11 c y Cs_2CO_3 de una manera como se describe previamente para el ejemplo 1 para dar un rendimiento del 51% de un sólido amarillo claro. ^{1}H RMN (DMSO-d_6) δ 8,50 (1H, d, J=5,6 Hz), 8,01 (1H, d, J=4,5 Hz), 7,88 (1H, s), 7,82 (1H, d, J=8,6 Hz), 7,64 (1H, s), 7,40 (1H, s), 7,25 (1H, d, J=8,3 Hz), 7,03 (1H, s), 6,66 (1H, d, J=5,6 Hz), 3,97 (3H, s), 2,81 (3H, d, J=4,5 Hz), 2,64 (3H, s). Análisis Calculado para $C_{22}H_{18}N_4O_3S$. 0,25 H_2O: C, 62,47; H, 4,41; N, 13,25; S, 7,29. Encontrado: C, 62,57; H, 4,37; N, 13,05; S, 7,29.

Ejemplo 14(a): 6-metoxi-2-etilbenzofurano



Este material se preparó a partir de 2-yodo-5-metoxifenol (1 g, 4 mmol) y 1-butino de una manera como se describe previamente para el ejemplo 12 a para dar 570 mg (81%) de un aceite marrón. ^{1}H RMN ($CDCl_3$) δ 7,33 (1H, d, J=8,6 Hz), 6,97 (1H, d, J=2,2 Hz), 6,80 (1H, dd, J=2,2, 8,6 Hz), 6,26 (1H, s), 3,83 (3H, s), 3,04 (2H, q, J=7,3 Hz), 1,28 (3H, t, J=7,3 Hz).

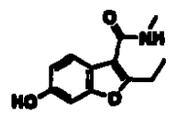
Ejemplo 14(b): metilamida del ácido metoxi-2-etilbenzofuran-3-carboxílico.



El ejemplo 14(b) se preparó a partir de 6-metoxi-2-etilbenzofurano 14 a (522 mg, 2,96 mmol) por acilación con cloruro de oxalilo en presencia de $AlCl_3$ seguido de

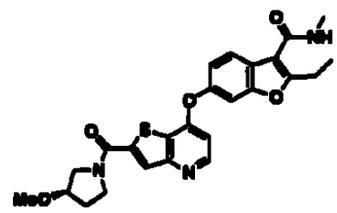
tratamiento con metilamina de una manera como se describe previamente en el Ejemplo 1 c para dar 433 mg (63%) de un sólido blancuzco. ^{1}H RMN (DMSO-d_6) δ 7,83 (1H, d, J=4,8 Hz), 7,56 (1H, d, J=8,8 Hz), 7,23 (1H, d, J=2,3 Hz), 6,83 (1H, dd, J=2,3, 8,8 Hz), 3,78 (3H, s), 3,05 (2H, q, J=7,2 Hz), 2,80 (3H, d, J=4,8 Hz), 1,26 (3H, t, J=7,2 Hz). Análisis Calculado para $C_{13}H_{15}NO_3$: C, 66,93; H, 6,48; N, 6,00. Encontrado: C, 66,96; H, 6,46; N, 5,95.

Ejemplo 14(c): metilamida del ácido 6-hidroxi-2-etilbenzofuran-3-carboxílico.



El ejemplo 14(c) se preparó a partir de metilamida del ácido 6-metoxi-2-etilbenzo[b]furan-3-carboxílico 14 b (401 mg, 1,72 mmol) por tratamiento con BBr_3 de una manera como se describe previamente para el ejemplo 1 d para dar 318 mg (84%) de un sólido blancuzco. ^{1}H RMN (DMSO-d_6) δ 9,53 (1H, s), 7,79 (1H, d, J=4,6 Hz), 7,45 (1H, d, J=8,6 Hz), 6,88 (1H, d, J=2,0 Hz), 6,74 (1H, dd, J=2,0, 8,6 Hz), 3,03 (2H, q, J=7,3 Hz), 2,77 (3H, d, J=4,6 Hz), 1,24 (3H, t, J=7,3 Hz). Análisis Calculado para $C_{12}H_{13}NO_3$: C, 65,74; H, 5,98; N, 6,39. Encontrado: C, 65,61; H, 6,06; N, 6,32.

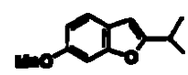
Ejemplo 14: metilamida del ácido 6-(2-[3-metoxipirrolidina-1-carbonil]tieno[3,2-b]piridin-7-iloxi)-2-etilbenzofuran-3-carboxílico.



El ejemplo 14 se preparó por la reacción de 7-cloro-2-[(R)-3-metoxipirrolidina-1-carbonil]tieno[3,2-b]piridina 4 b (135 mg, 0,46 mmol) con metilamida del ácido 6-hidroxi-2-etilbenzo[b]furan-3-carboxílico 14 c (120 mg, 0,55 mmol) y Cs_2CO_3 (594 mg, 1,82 mmol) de una manera como se describe previamente para el ejemplo 1 para dar 75 mg (34%) de un sólido blancuzco. ^{1}H RMN (DMSO-d_6) δ 8,57 (1H, d, J=5,4 Hz), 8,07 (1H, s), 8,01 (1H, d, J=4,5 Hz), 7,83 (1H, d, J=8,6 Hz), 7,68 (1H, d, J=2,0 Hz), 7,26 (1H, dd, J=2,0, 8,6 Hz), 6,73 (1H, d, J=5,4 Hz), 4,11-3,82 (3H, m), 3,69-3,43 (2H, m), 3,27, 3,24 (3H, s), 3,05 (2H, q, J=7,5 Hz), 2,82 (3H, d, J=4,5 Hz), 2,18-1,94 (2H,

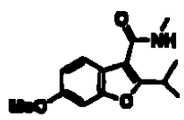
m), 1,27 (3H, t, J=7,5 Hz). Análisis Calculado para $C_{25}H_{25}N_3O_5S$. 0,2 CH_2Cl_2. 0,25 hexano: C, 61,90; H, 5,62; N, 8,11; S, 6,19. Encontrado: C, 61,88; H, 5,64; N, 8,03; S, 6,11.

Ejemplo 15(a): 6-metoxi-2-(1-metiletil)benzofurano.



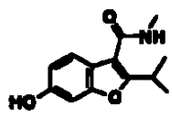
El ejemplo 15(a) se preparó a partir de 2-yodo-5-metoxifenol (896 mg, 3,6 mmol) y 3-metil-1-butino de una manera como se describe previamente para el ejemplo 12 a para dar 265 mg (38%) de un aceite ámbar. ^{1}H RMN ($CDCl_3$) δ 7,33 (1H, d, J=8,6 Hz), 6,97 (1H, d, J=2,2 Hz), 6,80 (1H, dd, J=2,2, 8,6 Hz), 6,26 (1H, s), 3,83 (3H,s), 3,07-3,01 (1H, m), 1,31 (6H, d, J=7,1 Hz).

Ejemplo 15(b): metilamida del ácido 6-metoxi-2-(1-metiletil)benzofuran-3-carboxílico.



El ejemplo 15(b) se preparó a partir de 6-metoxi-2-(1-metiletil)benzofurano 15 a (263 mg, 1,36 mmol) por acilación con cloruro de oxalilo en presencia de $AlCl_3$, seguido de tratamiento con metilamina de una manera como se describe previamente para el ejemplo 1 c para dar 200 mg (60%) de un sólido blancuzco. ^{1}H RMN (DMSO-d_6) δ 7,83 (1H, d, J=4,8 Hz), 7,56 (1H, d, J=8,8 Hz), 7,20 (1H, d, J=2,3 Hz), 6,89 (1H, dd, J=2,3, 8,8 Hz), 3,78 (3H, s), 3,68-3,61 (1H, m), 2,78 (3H, d, J=4,8 Hz), 1,26 (6H, d, J=6,8 Hz).

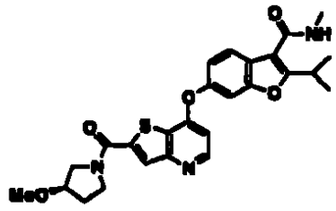
Ejemplo 15(c): metilamida del ácido 6-hidroxi-2-(1-metiletil)benzofuran-3-carboxílico.



Este material se preparó a partir de metilamida del ácido 6-metoxi-2-(1-metiletil)benzo[b]furan-3-carboxílico 15 b (173 mg, 0,84 mmol) por tratamiento con BBr_3 de una manera como se describe previamente para el ejemplo 1 d para dar 157

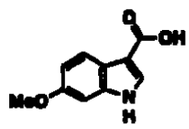
mg (80%) de una espuma crujiente. ^{1}H RMN (DMSO-d_6) δ 9,54 (1H, s), 7,76 (1H, d, J=4,6 Hz), 7,45 (1H, d, J=8,6 Hz), 6,88 (1H, d, J=2,0 Hz), 6,74 (1H, dd, J=2,0, 8,6 Hz), 3,68-3,61 (1H, m), 2,75 (3H, d, J=4,6 Hz), 1,24 (6H, d, J=7,1 Hz).

Ejemplo 15: metilamida del ácido 6-(2-[3-metoxipirrolidina-1-carbonil]tieno[3,2-b]piridin-7-iloxi)-2-(1-metiletil)benzofuran-3-carboxílico.



Este material se preparó por la reacción de 7-cloro-2-[(R)-3-metoxipirrolidina-1-carbonil]tieno[3,2-b]piridina 4 b (122 mg, 0,41 mmol) con metilamida del ácido 6-hidroxi-2-(1-metiletil)benzo[b]furan-3-carboxilico 15 c (125 mg, 0,53 mmol) y Cs_2CO_3 (200 mg, 0,61 mmol) de una manera como se describe previamente para el ejemplo 1 par dar 82 mg (40%) de un sólido blanco. ^{1}H RMN (DMSO-d_6) δ 8,56 (1H, d, J=5,3 Hz), 8,06 (1H, s), 8,01 (1H, d, J=4,6 Hz), 7,79 (1H, d, J=8,6 Hz), 7,68 (1H, d, J=2,2 Hz), 7,25 (1H, dd, J=2,2, 8,6 Hz), 6,73 (1H, d, J=5,3 Hz), 4,15-3,85 (3H, m), 3,70-3,45 (3H, m), 3,27, 3,24 (3H, s), 2,82 (3H, d, J=4,6 Hz), 2,15-1,95 (2H, m), 1,30 (6H, d, J=7,1 Hz). Análisis Calculado para $C_{28}H_{27}N_3O_5S$. 0,2 H_2O/0,2 MTBE: C, 62,99; H, 5,84; N, 8,186; S, 6,23. Encontrado: C, 62,92; H, 5,93; N, 7,97; S, 6,07.

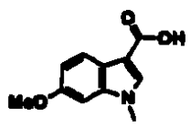
Ejemplo 16(a): ácido 6-metoxi-1H-indol-3-carboxílico.



La preparación del compuesto del título se adaptó del trabajo previamente publicado por Swain et al. (J. Med. Chem. 1992. 35, 1019-1031). A una disolución agitada de 6-metoxi-1H-indol (10 g, 68 mmol) en DMF (100 ml) a 0°C se añadió anhídrido trifluoroacético (21,4 ml, 150 mmol) gota a gota. Después de la adición, la mezcla se calentó a 165°C durante 18 horas. La mezcla se retiró del calor y se añadió gota a gota a agua con hielo (1 l). El precipitado resultante se recogió por filtración, se lavó con agua y a continuación se suspendió en NaOH acuoso al 20% (200 ml). La suspensión se calentó a 90°C hasta homogeneidad (~ 2 h). La mezcla oscura se dejó

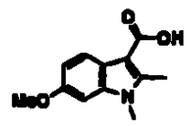
enfriar hasta ta. y se lavó con Et_2O (200 ml). La capa acuosa se lavó con CH_2Cl_2. Durante la extracción se formó un precipitado que fue recogido por filtración. El filtrado se dividió en capas y la capa acuosa se acidificó a pH 3 usando HCl 6 N, dando como resultado la formación de un precipitado. Los sólidos recogidos previamente se añadieron a la suspensión y la mezcla se agitó durante 3 horas. La mezcla se acidificó a pH 2 usando HCl 6 N y los sólidos se recogieron por filtración. Los sólidos se lavaron con agua y se secaron en aire para dar 10,08 g (77%) de un sólido blancuzco que se utilizó a continuación sin purificación adicional. ^{1}H RMN (DMSO-d_6) δ 11,53 (1H, s ancho), 7,88 (1H, d, J=8,7 Hz), 7,75 (1H, s), 6,91 (1H, d, J=2,0 Hz), 6,74 (1H, dd, J=2,0, 8,7 Hz), 3,75 (3H, s).

Ejemplo 16(b): ácido 6-metoxi-1-metil-1H-indol-3-carboxílico



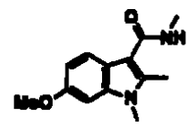
A una disolución agitada de ácido 6-metoxi-1H-indol-3-carboxílico 16 a (8,0 g, 41,2 mmol) en DMF anhidro (100 ml) a 0°C se añadió NaH (dispersión al 60% en aceite, 4,12 g, 103 mmol) en una única porción. Después de agitar a 0°C durante 1,3 horas, se añadió yodometano (7,5 ml, 120 mmol) vía una jeringa. La mezcla resultante se agitó durante 18 horas, calentando gradualmente hasta temperatura ambiente, a continuación se vertió en NaOH 0,2 N (1 l) y se extrajo con EtOAc (3 x 250 ml). Los extractos combinados se lavaron secuencialmente con NaOH 1 N (50 ml), agua (3x 50 ml), y salmuera (50 ml), a continuación se secaron sobre Na_2SO_4 y se concentraron a vacío. El éster metílico del ácido 6-metoxi-1-metil-1H-indol-3-carboxílico en bruto resultante se trituró con hexanos y se recogió por filtración. Este material se suspendió en KOH acuoso (3,36 g, 60 mmol en 150 ml) y la suspensión resultante se calentó a reflujo durante 3,5 horas. La mezcla se vertió a continuación sobre 200 g de hielo y se lavó con CH_2Cl_2 (2 x 50 ml). La capa acuosa se acidificó con HCl 6 N hasta pH 2 dando como resultado un precipitado blanco que se recogió por filtración, se lavó con agua y se secó al aire para dar 7,25 g (86%) del compuesto del título que se utilizó a continuación sin ninguna purificación adicional. ^{1}H RMN (DMSO-d_6) δ 11,84 (1H, s ancho), 7,88 (1H, s), 7,84 (1H, d, J=8,7 Hz), 7,02 (1H, d, J=2,2 Hz), 6,82 (1H, dd, J=2,2, 8,7 Hz), 3,81 (3H, s), 3,79 (3H, s). Análisis Calculado para $C_{11}H_{11}NO_3$. 0,2 H_2O: C, 63,27; H, 5,50; N, 6,71. Encontrado: C, 63,36; H, 5,35; N, 6,63.

Ejemplo 16(c): ácido 1,2-dimetil-6-metoxi-1H-indol-3-carboxílico.



La preparación del compuesto del título se adaptó del trabajo previamente publicado por Buttery et al. (J. Chem. Soc. Perkin Trans. **1993**, 1425-1431). Una disolución de ácido 6-metoxi-1-metil-1H-indol-3-carboxílico **16 b** (5,2 g, 25,4 mmol) en THF anhidro (100 ml) se añadió gota a gota durante 30 minutos a una disolución agitada de LDA [preparada de N-BuLi (69 mmol) y diisopropilamina (60 mmol)] en THF anhidro (50 ml) a –78°C. La mezcla resultante se dejó calentar hasta –10°C durante 30 minutos, a continuación se enfrió hasta –78°C previamente a la adición de yodometano (8 ml, 128,5 mmol) vía una jeringa. La mezcla ámbar resultante se dejó calentar hasta 15°C durante 3 horas, a continuación se lavó con NaOH 1 N (100 ml). Durante la separación se formó un precipitado que se recogió por filtración. El filtrado se separó en capas. La capa orgánica se lavó de nuevo con NaOH 1 N (50 ml). Los sólidos se suspendieron en agua y la suspensión resultante se acidificó hasta pH 3 usando HCl 0,5 N. Las suspensión espesa resultante se sonicó y agitó durante 15 minutos, a continuación se recogieron los sólidos por filtración y se lavaron con agua. Las capas de NaOH combinadas anteriores se acidificaron hasta pH 4 usando HCl 6 N para dar otro lote de sólidos que se recogió por filtración y se lavó con agua. El primer lote de sólidos se suspendió en $CHCl_3$:MeOH (3:1) caliente y el material insoluble se recogió por filtración. Se encontró que este material aislado era el producto deseado. El filtrado se concentró a sequedad a presión reducida y el residuo se trituró dos veces con $CHCl_3$ caliente para dar una segunda cosecha de producto. Los sólidos obtenidos de la acidificación de la capa acuosa básica se trituraron tres veces con $CHCl_3$ caliente para dar una tercera cosecha de producto. Las tres cosechas se combinaron, se trituraron con MTBE y se filtraron para dar 3,13 g (56%) de un sólido blanco. Este material era de pureza apropiada para ser utilizado a continuación sin purificación adicional. ^{1}H RMN (DMSO-d_6) δ 11,83 (1H, s ancho), 7,81 (1H, d, J=8,6 Hz), 7,03 (1H, d, J=2,3 Hz), 6,76 (1H, dd, J=2,3, 8,6 Hz), 3,79 (3H,s), 3,67 (3H, s), 2,67 (3H, s). Análisis Calculado para $C_{12}H_{13}NO_3$. 0,2 H_2O: C, 64,68; H, 6,06; N, 6,29. Encontrado: C, 64,89; H, 5,91; N, 6,29.

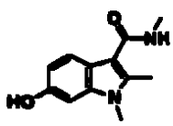
Ejemplo 16(d): metilamida del ácido 6-metoxi-1,2-dimetil-1H-indol-3-carboxílico.



A una disolución agitada del carboxilato **16 c** (700 mg, 3,2 mmol) en CH_2Cl_2 anhidro (15 ml) a 0°C se añadió una gota de DMF, seguida de cloruro de oxalilo (0,55 ml, 6,4 mmol) vía una jeringa. Después de agitar a 0°C durante 15 minutos se retiró el baño de hielo y la mezcla se agitó a temperatura ambiente durante 55 minutos. La mezcla se diluyó con benceno y se concentró hasta sequedad a presión reducida. El residuo se disolvió en CH_2Cl_2 (10 ml) y se añadió vía una jeringa a una disolución 2 M de metilamina en THF (30 ml). Después de observar una ligera exoterma al comienzo de la adición, la mezcla se enfrió hasta 0°C durante el resto de la adición. La reacción se agitó durante unas 16 horas adicionales, calentando gradualmente hasta temperatura ambiente, a continuación se repartió entre CH_2Cl_2 (100 ml) y NaOH 1 N (100 ml). La capa orgánica se lavó secuencialmente con NaOH 1 N (50 ml), salmuera (50 ml), a continuación se secó sobre Na_2SO_4 y se concentró a vacío. El residuo en bruto se trituró con MTBE y se filtró para dar 590 mg (79%) de un sólido blanco. ^1H RMN (DMSO-d_6) δ 7,60 (1H, d, J=8,6 Hz), 7,39-7,35 (1H, m), 7,00 (1H, d, J=2,3 Hz), 6,72 (1H, dd, J=2,3, 8,6 Hz), 3,79 (3H, s), 3,63 (3H, s), 2,76 (3H, d, J=4,6 Hz), 2,53 (3H, s).

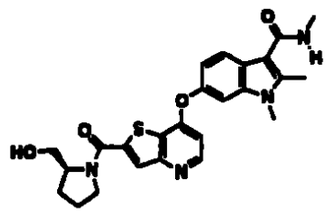
Análisis Calculado para $C_{13}H_{16}N_2O_2$: C, 67,22; H, 6,54; N, 12,06. Encontrado: C, 67,00; H, 6,95; N, 11,99.

Ejemplo 16(e):metilamida del ácido 6-hidroxi-1,2-dimetil-1H-indol-3-carboxílico



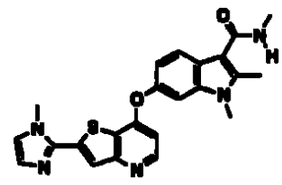
El ejemplo 16(e) se preparó a partir de metilamida del ácido 6-metoxi-1,2-dimetil-1H-indol-3-carboxílico **16 d** (560 mg, 2,4 mmol) por tratamiento con BBr_3 de una manera como se describe previamente para el ejemplo **1 d** para obtener 380 mg (73%) de sólido blanco. ^1H RMN (DMSO-d_6) δ 9,05 (1H, s), 7,50 (1H, d, J=8,59 Hz), 7,35-7,28 (1H, m), 6,73 (1H, d, J=1,77 Hz), 6,60 (1H, dd, J=8,5, 2,27 Hz), 3,54 (3H, s), 2,75 (3H, d, J=4,55 Hz), 2,53 (3H, s). Análisis Calculado para $C_{12}H_{14}N_2O_2$. 0,3 H_2O: C, 64,44; H, 6,58; N, 12,53. Encontrado: C, 64,55; H, 6,49; N, 12,35.

Ejemplo 16: metilamida del ácido 6-[2-(2-hidroximetil-pirrolidina-1-carb nil)-tieno[3,2-b]piridin-7-iloxi]-1,2-dimetil-1H-indol-3-carboxílico.



Este material se preparó por la reacción de 7-cloro-2-[(S)-2-([t-butildimetilsililoxi]metil)-pirrolidina-1-carbonil]tieno[3,2-b]piridina **3 b** (76 mg, 0,3 mmol) con metilamida del ácido 6-hidroxi-1,2-dimetil-1H-indol-3-carboxílico **16 e** (100 mg, 0,46 mmol) y Cs_2CO_3 (488 mg, 1,5 mmol) de una manera como se describe previamente para el ejemplo 1 para dar 53 mg (43%) de un sólido blancuzco. ^{1}H RMN (DMSO-d_6) δ 8,54 (1H, d, J=5,46 Hz), 7,99 (1H, s), 7,83 (1H, d, J=8,67 Hz), 7,61-7,55 (1H, m), 7,54 (1H, d, J=2,07 Hz), 7,03 (1H, dd, J=8,48, 2,07 Hz), 6,64 (1H, d, J=5,27 Hz), 5,10-4,80 (1H, 2m), 4,41-4,16 (1H, 2m), 3,91-3,77 (1H, m), 3,67 (3H, s), 3,64-3,47 (2H, m), 2,80 (3H, d, J=4,52 Hz), 2,60 (3H, s), 2,04-1,81 (4H, m). Análisis Calculado para $C_{25}H_{26}N_4O_4S$. 0,4 H_2O. 0,2 EtOAc: C, 61,56; H, 5,69;

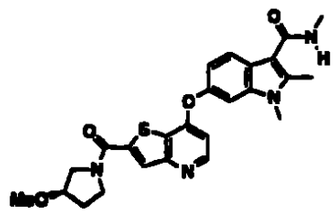
Ejemplo 17: metilamida del ácido 1,2-dimetil-6-[2-[1-metil-1H-imidazol-2-il]tieno[3,2-b]piridin-7-iloxi)-1H-indol-3-carboxílico.



Este material se preparó por la reacción de 7-cloro-2-(1-metil-1H-imidazol-2-il)tieno[3,2-b]piridina **1 e** (76 mg, 0,3 mmol) con metilamida del ácido 6-hidroxi-1,2-dimetil-1H-indol-3-carboxílico **16 e** (100 mg, 0,46 mmol) y Cs_2CO_3 (488 mg, 1,5 mmol) de una manera como se describe previamente para el ejemplo 1 para dar 51 mg (39%) de producto en forma de sólido blancuzco. ^{1}H RMN (DMSO-d_6) δ 8,48 (1H, d, J=5,5 Hz), 7,88 (1H, s), 7,83 (1H, d, J=8,6 Hz), 7,61-7,55 (1H, m), 7,53 (1H, t, J=2,3 Hz), 7,41 (1H, d, J=1,0 Hz), 7,0-6,99 (2H, m), 6,59 (1H, d, J=5,5 Hz), 3,98 (3H, s), 3,67 (3H, s), 2,80 (3H, d, J=4,6 Hz), 2,60 (3H, s). Análisis Calculado para $C_{23}H_{21}N_5O_2S$. 0,3 H_2O.

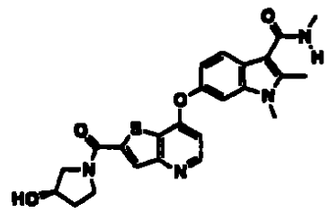
0,1 EtOAc: C, 63,05; H, 5,07; N, 15,71; S, 7,19. Encontrado: C, 63,06; H, 5,06; N, 15,56; S, 6,96.

Ejemplo 18: metilamida del ácido 1,2-dimetil-6-(2-[3-metoxi-pirrolidina-1-carbonil]tieno[3,2-b]piridin-7-iloxi)-1H-indol-3-carboxílico



Este material se preparó por la reacción de 7-cloro-2-[(R)-3-metoxipirrolidina-1-carbonil]tieno[3,2-b]piridina **4 b** (157 mg, 0,5 mmol) con metilamida del ácido 6-hidroxi-1,2-dimetil-1H-indol-3-carboxílico **16 e** (150 mg, 0,7 mmol) y Cs_2CO_3 (673 mg, 2,1 mmol) de una manera como se describe previamente para el ejemplo 1 para dar 51 mg (39%) de una espuma crujiente. ^{1}H RMN (DMSO-d_6) δ 8,54 (1H, dd, J=5,5, 1,13 Hz), 8,05 (1H, s), 7,84 (1H, d, J=8,6 Hz), 7,61-7,55 (1H, m), 7,54 (1H, d, J=2,1 Hz), 7,03 (1H, dd, J=2,01, 8,6 Hz), 6,64 (1H, d, J=5,5 Hz), 4,12-3,51 (5H, m), 3,67 (3H, s), 3,27, 3,24 (3H, 2s), 2,80 (3H, d, J=4,5 Hz), 2,60 (3H, s), 2,35-1,95 (2H, m). Análisis Calculado para $C_{25}H_{28}N_4O_4S$. 0,9 H_2O. 0,2 EtOAc: C, 60,47; H, 5,78; N, 10,93; S, 6,26. Encontrado: C, 60,46; H, 5,56; N, 10,81; S, 6,34.

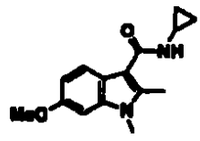
Ejemplo 19: metilamida del ácido 1,2-dimetil-6-(2-[3-hidroxi-pirrolidina-1-carbonil]tieno[3,2-b]piridin-7-iloxi)-1H-indol-3-carboxílico.



Este material se preparó a partir de metilamida del ácido 1,2-dimetil-6-(2-[3-metoxi-pirrolidina-1-carbonil]tieno[3,2-b]piridin-7-iloxi)-1H-indol-3-carboxílico **18** (128 mg, 0,27 mmol) por tratamiento con BBr_3 de una manera como se describe previamente para el ejemplo 1 d para dar 70 mg (56%) de un sólido blanco. ^{1}H RMN (DMSO-d_6) δ 8,54 (1H, dd, J=5,3, 1,1 Hz), 8,05, 7,99 (1H, 2s), 7,83 (1H, d, J=8,6 Hz), 7,61-7,55 (1H, m), 7,54 (1H, d, J=2,2 Hz), 7,03 (1H, dd, J=2,2, 8,6 Hz), 6,64 (1H, dd,

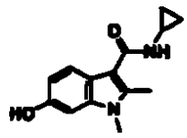
J=5,3, 1,1 Hz), 5,10-5,05 (1H, m), 4,41-4,31 (1H, m), 4,00-3,90 (1H, m), 3,67 (3H, s), 3,66-3,42 (3H, m), 2,80 (3H, d, J=4,5 Hz), 2,60 (3H, s), 2,06-1,92 (2H, m). Análisis Calculado para $C_{24}H_{24}N_4O_4S$. 0,9 H_2O: C, 59,96; H, 5,41; N, 11,65; S, 6,67. Encontrado: C, 59,87; H, 5,19; N, 11,51; S, 6,48.

Ejemplo 20(a): ciclopropilamida del ácido 6-metoxi-1,2-dimetil-1H-indol-3-carboxílico.



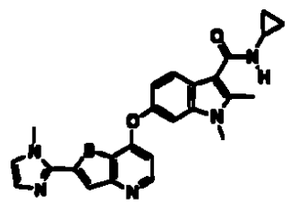
Este material se preparó a partir de ácido 1,2-dimetil-6-metoxi-1H-indol-3-carboxílico **16 c** (500 mg, 2,3 mmol), cloruro de oxalilo (0,4 ml, 4,6 mmol) y ciclopropilamina (1,6 ml, 23 mmol) de una manera como se describe previamente para el ejemplo **16 d** para dar 480 mg (82%) de un sólido blanco. ^{1}H RMN (DMSO-d_6) δ 7,57 (1H, d, J=3,8 Hz), 7,50 (1H, d, J=8,8 Hz), 6,99 (1H, d, J=2,3 Hz), 6,71 (1H, dd, J=2,3, 8,8 Hz), 3,78 (3H, s), 3,63 (3H, s), 2,83-2,80 (1H, m), 2,51 (3H, s), 0,68-0,62 (2H, m), 0,57-0,53 (2H, m).

Ejemplo 20(b): ciclopropilamida del ácido 6-hidroxi-1,2-dimetil-1H-indol-3-carboxílico.



Este material se preparó a partir de ciclopropilamida del ácido 6-metoxi-1,2-dimetil-1H-indol-3-carboxílico **20 a** (655 mg, 2,5 mmol) por tratamiento con BBr_3 de una manera como se describe previamente para el ejemplo **1 d** para dar 130 mg (21%) de un sólido blanco. ^{1}H RMN (DMSO-d_6) δ 9,06 (1H, s), 7,51 (1H, d, J=4,0 Hz), 7,41 (1H, d, J=8,5 Hz), 6,73 (1H, d, J=1,8 Hz), 6,60 (1H, dd, J=1,8, 8,5 Hz), 3,56 (3H, s), 2,82 (1H, m), 2,50 (3H, s), 0,62 (2H, m), 0,52 (2H, m).

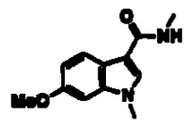
Ejemplo 20: ciclopropilamida del ácido 1,2-dimetil-6-[2-(1-metil-1H-imidazol-2-il)-tieno[3,2-b]piridin-7-iloxi]-1H-indol-3-carboxílico.



Este material se preparó por la reacción de 7-cloro-2-(1-metil-1H-imidazol-2-il)tieno[3,2-b]piridina **1 e** (79 mg, 0,3 mmol) con ciclopropilamida del ácido 1,2-dimetil-6-hidroxi-1H-indol-3-carboxílico **20 b** (93 mg, 0,4 mmol) y Cs_2CO_3 (517 mg, 1,6 mmol) de una manera como se describe previamente para el ejemplo 1 para dar 84 mg (58%) de un sólido blanco. ^{1}H RMN (DMSO-d_6) δ 8,47 (1H, d, J=4,9 Hz), 7,87 (1H, s), 7,78 (1H, d, J=3,7 Hz), 7,72 (1H, d, J=8,5 Hz), 7,52 (1H, s), 7,40 (1H, s), 7,02 (1H, s), 7,01 (1H, d, J=8,9 Hz), 6,58 (1H, d, J=5,3 Hz), 3,98 (3H, s), 3,67 (3H, s), 2,85 (1H, m), 2,57 (3H, s), 0,68 (2H, m), 0,58 (2H, m).

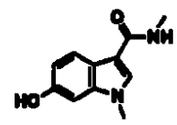
Análisis Calculado para $C_{25}H_{23}N_5O_2S$. 0,5 MeOH: C, 64,67; H, 5,32; N, 14,79; S, 6,77. Encontrado: C, 64,57; H, 5,24; N, 14,72; S, 6,81.

Ejemplo 21(a): metilamida del ácido 6-metoxi-1-metil-1H-indol-3-carboxílico



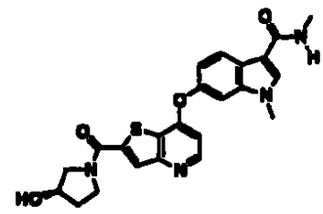
Este material se preparó a partir del ácido 6-metoxi-1-metil-indol-3-carboxílico **16 b** (515 mg, 2,5 mmol), cloruro de oxalilo (0,9 ml, 12,6 mmol) y metilamina (7,5 mmol) de una manera como se describe previamente para el ejemplo **16 d** para dar 457 mg de un sólido marrón pálido (83%). ^{1}H RMN (CD_3OD) δ 7,83 (1H, d, J=8,7 Hz), 7,51 (1H, s), 6,81 (1H, d, J=2,3 Hz), 6,72 (1H, dd, J=2,3, 8,7 Hz), 3,75 (3H, s), 3,67 (3H, s),2,80 (3H, s); ESIMS (MH^+): 219,05.

Ejemplo 21(b): metilamida del ácido 6-hidroxi-1-metil-1H-indol-3-carboxílico



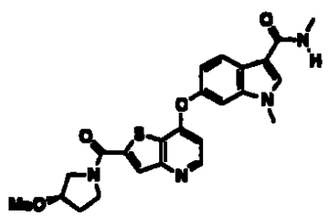
Este material se preparó a partir de metilamida del ácido 6-metoxi-1-metil-1H-indol-3-carboxílico **21 a** (453 mg, 2,1 mmol) por tratamiento con BBr_3 de una manera como se describe previamente para el ejemplo 1 d para dar 219 mg (51%) de un sólido naranja pálido. ^{1}H RMN (CD_3OD) δ 7,75 (1H, d, J=8,5 Hz), 7,47 (1H, s), 6,61-6,66 (2H, m), 3,62 (3H, s), 3,24 (1H, s), 2,79 (3H, s). ESIMS (MH^+): 205,10.

Ejemplo 21: metilamida del ácido 6-{2-[3-(R)-hidroxi-pirrolidina-1-carbonil]tieno[3,2-b]piridin-7-iloxi}-1-metil-1H-indol-3-carboxílico.



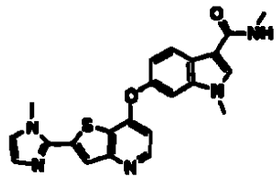
Este material se preparó por la reacción de 7-cloro-2-[(R)-3-hidroxipirrolidina-1-carbonil]tieno[3,2-b]piridina **4 a** (152 mg, 0,5 mmol) con metilamida del ácido 6-hidroxi-1-metil-1H-indol-3-carboxílico **21 b** (110 mg, 0,5 mmol) y Cs_2CO_3 (176 mg, 0,5 mmol) de una manera como se describe previamente para el ejemplo 1 para dar 65 mg (27%) de un sólido blanco. ^{1}H RMN (CD_3OD) δ 8,39 (1H, d, J=5,5 Hz), 8,12 (1H, d, J=8,7 Hz), 7,77 (1H, d, J=17,33 Hz), 7,72 (1H, s), 7,32 (2H, m), 6,99 (1H, dd, J_1=6,59 Hz, J_2=2,08 Hz), 6,60 (1H, d, J=5,5 Hz), 4,43 (1H, m), 3,95 (1H, m), 3,73 (3H, s), 3,59-3,69 (3H, m), 2,83 (3H, s), 2,01 (2H, m), ESIMS (MH^+): 451,10; Análisis Calculado para $C_{23}H_{22}N_4O_4S$. 0,6 CH_3OH. 0,2 CH_2Cl_2: C, 57,91; H, 5,02; N, 11,35. Encontrado: C, 57,68; H, 5,06; N, 11,43.

Ejemplo 22: metilamida del ácido 6-[2-(3-metoxipirrolidina-1-carbonil)-tieno[3,2-b]piridin-7-iloxi]-1-metil-1H-indol-3-carboxílico.



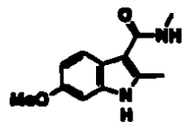
Este material se preparó por la reacción de 7-cloro-2-[(R)-3-metoxipirrolidina-1-carbonil]tieno[3,2-b]piridina **4 b** con metilamida del ácido 6-hidroxi-1-metil-1H-indol-3-carboxílico **21 b** y Cs_2CO_3 de una manera como se describe previamente para el ejemplo 1. ^1H RMN (CD_3OD) δ 8,53 (1H, d, J=5.5 Hz), 8,25 (1H, d, J=8,7 Hz), 7,96 (1H, d, J=6,2 Hz), 7,86 (1H, s), 7,46 (1H, d, J=1,9 Hz), 7,12 (1H, d, J=8,5 Hz), 6,74 (1H, d, J=5,5 Hz), 4,19-4,11 (1H, m), 4,05-3,95 (2H, m), 3,38 (3H, s), 3,85-3,72 (2H, m), 3,40 (3H, d, J=13,9 Hz), 2,96 (3H, s), 2,30-2,09 (2H, m), LCMS (ESI+): [M+H]/z Calculado 465, encontrado 465. Análisis Calculado para $C_{24}H_{24}N_4O_4S$. 0,4 CH_2Cl_2: C, N,. H.

Ejemplo 23: metilamida del ácido 1-metil-6-[2-(1-metil-1H-imidazol-2-il)-tieno[3,2-b]piridin-7-iloxi]-1H-indol-3-carboxílico.



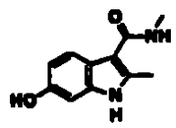
Este material se preparó por la reacción de 7-cloro-2-(1-metil-1H-imidazol-2-il)tieno[3,2-b]piridina **1 e** con metilamida del ácido 6-hidroxi-1-metil-1H-indol-3-carboxílico **21 b** y Cs_2CO_3 de una manera como se describe previamente para el ejemplo 1. ^1H RMN (300 MHz, $CDCl_3$) δ 8,43 (1H, d, J=5,5 Hz), 8,05 (1H, d, J=8,7 Hz), 7,67 (1H, s), 7,61 (1H, s), 7,17 (1H, d, J=2,1 Hz), 7,13 (1H, s), 7,08 (1H, dd, J=2,1, 8,7 Hz), 7,02 (1H, s), 6,54 (1H, d, J=5,5 Hz), 3,95 (3H, s), 3,75 (3H, s), 3,01 (3H, s). LCMS (ESI+) [M+H]/z Calculado 418, encontrado 418. Análisis ($C_{22}H_{19}N_5O_2S$. 0,25 EtOAc) C, H, N.

Ejemplo 24(a): metilamida del ácido 6-metoxi-2-metil-1H-indol-3-carboxílico.



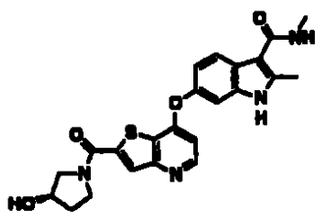
A una disolución agitada de 6-metoxi-2-metil-1H-indol (500 mg, 3,1 mmol) (preparada según JACS 1988, 110, 2242) en 8 ml de THF anhidro mantenida a temperatura ambiente se añadió bromuro de metilmagnesio (1,13 ml, disolución 3,0 M en éter dietílico, 3,41 mmol). Después de agitar durante 1 hora a temperatura ambiente, se introdujo una disolución de cloruro de cinc 0,5 M en THF (7,44 ml, 3,72 mmol) y la mezcla se agitó durante 1 hora a temperatura ambiente antes de la adición de isocianato de metilo (424 mg, 7,44 mmol). La mezcla resultante se agitó a temperatura ambiente durante la noche, se enfrió rápidamente con agua, y se extrajo con EtOAc. La capa orgánica combinada se lavó con salmuera, se secó sobre Na_2SO_4, se filtró y se concentró. El residuo se purificó por cromatografía flash en columna eluyendo con MeOH al 2-5% en CH_2Cl_2 para dar 200 mg de producto (rendimiento del 30%). ^1H RMN (300 MHz, CD_3OD) δ 7,55 (1H, d, J=8,6 Hz), 6,78 (1H, d, J=2,2 Hz), 6,70 (1H, dd, J=2,2, 8,6 Hz), 3,73 (3H, s), 2,90 (3H, s), 2,52 (3H, s). LCMS (ESI+) [M+H]/z Calculado 219, encontrado 219.

Ejemplo 24(b): metilamida del ácido 6-hidroxi-2-metil-1H-indol-3-carboxílico.



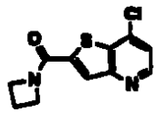
Este material se preparó a partir de metilamida del ácido 6-metoxi-2-metil-1H-indol-3-carboxílico **24 a** por tratamiento con BBr_3 de una manera como se describe previamente para el ejemplo 1 d. ^1H RMN (300 MHz, CD_3OD) δ 7,52 (1H, d, J=8,7 Hz), 6,72 (1H, d, J=2,3 Hz), 6,65 (1H, dd, J=2,3, 8,7 Hz), 2,93 (3H, s), 2,55 (3H, s), LCMS (ESI+) [M+H]/z Calculado 205, encontrado 205.

Ejemplo 24: metilamida del ácido 6-[2-(3-hidroxi-pirrolidina-1-carbonil)-tieno[3,2-b]piridin-7-iloxi]-2-metil-1H-indol-3-carboxílico.



Este material se preparó por la reacción de 7-cloro-2-[(R)-3-hidroxipirrolidina-1-carbinil]tieno[3,2-b]piridina 4 a con metilamida del ácido 6-hidroxi-2-metil-1H-indol-3-carboxílico y Cs_2CO_3 de una manera como se describe previamente para el Ejemplo 1. ^{1}H RMN (300 MHz, CD_3OD) δ 8,48 (1H, d, J=5,5 Hz), 7,91 (1H, d, J=17,3 Hz), 7,86 (1H, d, J=8,6 Hz), 7,21 (1H, s), 7,00 (1H, d, J=8,6 H), 6,69 (1H, d, J=5,5 Hz), 4,50 (1H, m), 4,05-3,70 (4H, m), 2,97 (3H, s), 2,63 (3H, s), 2,40-1,90 (2H, m). LCMS (ESI+) [M+H]/z Calculado 451, encontrado 451.

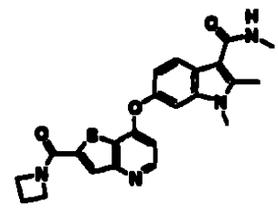
Ejemplo 25(a): 2-(azetidin-1-il-carbonil)-7-clorotieno[3,2-b]piridina.



Este material se preparó a partir de 7-clorotieno[3,2-b]piridina-2-carboxilato de litio (100 mg, 0,47 mmol) por tratamiento con cloruro de tionilo seguido de copulación con azetidina, de una manera como se describe para el ejemplo 9 d para dar 98 mg (83%) de un sólido amarillo oscuro. ^{1}H RMN (DMSO-d_6) δ 8,72 (1H, d, J=5,1 Hz), 7,96 (1H, s), 7,70 (1H, d, J=5,1 Hz), 4,62 (2H, t, J=7,4 Hz), 4,12 (2H, t, J=7,7 Hz), 2,34 (2H, tt, J=7,4, 7,7 Hz).

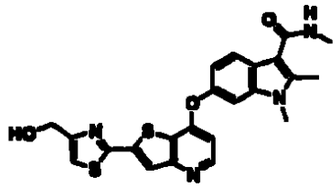
Análisis Calculado para $C_{11}H_9N_2OSCl$: C, 52,28; H, 3,59; Cl, 14,03; N, 11,09; S, 12,69. Encontrado: C, 52,39; H, 3,63; Cl, 14,29; 10,99; S, 12,74.

Ejemplo 25: metilamida del ácido 6-[2-(azetidina-1-carbonil)-tieno[3,2-b]piridin-7-iloxi]-1,2-dimetil-3H-indol-3-carboxílico.



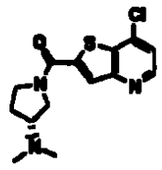
Este material se preparó por la reacción de 2-(azetidin-1-il-carbonil)-7-clorotieno[3,2-b]piridina **25 a** con metilamida del ácido 6-hidroxi-1,2-dimetil-1H-indol-3-carboxílico **16 e** y Cs_2CO_3 de una manera como se describe previamente para el ejemplo 1. ^1H RMN (300 MHz, CD_3OD) δ 8,41 (1H, d, J=5,5 Hz), 7,80 (1H, d, J=3,20 Hz), 7,74 (1H, d, J=11,68 Hz), 7,30 (1H, s), 6,94 (1H, d, J=8,66 Hz), 6,62 (1H, d, J=5,5 Hz), 4,64-4,59 (2H, m), 4,20-4,15 (2H, m), 3,63 (3H, s), 2,85 (3H, s), 2,57 (3H, s), 2,44-2,36 (2H, m). LCMS (ESI+) [M+H]/z Calculado 435, encontrado 435.
Análisis ($C_{23}H_{22}N_4O_3S$. 0,35 CH_2Cl_2) C, H, N.

Ejemplo 26: metilamida del ácido 1,2-dimetil-6-(2-[4-(hidroximetil)tiazol-2-il]tieno[3-2-b]piridin-7-iloxi)-1H-indol-3-carboxílico.



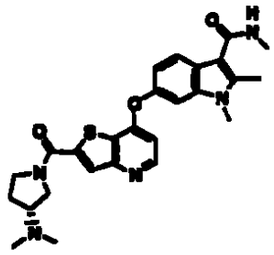
Este material se preparó por la reacción de [2-(7-cloro-tieno[3,2-b]piridin-2-il)-tiazol-4-il]-metanol con metilamida del ácido 6-hidroxi-1,2-dimetil-1H-indol-3-carboxílico **16 e** y Cs_2CO_3 de una manera como se describe previamente para el ejemplo 1. ^1H RMN (300 MHz, DMSO-d_6) δ 8,52 (1H, d, J=5,5 Hz), 8,14 (1H, s), 7,83 (1H, d, J= 8,6 Hz), 7,63 (1H, s), 7,58 (1H, d, J=4,7 Hz), 7,54 (1H, d, J=2,0 Hz), 7,04 (1H, dd, J=2,0, 8,6 Hz), 6,64 (1H, d, J=5,5 Hz), 4,60 (2H, s), 3,67 (3H, s), 2,80 (3H, d, J=4,3 Hz), 2,61 (3H, s). LCMS (ESI+) [M+H]/z Calculado 465, encontrado 465. Análisis ($C_{23}H_{20}N_4O_3S_2$. 0,6 CH_3OH) C, H, N.

Ejemplo 27(a): (3R)-1-[(7-clorotieno[3,2-b]piridin-2-il)carbonil]-N,N-dimetilpirrolidin-3-amina



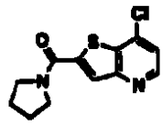
Este material se preparó a partir de 7-clorotieno[3,2-b]piridina-2-carboxilato de litio (0,214 g, 1,0 mmol) por tratamiento con cloruro de tionilo seguido de reacción del cloruro de acilo resultante con (3R)-N,N-dimetilpirrolidin-3-amina (0,114 g, 1,0 mmol) y Et_3N (0,139 ml, 1,0 mmol), de una manera como se describe previamente para el ejemplo 9 d para dar un sólido marrón (0,134 g, 43%). ^1H RMN (300 MHz, CD_3OD) δ 7,24 (1H, d, J=5,1 Hz), 6,57 (1H, d, J=8,48 Hz), 6,15 (1H, d, J=5,1 Hz), 2,70 (1H, m), 2,51 (2H, m), 2,24 (1H, m), 2,04 (1H, m), 1,49 (1H, m), 0,93 (3H, s), 0,90 (3H, s), 0,52 (1H, m); ESIMS (MH^+): 310,10.

Ejemplo 27: 6-[(2-{[(3R)-3-(dimetilamino)pirrolidin-1-il]carbonil}tieno[3,2-b]piridin-7-il)oxi]-N,1,2-trimetil-1H-indol-3-carboxamida.



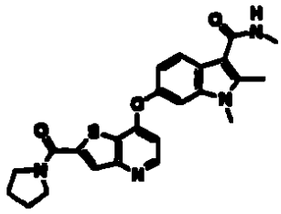
Este material se preparó por la reacción de (3R)-1-[(7-clorotieno[3,2-b]piridin-2-il)carbonil]-N,N-dimetilpirrolidin-3-amina 27 a (0,136 g, 0,44 mmol) con 6-hidroxi-N,1,2-trimetil-1H-indol-3-carboxamida 16 e (0,064 g, 0,294 mmol) y Cs_2CO_3 (0,096 g, 0,29 mmol) de una manera como se describe previamente para el ejemplo 1 para dar una espuma de color marrón (0,059 g, 17%). ^1H RMN (300 MHz, CD_3OD) δ 8,40 (1H, d, J=5,46 Hz), 7,84 (1H, d, J=6,59 Hz), 7,76 (1H, d, J=8,67 Hz), 7,29 (1H, d, J=2,07 Hz), 6,95 (1H, dd, J=8,57, 2,17 Hz), 6,62 (1H, d, J=5,65 Hz), 4,06 (1H, m), 3,87 (2H, m), 3,63 (3H, s), 3,03 (2H, m), 2,88 (3H, s), 2,57 (3H, s), 2,37 (3H, s), 2,32 (3H, s), 2,23 (1H, m), 1,95 (1H, m); HRMS (MH^+): Calculado: 492,2085; Encontrado: 492,2069.

Ejemplo 28 (a): (7-cloro-tieno[3,2-b]piridin-2-il)-pirrolidin-1-il-metanona.



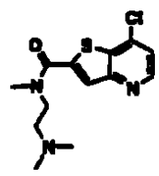
Este material se preparó a partir de la copulación de ácido 7-clorotieno[3,2-b]piridina-2-carboxílico y pirrolidina de una manera como se describe previamente para el ejemplo **9** d. ^{1}H RMN (300 MHz, CD_3OD) δ 8,60 (1H, d, J=5,1 Hz), 7,84 (1H, s), 7,32 (1H, d, J=5,1 Hz), 3,82 (2H, t, J=6,4 Hz), 3,70 (2H, t, J=6,6 Hz), 2,02 (4H, m). LCMS (ESI+) [M+H]/z Calculado 267, encontrado 267.

Ejemplo 28: metilamida del ácido 1,2-dimetil-6-[2-(pirrolidina-1-carbonil)-tieno[3,2-b]piridin-7-iloxi]-1H-indol-3-carboxílico.



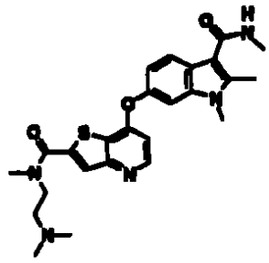
Este material se preparó por la reacción de (7-cloro-tieno[3,2-b]piridin-2-il)-pirrolidin-1-il-metanona **28** a con metilamida del ácido 6-hidroxi-1,2-dimetil-1H-indol-3-carboxílico **16** e y Cs_2CO_3 de una manera como se describe previamente para el ejemplo **1**. ^{1}H RMN (300 MHz, CD_3OD) δ 8,47 (1H, d, J=5,3 Hz), 7,82 (1H, s), 7,74 (1H, d, J=8,4 Hz), 7,14 (1H, d, J=1,7 Hz), 7,02 (1H, dd, J=1,7, 8,4 Hz), 6,55 (1H, d, J=5,3 Hz), 5,91 (1H, s ancho), 3,84 (2H, m), 3,70 (2H, m), 3,65 (3H, s), 3,05 (3H, d, J=4,5 Hz), 2,72 (3H, s), 2,02 (4H, m). LCMS (ESI+) [M+H]/z Calculado 449, encontrado 449. Análisis ($C_{24}H_{24}N_4O_3S$. 0,5 CH_3OH) C, H, N.

Ejemplo 29(a): 7-cloro-N-[2-(dimetilamino)etil]-N-metiltieno[3,2-b]piridina-2-carboxamida.



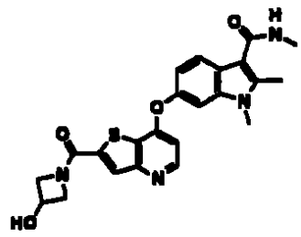
Este material se preparó a partir de 7-clorotieno[3,2-b]piridina-2-carboxilato de litio (0,957 g, 4,48 mmol) por tratamiento con cloruro de tionilo seguido de reacción del cloruro de acilo resultante con N,N,N-trimetiletano-1,2-diamina (0,640 ml, 4,93 mmol) y Et_3N (0,624 ml, 4,48 mmol), de una manera como se describe previamente para el ejemplo 9 d para dar un sólido marrón (0,167 g, 13%). ^1H RMN (400 MHz, $CDCl_3$) δ 8,60 (1H, d, J=5,1 Hz), 7,74 (1H, s), 7,32 (1H, d, J=5,1 Hz), 3,66 (2H, t, J=6,4 Hz), 3,26 (3H, s), 2,57 (2H, t, J=6,4 Hz), 2,25 (6H, s); ESIMS (MH^+): 298,05.

Ejemplo 29: N-[2-(dimetilamino)etil]-7-({1,2-dimetil-3-[(metilamino)carbonil]-1H-indol-6-il}oxi)-N-metiltieno[3,2-b]piridina-2-carboxamida



Este material se preparó por la reacción de 7-cloro-N-[2-(dimetilamino)etil]-N-metiltieno[3,2-b]piridina-2-carboxamida **29 a** (0,167 g, 0,56 mmol) con 6-hidroxi-N,1,2-trimetil-1H-indol-3-carboxamida **16 e** (0,123 g, 0,56 mmol) y Cs_2CO_3 (0,182 g, 0,56 mmol) de una manera como se describe previamente para el ejemplo 1 para dar un sólido amarillo (0,040 g, 13%). ^1H RMN (400 MHz, CD_3OD) δ 8,71 (1H, d, J=6,8 Hz), 8,06 (1H, s); 7,83 (1H, d, J=8,6 Hz), 7,46 (1H, d, J=2,0 Hz), 7,09 (1H, d, J=6,8 Hz), 7,05 (1H, dd, J=2,0, 8,6 Hz), 3,90 (2H, t, J=5,8 Hz), 3,64 (3H, s), 3,42 (2H, t, J=5,8 Hz), 3,23 (6H, s), 2,93 (3H, s), 2,88 (3H, s), 2,58 (3H, s). HRMS (MH^+): Calculado 480,2090; Encontrado 480,2069.

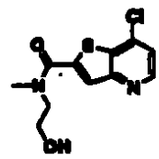
Ejemplo 30: metilamida del ácido 6-[2-(3-hidroxi-azetidina-1-carbonil)tieno[3,2-b]piridin-7-iloxi]-1,2-dimetil-1H-indol-3-carboxílico



Este material se preparó por la reacción de (7-cloro-tieno[3,2-b]piridin-2-il)-(3-hidroxi-azetidin-1-il)-metanona **9 d** con metilamida del ácido 6-hidroxi-1,2-dimetil-1H-indol-3-carboxílico **16 e** y Cs_2CO_3 de una manera como se describe previamente para el ejemplo 1. ^{1}H RMN (300 MHz, CD_3OD) δ 8,41 (1H, d, J=5,5 Hz), 7,78-7,74 (2H, m), 7,29 (1H, d, J=2,1 Hz), 6,95 (1H, dd, J=2,1, 8,6 Hz), 6,62 (1H, d, J=5,5 Hz), 4,76-4,73 (2H, m), 4,63 (1H, s ancho), 4,35-4,32 (2H, m), 3,97-3,94 (1H, m), 3,62 (3H, s), 2,89 (3H, s), 2,57 (3H, s), LCMS (ESI+) [M+H]/z Calculado 451, encontrado 451.

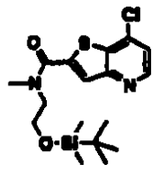
Análisis ($C_{23}H_{22}N_4O_4S$. 1,1 CH_2Cl_2) C, H, N.

Ejemplo 31(a): 7-cloro-N-(2-hidroxietil)-N-metiltieno[3,2-b]piridina-2-carboxamida.



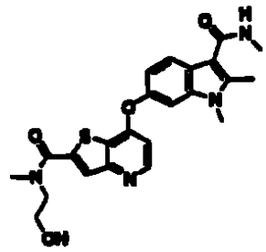
Este material se preparó a partir de 7-clorotieno[3,2-b]piridina-2-carboxilato de litio (1,0 g, 4,68 mmol) por tratamiento con cloruro de tionilo seguido de la reacción del cloruro de acilo resultante con 2-(metilamino)etanol (0,414 ml, 5,15 mmol) y Et_3N (0,718 ml, 5,15 mmol), de una manera como se describe previamente para el ejemplo **9 d** para dar un sólido marrón pálido (0,624 g, 49% de rendimiento). ^{1}H RMN (400 MHz, $CDCl_3$) δ 8,61 (1H, d, J=4,8 Hz), 7,80 (1H, s), 7,33 (1H, d, J=4,8 Hz), 3,92 (2H, m), 3,76 (2H, t, J=5,1 Hz), 3,37 (3H, s), 3,19 (1H, s); ESIMS (MH^+): 259,10.

Ejemplo 31(b): N-(2-{[terc-butil(dimetil)silil]oxi}etil)-7-cloro-N-metiltieno[3,2-b]piridina-2-caraboxamida.



Este material se preparó a partir de 7-cloro-N-(hidroxietil)-N-metiltieno[3,2-b]piridina-2-carboxamida **31** a (1,27 g, 4,68 mmol), cloruro de t-butildimetilsililo (0,705 g, 4,68 mmol) y Et_3N (0,718 ml, 4,68 mmol) de una manera como se describe previamente para **3 b** para dar un aceite naranja (1,40 g, 78%). ^1H RMN (300 MHz, $CDCl_3$) δ 8,61 (1H, d, J=5,1 Hz), 7,74 (1H, s), 7,32 (1H, d, J=5,1 Hz), 3,89 (2H, m), 3,71 (2H, m), 3,37 (3H, s), 0,89 (9H, m), 0,07 (6H, m); ESIMS (MH^+): 385,10.

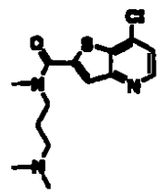
Ejemplo 31: N-({1,2-dimetil-3-[(metilamino)carbonil]-1H-inden-6-il}oxi)-N-(2-hidroxietil)-N-metiltieno[3,2-b]piridina-2-carboxamida.



Este material se preparó por la reacción de N-(2-{[terc-butil(dimetil)silil]oxi}etil)-7-cloro-N-metiltieno[3,2-b]piridina-2-carboxamida **31 b** (0,133 g, 0,35 mmol) con 6-hidroxi-N,1,2-trimetil-1H-indol-3-carboxamida **16 e** (0,76 g, 0,35 mmol) y Cs_2CO_3 (0,114 g, 0,35 mmol) de una manera como se describe previamente para el ejemplo 1 para dar una mezcla de N-(2-{[terc-butil(dimetil)silil]oxi}etil)-7-({1,2-dimetil-3-[(metilamino)carbonil]-1H-indol-6-il}oxi)-N-metiltieno[3,2-b]piridina-2-caraboxamida y 7-({1,2-dimetil-3-[(metilamino)carbonil]-1H-inden-6-il}oxi)-N-(2-hidroxietil)-N-metiltieno[3,2-b]piridina-2-carboxamida, que se disolvió en THF (10 ml) y se trató con TBAF (0,7 ml) durante 2 h. La mezcla de reacción se enfrió rápidamente con H_2O y se repartió entre CH_2Cl_2 (50 x 2 ml) y H_2O (50 ml). Las capas orgánicas combinadas se secaron sobre $MgSO_4$ y se concentraron. El residuo se purificó por cromatografía flash

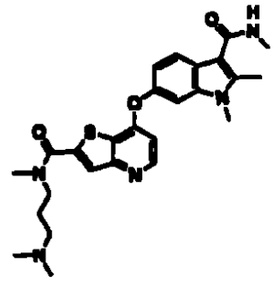
en columna eluyendo con CH_3OH al 5-8% en CH_2Cl_2 para dar un sólido blancuzco (0,064 g, 41% de rendimiento). ^1H RMN (400 MHz, CD_3OD) δ 8,38 (1H, d, J=5,4 Hz), 7,76 (2H, m), 7,29 (1H, s), 6,95 (1H, dd, J=2,1, 8,7 Hz), 6,61 (1H, d, J=5,4 Hz), 3,72 (2H, m), 3,62 (3H, s), 3,22 (3H, s), 3,12 (2H, m), 2,88 (3H, s), 2,57 (3H, s); HRMS (MH^+): Calculado: 453,1606; Encontrado: 453,1597.

Ejemplo 32(a): 7-cloro-N-[3-(dimetilamino)propil]-N-metiltieno[3,2-b]piridina-2-carboxamida.



Este material se preparó a partir de ácido 7-clorotieno[3,2-b]piridina-2-carboxílico (1,0 g, 4,68 mmol), $SOCl_2$ (10 ml), N,N,N-trimetilpropano-1,3-diamina (0,868 ml, 4,68 mmol) y Et_3N (1,96 ml, 14,04 mmol) de una manera como se describe previamente para el ejemplo 9 d para dar una espuma blanca (1,07 g, 77%). ^1H RMN (300 MHz, CD_3OD) δ 8,56 (1H, d, J=5,2 Hz), 7,76 (1H, s), 7,46 (1H, d, J=5,2 Hz), 3,51 (2H, m), 3,20 (3H, s), 2,33 (2H, m), 2,18 (6H, s), 1,79 (2H, m); ESIMS (MH^+): 312,05.

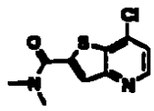
Ejemplo 32: N-[3-(dimetilamino)propil]-7-({1,2-dimetil-3-[(metilamino)carbonil]-1H-indol-6-il}oxi)-N-metiltieno[3,2-b]piridina-2-carboxamida.



Este material se preparó por la reacción de 7-cloro-N-[3-(dimetilamino)propil]-N-metiltieno[3,2-b]piridina-2-carboxamida **32 a** (0,095 g, 0,32 mmol) con 6-hidroxi-N,1,2-trimetil-1H-indol-3-carboxamida (0,070 g, 0,32 mmol) **16 e** y Cs_2CO_3 (0,104 g, 0,32 mmol) de una manera como se describe previamente para el ejemplo 1 para dar un sólido blanco (0,098 g, 62%) ^1H RMN (300 MHz, CD_3OD) δ 8,53 (1H, d, J=5,3 Hz),

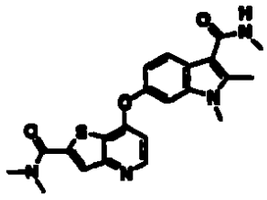
7,91 (2H, m), 7,38 (1H, s), 7,09 (1H, dd, J=2.1, 8,7 Hz), 6,81 (1H, d, J=5,3 Hz), 3,73 (3H, s), 3,66 (2H, m), 3,28 (2H, m), 3,01 (3H, s), 2,68 (9H, m), 2,06 (2H,m), 1,94 (3H, s); HRMS (MH^+); Calculado: 494,2223; Encontrado: 494,2226.

Ejemplo 33(a): 7-cloro-N,N-dimetiltieno[3,2-b]piridina-2-carboxamida



Este material se preparó a partir de ácido 7-clorotieno[3,2-b]piridina-2-carboxílico (0,57 g, 2,67 mmol), $SOCl_2$ (5 ml), N,N-dimetilamina 2,0 M en THF (1,60 ml, 3,20 mmol) y Et_3N (0,447 ml, 3,20 mmol) de una manera como se describe previamente para el ejemplo 9 d para dar un sólido marrón (0,54 g, 84%). ^1H RMN (300 MHz, $CDCl_3$) δ (1H, d, J=5,0 Hz), 7,74 (1H, s), 7,35 (1H, d, J=5,0 Hz), 3,28 (3H, s), 3,22 (3H, s); ESIMS (MH^+): 240,95

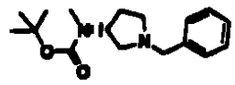
Ejemplo 33: 7-({1,2-dimetil-3-[(metilamino)carbonil]-1H-indol-6-il}oxi)-N,N-dimetiltieno[3,2-b]piridina-2-carboxamida.



Este material se preparó por la reacción de 7-cloro-N,N-dimetiltieno[3,2-b]piridina-2-carboxamida **33 a** (0,077 g, 0,32 mmol) y 6-hidroxi-N,1,2-trimetil-1H-indol-3-carboxamida **16 e** (0,070 g, 0,32 mmol) y Cs_2CO_3 (0,104 g, 0,32 mmol) de una manera como se describe previamente para el ejemplo 1 para dar un sólido amarillo pálido (0,098 g, 73%). ^1H RMN (300 MHz, CD_3OD) δ 8,38 (1H, d, J=5,5 Hz), 7,75 (1H, d, J=8,7 Hz), 7,66 (1H, s), 7,28 (1H, d, J=2,1 Hz), 6,94 (1H, dd, J=2,1, 8,7 Hz), 6,60 (1H, d, J=5,5 Hz), 3,61 (3H, s), 3,21 (6H, m), 2,87 (3H, s), 2,56 (3H, s), ESIMS (MH^+): 423,05.

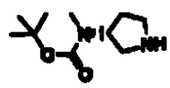
Análisis Calculado para $C_{22}H_{22}N_4O_3S$. 0,6 H_2O: C, 59,21; H, 5,28; N, 12,44. Encontrado: C, 59,20; H, 5,28; N, 12,44.

Ejemplo 34(a): (3R)-3-[(terc-butoxicarbonil)(metil)amino]pirrolidina-1-carboxilato de bencilo



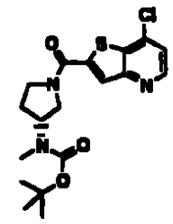
Se añadió Boc_2O (1,26 g, 5,78 mmol) y DMAP (6,4 mg, 0,053 mmol) a una disolución de metil[(3R)-pirrolidin-3-il]carbamato de terc-butilo (1,0 g, 5,26 mmol). La mezcla de reacción se agitó a temperatura ambiente durante la noche y se repartió entre CH_2Cl_2 (2 x 100 ml) y H_2O (100 ml). Las capas orgánicas combinadas se secaron sobre $MgSO_4$ y se concentraron. El residuo se purificó por cromatografía flash en columna eluyendo con CH_3OH al 1-2% en CH_2Cl_2 para dar un aceite amarillo pálido (1,51 g, 99%). ^1H RMN (300 MHz, $CDCl_3$) δ 7,30 (5H, m), 3,56 (2H, m), 2,82 (3H, s), 2,76 (2H, m), 2,53 (2H, m), 2,33 (1H, m), 2,09 (1H, m), 1,73 (1H, m), 1,42 (9H, m); ESIMS (MH^+): 291,20.

Ejemplo 34(b): metil[(3R)-pirrolidin-3-il]carbamato de terc-butilo.



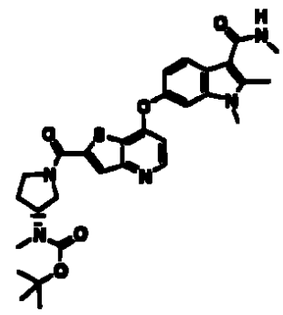
A una disolución agitada de (3R)-3-[(terc-butoxicarbonil)(metil)amino]pirrolidina-1-carboxilato de bencilo 34 a (1,5 g, 5,17 mmol) en MeOH (10 ml) se añadió $Pd(OH)_2$ sobre carbono (150 mg). La mezcla de reacción estuvo en una atmósfera de H_2 durante la noche, se filtró a través de celite y se concentró a vacío. El residuo obtenido se usó directamente en la subsecuente reacción sin ninguna purificación adicional, vide infra. ^1H RMN (300 MHz, CD_3OD) δ 4,47 (1H, m), 3,20 (1H, m), 2,91 (2H, m), 2,76 (1H, m), 2,69 (3H, s), 1,89 (1H, m), 1,68 (1H, m), 1,35 (9H, s).

Ejemplo 34(c): (3R)-1-[(7-clorotieno[3,2-b]piridin-2-il)carbonil]pirrolidin-3-il(metil)carbamato de terc-butilo.



Este material se preparó a partir de ácido 7-clorotieno[3,2-b]piridina-2-carboxílico (1,05 g, 4,94 mmol), $SOCl_2$ (10 ml), metil[(3R)-pirrolidin-3-il)carbamato de terc-butilo **34 b** (0,989 g, 4,94 mmol) y Et_3N (0,689 ml, 4,94 mmol) de una manera como se describe previamente para el ejemplo 9 d para dar un aceite marrón (0,723 g, 0,30%). ^1H RMN (300 MHz, $CDCl_3$) δ 8,62 (1H, d, J=5,1 Hz), 7,58 (1H, s), 7,35 (1H, d, J=5,1 Hz), 4,82 (1H, m), 3,93 (3H, m), 3,63 (1H, m), 2,82 (3H, s), 2,12 (2H, m), 1,47 (9H, s); ESIMS (MH^+): 396,05.

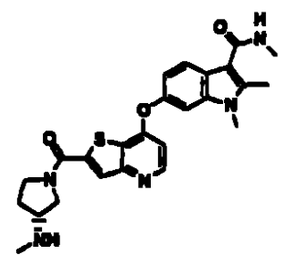
Ejemplo 34: (3R)-1-{[7-({1,2-dimetil-3-[(metilamino)carbonil]-1H-indol-6-il}oxi)tieno[3,2-b]piridin-2-il]carbonil}pirrolidin-3-il(metil)carbamato de ter-butilo.



Este material se preparó por la reacción de (3R)-1-[(7-clorotieno[3,2-b]piridin-2-il)carbonil]pirrolidin-3-il(metil)carbamato de terc-butilo **34 c** (0,161 g, 0,46 mmol) con 6-hidroxi-N,1,2-trimetil-1H-indol-3-carboxamida **16 e** (0,10 g, 0,46 mmol) y Cs_2CO_3 (0,149 g, 0,46 mmol) de una manera como se describe previamente para el ejemplo 1 para dar un sólido amarillo (0,105 g, 40%). ^1H RMN (300 MHz, $CDCl_3$) δ 8,48 (1H, d; J=5,4 Hz), 7,82 (1H, s), 7,75 (1H, d, J=8,7 Hz), 7,15 (1H, d, J=2,1 Hz), 7,02 (1H, dd, J=2,1, 8,7 Hz), 6,56 (1H, d, J=5,4 Hz), 5,91 (1H, d, J=4,7 Hz), 4,82 (1H, m), 4,07 (2H, m), 3,87 (1H, m), 3,68 (1H, m), 3,65 (3H, s), 3,05 (3H, d, J=4,7 Hz), 2,84 (3H, s), 2,73

(3H, s), 2,17 (2H, m), 1,45 (9H, s); HRMS (MH^+): Calculado: 578,2450; Encontrado: 578,2437.

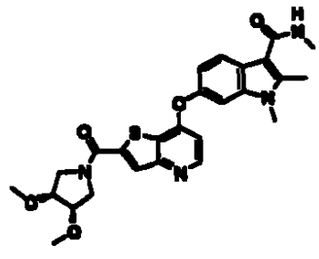
Ejemplo 35: metilamida del ácido 1,2-dimetil-6-[2-(3-metilamino-pirrolidina-1-carbonil)-tieno[3,2-b]piridin-7-iloxi]-1H-indol-3-carboxílico.



Se añadió HCl 4 N en 1,4-dioxano (1,0 ml) a una disolución de (3R)-1-{[7-({1,2-dimetil-3-[(metilamino)carbonil]-1H-indol-6-il}oxi)tieno[3,2-b]piridin-2-il]carbonil}pirrolidin-3-il(metil)carbamato de terc-butilo **34** (0,090 g, 0,16 mmol) en 1,4-dioxano (5 ml). La mezcla de reacción se agitó a temperatura ambiente durante 3 h, a continuación se concentró a vacío. El residuo se purificó por cromatografía en fase inversa eluyendo con CH_3CN al 10-60% en H_2O para dar un sólido blanco (0,020 g, 26%). ^1H RMN (300 MHz, $CDCl_3$) δ 8,54 (1H, d, J=5,3 Hz), 8,01 (1H, s), 7,83 (1H, d, J=8,7 Hz), 7,53-7,57 (2H, m), 7,03 (1H, dd, J=1,9, 8,7 H), 6,63 (1H, d, J=5,3 Hz), 3,88-3,99 (2H, m), 3,67 (3H, s), 3,61 (1H, m), 3,29 (3H, m), 2,80 (3H, d, J=4,50 Hz), 2,61 (3H, s), 2,30 (3H, d, J=10,55 Hz), 1,78-1,83 (1H, m); ESIMS (MH^+): 478,10.

Análisis Calculado para $C_{25}H_{27}N_5O_3S$. 1,2 CH_2Cl_2: C, 54,30; H, 5,11; N, 12,09; Encontrado: C, 53,95; H, 5,52; N, 11,96.

Ejemplo 36: metilamida del ácido 6-[2-(3,4-dimetoxi-pirrolidina-1-carbonil)-tieno[3,2-b]piridin-7-iloxi]-1,2-dimetil-1H-indol-3-carboxílico (36).

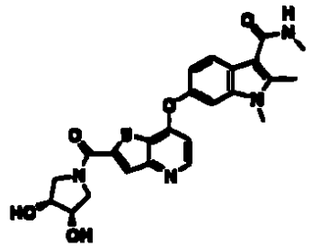


Este material se preparó por la reacción de 7-cloro-2-{[(3R,4S)-3,4-dimetoxipirrolidin-1-il]carbonil}tieno[3,2-b]piridina **5 d** (0,152 g, 0,47 mmol) con 6-

hidroxi-N,1,2-trimetil-1H-indol-3-carboxamida **16 e** (0,102 g, 0,47 mmol) y Cs_2CO_3 (0,153 g, 0,47 mmol) de una manera como se describe previamente para el ejemplo 1 para dar un sólido blancuzco (0,093 g, 39%). ^{1}H RMN (300 MHz, $CDCl_3$) δ 8,42 (1H, d, J=5,3 Hz), 7,84 (1H, s), 7,77 (1H, dd, J=3,8, 8,7 Hz), 7.31 (1H, d, J=2,30 Hz), 3,97 (1H, dd, J=2,3, 8,7 Hz), 6,63 (1H, d, J=5,3 Hz), 4,04 (4H, m), 3,68 (2H, m), 3,64 (3H, s), 3,42 (3H, s), 3,38 (3H, s), 2,90 (3H, s), 2,59 (3H. s); ESIMS (MH^+): 409,15.

Análisis Calculado para $C_{23}H_{28}N_4O_5S$. 0,2 CH_2Cl_2. 0,5 EtOAc: C, 59,46; H, 5,73; N, 9,84; Encontrado: C, 59,09; H, 5,95; N, 9,93.

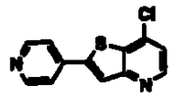
Ejemplo 37: metilamida del ácido 6-[2-(3,4-dihidroxi-pirrolidina-1-carbonil)-tieno[3,2-b]piridin-7-iloxi]-1,2-dimetil-1H-indol-3-carboxílico (37).



Este material se preparó tratando metilamida del ácido 6-[(2-{[(3R,4S)-3,4-dimetoxipirrolidin-1-il]carbonil}tieno[3,2-b]piridin-7-il)oxi]-1,2-dimetil-1H-indol-3-carboxílico **38** (0,065 g, 0,13 mmol) con BBr_3 1,0 M en CH_2Cl_2 (0,070 ml, 0,77 mmol) de una manera como se describe previamente para el ejemplo 1 d para dar un sólido blanco (0,017 g, 33%). ^{1}H RMN (300 MHz, CD_3OD) δ 8.38 (1H, d, J=5,5 Hz), 7,79 (2H, m), 7,28 (1H, d, J=2,1 Hz), 6,94 (1H, dd, J=2,1, 8,7 Hz), 6,60 (1H, d, J=5,5 Hz), 5,07-5,13 (2H, m), 4,41 (1H, m), 3,95 (2H, m), 3,70 (1H, m), 3,61 (3H, s), 2,55 (3H, m), 1,90 (3H, s); ESIMS (MH^+): 481,10.

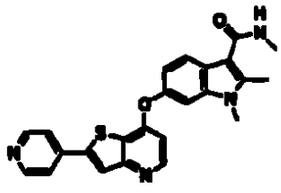
Análisis Calculado para $C_{24}H_{24}N_4O_5S$. 0,2 CH_2Cl_2. H_2O: C, 56,38; H, 5,16; N, 10,87; Encontrado: C, 56,36; H, 5,09; N, 10,60.

Ejemplo 38(a): 7-cloro-2-piridin-4-iltieno[3,2-b]piridina



Se añadió tetraquis(trifenilfosfina)paladio (54 mg, 0,05 mmol) a una disolución de 4-(tributilestannil)piridina (0,432 g, 1,17 mmol) y 7-cloro-2-yodotieno[3,2-b]piridina (0,347 g, 1,17 mmol) en DMF (5 ml). La mezcla de reacción se agitó a reflujo durante 3 h, se enfrió hasta temperatura ambiente. La mezcla se filtró, se lavó con CH_2Cl_2 y se repartió entre H_2O (50 ml), y CH_2Cl_2 (2 x 50 ml). Las capas orgánicas combinadas se secaron sobre $MgSO_4$ y se concentraron. El residuo se purificó por cromatografía flash en columna eluyendo con EtOAc al 30-60% en hexano para dar un sólido de color amarillo pálido (0,103 g, 36%); ^{1}H RMN (300 MHz, $CDCl_3$) δ 8,61 (1H, d, J=5,1 Hz), 7,95 (1H, s), 7,66 (2H, m), 7,44 (2H, m), 7,31 (1H, d, J=5,1 Hz); ESIMS (MH^+): 481,10.

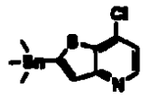
Ejemplo 38: metilamida del ácido 1,2-dimetil-6-(2-piridin-4-il-tieno[3,2-b]piridin-7-iloxi)-1H-indol-3-carboxílico.



Este material se preparó por la reacción de 7-cloro-2-piridin-4-iltieno[3,2-b]piridina **38 a** (0,103 g, 0,42 mmol) con 6-hidroxi-N,1,2-trimetil-1H-indol-3-carboxamida **16 e** (0,070 g, 0,32 mmol) y Cs_2CO_3 (0,104 g, 0,32 mmol) de una manera como se describe previamente para el ejemplo 1 para dar un sólido blancuzco (0,055 g, 31%). ^{1}H RMN (300 MHz, DMSO-d_6) δ 8,70 (2H, m), 8,52 (1H, m), 8,37 (1H, m), 7,87 (3H, m), 7,56 (2H, m), 7,05 (1H, d, J=8,3 Hz), 6,59 (1H, m), 3,68 (3H, s), 2,80 (3H, s), 2,61 (3H, s); ESIMS (MH^+): 429,05.

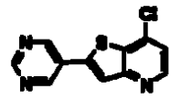
Análisis Calculado para $C_{24}H_{20}N_4O_2S$. 0,5 CH_2Cl_2. 0,4 EtOAc: C, 61,92; H, 4,82; N, 11,07; Encontrado: C, 61,93; H, 4,97; N, 10,99.

Ejemplo 39(a): 7-cloro-2-(trimetilestannil)tieno[3,2-b]piridina



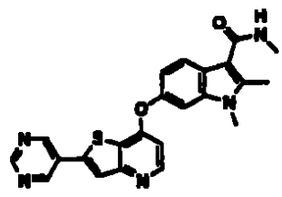
Se añadió tetraquis(trifenilfosfina)paladio (238 mg, 0,2 mmol) a una disolución de hexametildiestannano (1,68 g, 5,1 mmol) y 7-cloro-2-yodotieno[3,2-b]piridina (1,52 g, 5,1 mmol) en 1,4-dioxano (20 ml). La mezcla de reacción se agitó a 110°C durante 3 h. Después de enfriar hasta temperatura ambiente, la mezcla se filtró, se lavó con CH_2Cl_2 y se repartió entre H_2O (100 ml), y CH_2Cl_2 (2 x 100 ml). Las capas orgánicas combinadas se secaron sobre $MgSO_4$ y se concentraron. El residuo se purificó por cromatografía flash en columna eluyendo con EtOAc al 10-15% en hexano para dar un sólido naranja (1,09 g, 63%); ^1H RMN (300 MHz, $CDCl_3$) δ 8,16 (1H, d, J=5,1 Hz), 6,87 (1H, s), 6,82 (H, d, J=5,1 Hz), 0,08 (9H, m); ESIMS (MH^+): 333,95.

Ejemplo 39(b): 7-cloro-2-pirimidin-5-iltieno[3,2-b]piridina



Se añadió tetraquis(trifenilfosfina)paladio (17 mg) a una disolución de 5-bromopirimidina (0,057 g, 0,36 mmol) y 7-cloro-2-(trimetilestannil)tieno[3,2-b]piridina **39 a** (0,119 g, 0,36 mmol) en tolueno (10 ml). La mezcla de reacción se agitó a 90°C durante la noche. Después de enfriar hasta temperatura ambiente, la mezcla se filtró, se lavó con CH_2Cl_2 y se repartió entre H_2O (20 ml) y CH_2Cl_2 (2 x 20 ml). Las capas orgánicas combinadas se secaron sobre $MgSO_4$ y se concentraron. El residuo se purificó por cromatografía flash en columna eluyendo con MeOH 0-1% en CH_2Cl_2 para dar un sólido blanco (0,045 g, 51%); ^1H RMN (300 MHz, C_6D_6) δ 9,25 (1H, s), 9,10 (2H, s), 8,64 (1H, d, J=5,1 Hz), 7,89 (1H, s),7,34 (1H, d, J=5,1 Hz); ESIMS (MH^+): 248,00

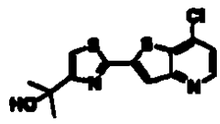
Ejemplo 39: metilamida del ácido 1,2-dimetil-6-(2-pirimidin-5-il-tieno[3,2-b]piridin-7-iloxi)-1H-indol-3-carboxílico.



Este material se preparó por la reacción de 7-cloro-2-pirimidin-5-iltieno[3,2-b]piridina **39 b** (0,045 g, 0,18 mmol) con 6-hidroxi-N,1,2-trimetil-1H-indol-3-carboxamida **16 e** (0,040 g, 0,18 mmol) y Cs_2CO_3 (0,059 g, 0,18 mmol) de una manera como se describe previamente para el ejemplo 1 para dar un sólido blancuzco (0,018 g, 23%). ^{1}H RMN (300 MHz, CD_3OD) δ 9,23 (3H, m), 8,63 (1H, d, J=6,2 Hz), 8,11 (1H, s), 7,82 (1H, d, J=8,5 Hz), 7,43 (1H, s), 7,01 (2H, m), 3,63 (3H, s), 2,88 (3H, s), 2,55 (3H, s); ESIMS (MH^+): 430,10.

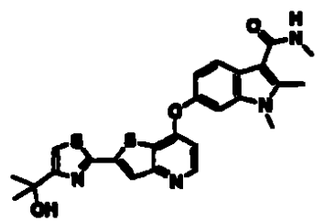
Análisis Calculado para $C_{24}H_{20}N_4O_2S$. 1,0 CH_2Cl_2. 1,5 CH_3OH: C, 54,45; H, 4,84; N, 12,45; Encontrado: C, 54,12; H, 4,89; N, 12,30.

Ejemplo 40(a): 2-[2-(7-clorotieno[3,2-b]piridin-2-il)-1,3-tiazol-4-il]propan-2-ol.



El compuesto del título se preparó por el método descrito en el documento PC10795A, ejemplo 27.

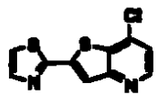
Ejemplo 40: metilamida del ácido 6-{2-[4-(1-hidroxi-1-metil-etil)-tiazol-2-il]-tieno[3,2-b]piridin-7-iloxi}-1,2-dimetil-1H-indol-3-carboxílico.



Este material se preparó por la reacción de 2-[2-(7-clorotieno[3,2-b]piridin-2-il)-1,3-tiazol-4-il]propan-2-ol **40 a** (0,099 g, 0,32 mmol) con 6-hidroxi-N,1,2-trimetil-1H-indol-3-carboxamida **16 e** (0,071 g, 0,32 mmol) y Cs_2CO_3 (0,106 g, 0,32 mmol) de una manera como se describe previamente para el ejemplo 1 para dar un sólido de color amarillo (0,116 g, 73%). ^{1}H RMN (300 MHz, DMSO-d_6) δ 8,50 (1H, d, J=5,46 Hz), 8,12 (1H, s), 7,84 (1H, d, J=8,67 Hz), 7,58 (2H, m), 7.54 (1H. d, J=2,07 Hz), 7,04 (1H, dd, J=8,67, 2,26 Hz), 6,59 (1H, d, J=5,46 Hz), 3,68 (3H, s), 2,80 (1H, d, J=4,71 Hz), 2,61 (3H, s), 2,53 (3H, s), 1,50 (6H, s).

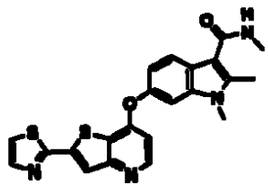
Análisis Calculado para $C_{25}H_{24}N_4O_3S_2$. 0,45 CH_2Cl_2. 1,0 CH_3OH: C, 55,64; H, 5,18; N, 9,95; Encontrado: C, 56,37; H, 5,22; N, 9,89.

Ejemplo 41(a): 7-cloro-2-(1,3-tiazol-2-il)tieno[3,2-b]piridina



Este material se preparó por copulación de 7-cloro-2-(trimetilestannil)tieno[3,2-b]piridina **39 a** (0,140 g, 0,42 mmol) y 2-bromo-1,3-tiazol (0,038 ml, 0,42 mmol) con tetraquis(trifenilfosfina)paladio (0,019 g) de una manera como se describe previamente en el ejemplo **39 b** para dar un sólido amarillo (0,049 g, 46%). ^{1}H RMN (300 MHz, $CDCl_3$) δ 8,59 (1H, d, J=5,1 Hz), 7,93 (1H, s), 7,89 (1H, d, J=3,4 Hz), 7,45 (1H, d, J=3,4 Hz), 7,30 (1H, d, J=5,1 Hz).

Ejemplo 41: metilamida del ácido 1,2-dimetil-6-(2-tiazol-2-il-tieno[3,2-b]piridin-7-iloxi)-1H-indol-3-carboxílico.

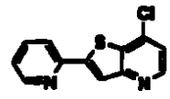


Este material se preparó por la reacción de 7-cloro-2-(1,3-tiazol-2-il)tieno[3,2-b]piridina **41 a** (0,049 g, 0,19 mmol) con 6-hidroxi-N,1,2-trimetil-1H-indol-3-carboxamida **16 e** (0,043 g, 0,19 mmol) y Cs_2CO_3 (0,062 g, 0,19 mmol) de una manera como se describe previamente para el ejemplo 1 para dar un sólido blancuzco (0,050 g, 60%). ^{1}H RMN (300 MHz, DMSO-d_6) δ 8,52 (1H, d, J=5,4 Hz), 8,18 (1H, s), 7,93

(2H, m), 7,84 (1H, d, J=8,9 Hz), 7,56 (2H, m), 7,05 (1H, m), 6,63 (1H, d, J=5,4 Hz), 3,68 (3H, s), 2,80 (3H, d, J=4,5 Hz), 2,61 (3H, s); ESIMS (MH^+): 430,10.

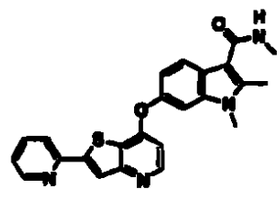
Análisis Calculado para $C_{22}H_{18}N_4O_2S_2$. 0,45 CH_2Cl_2. 1,0 CH_3OH: C, 55,64; H, 5,18; N, 9,95; Encontrado: C, 56,37; H, 5,22; N, 9,89.

Ejemplo 42(a): 7-cloro-2-piridin-2-iltieno[3,2-b]piridina



Este material se preparó por copulación de 7-cloro-2-(trimetilestannil)tieno[3,2-b]piridina **39 a** (0,255 g, 0,77 mmol) con 2-bromopiridina (0,121 g, 0,77 mmol) usando tetraquis(trifenilfosfina)paladio(0) (0,036 g) como catalizador de una manera como se describe previamente en el ejemplo **39 b** para dar un sólido blanco (0,058 g, 31%). ^1H RMN (300 MHz, $CDCl_3$) δ 8,66 (1H, m), 8,57 (1H, d, J=5,1 Hz), 8,00 (1H, s), 7,83 (3H, m), 7,27 (1H, d, J=5,1 Hz); ESIMS (MH^+): 246,95.

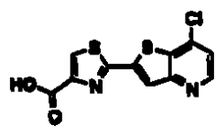
Ejemplo 42: metilamida del ácido 1,2-dimetil-6-(2-piridin-2-il-tieno[3,2-b]piridin-7-iloxi)-1H-indol-3-carboxílico.



Este material se preparó por la reacción de 7-cloro-2-piridin-2-iltieno[3,2-b]piridina (0,100 g, 0,41 mmol) **42 a** con 6-hidroxi-N,1,2-trimetil-1H-indol-3-carboxamida **16 e** (0,089 g, 0,41 mmol) y Cs_2CO_3 (0,134 g, 0,41 mmol) de una manera como se describe previamente para el ejemplo 1 para dar un sólido blancuzco (0,048 g, 27%). ^1H RMN (300 MHz, DMSO-d_6) δ 8,63 (1H, d, J=4,5 Hz), 8,49 (1H, d, J=5,5 Hz), 8,35 (1H, s), 8,28 (1H, d, J=7,72 Hz), 7,95 (1H, t, J=8,4 Hz), 7,84 (1H, d, J=8,6 Hz), 7,58 (1H, d, J=4,5 Hz), 7,54 (1H, d, J=1,9 Hz), 7,43 (1H, m), 7,04 (1H, dd, J=1,9, 8,6 Hz), 6,58 (1H, d, J=5,5 Hz), 3,68 (3H, s), 2,80 (3H, s), 2,62 (3H, s); ESIMS (MH^+): 429,05.

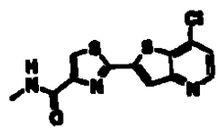
Análisis Calculado para $C_{24}H_{20}N_4O_2S$. 0,8 H_2O; C, 65,08; H, 4,92; N, 12,65; Encontrado: C, 65,16; H, 4,93; N, 12,40.

Ejemplo 43(a): ácido 2-(7-clorotieno[3,2-b]piridin-2-il)-1,3-tiazol-4-carboxílico



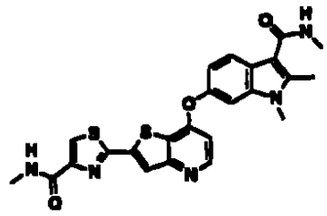
A una disolución de 2-(7-clorotieno[3,2-b]piridin-2-il)-1,3-tiazol-4-carboxilato de metilo (0,200 g, 0,62 mmol), preparada por el método descrito en el documento PC10795A, sección A, ejemplo 26, en EtOAc (5 ml) se añadió disolución acuosa 1 N de NaOH (1,85 ml, 1,85 mmol). La mezcla de reacción se agitó a 50°C durante 1 h, se enfrió hasta temperatura ambiente, se diluyó con H_2O (10 ml) y se acidificó con HCl 1 N hasta pH 2. La disolución resultante se extrajo con MeOH al 10% en CH_2Cl_2 (5 x 10 ml), se secó sobre $MgSO_4$ y se concentró y secó a vacío para dar un sólido amarillo (0,181 g, 98%). ^{1}H RMN (300 MHz, DMSO-d_6) δ 7,67 (1H, d, J=5,09 Hz), 8,41 (1H, s), 8,65 (1H, s), 8,71 (1H, s ancho); ESIMS (MH^+): 309,95.

Ejemplo 43(b): 2-(7-clorotieno[3,2-b]piridin-2-il)-N-metil-1,3-tiazol-4-carboxamida.



A una disolución de ácido 2-(7-clorotieno[3,2-b]piridin-2-il)-1,3-tiazol-4-carboxílico **43 a** (0,123 g, 0,41 mmol) en CH_2Cl_2 enfriada a 0°C se añadió cloruro de oxalilo 2,0 M en CH_2Cl_2 (0,520 ml, 1,04 mmol) y DMF (2 gotas). La mezcla de reacción se agitó a temperatura ambiente durante 1 h, se concentró y se secó. El residuo se recogió en CH_2Cl_2 (10 ml) y se añadió metilamina 2,0 M en CH_2Cl_2 (0,250 ml, 0,492 mmol). La mezcla de reacción se agitó a temperatura ambiente durante 1 h y a continuación se repartió entre H_2O (100 ml) y CH_2Cl_2 (2 x 100 ml). Las capas orgánicas combinadas se secaron sobre $MgSO_4$ y se concentraron. El residuo se purificó por cromatografía flash en columna eluyendo con CH_3OH al 2-8% en CH_2Cl_2 para dar un sólido amarillo (0,116 g, 91%). ^{1}H RMN (300 MHz, $CDCl_3$) δ 8,62 (1H, d, J=5,1 Hz), 8,19 (1H, s), 7,96 (1H, s), 7,33 (1H, d, J=5,1 Hz), 3,06 (3H, d, J=4,9 Hz); ESIMS (MH^+): 309,95.

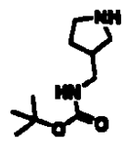
Ejemplo 43: metilamida del ácido 1,2-dimetil-6-[2-(4-metilcarbamoil-tiazol-2-il)-tieno[3,2-b]piridin-7-iloxi]-1H-indol-3-carboxílico.



Este material se preparó por reacción de 2-(7-clorotieno[3,2-b]piridin-2-il)-N-metil-1,3-tiazol-4-carboxamida **43 b** (0,125 g, 0,403 mmol) con metilamida del ácido 6-hidroxi-1,2-dimetil-1H-indol-3-carboxílico **16 e** (0,092 g, 0,403 mmol) y Cs_2CO_3 (0,137 g, 0,42 mmol) de una manera como se describe previamente para el ejemplo 1 para dar un sólido blancuzco (0,015 g, 9%). ^{1}H RMN (300 MHz, DMSO-d_6) δ 8,54 (1H, d, J=5,3 Hz), 8,43 (1H, d, J=4,7 Hz), 8,40 (1H, s), 8,30 (1H, s), 7,84 (1H, d, J=8,7 Hz), 7,56 (2H, m), 7,05 (1H, dd, J=2,1, 8,7 Hz), 6,63 (1H, d, J=5,3 Hz), 3,68 (3H, s), 2,81 (6H, m), 2,61 (3H, s); ESIMS (MH^+): 492,05.

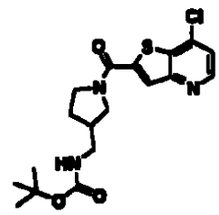
Análisis Calculado para $C_{24}H_{21}N_4O_3S_2Cl$. 0,5 CH_2Cl_2: C, 55,10; H, 4,15; N, 13,11; Encontrado: C, 55,14; H, 4,42; N, 12,99.

Ejemplo 44 (a): pirrolidin-3-il-metilcarbamato de terc-butilo



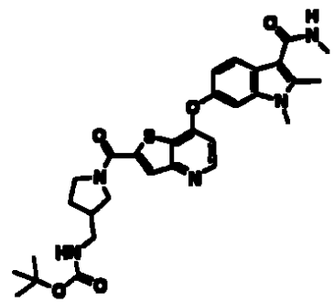
A una disolución de (1-bencilpirrolidin-3-il)metilcarbamato de terc-butilo (3,0 g, 10,33 mmol) en EtOAc (100 ml) se añadió $Pd(OH)_2$ en carbono (0,3 g). La mezcla se agitó en un globo de H_2 a temperatura ambiente durante 3 h y se filtró a través de celite. El filtrado se concentró para dar un aceite incoloro (1,87 g, 90%)

Ejemplo 44(b): {1-[7-clorotieno[3,2-b]piridin-2-il)carbonil]pirrolidin-3-il}metilcarbamato de terc-butilo.



Este material se preparó a partir de sal de litio del ácido 7-clorotieno[3,2-b]piridina-2-carboxílico (2,27 g, 10,33 mmol), $SOCl_2$ (10 ml), pirrolidin-3-il-metilcarbamato de terc-butilo **44 a** (2,07 g, 10,33 mmol) y Et_3N (1,44 ml, 10,33 mmol) de una manera como se describe previamente para el ejemplo **9 d** para dar un sólido amarillo (2,44 g, 60%). ^1H RMN (300 MHz, $CDCl_3$) δ 7,85 (1H, s), 7,34 (1H, d, J=5,1 Hz), 4,73 (1H, s), 3,96 (1H, m), 3,85 (1H, m), 3,70 (1H, m), 3,55 (1H, m), 3,42 (1H, m), 3,22 (2H, m), 2,54 (1H, m), 2,12 (1H, m), 1,43, 1,41 (9H, s); ESIMS (M^+): 396,05.

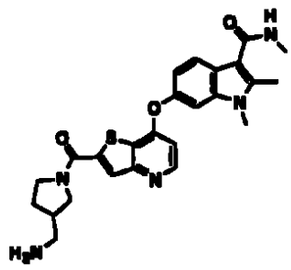
Ejemplo 44: (1-{[7-({1,2-dimetil-3-[(metilamino)carbonil]-1H-indol-6-il}oxi)tieno[3,2-b]piridin-2-il]carbonil}pirrolidin-3-il)metilcarbamato de terc-butilo.



Este material se preparó por la reacción de {1-[7-clorotieno[3,2-b]piridin-2-il)carbonil]pirrolidin-3-il}metilcarbamato de terc-butilo.**44 b** (0,206 g, 0,52 mmol) con 6-hidroxi-N,1,2-trimetil-1H-indol-3-carboxamida **16 e** (0,113 g, 0,52 mmol) y Cs_2CO_3 (0,169 g, 0,52 mmol) de una manera como se describe previamente para el ejemplo **1** para dar un sólido blancuzco (0,168 g, 56%). ^1H RMN (300 MHz, $CDCl_3$) δ 8,48 (1H, d, J=5,3 Hz), 7,82 (1H, s), 7,75 (1H, d, J=8,7 Hz), 7,25 (1H, s), 7,15 (1H, d, J=2,0 Hz), 7,02 (1H, dd, J=2,0, 8,7 Hz), 6,56 (1H, d, J=5,3 Hz), 5,89 (1H, s), 4,74 (1H, s), 3,97 (1H, m), 3,84 (1H, m), 3,65 (3H, s), 3,44 (1H, m), 3,20 (2H, m), 3,06 (3H, d, J=4,71 Hz), 2,72 (3H, s), 1,77 (1H, m), 1,44, 1,42 (9H, s), 0,84 (2H, m).

Análisis Calculado para $C_{30}H_{35}N_5O_5S$. 1,0 H_2O. 1,2 EtOAc: C, 59,59; H, 6,70; N, 9,98; Encontrado: C, 59,54; H, 6,44; N, 9,85.

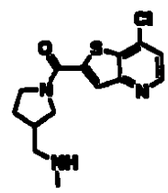
Ejemplo 45: metilamida del ácido 6-[2-(3-aminometil-pirrolidina-1-carbonil)tieno[3,2-b]piridin-7-iloxi]-1,2-dimetil-1H-indol-3-carboxílico.



Se añadió ácido trifluoroacético (1 ml) a una disolución agitada de (1-{[7-({1,2-dimetil-3-[(metilamino)carbonil]-1H-indol-6-il}oxi)tieno[3,2-b]piridin-2-il]carbonil}pirrolidin-3-il)metilcarbamato de terc-butilo 44 (0,148 g, 0,26 mmol). La mezcla de reacción se agitó a temperatura ambiente durante 15 minutos y se concentró. El residuo se trituró con Et_2O, se filtró para dar un sólido amarillo (0,050 g, 40%). ^1H RMN (300 MHz, DMSO-d_6) δ 8,56 (1H, d, J=5,5 Hz), 8,05 (1H, s), 7,84 (3H, m), 7,58 (1H, d, J=4,5 Hz), 7,54 (1H, d, J=1,7 Hz), 7,02 (1H, d, J=8,8 Hz), 6,67 (1H, d, J=5,5 Hz), 4,08 (1H, m), 3,92 (1H, m), 3,78 (1H, m), 3,67 (3H, s), 3,54 (1H, m), 3,36 (1H, m), 2,96 (2H, m), 2,80 (3H, d, J=4,33 Hz), 2,61 (3H, s), 2,09 (1H, m), 1,78 (1H, m); ESIMS (MH^+); 478,10.

Análisis Calculado para $C_{25}H_{27}N_5O_3S$. 1,0 CF_3CO_2H. 2,7 CH_2Cl_2: C, 46,69; H, 4,41; N, 9,17; Encontrado: C, 46,87; 4,27; N, 9,06.

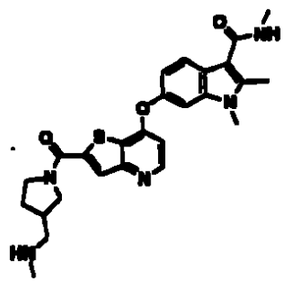
Ejemplo 46(a): N-{(1-[(7-clorotieno[3,2-b]piridin-2-il)carbonil]pirrolidin-3-il}metil)-N-metilamina.



Se añadió NaH (0,033 g, 0,82 mmol) y CH_3I (0,064 ml, 1,02 mmol) a una disolución de {1-[(7-clorotieno[3,2-b]piridin-2-il)carbonil]pirrolidin-3-il}metil-carbamato de terc-butilo **43** (0,271 g, 0,68 mmol) en THF a 0°C. La mezcla de reacción se agitó y calentó hasta temperatura ambiente durante la noche y se repartió entre H_2O (50 ml) y EtOAc (2 x 50 ml). Las capas orgánicas combinadas se secaron sobre $MgSO_4$ y se

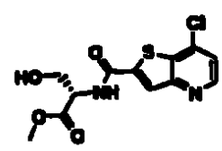
concentraron. El residuo se purificó por cromatografía flash en columna eluyendo con CH_3OH al 0-2% en CH_2Cl_2 para dar un sólido amarillo (0,283 g, 82%). ^1H RMN (300 MHz, $CDCl_3$) δ 8,62 (1H, d, J=5,1 Hz), 7,85 (1H, s), 7,34 (1H, d, J=5,1 Hz), 4,72 (1H, s), 3,99 (1H, m), 3,77 (2H, m), 3,50 (1H, m), 3,19 (2H, m), 2,88 (3H, d, J=12,06 Hz), 2,62 (1H, m), 2,14 (1H, m), 1,83 (1H, m); ESIMS (MH^+): 310,10.

Ejemplo 46: metilamida del ácido 1,2-dimetil-6-[2-(3-metilaminometil-pirrolidina-1-carbonil)-tieno[3,2-b]piridin-7-iloxi]-1H-indol-3-carboxílico.



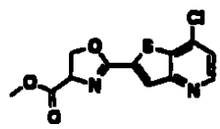
Este material se preparó por la reacción de N-({1-[(7-clorotieno[3,2-b]piridin-2-il)carbonil]pirrolidin-3-il}metil)-N-metilamina **46 a** (0,115 g, 0,41 mmol) con 6-hidroxi-N,1,2-trimetil-1H-indol-3-carboxamida **16 e** (0,090 g, 0,41 mmol) y Cs_2CO_3 (0,147 g, 0,41 mmol) de una manera como se describe previamente para el ejemplo 1 para dar un sólido blancuzco (0,110 g, 54%). ^1H RMN (300 MHz, DMSO-d_6) δ 8,54 (1H, s), 8,01 (1H, s), 7,83 (1H, m), 7,54 (2H, m), 7,02 (1H, s), 6,64 (1H, d, J=5,46 Hz), 3,93 (2H, m), 3,68 (3H, s), 3,54 (2H, m), 3,16 (2H, m), 2,99 (1H, m), 2,80 (3H, s), 2,79 (3H, s), 1,98 (2H, m), 1,65 (1H, m); HRMS (MH^+): Calculado: 492,2064; Encontrado: 492,2048.

Ejemplo 47(a): N-[(7-clorotieno[3,2-b]piridin-2-il)carbonil]-L-serinato de metilo



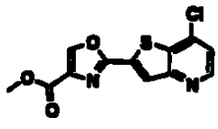
Este material se preparó a partir de ácido 7-clorotieno[3,2-b]piridina-2-carboxílico y Li (2,69 g, 12,25 mmol), $SOCl_2$ (10 ml), hidrocloruro del éster metílico de L-serina (2,86 g, 18,4 mmol) y Et_3N (5,12 ml, 37,7 mmol) de una manera como se describe previamente para el ejemplo 9 d para dar un sólido blanco (2,09 g, 54%). ^1H RMN (300 MHz, $CDCl_3$) δ 8,61 (1H, d, J=5,1 Hz), 8,02 (1H, s), 7,35 (1H, d, J=5,1 Hz), 4,89 (1H, m), 4,15 (2H, m), 3,84 (3H, m).

Ejemplo 47(b): 2-[2-(7-clorotieno[3,2-b]piridin-2-il)-4,5-dihidro-1,3-oxazol-4-il]propan-2-ol.



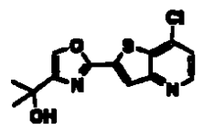
Se añadió reactivo de Burgess (0,606 g, 2.54 mmol) a una disolución agitada de N-[(7-clorotieno[3,2-b]piridin-2-il)carbonil]-L-serinato de metilo 47 a (0,728 g, 2,31 mmol) en THF (10 ml). La mezcla de reacción se agitó a reflujo durante 2 h, se enfrió rápidamente con MeOH (1 ml) y se repartió entre H_2O (30 ml) saturada y EtOAc (2 x 30 ml). Las capas orgánicas combinadas se secaron sobre $MgSO_4$ y se concentraron. El residuo se purificó por cromatografía flash en columna eluyendo con EtOAc al 20-60% en hexano para dar un sólido blanco (0,314 g, 46%). ^{1}H RMN (300 MHz, $CDCl_3$) δ 8,66 (1H, d, J=5,1 Hz), 8,08 (1H, s), 7,37 (1H, d, J=5,1 Hz), 5,03 (1H, m), 4,81 (1H, t, J=8,4 Hz), 4,70 (1H, m), 3,85 (3H, s); ESIMS (MH^+): 296,95.

Ejemplo 47(c): 2-(7-clorotieno[3,2-b]piridin-2-il)-1,3-oxazol-4-carboxilato de metilo



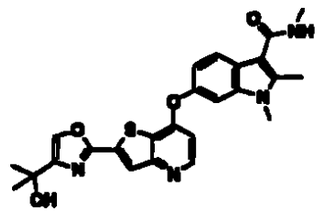
Se añadió MnO_2 (0,628 mg) a una disolución de 2-[2-(7-clorotieno[3,2-b]piridin-2-il)-4,5-dihidro-1,3-oxazol-4-il]propan-2-ol 47 b (0,314 g, 1,06 mmol) en benceno (15 ml). La mezcla de reacción se calentó a reflujo durante 2 h, a continuación se filtró a través de celite. El filtrado se concentró y el residuo se purificó por cromatografía flash en columna eluyendo con EtOAc al 10-60% en hexano para dar un sólido blanco (0,220 g, 71%). ^{1}H RMN (300 MHz, $CDCl_3$) δ 8,65 (1H, d, J=5,0 Hz), 8,35 (1H, s), 8,20 (1H, s), 7,36 (1H, d, J=5,0 Hz), 3,97 (3H, s); ESIMS (MH^+): 294,95.

Ejemplo 47(d): 2-[2-(7-clorotieno[3,2-b]piridin-2-il)-1,3-oxazol-4-il]propan-2-ol.



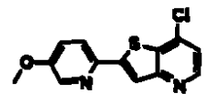
Se añadió MeMgBr (0,483 ml, 1,45 mmol) a una disolución de 2-(7-clorotieno[3,2-b]piridin-2-il)-1,3-oxazol-4-carboxilato de metilo 47 c (0,171 g, 0,58 mmol) en THF (10 ml) a 0°C. La mezcla de reacción se agitó a 0°C durante 1 h, se enfrió rápidamente con NH_4Cl (1 ml) saturado y se repartió entre $NaHCO_3$ (20 ml) saturado y EtOAc (2 x 20 ml). Las capas orgánicas combinadas se secaron sobre $MgSO_4$ y se concentraron. El residuo se purificó por cromatografía flash en columna eluyendo con CH_3OH al 0-2% en 1:1 EtOAc y CH_2Cl_2 para dar un sólido blancuzco (0,070 g, 41%). ^1H RMN (300 MHz, $CDCl_3$) δ 8,65 (1H, d, J=5,0 Hz), 8,35 (1H, s), 8,20 (1H, s), 7,36 (1H, d, J=5,0 Hz), 3,97 (6H, s); ESIMS (MH^+): 294,95.

Ejemplo 47: metilamida del ácido 6-(2-[4-(1-hidroxi-1-metil-etil)-oxazol-2-il]-tieno[3,2-b]piridin-7-iloxi)-1,2-dimetil-1H-indol-3-carboxílico (47).



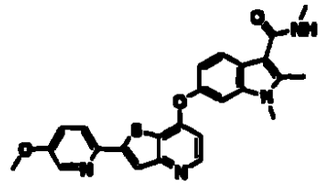
Este material se preparó por la reacción de 2-[2-(7-clorotieno[3,2-b]piridin-2-il)1,3-oxazol-4-il]propan-2-ol 47 d (0,068 g, 0,23 mmol) con 6-hidroxi-N,1,2-trimetil-1H-indol-3-carboxamida 16 e (0,051 g, 0,23 mmol) y Cs_2CO_3 (0,081g, 0,23 mmol) de una manera como se describe previamente para el ejemplo 1 para dar un sólido amarillo (0,046 g, 42%). ^1H RMN (300 MHz, CD_3OD) δ 8,39 (1H, d, J=5,3 Hz), 7,94 (1H, d, J=1,0 Hz), 7,79 (1H, s), 7,77 (1H, s), 7,32 (1H, s), 6,98 (1H, d, J=8,6 Hz), 6,62 (1H, d, J=5,3 Hz), 3,63 (3H, s), 2,90 (3H, s), 2,58 (3H, s), 1,51 (6H, s); ESIMS (MH^+): 477,10. Análisis Calculado para $C_{25}H_{25}N_4O_4S$. 0,25 CH_2Cl_2: C, 60,80; H, 5,15; N, 11,26; Encontrado: C, 60,84; H, 5,21; N, 10,98.

Ejemplo 48(a): 7-cloro-2-(5-metoxipiridin-2-il)tieno[3,2-b]piridina.



Este material se preparó por copulación de 7-cloro-2-(trimetilestannil)tieno[3,2-b]piridina **39 a** (0,214 g, 0,64 mmol) con 2-yodo-5-metoxipiridna (0,152 g, 0,64 mmol) usando tetraquis(trifenilfosfina)paladio(0) (30 mg) como catalizador de una manera como se describe previamente para el ejemplo **39 b** para dar un sólido amarillo (0,060 g, 34%). ^{1}H RMN (300 MHz, $CDCl_3$) δ 8,55 (1H, d, J=5,1 Hz), 8,43 (1H, s), 8,28 (1H, dd, J=1,3, 4,6 Hz), 7,34 (1H, m), 7,28 (1H, m), 7,24 (1H, d, J=5,8 Hz), 4,04 (3H, s).

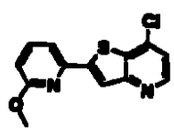
Ejemplo 48: metilamida del ácido 6-[2-(5-metoxi-piridin-2-il)tieno[3,2-b]piridin-7-iloxi]-1,2-dimetil-1H-indol-3-carboxílico.



Este material se preparó por la reacción de 7-cloro-2-(5-metoxipiridin-2-il)tieno[3,2-b]piridina **48 a** (0,058 g, 0,21 mmol) con 6-hidroxi-N,1,2-trimetil-1H-indol-3-carboxamida **16 e** (0,046 g, 0,21 mmol) y Cs_2CO_3 (0,068 g, 0,21 mmol) de una manera como se describe previamente para el ejemplo 1 para dar un sólido amarillo pálido (0,014 g, 15%) .^{1}H RMN (300 MHz, $CDCl_3$) δ 8,42 (2H, m), 8,26 (1H, dd, J=1,1, 4,6 Hz), 7,73 (1H, d, J=8,6 Hz), 7,34 (1H, m), 7,27 (1H, d, J=4,6 Hz), 7,15 (1H, d, J=2,0 Hz), 7,05 (1H, dd, J=2,0, 8,6 Hz), 6,49 (1H, d, J=5,31 Hz), 5,91 (1H, s ancho), 4,03 (3H, s), 3,64 (3H, s), 3,06 (3H, d, J=4,8 Hz), 2,72 (3H, s); ESIMS (MH^+): 459,03.

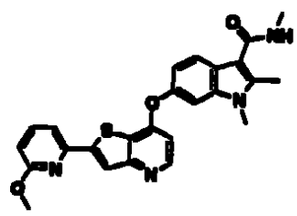
Análisis Calculado para $C_{25}H_{22}N_4O_3S$. 0,7 CH_3OH: C, 64,18; H, 5,20; N, 11,65; Encontrado: C, 64,28; H, 5,27; N, 11,47.

Ejemplo 49(a): 7-cloro-2-(6-metoxipiridin-2-il)tieno[3,2-b]piridina.



Este material se preparó por copulación de 7-cloro-2-(trimetilestannil)tieno[3,2-b]piridina **39 a** (0,478 g, 1,44 mmol) con 2-bromo-6-metoxipiridina (0,177 g, 1,44 mmol) usando tetraquis(trifenilfosfina)paladio(0) (67 mg) como catalizador de una manera como se describe previamente para el ejemplo **39 b** para dar un sólido amarillo pálido (0,249 g, 63%). ^{1}H RMN (300 MHz, $CDCl_3$) δ 8,56 (1H, d, J=5,1 Hz), 7,98 (1H, s), 7,66 (3H, m), 6,75 (1H, d, J=8,3 Hz), 4,05 (3H, s); ESIMS (MH^+): 276,95.

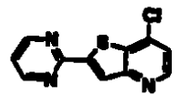
Ejemplo 49: metilamida del ácido 6-[2-(6-metoxi-piridin-2-il)-tieno[3,2-b]piridin-7-iloxi]-1,2-dimetil-1H-indol-3-carboxílico.



Este material se preparó por la reacción de 7-cloro-2-(6-metoxipiridin-2-il)tieno[3,2-b]piridina **49 a** (0,093 g, 0,34 mmol) con 6-hidroxi-N,1,2-trimetil-1H-indol-3-carboxamida **16 e** (0,074 g, 0,34 mmol) y Cs_2CO_3 (0,111 g, 0,34 mmol) de una manera como se describe previamente para el ejemplo 1 para dar un sólido blanco (0,029 g, 19%). ^{1}H RMN (300 MHz, $CDCl_3$) δ 8,43 (1H, d, J=5,46 Hz), 7,99 (1H, s), 7,76 (1H, d, J=8,7 Hz), 7,65 (1H, m), 7,45 (1H, d, J=7,4 Hz), 7,18 (1H, d, J=2,0 Hz), 7,07 (1H, dd, J=2,0, 8,7 Hz), 6,73 (1H, d, J=8,1 Hz), 6,47 (1H, m), 5,87 (1H, s), 4,03 (3H, s), 3,66 (3H, s), 3,07 (3H, d, J=4,9 Hz), 2,74 (3H, s); ESIMS (MH^+): 459,20.

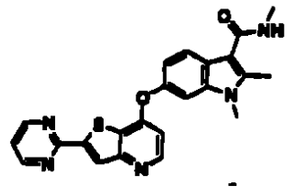
Análisis Calculado para $C_{25}H_{22}N_4O_3S$. 0,85 H_2O: C, 63,37; H, 5,04; N, 11,82; Encontrado: C, 63,48; H, 4,98; N, 11,43.

Ejemplo 50(a): 7-cloro-2-pirimidin-2-il-tieno[3,2-b]piridina.



Este material se preparó por copulación de 7-cloro-2-(trimetilestannil)tieno[3,2-b]piridina **39 a** (0,218 g, 0,66 mmol) con 2-bromopiridina (0,104 g, 0,66 mmol) usando tetraquis(trifenilfosfina)paladio(0) (31 mg) como catalizador de una manera como se describe previamente para el ejemplo **39 b** para dar un sólido blanco (0,066 g, 40%). ^{1}H RMN (300 MHz, $CDCl_3$) δ 8,76 (2H, d, J=4,90 Hz), 8,57 (1H, d, J=5,1 Hz), 8,41 (1H, s), 7,26 (1H, d, J=5,1 Hz), 7,20 (1H, m); ESIMS (MH^+): 248,00.

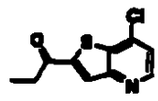
Ejemplo 50: metilamida del ácido 1,2-dimetil-6-(2-pirimidin-2-il-tieno[3,2-b]piridin-7-iloxi)-1H-indol-3-carboxílico.



Este material se preparó por la reacción de 7-cloro-2-pirimidin-2-iltieno[3,2-b]piridina **50 a** (0,066 g, 0,23 mmol) con 6-hidroxi-N,1,2-trimetil-1H-indol-3-carboxamida **16 e** (0,050 g, 0,23 mmol) y Cs_2CO_3 (0,075 g, 0,23 mmol) de una manera como se describe previamente para el ejemplo 1 para dar un sólido blanco (0,041 g, 41%). ^{1}H RMN (300 MHz, DMSO-d_6) δ 8,90 (2H, d, J=4,9 Hz), 8,50 (1H, d, J=5,3 Hz), 8,29 (1H, s), 7,81 (1H, d, J=8,5 Hz), 7,50 (3H, m), 7.01 (1H, dd, J=2,2, 8,5 Hz), 6,60 (1H, d, J=5,3 Hz), 3,64 (3H, s), 2,76 (3H, d, J=4,5 Hz), 2,57 (3H, s); ESIMS (MH^+): 430,10.

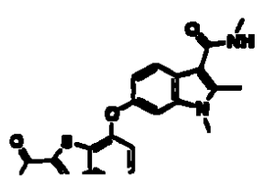
Análisis Calculado para $C_{23}H_{19}N_5O_2S$. 0,75 CH_3OH: C, 62,90; H, 4,89; N, 15,44; Encontrado: C, 62,92; H, 4,61; N, 15,39.

Ejemplo 51(a): 1-(7-clorotieno[3,2-b]piridin-2-il)propan-1-ona.



Se añadió nBuLi 2,5 M en hexano (0,619 ml, 1,55 mmol) a una disolución de 7-clorotieno[3,2-b]piridina (0,250 g, 1,47 mmol) en THF (5 ml) a –78°C. La mezcla de reacción se agitó a –78°C durante 30 min, y a continuación se añadió cloruro de propanoilo (0,162 ml, 1,76 mmol). La mezcla de reacción se agitó a –78°C y se calentó lentamente hasta 0°C y se enfrió rápidamente con agua (10 ml), y se extrajo con EtOAc (2 x 10 ml). La capa orgánica se secó sobre $MgSO_4$ y se concentró. El residuo se purificó por cromatografía flash en columna eluyendo con EtOAc al 10-70% en hexano para dar un sólido blancuzco (0,084 g, 25%). ^{1}H RMN (300 MHz, $CDCl_3$) δ 8,66 (1H, d, J=4,9 Hz), 8,12 (1H, s), 7,38 (1H, d, J=4,9 Hz), 3,09 (2H, q, J=7,3 Hz), 1,29 (3H, t, J=7,3 Hz); ESIMS (MH^+): 225,95.

Ejemplo 51: metilamida del ácido 1,2-dimetil-6-(2-propionil-tieno[3,2-b]piridin-7-

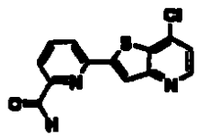


iloxi)-1H-indol-3-carboxílico.

Este material se preparó por la reacción de 1-(7-clorotieno[3,2-b]piridin-2-il)propan-1-ona **51 a** (0,062 g, 0,28 mmol) con 6-hidroxi-N,1,2-trimetil-1H-indol-3-carboxamida **16 e** (0,061 g, 0.28 mmol) y Cs_2CO_3 (0,091 g, 0,28 mmol) de una manera como se describe previamente para el ejemplo 1 para dar un sólido blancuzco (0,035 g, 31%). ^{1}H RMN (300 MHz, $CDCl_3$) δ 8,51 (1H, d, J=5,5 Hz), 8,11 (1H, s), 7,76 (1H, d, J=8,6 Hz), 7,15 (1H, d, J=2,1 Hz), 7,02 (1H, dd, J=2,1, 8,6 Hz), 6,58 (1H, d, J=5,5 Hz), 5,87 (1H, d, J=4,3 Hz), 3,66 (3H, s), 3,10 (2H, m), 3,06 (3H, d, J=4,9 Hz), 2,73 (3H, s), 1,31 (3H, t, J=7,3 Hz); ESIMS (MH^+): 408,05.

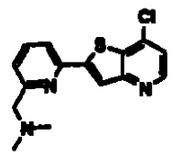
Análisis Calculado para $C_{22}H_{21}N_3O_3S$. 0,15 CH_2Cl_2: C, 63,31; H, 5,11; N, 10,00; Encontrado: C, 63,42; H, 5,03; N, 9,83.

Ejemplo 52(a): 6-(7-clorotieno[3,2-b]piridin-2-il)piridina-2-carbaldehído.



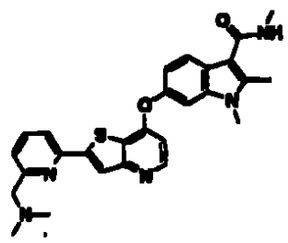
Este material se preparó por copulación de 7-cloro-2-(trimetilestannil)tieno[3,2-b]piridina **39 a** (0,707 g, 2,17 mmol) con 6-bromopiridina-2-carbaldehído (0,396 g, 2,17 mmol) usando tetraquis(trifenilfosfina)paladio(0) (100 mg) como catalizador de una manera como se describe previamente para el ejemplo **39 b** para dar un sólido blanco (0,161 g, 27%). ^{1}H RMN (300 MHz, $CDCl_3$) δ 10,15 (1H, s), 8,61 (1H, d, J=5,1 Hz), 7,93-8,09 (4H, m), 7,31 (1H, d, J=5,1 Hz); ESIMS (MH^+): 275,00.

Ejemplo 52(b): N-{[6-(7-clorotieno[3,2-b]piridin-2-il)piridin-2-il]metil}-N,N-dimetilamina



A una disolución de 6-(7-clorotieno[3,2-b]piridin-2-il)piridina-3-carbaldehído **52 a** (0,127 g, 0,46 mmol) en THF (20 ml) se añadió dimetilamina 2,0 M en THF (1,5 ml, 2,3 mmol), $NaCNBH_3$ (0,063 g, 0,92 mmol) y NaOAc (0,076 g, 0,92 mmol). La mezcla de reacción se agitó a temperatura ambiente durante la noche y se concentró. El residuo se purificó por cromatografía flash en columna eluyendo con CH_3OH al 2-10% en $CHCl_3$ para dar un sólido amarillo (0,086 g, 61%). ^1H RMN (300 MHz, CD_3OD) δ 8,50 (1H, d, J=5,3 Hz), 8,11 (1H, s), 8,03 (1H, d, J=7,9 Hz), 7,90 (1H, t, J=7,9 Hz), 7,41 (2H, m), 4,16 (2H, s), 2,71 (6H, s).

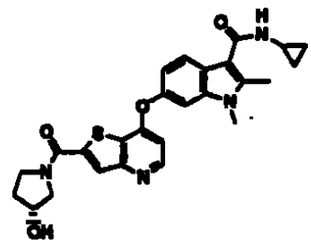
Ejemplo 52: metilamida del ácido 6-[2-(6-dimetilaminometil-piridin-2-il)tieno[3,2-b]piridin-7-iloxi]-1,2-dimetil-1H-indol-3-carboxílico.



Este material se preparó por la reacción de N-{[6-(7-clorotieno[3,2-b]piridin-2-il)piridin-2-il]metil}-N,N-dimetilamina **52 b** (0,080g, 0,26 mmol) con 6-hidroxi-N,1,2-trimetil-1H-indol-3-carboxamida **16 e** (0,058 g, 0,26 mmol) y Cs_2CO_3 (0,085 g, 0,26 mmol) de una manera como se describe previamente para el ejemplo 1 para dar un sólido blanco (0,016 g, 13%). ^1H RMN (300 MHz, CD_3OD) δ 8,27 (1H, d, J=5,5 Hz), 7,91 (1H, s), 7,77 (3H, m), 7,31 (1H, d, J=7,0 Hz), 7,24 (1H, d, J=2,0 Hz), 6,93 (1H, dd, J=2,0, 8,6 Hz), 6,49 (1H, d, J=5,5 Hz), 3,57 (5H, m), 2,88 (3H, s), 2,54 (3H, s), 2,26 (6H, s).

Análisis Calculado para $C_{27}H_{27}N_5O_2S$. 1,5 CH_2Cl_2: C, 55,84; H, 4,93; N, 11,43; Encontrado: C, 55, 75; H, 5,15; N, 11,01.

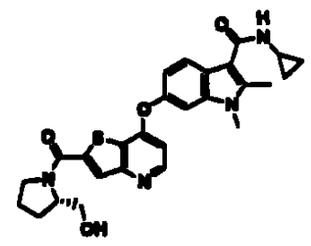
Ejemplo 53: ciclopropilamida del ácido 6-[2-((R)-3-hidroxi-pirrolidina-1-carbonil)-tieno[3,2-b]piridin-7-iloxi]-1,2-dimetil-1H-indol-3-carboxílico.



Este material se preparó por la reacción de (7-cloro-tieno[3,2-b]piridin-2-il)-((R)-3-hidroxi-pirrolidin-1-il)-metanona **4 a** con ciclopropilamida del ácido 6-hidroxi-1,2-dimetil-1H-indol-3-carboxílico **20 b** y Cs_2CO_3 de una manera como se describe previamente para el ejemplo 1. ^{1}H RMN (300 MHz, CD_3OD) δ 8,50 (1H, d, J=5,5 Hz), 7,93 (1H, d, J=17,33 Hz), 7,80 (1H, d, J=8,6 Hz), 7,39 (1H, d, J=2,1 Hz), 7,05 (1H, dd, J=2,1, 8,6 Hz), 6,71 (1H, d, J=5,5 Hz), 4,54 (1H, s ancho), 4,11-4,00 (2H, m), 3,85-3,72 (6H, m), 2,93-2,86 (1H, m), 2,66 (3H, s), 2,19-2,07 (2H, m), 0,90-0,84 (2H, m), 0,76-0,68 (2H, m), CLEM (ESI+) [M+H]/z Calculado 491, Encontrado 491.

Análisis ($C_{28}H_{26}N_4O_4S$. 0,2 CH_2Cl_2) C, H, N.

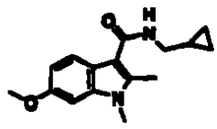
Ejemplo 54: N-ciclopropil-6-[(2-{[(2S)-2-(hidroximetil)pirrolidin-1-il]carbonil}tieno[3,2-b]piridin-7-il)oxi]-1,2-dimetil-1H-indol-3-carboxamida.



Este material se preparó por la reacción de {(2S)-1-[(7-clorotieno[3,2-b]piridin-2-il)carbonil]pirrolidin-2-il}metanol **3 b** (0,107 g, 0,345 mmol) con N-ciclopropil-6-hidroxi-1,2-dimetil-1H-indol-3-carboxamida **20 b** (0,055 g, 0,23 mmol) y Cs_2CO_3 (0,073 g, 0,23 mmol) de una manera como se describe previamente para el ejemplo 1 para dar un sólido marrón (0,059 g, 51%). ^{1}H RMN (300 MHz, CD_3OD) δ 8,37 (1H, d, J=5,6 Hz), 7,81 (1H, s), 7,67 (1H, d, J=8,6 Hz), 7,27 (1H, d, J=2,1 Hz), 6,92 (1H, dd, J=2,1, 8,6

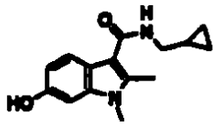
Hz), 6,59 (1H, d, J=5,6 Hz), 4,25 (1H, m), 3,82 (3H. m), 3,61 (3H, s), 2,76 (1H, m), 2,54 (3H, s), 2,00 (4H, m), 1,84 (1H, m), 1,14 (2H, m), 0,77 (2H, m). ESIMS (MH^+): 505,15. Análisis Calculado para $C_{27}H_{28}N_4O_4S$. 0,45 CH_2Cl_2: C, 60,74; H, 5,37; N, 10,32; Encontrado: C, 60,40; H, 5,56; N, 10,06.

Ejemplo 55(a): N-(ciclopropilmetil)-6-metoxi-1,2-dimetil-1H-indol-3-carboxamida.



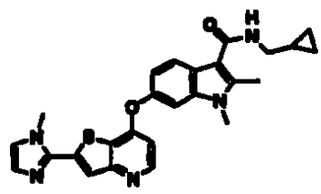
Este material se preparó a partir de ácido 6-metoxi-1,2-dimetil-1H-indol-3-carboxílico **16 c** (0,80 g, 3,65 mmol) con $SOCl_2$ (0,799 ml, 10,95 mmol) y ciclopropilmetilamina (0,38 ml, 4,38 mmol) de una manera como se describe previamente para el ejemplo 9 d para dar un sólido amarillo pálido (0,382 g, 38%). ^1H RMN (300 MHz, CD_3OD) δ 7,50 (1H, d, J=8,7 Hz), 6,81 (1H, d, J=2,2 Hz), 6,69 (1H, dd, J=2,2, 8,7 Hz), 3,74 (3H, s), 3,56 (3H, s), 3,20 (2H, m), 2,50 (3H, m), 1,07 (1H, m), 0,44 (2H, m), 0,21 (2H, m); ESIMS (MH^+): 273,10.

Ejemplo 55(b): N-(ciclopropilmetil)-6-hidroxi-1,2-dimetil-1H-indol-3-carboxamida.



Este material se preparó por reacción de N-(ciclopropilmetil)-6-metoxi-1,2-dimetil-1H-indol-3-carboxamida **55a** (0,38 g, 1,4 mmol) con BBr_3 1,0 M en CH_2Cl_2 (4,19 ml, 4,19 mmol) de una manera como se describió previamente para el ejemplo 1 d para dar un sólido amarillo pálido (0,278 g, 77%). ^1H RMN (400 MHz, CD_3OD) δ 7,55 (1H, d, J=8,5 Hz), 6,77 (1H, s), 6,71 (1H, d, J=8,5 Hz), 3,63 (3H, s), 3,28 (2H, m), 2,61 (3H, s), 1,18 (1H, m), 0,56 (2H, m); ESIMS (MH^+): 259,10

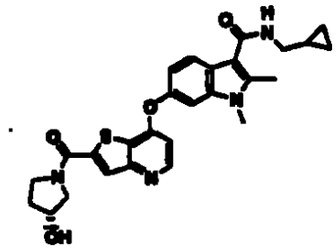
Ejemplo 55: N-(ciclopropilmetil)-1,2-dimetil-6-{[2-(1-metil-1H-imidazol-2-il)tieno[3,2-b]piridin-7-il]oxi}-1H-indol-3-carboxamida



Este material se preparó por la reacción de 7-cloro-2-(1-metil-1H-imidazol-2-il)tieno[3,2-b]piridina **1 e** (0,76 g, 0,32 mmol) con 6-hidroxi-N,1,2-trimetil-1H-indol-3-carboxamida **55 b** (0,074 g, 0,32 mmol) y Cs_2CO_3 (0,098 g, 0,30 mmol) de una manera como se describe previamente para el ejemplo 1 para dar un sólido amarillo pálido (0,060 g, 40%). ^{1}H RMN (400 MHz, CD_3OD) δ 8,33 (1H, d, J=5,6 Hz), 7,75 (1H, d, J=8,6 Hz), 6,77 (1H, s), 7,67 (1H, s), 7,28 (1H, d, J=2,2 Hz), 7,21 (1H, d, J=1,1Hz), 6,99 (1H, d, J=1,1 Hz), 6,95 (1H, dd, J=2,2, 8,6 Hz), 6,57 (1H, d, J=5,6 Hz), 3,92 (3H, s), 3,61 (3H, s), 2,55 (3H, s), 1,06 (1H, m), 0,46 (2H, m); 0.23 (2H, m) ESIMS (MH^+): 472,10

Análisis calculado para $C_{28}H_{25}N_5O_2S$. 0,5 CH_3OH: C, 65,27; H, 5,58; N, 14,36; Encontrado: C, 65,52; H, 5,58; N, 14,12.

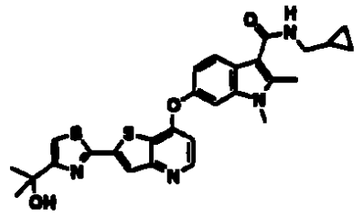
Ejemplo 56: N-(ciclopropilmetil)-6-[(2-{[(3R)-3-hidroxipirrolidin-1-il]carbonil}tieno[3,2-b]piridin-7-il)oxi]-1,2-dimetil-1H-indol-3-carboxamida



Este material se preparó por la reacción de (3R)-1-[(7-clorotieno[3,2-b]piridin-2-il)carbonil]pirrolidin-3-ol **4 a** (0,083 g, 0,29 mmol) con 6-hidroxi-N,1,2-trimetil-1H-indol-3-carboxamida **55 b** (0,075 g, 0,29 mmol) y Cs_2CO_3 (0,094 g, 0,29 mmol) de una manera como se describe previamente para el ejemplo 1 para dar un sólido amarillo pálido (0,050 g, 34%). ^{1}H RMN (300 MHz, CD_3OD) δ 8,50 (1H, d, J=5,3 Hz), 7,83 (1H, s), 7,73 (1H, d, J=8,7 Hz), 7,50 (1H, d, J=4,7 Hz), 7,42 (1H, d, J=2,1 Hz), 6,99 (1H, d, J=2,1 8,7 Hz), 4,53 (1H, m), 3,96 (2H, m), 3,65 (2H, m), 3,61 (3H, s), 3,10 (4H, m), 2,35 (3H, s), 1,09 (1H, m), 0,88 (2H, m); 0,45 (2H, m); ESIMS (MH^+): 505,20

Análisis calculado para $C_{27}H_{28}N_4O_4S$. 0,25 CH_2Cl_2: C, 62,24; H, 4,56; N, 10,66; Encontrado: C, 62,10; H, 5,74; N, 10,33.

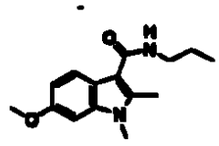
Ejemplo 57: ciclopropilmetilamida del ácido 6-[2-[4-(1-hidroxi-1-metil-etil)tiazol-2-il]tieno[3,2-b]piridin-7-iloxi]-1,2-dimetil-1H-indol-3-carboxílico.



Este material se preparó por la reacción de 2-[2-(7-clorotieno[3,2-b]piridin-2-il)-1,3-tiazol-4-il]propan-2-ol **40 a** (0,102 g, 0,33 mmol) con N-(ciclopropilmetil)-6-hidroxi-1,2-dimetil-1H-indol-3-carboxamida **55 b** (0,085 g, 0,33 mmol) y Cs_2CO_3 (0,108 g, 0,33 mmol) de una manera como se describe previamente para el ejemplo 1. ^{1}H RMN (300 MHz, DMSO-d_6) δ 8,50 (1H, d, J=5,5 Hz), 8,12 (1H, s), 7,83 (1H, d, J=8,6 Hz), 7,73 (1H, t, J=5,8 Hz), 7,58 (1H, s), 7,54 (1H, d, J=2,1 Hz), 7,05 (1H, dd, J=2,1 8,6 Hz), 6,59 (1H, d, J=5,5 Hz), 3,68 (3H, s), 3,17 (2H, t, J=6,1 Hz), 2,61 (3H, s), 1,50 (6H, s), 1,08 (2H, m), 0,43 (2H, m); 0,25 (2H, m); ESIMS (MH^+): 533,15

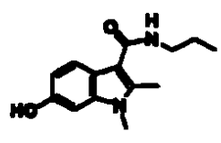
Análisis calculado para $C_{28}H_{28}N_4O_3S_2$. 0,25 H_2O: C, 62,60; H, 5,35; N, 10,43; Encontrado: C, 62,65; H, 5,37; N, 10,20.

Ejemplo 58(a): propilamida del ácido 6-metoxi-1,2-dimetil-1H-indol-3-carboxílico



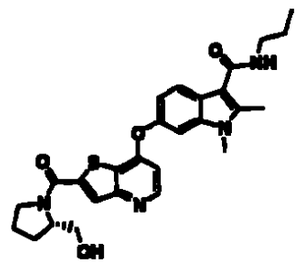
Este material se preparó a partir de ácido 1,2-dimetil-6-metoxi-1H-indol-3-carboxílico **16 c**, cloruro de tionilo y propilamina de una manera como se describe previamente para el ejemplo 9 d. ^{1}H RMN (300 MHz, $CDCl_3$) δ 7,55 (1H, d, J=8,6 Hz), 6,84 (1H, dd, J=2,2, 8,6 Hz), 6,78 (1H, d, J=2,2 Hz), 5,87 (1H, s ancho), 3,87 (3H, s), 3,63 (3H, s), 3,45 (2H, m), 2,69 (3H, s), 1,67 (2H, m), 1,02 (3H, t, J=7,4 Hz) LCMS (ESI+) [M+H]/z) Calculado 261, encontrado 261.

Ejemplo 58(b): propilamida del ácido 6-hidroxi-1,2-dimetil-1H-indol-3-carboxílico



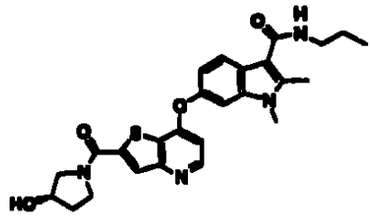
Este material se preparó a partir de propilamida del ácido 6-metoxi-1,2-dimetil-1H-indol-3-carboxílico **18 a**, por tratamiento con BBr_3, de una manera como se describe previamente para el ejemplo 1 **d**. ^1H RMN (300 MHz, CD_3OD) δ 7,50 (1H, d, J=8,7 Hz), 6,74 (1H, d, J=1,9 Hz), 6,68 (1H, dd, J=1,9, 8,7 Hz), 3,61 (3H, s), 3,32 (2H, m), 2,58 (3H, s), 1,66 (2H, m), 1,01 (3H, t, J=7,4 Hz) LCMS (ESI+) [M+H]/z) Calculado 247, encontrado 247.

Ejemplo 58: propilamida del ácido 6-(2-[2-(S)-hidroximetil-pirrolidina-1-carbonil]tieno[3,2-b]piridin-7-iloxi)-1,2-dimetil-1H-indol-3-carboxílico.



Este material se preparó por la reacción de (7-cloro-tieno[3,2-b]piridin-2-il)-(3-hidroximetil-pirrolidin-1-il)-metanona **3 a** (0,127 g, 0,43 mmol) con propilamida del ácido 6-hidroxi-1,2-dimetil-1H-indol-3-carboxílico **58 b** (0,070 g, 0,285 mmol) y Cs_2CO_3 (0,099 g, 0,35 mmol) de una manera como se describe previamente para el ejemplo 1 para dar 30 mg (14% de rendimiento) de un sólido amarillo pálido. ^1H RMN (CD_3OD) δ 8,33 (1H, d, J=5,1 Hz), 7,69-7,75 (2H, m), 7,24 (1H, s), 6,9 (1H, d, J=8,1 Hz), 6,56 (1H, d, J=5,1 Hz), 4,22 (1H, m), 3,64-3,78 (4H, m), 3,56 (3H, s), 3,20-3,31 (2H, m), 2,52 (3H, s), 1,90-1,98 (4H, m), 1,62-1,55 (2H, m), 0,95-0,90 (3H, m). ESIMS (MH^+): 507,20. Análisis calculado para $C_{27}H_{30}N_4O_4S$. 1,0 CH_3OH: C, 62,43; H, 6,36; N, 10,40. Encontrado: C, 62,44; H, 6,13; N, 10,13.

Ejemplo 59: propilamida del ácido 6-[2-(3-hidroxi-pirrolidina-1-carbonil)tieno[3,2-b]piridin-7-iloxi]-1,2-dimetil-3H-indol-3-carboxílico.

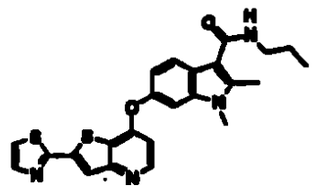


Este material se preparó por la reacción de 7-cloro-2-[(R)-3-hidroxipirrolidina-1-carbonil]tieno[3,2-b]piridinina **4 a** con propilamida del ácido 6-hidroxi-1,2-dimetil-1H-

indol-3-carboxílico **58 b** y Cs_2CO_3 de una manera como se describe previamente para el ejemplo 1. ^1H RMN (300 MHz, CD_3OD) δ 8,50 (1H, d, J=5,6 Hz), 7,96 (1H, d, J=17,3 Hz), 7,86 (1H, d, J=8,7 Hz), 7,40 (1H, s), 7,06 (1H, d, J=10,7 Hz), 6,72 (1H, d, J=5,6 Hz), 4,61-4,53 (1H, m), 4,15-4,00 (2H, m), 3,91-3,73 (3H, m), 3,73 (3H, s), 3,53-3,40 (2H, m), 2,67 (3H, s), 2,28-2,07 (2H, m), 1,78-1,69 (2H, m), 1,18-1,04 (3H, m). LCMS (ESI+) [M+H]/z. Calculado 493, encontrado 493.

Análisis $C_{28}H_{28}N_4O_4S$. 0,3 CH_2Cl_2: C, H, N.

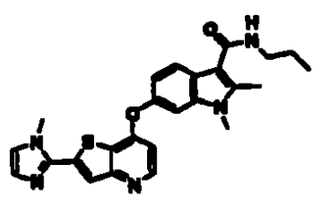
Ejemplo 60: propilamida del ácido 1,2-dimetil-6-(2-tiazol-2-il-tieno[3,2-b]piridin-7-iloxi)-1H-indol-3-carboxílico.



Este material se preparó por la reacción de 7-cloro-2-(1,3-tiazol-2-il)tieno[3,2-b]piridina **41 a** (0,078 g, 0,314 mmol) con 6-hidroxi-1,2-dimetil-N-propil-1H-indol-3-carboxamida **58 b** (0,076 g, 0,31 mmol) y Cs_2CO_3 (0,101 g, 0,31 mmol) de una manera como se describe previamente para el ejemplo 1 para dar un sólido amarillo (0,035 g, 24%). ^1H RMN (300 MHz, $CDCl_3$) δ 8,46 (1H, d, J=5,3 Hz), 7,92 (1H, s), 7,88 (1H, d, J=3,2 Hz), 7,74 (1H, d, J=8,7 Hz), 7,42 (1H, d, J=3,2 Hz), 7,17 (1H, d, J=1,7 Hz), 7,05 (1H, dd, J=1,7, 8,7 Hz), 6,55 (1H, d, J=5,3 Hz), 5,90 (1H, m), 3,66 (3H, s), 3,47 (2H, m), 2,73 (3H, s), 1,69 (2H, m), 1,03 (3H, t, J=7,4 Hz); ESIMS (MH^+): 463,10.

Análisis Calculado para $C_{24}H_{22}N_4O_2S_2$. 0,05 CH_2Cl_2: C, 61,87; H, 4,77; N, 12,00; Encontrado: C, 61,90; H, 4,77; N, 11,90.

Ejemplo 61: propilamida del ácido 1,2-dimetil-6-[2-(1-metil-1H-imidazol-2-il)tieno[3,2-b]piridin-7-iloxi]-1H-indol-3-carboxílico.

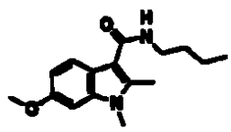


Este material se preparó a partir de 7-cloro-2-(1-metil-1H-imidazol-2-il)tieno[3,2-b]piridina **1 e** con propilamida del ácido 6-hidroxi-1,2-dimetil-1H-indol-3-carboxílico **58**

b y Cs_2CO_3, de una manera como se describe previamente para el ejemplo 1. ^1H RMN (300 MHz, $CDCl_3$) δ 8,42 (1H, d, J=5,5 Hz), 7,82 (1H, d, J=8,7 Hz), 7,76 (1H, s), 7,37 (1H, d, J=1,8 Hz), 7,30 (1H, s), 7,08 (1H, s), 7,03 (1H, dd, J=1,8, 8,7 Hz), 6,65 (1H, d, J=5,5 Hz), 4,01 (3H, s), 3,70 (3H, s), 3,39 (2H, m), 2,64 (3H, s), 1,70 (2H, m), 1,03 (3H, m). LCMS (ESI+) [M+H]/z Calculado 460, encontrado 460.

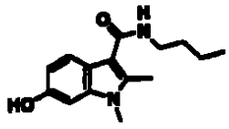
Análisis ($C_{25}H_{25}N_5O_2S$. 1,0 CH_3OH), C, H, N.

Ejemplo 62(a): butilamida del ácido 6-metoxi-1,2-dimetil-1H-indol-3-carboxílico.



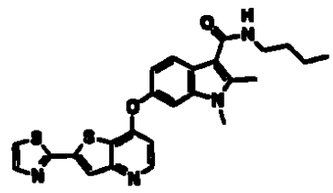
Este material se preparó por la reacción de ácido 6-metoxi-1,2-dimetil-1H-indol-3-carboxílico (1,12 g, 5,11 mmol) **16 c** con cloruro de oxalilo (0,682 g, 13,6 mmol) y butan-1-amina (1,51 ml, 15,33 mmol) de una manera como se describe previamente para el ejemplo **16 d** para dar un sólido amarillo (0,990 g, 71%). ^1H RMN (300 MHz, $CDCl_3$) δ 8,01 (1H, d, J=8,6 Hz), 7,31 (1H, dd, J=2,3, 8,6 Hz), 7,25 (1H, d, J=2,3 Hz), 6,32 (1H, s), 4,34 (3H, s), 4,09 (3H, s), 3,95 (2H, m), 3,16 (3H, s), 2,10 (2H, m), 1,92 (2H, m), 1,44 (3H, t, J=7,4 Hz); ESIMS (MH^+): 275,15.

Ejemplo 62 (b): butilamida del ácido 6-hidroxi-1,2-dimetil-1H-indol-3-carboxílico.



Este material se preparó por la reacción de butilamida del ácido 6-metoxi-1,2-dimetil-1H-indol-3-carboxílico **62 a** (0,78 g, 2,84 mmol) con BBr_3 1,0 M en CH_2Cl_2 (8,53 ml, 8,53 mmol) de una manera como se describe previamente para el ejemplo **1 d** para dar un sólido blancuzco (0,623 g, 96%). ^1H RMN (300 MHz, CD_3OD) δ 7,40 (1H, d, J=8,5 Hz), 6,64 (1H, d, J=2,1 Hz), 6,59 (1H, dd, J=2,1, 8,5 Hz), 3,50 (3H, s), 3,29 (2H, m), 2,48 (3H, s), 1,54 (2H, m), 1,36 (2H, m), 0,90 (3H, t, J=7,3 Hz); ESIMS (MH^+): 261,15.

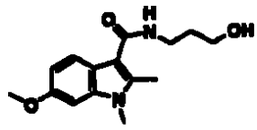
Ejemplo 62: butilamida del ácido 1,2-dimetil-6-(2-tiazol-2-il-tieno[3,2-b]piridin-7-iloxi)-1H-indol-3-carboxílico.



Este material se preparó por la reacción de 7-cloro-2-(1,3-tiazol-2-il)tieno[3,2-b]piridina 41 a (0,085 g, 0,33 mmol) con butilamida del ácido 6-hidroxi-1,2-dimetil-1H-indol-3-carboxílico **62 b** (0,087 g, 0,33 mmol) y Cs_2CO_3 (0,108 g, 0,33 mmol) de una manera como se describe previamente para el ejemplo 1 para dar un sólido amarillo (0,090 g, 57%). ^{1}H RMN (300 MHz, CD_3OD) δ 8,32 (1H, d, J=5,5 Hz), 7,83 (1H, s), 7,78 (1H, d, J=3,2 Hz), 7,72 (1H, d, J=8,7 Hz), 7,63 (1H, d, J=3,2 Hz), 7,28 (1H, d, J=2,0 Hz), 6,94 (1H, dd, J=2,0, 8,7 Hz), 6,56 (1H, d, J=5,5 Hz), 3,59 (3H, s), 3,34 (2H, m), 2,54 (3H, s), 1,57 (2H, m), 1,38 (2H, m), 0,90 (3H, t, J=7,4 Hz); ESIMS (MH^+); 477,05.

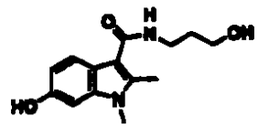
Análisis Calculado para $C_{25}H_{24}N_4O_2S_2$. 0,7 H_2O: C, 61,37; H, 5,23; N, 11,45; Encontrado: C, 61,34; H, 5,22; N, 11,11.

Ejemplo 63 (a): (3-hidroxi-propil)amida del ácido 6-metoxi-1,2-dimetil-1H-indol-3-carboxílico.



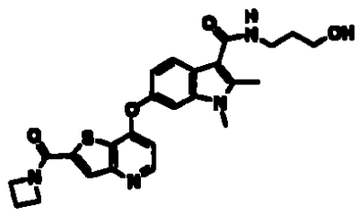
Este material se preparó por la reacción del ácido 1,2-dimetil-6-metoxi-1H-indol-3-carboxílico **16 c** con 3-hidroxipropilamina y cloruro de oxalilo de una manera como se describe previamente para **16 d**. ^{1}H RMN (300 MHz, CD_3OD) δ 7,52 (1H, d, J=8,6 Hz), 6,73 (1H, d, J=2,1 Hz), 6,68 (1H, dd, J=2,1, 8,6 Hz), 3,69 (2H, t, J=6,1 Hz), 3,79 (3H, s), 3,63 (3H, s), 3,51 (2H, m), 2,57 (3H, s), 1,85 (2H, m), LCMS (ESI+) [M+H]/z Calculado 291, encontrado 291.

Ejemplo 63 (b): (3-hidroxi-propil)amida del ácido 6-hidroxi-1,2-dimetil-1H-indol-3-carboxílico.



Este material se preparó por la reacción de (3-metoxipropil)amida del ácido 6-metoxi-1,2-dimetil-1H-indol-3-carboxílico **63 a** por tratamiento con BBr_3 de una manera como se describe previamente para **1 d**. ^{1}H RMN (300 MHz, CD_3OD) δ 7,52 (1H, d, J=8,6 Hz), 6,73 (1H, d, J=2,1 Hz), 6,68 (1H, dd, J=2,1, 8,6 Hz), 3,69 (2H, t, J=6,1 Hz), 3,57 (3H, s), 3,51 (2H, m), 2,57 (3H, s), 1,85 (2H, m), LCMS (ESI+) [M+H]/z Calculado 263, encontrado 263.

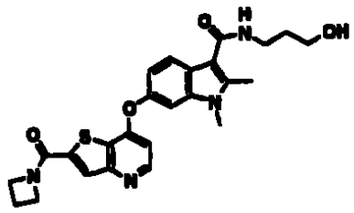
Ejemplo 63: (3-hidroxipropil)amina del ácido 6-[2-(azetidina-1-carbonil)tieno[3,2-b]piridin-7-iloxi]-1,2-dimetil-1H-indol-3-carboxílico



Este material se preparó por la reacción de 2-(azetidin-1-il-carbonil)-7-clorotieno[3,2-b]piridina **25 a** con (3-hidroxipropil)amida del ácido 6-hidroxi-1,2-dimetil-1H-indol-3-carboxílico **63 b** y Cs_2CO_3 de una manera como se describe previamente para el ejemplo **1**. ^{1}H RMN (300 MHz, CD_3OD) δ 8,50 (1H, d, J=5,5 Hz), 7,89 (1H, d, J=8,7 Hz), 7,82 (1H, s), 7,40 (1H, s), 7,06 (1H, d, J=6,6 Hz), 6,72 (1H, d, J=5,5 Hz), 4,74-4,65 (2H, m), 4,31-3,68 (5H, m), 3,60-3,55 (2H, m), 2,68 (3H, s), 2,54-2,46 (2H, m), 1,95-1,87 (2H, m). LCMS (ESI+) [M+H]/z Calculado 478, encontrado 478.

Análisis ($C_{25}H_{26}N_4O_3S$. 0,9 CH_2Cl_2) C, H, N.

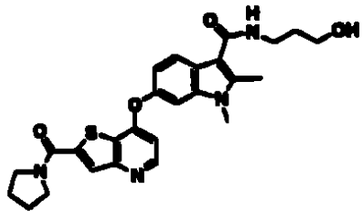
Ejemplo 64: (3-hidroxipropil)amida del ácido 6-[2-((R)-3-hidroxi-pirrolidina-1-carbonil)-tieno[3,2-b]piridin-7-iloxi]-1,2-dimetil-1H-indol-3-carboxílico.



Este material se preparó por la reacción de (7-cloro-tieno[3,2-b]piridin-2-il)-((R)-3-hidroxi-pirrolidin-1-il)metanona 4 a con (3-hidroxipropil)amida del ácido 6-hidroxi-1,2-dimetil-1H-indol-3-carboxílico 63 b y Cs_2CO_3 de una manera como se describe previamente para el ejemplo 1. ^1H RMN (300 MHz, CD_3OD) δ 8,38 (1H, d, J=5,5 Hz), 7,84-7,74 (2H, m), 7,28 (1H, d, J=2,1 Hz), 6,94 (1H, dd, J=2,1, 8,6 Hz), 6,60 (1H, d, J=5,5 Hz), 4,45-4,42 (1H, m), 3,93-3,91 (2H, m), 3,71-3,60 (8H, m), 3,45 (2H, m), 2,56 (3H, s), 2,02-1,98 (2H, m), 1,72-1,68 (2H, m). LCMS (ESI+) [M+H]/z Calculado 509, encontrado 509.

Análisis ($C_{28}H_{28}N_4O_5S$. 0,6 CH_2Cl_2) C, H, N.

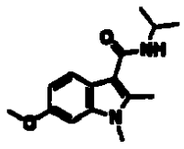
Ejemplo 65: (3-hidroxipropil)amida del ácido 1,2-dimetil-6-[2-(pirrolidina-1-carbonil)tieno[3,2-b]piridin-7-iloxi]-1H-indol-3-carboxílico.



Este material se preparó a partir de la reacción de (7-cloro-tieno[3,2-b]piridin-2-il)pirrolidin-1-il-metanona con (3-hidroxipropil)amida del ácido 6-hidroxi-1,2-dimetil-1H-indol-3-carboxílico 63 b y Cs_2CO_3, de una manera como se describe previamente para el ejemplo 1. ^1H RMN (300 MHz, CD_3OD) δ 8,44 (1H, d, J=5,5 Hz), 7,85 (1H, s), 7,83 (1H, d, J=10,0 Hz), 7,35 (1H, d, J=1,9 Hz), 7,01 (1H, dd, J=1,9, 8,5 Hz), 6,66 (1H, d, J=5,5 Hz), 3,88 (2H, m), 3,76 (7H, m), 3,54 (2H, m), 2,63 (3H, s), 1,83-2,10 (6H, m). LCMS (ESI+) [M+H]/z Calculado 493, encontrado 493.

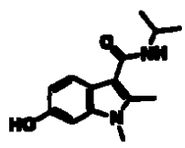
Análisis ($C_{28}H_{28}N_4O_4S$. 0,5 CH_3OH) C, H, N.

Ejemplo 66(a): Isopropilamida del ácido 6-metoxi-1,2-dimetil-1H-indol-3-carboxílico.



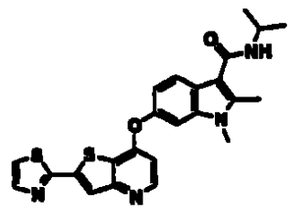
Este material se preparó a partir de ácido 1,2-dimetil-6-metoxi-1H-indol-3-carboxílico **16 c**, cloruro de oxalilo e isopropilamina de una manera como se describe previamente para el ejemplo **16 d**. ^{1}H RMN (300 MHz, $CDCl_3$) δ 7,53 (1H, d, J=8,7 Hz), 6,85 (1H, dd, J=2,3, 8,7 Hz), 6,77 (1H, d, J=2,3 Hz), 4,35 (1H, m), 3,87 (3H, s), 3,63 (3H, s), 2,69 (3H, s), 1,30 (3H, s), 1,27 (3H, s). LCMS (ESI+) [M+H]/z Calculado 261, encontrado 261.

Ejemplo 66(b): Isopropilamida del ácido 6-hidroxi-1,2-dimetil-1H-indol-3-carboxílico.



Este material se preparó de isopropilamida del ácido 6-metoxi-1,2-dimetil-1H-indol-3-carboxílico **66 a**, por tratamiento con BBr_3 de una manera como se describe previamente para el ejemplo **1 d**. ^{1}H RMN (300 MHz, CD_3OD) δ 7,47 (1H, d, J=8,5 Hz), 6,74 (1H, d, J=2,1 Hz), 6,67 (1H, dd, J=2,1, 8,5 Hz), 4,22 (1H, m), 3,61 (3H, s), 2,56 (3H, s), 1,28 (3H, s), 1,26 (3H, s). LCMS (ESI+) [M+H]/z Calculado 247, encontrado 247.

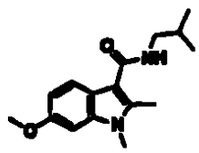
Ejemplo 66: isopropilamida del ácido 1,2-dimetil-6-(2-tiazol-2-il-tieno[3,2-b]piridin-7-iloxi)-1H-indol-3-carboxílico.



Este material se preparó por reacción de 7-cloro-2-(1,3-tiazol-2-il)tieno[3,2-b]piridina **41 a** (0,084 g, 0,33 mmol) con 6-hidroxi-N-isopropil-1,2-dimetil-1H-indol-3-carboxamida **66 b** (0,082 g, 0,33 mmol) y Cs_2CO_3 (0,116 g, 0,33 mmol) para dar un sólido blancuzco (0,058 g, 38%). ^{1}H RMN (300 MHz, $CDCl_3$) δ 8,46 (1H, d, J=5,4 Hz), 7,93 (1H, s), 7,88 (1H, d, J=3,2 Hz), 7,73 (1H, d, J=8,6 Hz), 7,42 (1H, d, J=3,2 Hz), 7,17 (1H, d, J=2,1 Hz), 7,07 (1H, dd, J=2,1, 8,6 Hz), 6,54 (1H, d, J=5,4 Hz), 5,71 (1H, d, J=7,7 Hz), 4,36 (1H, m), 3,66 (3H, s), 2,72 (3H, s), 1,31 (6H, d, J=6,6 Hz); ESIMS (MH+): 463,10.

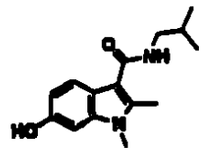
Análisis Calculado para $C_{24}H_{22}N_4O_2S_2$. 0,33 H_2O: C, 61,59; H, 4,87; N, 11,97; Encontrado: C, 61,48; H, 4,67; N, 11,86.

Ejemplo 67(a): isobutilamida del ácido 6-metoxi-1,2-dimetil-1H-indol-3-carboxílico.



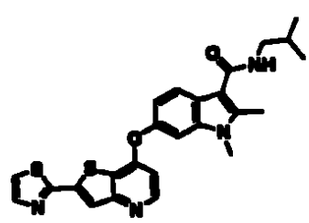
Este material se preparó a partir de ácido 1,2-dimetil-6-metoxi-1H-indol-3-carboxílico **16 c**, cloruro de oxalilo e isopropilamina de una manera como se describe previamente para el ejemplo **16 d**. ^{1}H RMN (300 MHz, $CDCl_3$) δ 7,56 (1H, d, J=8,6 Hz), 6,85 (1H, dd, J=2,2, 8,6 Hz), 6,78 (1H, d, J=2,2 Hz), 3,87 (3H, s), 3,63 (3H, s), 3,32 (2H, m), 2,69 (3H, s), 1,93 (1H, m), 1,02 (3H, s), 1,00 (3H, s). LCMS (ESI+) [M+H]/z Calculado 275, encontrado 275.

Ejemplo 67(b): isobutilamida del ácido 6-hidroxi-1,2-dimetil-1H-indol-3-carboxílico.



Este material se preparó de isobutilamida del ácido 6-metoxi-1,2-dimetil-1H-indol-3-carboxílico **66 a**, por tratamiento con BBr_3 de una manera como se describe previamente para el ejemplo 1 d. ^1H RMN (300 MHz, CD_3OD) δ 7,52 (1H, d, J=8,5 Hz), 6,74 (1H, d, J=2,3 Hz), 6,68 (1H, dd, J=2,3, 8,5 Hz), 3,61 (3H, s), 3,22 (2H, m), 2,58 (3H, s), 1,95 (1H, m), 1,02 (3H, s), 1,00 (3H, s). LCMS (ESI+) [M+H]/z Calculado 261, encontrado 261.

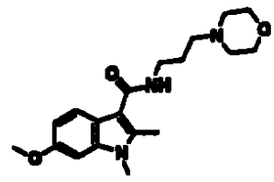
Ejemplo 67: isobutilamida del ácido 1,2-dimetil-6-(2-tiazol-2-il-tieno[3,2-b]piridin-7-iloxi)-1H-indol-3-carboxílico.



Este material se preparó por reacción de 7-cloro-2-(1,3-tiazol-2-il)tieno[3,2-b]piridina **41 a** (0,086 g, 0,34 mmol) con 6-hidroxi-N-isobutil-1,2-dimetil-1H-indol-3-carboxamida **67 b** (0,087g, 0,34 mmol) y Cs_2CO_3 (0,120 g, 0,34 mmol) para dar un sólido amarillo pálido (0,065 g, 40%). ^1H RMN (300 MHz, $CDCl_3$) δ 8,46 (1H, d, J=5,5 Hz), 7,93 (1H, s), 7,88 (1H, d, J=3,2 Hz), 7,75 (1H, d, J=8,6 Hz), 7,42 (1H, d, J=3,2 Hz), 7,18 (1H, d, J=2,1 Hz), 7,06 (1H, dd, J=2,1, 8,6 Hz), 6,55 (1H, d, J=5,5 Hz), 5,95 (1H, s), 3,66 (3H, s), 3,35 (1H, t, J=6,4 Hz), 2,73 (3H, s), 1,95 (1H, m), 1,03 (6H, d, J=6,8 Hz); ESIMS (MH+): 477,05.

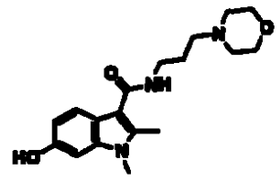
Análisis Calculado para $C_{25}H_{24}N_4O_2S_2$. 0,4 H_2O; C, 62,06; H, 5,17; N, 11,58; Encontrado: C, 61,97; H, 5,00; N, 11,47.

Ejemplo 68(a): 6-metoxi-1,2-dimetil-N-(3-morfolin-4-ilpropil)-1H-indol-3-carboxamida.



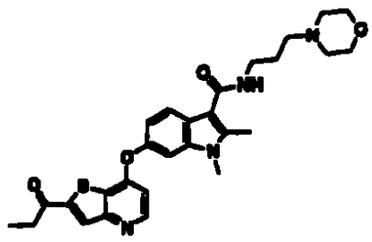
Este material se preparó a partir de ácido 6-metoxi-1,2-dimetil-1H-indol-3-carboxílico **16 c** (0,483 g, 2,20 mmol) con cloruro de oxalilo 2,0 M en CH_2Cl_2 (2,2 ml, 4,4 mmol) y 3-morfolin-4-il-propilamina de una manera como se describe previamente para el ejemplo **16 d**.para dar un sólido blanco (0,445 g, 59%) ^{1}H RMN (300 MHz, $CDCl_3$) δ 7,60 (1H, d, J=8,6 Hz), 6,82 (1H, dd, J=2,3, 8,6 Hz), 6,77 (1H, d, J=2,3 Hz), 6,71 (1H, s), 3,87 (3H, s), 3,62 (3H, s), 3,57 (6H, m), 2,69 (3H, s), 2,50 (2H, t, J=6,6 Hz), 2,43 (4H, m), 1,81 (2H, m). ESIMS (MH^+) 346,20.

Ejemplo 68(b): 6-hidroxi-1,2-dimetil-N-(3-morfolin-4-il-propil)-1H-indol-3-carboxamida.



Este material se preparó de 6-metoxi-1,2-dimetil-N-(3-morfolin-4-il-propil)-1H-indol-3-carboxamida **66 a** (0,445 g, 1,29 mmol) por tratamiento con BBr_3 1,0 M en CH_2Cl_2 (3,86 ml, 3,86 mmol) de una manera como se describe previamente para el ejemplo **1 d**.para dar un sólido blanco (0,445 g, 59%) ^{1}H RMN (300 MHz, CD_3OD) δ 7,49 (1H, d, J=8,6 Hz), 6,71 (1H, s), 6,64 (1H, dd, J=2,2, 8,6 Hz), 3,87 (4H, m), 3,56 (3H, s), 3,47 (2H, t, J=6,4 Hz), 3,10-3,24 (6H, m), 2,55 (3H, s), 2,00 (2H, m). ESIMS (MH^+): 332,15.

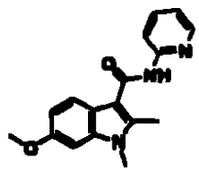
Ejemplo 68: (3-morfolin-4-il-propil)amida del ácido 1,2-dimetil-6-(2-propionil-tieno[3,2-b]piridin-7-iloxi)-1H-indol-3-carboxílico.



Este material se preparó por reacción de 1-(7-clorotieno[3,2-b]piridin-2-il)propan-1-ona **51 a** (0,074 g, 0,33 mmol) con 6-hidroxi-1,2-dimetil-N-(3-morfolin-4-il-propil)-1H-indol-3-carboxamida **68 b** (0,110 g, 0,33 mmol) y Cs_2CO_3 (0,108 g, 0,33 mmol). de una manera como se describe previamente en el ejemplo 1 para dar un sólido blanco (0,019 g, 11%).^{1}H RMN (300 MHz, DMSO-d_6) δ 8,58 (1H, d, J=5,5 Hz), 8,47 (1H, s), 7,82 (1H, d, J=8,5 Hz), 7,69 (1H, t, J=5,6 Hz), 7,55 (1H, d, J=2,1 Hz), 7,04 (1H, dd, J=2,1, 8,5 Hz), 6,67 (1H, d, J=5,5 Hz), 3,67 (3H, s), 3,54 (4H, m), 3,20 (2H, q, J=7,2 Hz), 2,60 (3H, s), 2,36 (8H, m), 1,71 (2H, m), 1,13 (3H, t, J=7,2 Hz); ESIMS (MH^+): 521,15.

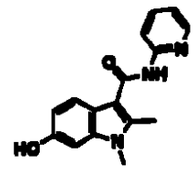
Análisis Calculado para $C_{28}H_{32}N_4O_4S$. 1,5 H_2O: C, 61,40; H, 6,44; N, 10,23; Encontrado: C, 61,40; H, 6,13; N, 10,09.

Ejemplo 69(a): piridin-2-il-amida del ácido 6-metoxi-1,2-dimetil-1H-indol-3-carboxílico.



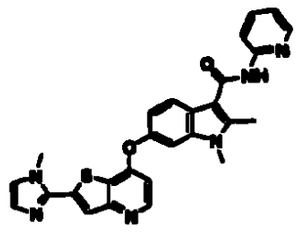
Este material se preparó a partir de ácido 1,2-dimetil-6-metoxi-1H-indol-3-carboxílico **16 c**, cloruro de oxalilo y propilamina de una manera como se describe previamente para el ejemplo **16 d**. ^{1}H RMN (300 MHz, $CDCl_3$) δ 8,34-8,37 (2H, m), 8,30 (1H, d, J=5,0 Hz), 7,78 (1H, d, J=8,7 Hz), 7,71 (1H, d, J=8,9 Hz), 7,03 (1H, m), 6,92 (1H, dd, J=2,3, 8,9 Hz), 6,82 (1H, d, J=2,3 Hz), 3,89 (3H, s), 3,68 (3H, s), 2,76 (3H, s). LCMS (ESI+) [M+H]/z Calculado 296, encontrado 296.

Ejemplo 69(b): piridin-2-il-amida del ácido 6-hidroxi-1,2-dimetil-1H-indol-3-carboxílico.



Este material se preparó a partir de piridin-2-il-amida del ácido 6-metoxi-1,2-dimetil-1H-indol-3-carboxílico **69 a**, por tratamiento con BBr_3 de una manera como se describe previamente para el ejemplo 1 **d**. ^1H RMN (300 MHz, CD_3OD) δ 8,29 (1H, m), 8,24 (1H, d, J=8,3 Hz), 7,82 (1H, m), 7,64 (1H, d, J=8,7 Hz), 7,12 (1H, m), 6,82 (1H, d, J=2,2 Hz), 6,76 (1H, dd, J=2,2, 8,7 Hz), 3,66 (3H, s), 2,69 (3H, s). LCMS (ESI+) [M+H]/z Calculado 282, encontrado 282.

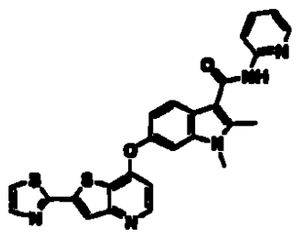
Ejemplo 69: piridin-2-il-amida del ácido 1,2-dimetil-6[2-(1-metil-1H-imidazol-2-il)tieno[3,2-b]piridin-7-iloxi]-1H-indol-3-carboxílico.



Este material se preparó por la reacción de 7-cloro-2-(1-metil-1H-imidazol-2-il)tieno[3,2-b]piridina **1 e** con piridin-2-il-amida del ácido 6-hidroxi-1,2-dimetil-1H-indol-3-carboxílico **69 b** y Cs_2CO_3, de una manera como se describe previamente para el ejemplo 1. ^1H RMN (300 MHz, DMSO-d_6) δ 8,43 (1H, d, J=5,5 Hz), 8,33 (1H, s), 8,20 (1H, d, J=3,8 Hz), 7,75-7,95 (3H, m), 7,61 (1H, s), 7,40 (1H, s), 7,11 (2H, m), 7,03 (1H, s), 6,60 (1H, d, J=5,5 Hz), 4,05 (3H, s), 3,73 (3H, s), 2,68 (3H, s). LCMS (ESI+) [M+H]/z Calculado 495, encontrado 495.

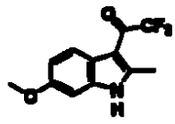
Análisis ($C_{27}H_{22}N_6O_2S$. 1,0 H_2O) C, H, N.

Ejemplo 70: piridin-2-il-amida del ácido 1,2-dimetil-6-(2-tiazol-2-il-tieno[3,2-b]piridin-7-iloxi)-1H-indol-3-carboxílico.



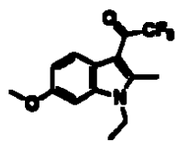
Este material se preparó por la reacción de 7-cloro-2-(1,3-tiazol-2-il)tieno[3,2-b]piridina **41 a** (0,117 g, 0,46 mmol) con 6-hidroxi-1,2-dimetil-N-piridin-2-il-1H-indol-3-carboxamida **69 b** (0,130 g, 0,46 mmol) y Cs_2CO_3 (0,150 g, 0,46 mmol) de una manera como se describe previamente para el ejemplo 1 para dar un sólido amarillo (0,151 g, 22%). ^{1}H RMN (300 MHz, $CDCl_3$) δ 8,48 (1H, d, J=5,5 Hz), 8,38 (1H, s), 8,35 (1H, s), 8,30 (1H, d, J=3,77 Hz), 7,95 (2H, s), 7,88 (1H, d, J=3,2 Hz), 7,75 (1H, m), 7,42 (1H, d, J=3,39 Hz), 7,22 (1H, d, J=1,9 Hz), 7,12 (1H, dd, J=1,9, 8,6 Hz), 7,04 (1H, dd, J=5,1, 6,6 Hz), 6,56 (1H, d, J=5,5 Hz), 3,70 (3H, m), 2,80 (3H, m); ESIMS (MH^+): 498,05.
Análisis Calculado para $C_{28}H_{19}N_5O_2S_2$. 0,1 H_2O: C, 62,53; H, 3,88; N, 14,02; Encontrado: C, 62,44; H, 3,96; N, 13,83.

Ejemplo 71(a): 2,2,2-trifluoro-1-(6-metoxi-2-metil-1H-indol-3-il)etanona



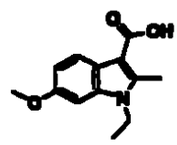
A una disolución de 6-metoxi-2-metil-1H-indol (1 g, 6,2 mmol) (preparada según JACS 1989, 110, 2242) en 25 ml de THF se añadió TFAA (1,56 g, 7,44 mmol) con enfriamiento en un baño de hielo. La mezcla se calentó hasta temperatura ambiente y se agitó durante dos horas y se concentró a vacío. El residuo se purificó adicionalmente por cromatografía en columna (eluyendo con CH_2Cl_2) para dar 1,34 g de producto en forma de sólido amarillo pálido (rendimiento del 82%). ^{1}H RMN (300 MHz, $CDCl_3$) δ 7,90 (1H, d, J=8,9 Hz), 6,87 (1H, dd, J=2,2, 8,9 Hz), 6,80 (1H, d, J=2,2 Hz), 3,82 (3H, s), 2,69 (3H, s).

Ejemplo 71(b): 1-(1-etil-6-metoxi-2-metil-1H-indol-3-il)-2,2,2-trifluoroetanona



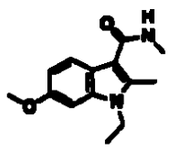
A una disolución de 2,2,2-trifluoro-1-(6-metoxi-2-metil-1H-indol-3-il)etanona 71 a (1,3 g, 5,05 mmol) en 20 ml de THF anhidro se añadió yoduro de etilo (2,36 g, 15,15 mmol) e hidruro de sodio (404 mg, al 60% en aceite mineral, 10,1 mmol) con enfriamiento en un baño de hielo. La mezcla se calentó lentamente hasta temperatura ambiente y se agitó durante unas cuatro horas adicionales. La reacción se enfrió rápidamente con agua y se extrajo con EtOAc. La capa orgánica combinada se secó sobre Na_2SO_4, se filtró y concentró en un rotavapor. El residuo se purificó por cromatografía en columna (eluyendo con EtOAc al 20-30% en hexanos) para dar un aceite marrón (580 mg, 40% de rendimiento). ^{1}H RMN (300 MHz, $CDCl_3$) δ 7,91 (1H, d, J=8,9 Hz), 6,93 (1H, dd, J=2,3, 8,9 Hz), 6,82 (1H, d, J=2,3 Hz), 4,18 (2H, m), 3,88 (3H, s), 2,76 (3H, s), 1,40 (3H, m).

Ejemplo 71(c): ácido 1-etil-6-metoxi-2-metil-1H-indol-3-carboxílico.



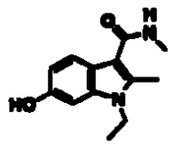
A una disolución de 1-(1-etil-6-metoxi-2-metil-1H-indol-3-il)-2,2,2-trifluoroetanona 71 b (580 mg, 2,03 mmol) en 10 ml de etanol se añadió una disolución de KOH (1,1 g, 20 mmol) en 10 ml de agua. La mezcla se calentó a reflujo durante 1 hora y se enfrió hasta temperatura ambiente. Se añadió HCl concentrado para ajustar el pH a 1. La mezcla se extrajo con EtOAc y la capa orgánica combinada se secó sobre Na_2SO_4, se filtró y concentró a vació. El residuo se purificó adicionalmente por cromatografía en columna (eluyendo con MeOH al 1-2% en CH_2Cl_2) para dar 350 mg de producto en forma de sólido marrón (rendimiento del 74%). ^{1}H RMN (400 MHz, $CDCl_3$) δ 8,07 (1H, d, J=8,7 Hz), 6,90 (1H, dd, J=2,2, 8,7 Hz), 6,80 (1H, d, J=2,2 Hz), 4,14 (2H, q, J=7,2 Hz), 3,88 (3H, s), 2,77 (3H, s), 1,37 (3H, t, J=7,2 Hz).

Ejemplo 71(d): metilamida del ácido 1-etil-6-metoxi-2-metil-1H-indol-3-carboxílico.



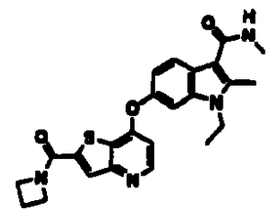
Este material se preparó por la reacción de ácido 1-etil-6-metoxi-2-metil-1H-indol-3-carboxílico 71 c (350 mg, 1,5 mmol), cloruro de oxalilo (1,1 ml, disolución 2,0 M) y metilamina (1,5 ml, disolución 2,0 M) de una manera como se describe previamente para el ejemplo 16 d para dar 350 mg de producto en forma de sólido beis (rendimiento del 95%). ^{1}H RMN (300 MHz, $CDCl_3$) δ 7,56 (1H, d, J=8,7 Hz), 6,84 (1H, dd, J=2,3, 8,7 Hz), 6,80 (1H, d, J=2,3 Hz), 5,84 (1H, s ancho), 4,10 (2H, q, J=7,2 Hz), 3,87 (3H, s), 3,03 (3H, d, J=4,9 Hz), 2,70 (3H, s), 1,33 (3H, t, J=7,2 Hz).

Ejemplo 71(e): metilamida del ácido 1-etil-6-hidroxi-2-metil-1H-indol-3-carboxílico



Este material se preparó a partir de metilamida del ácido 1-etil-6-metoxi-2-metil-1H-indol-3-carboxílico 71 d (350 mg, 1,42 mmol) por tratamiento con BBr_3 de una manera como se describe previamente para el ejemplo 1 d para dar 280 mg de producto en forma de sólido blanco (rendimiento del 85%). ^{1}H RMN (400 MHz, $CDCl_3$) δ 7,48 (1H, d, J=8,3 Hz), 6,73-6,77 (2H, m), 6,01 (1H, s ancho), 4,04 (2H, q, J=7,2 Hz), 3,03 (3H, d, J=4,9 Hz), 2,66 (3H, s), 1,31 (3H, t, J=7,2 Hz).

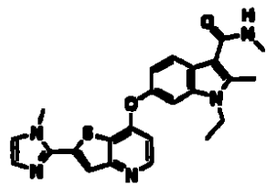
Ejemplo 71: metilamida del ácido 6-[2-(azetidina-1-carbonil)-tieno[3,2-b]piridin-7-iloxi]-1-etil-2-metil-1H-indol-3-carboxílico.



Este material se preparó por la reacción de 2-(azetidin-1-il-carbonil)-7-clorotieno[3,2-b]piridina **25 a** con metilamida del ácido 1-etil-6-hidroxi-2-metil-1H-indol-3-carboxílico **71 e** y Cs_2CO_3 de una manera como se describe previamente para el ejemplo 1. ^{1}H RMN (300 MHz, $CDCl_3$) δ 8,47 (1H, d, J=5,5 Hz), 7,75 (2H, m), 7,16 (1H, d, J=1,7 Hz), 7,01 (1H, dd, J=1,7, 8,4 Hz), 6,56 (1H, d, J=5,5 Hz), 5,91 (1H, s ancho), 4,59 (2H, m), 4,28 (2H, m), 4,11 (2H, m), 3,05 (3H, d, J=4,0 Hz), 2,72 (3H, s), 2,45 (2H, m), 1,33 (3H, m). LCMS (ESI+) [M+H]/z Calculado 449, encontrado 449.

Análisis ($C_{24}H_{24}N_4O_3S$. 0,5 H_2O. 0,25 MeOH) C, H, N.

Ejemplo 72: metilamida del ácido 1-etil-2-metil-6-[2-(1-metil-1H-imidazol-2-il)-tieno[3,2-b]piridin-7-iloxi]-1H-indol-3-carboxílico.

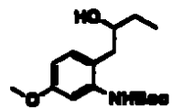


Este material se preparó por la reacción de 7-cloro-2-(1-metil-1H-imidazol-2-il)tieno[3,2-b]piridina **1 e** con metilamida del ácido 1-etil-6-hidroxi-2-metil-1H-indol-3-carboxílico **71 e** y Cs_2CO_3 de una manera como se describe previamente para el ejemplo 1. ^{1}H RMN (300 MHz, $CDCl_3$) δ 8,44 (1H, d, J=5,4 Hz), 7,74 (1H, d, J=8,7 Hz), 7,68 (1H, s), 7,18 (1H, d, J=1,9 Hz), 7,14 (1H, s), 7,05 (1H, d, J=1,9 Hz), 7,02 (1H, s), 6,54 (1H, d, J=5,4 Hz), 5,92 (1H, s ancho), 4,11 (2H, m), 3,96 (3H, s), 3,05 (3H, d, J=4,7 Hz), 2,72 (3H, s), 1,33 (3H, m). LCMS (ESI+) [M+H]/z Calculado 446, encontrado 446.

Análisis ($C_{24}H_{23}N_5O_2S$. 0,5 H_2O. 0,5 MeOH) C, H, N.

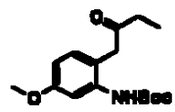
330

Ejemplo 73(a): éster t-butílico del ácido [2-(2-hidroxi-butil)-5-metoxi-fenil]carbámico.



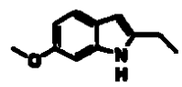
A una disolución de éster t-butílico del ácido (5-metoxi-2-metil-fenil)carbámico (6,95 g, 29,3 mmol) en 100 ml de THF enfriado a –45ºC se añadió sec-BuLi (45 ml, 58,5 mmol) lentamente para mantener la temperatura más baja de –45ºC. La mezcla de reacción se agitó y calentó a –20ºC, a continuación se enfrió a –45ºC y se añadió propionaldehído (2,67 ml, 36,63 mmol). La mezcla de reacción se agitó y calentó hasta temperatura ambiente durante 1 h, se enfrió rápidamente con HCl 1 N y se extrajo con EtOAc, se secó sobre $MgSO_4$ y se concentró. El residuo se purificó por cromatografía flash en columna (EtOAc al 10-15% en hexano) para dar un aceite incoloro (3,40 g, 39%). ^{1}H RMN ($CDCl_3$) δ 7,96 (1H, s), 7,44 (1H, s), 6,96-7,00 (1H, m), 6,55 (1H, m), 3,80 (3H, s), 2,60-2,76 (2H, m), 1,93-1,95 (2H, m), 1,50 (9H, s), 0,93-1,01 (4H, m). ESIMS (MNa^+): 318,20.

Ejemplo 73(b): éster t-butílico del ácido [5-metoxi-2-(2-oxo-butil)fenil]carbámico.



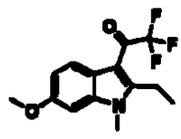
A una disolución del reactivo de Dess-Martin (2,82 g, 6,68 mmol) en 80 ml de THF enfriado a 0ºC se añadió éster t-butílico del ácido [2-(2-hidroxi-butil)-5-metoxi-fenil]carbámico 73 a (1,64 g, 5,57 mmol) en 20 ml de THF. La mezcla de reacción se agitó y calentó hasta temperatura ambiente durante 2 h, se enfrió rápidamente con $NaHCO_3$ medio saturado, se extrajo con EtOAc. La capa orgánica se secó sobre $MgSO_4$ y se concentró. El residuo se purificó por cromatografía flash en columna (EtOAc al 10-15% en hexano) para dar un aceite incoloro (1,36 g, 84%). ^{1}H RMN ($CDCl_3$) δ 7,67 (1H, s ancho), 7,48 (1H, s), 6,99-7,03 (1H, m), 6,56-6,60 (1H, m), 3,79 (3H, s), 3,59 (2H, s), 2,53-2,61 (2H, q, J=7,2 Hz), 1,51 (9H, s), 1,02 (3H, t, J=7,2 Hz). ESIMS (MNa^+): 316,10.

Ejemplo 73(a): 2-etil-6-metoxi-1H-indol



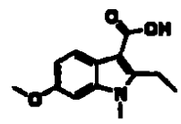
A una disolución de éster t-butílico del ácido [5-metoxi-2-(2-oxo-butil)-fenil]carbámico 73 b (1,36 g, 4,65 mmol) en 10 ml de THF se añadió 4 ml de TFA. La mezcla de reacción se agitó a temperatura ambiente durante 5 h, se enfrió rápidamente con 50 ml de H_2O y se extrajo con EtOAc. La capa orgánica se secó sobre $MgSO_4$ y se concentró. El residuo se purificó por cromatografía flash en columna (EtOAc al 10-15% en hexano) para dar un sólido amarillo pálido (1,36 g, 73%). ^1H RMN ($CDCl_3$) δ 7,75 (1H, s ancho), 7,49 (1H, d, J=8,6 Hz), 6,81 (1H, s), 6,73 (1H, d, J=8,6 Hz), 3,83 (3H, s), 2,75 (2H, q, J=7,5 Hz), 1,32 (3H, t, J=7,5 Hz). ESIMS (MH^+): 272,10.

Ejemplo 73(d): 1-(2-etil-6-metoxi-1-metil-1H-indol-3-il)-2,2,2-trifluoroetanona.



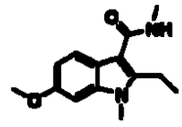
A una disolución de 2-etil-6-metoxi-1H-indol 73 c (1,79 g, 10,2 mmol) en 50 ml de THF a 0°C se añadió TFAA (1,58 ml, 11,22 mmol). La mezcla de reacción se agitó a 0°C durante 1 h, a continuación se concentró y se secó a vacío, y que se usó sin purificación. ESIMS (MH^+): 272,10. El residuo anterior se disolvió en 25 ml de THF y se enfrió a 0°C, se añadió MeI (1,59 ml, 25,5 mmol) y NaH (60%, 0,816 g, 20,4 mmol). La reacción se agitó a temperatura ambiente durante 1 h, se enfrió rápidamente con H_2O y se extrajo con EtOAc. La capa orgánica se secó sobre $MgSO_4$, y se concentró. El residuo se purificó por cromatografía flash en columna (EtOAc al 25% en hexano) para dar un sólido de color amarillo (2,42 g, 73%). ^1H RMN ($CDCl_3$) δ 7,88 (1H, d, J=8,9 Hz), 6,94 (1H, dd, J=2,4, 8,9 Hz), 6,81 (1H, s), 3,88 (3H, s), 3,72 (3H, s), 3,20 (2H, q, J=7,5 Hz), 1,27 (3H, t, J=7,5 Hz). ESIMS (MH^+): 286,10.

Ejemplo 73(e): ácido 2-etil-6-metoxi-1-metil-1H-indol-3-carboxílico.



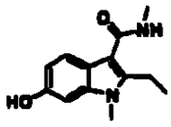
Se añadió KOH (1,9 g, 33,49 mmol) en 20 ml de H_2O a una disolución de 1-(2-etil-6-metoxi-1-metil-1H-indol-3-il)-2,2,2-trifluoroetanona 73 d (2,42 g, 8, 47 mmol) en 20 ml de EtOH. La mezcla de reacción se calentó a reflujo durante 8 h y se concentró. El residuo se disolvió en H_2O, se acidificó con HCl 1 N hasta pH 1 y se filtró. El sólido se purificó por cromatografía flash en columna (CH_3OH al 2-5% en CH_2Cl_2) para dar un sólido de color amarillo (1,3 g, 72%). ^1H RMN ($CDCl_3$) δ 11,88 (1H, s ancho), 7,82 (1H, d, J=8,7 Hz), 7,04 (1H, s), 6,77 (1H, d, J=8,7 Hz), 3,80 (3H, s), 3,70 (3H, s), 3,51 (2H, q, J=7,4 Hz), 1,15 (3H, t, J=7,4 Hz). ESIMS (MH^+): 234,05.

Ejemplo 73(f): metilamida del ácido 2-etil-6-metoxi-1-metil-1H-indol-3-carboxílico



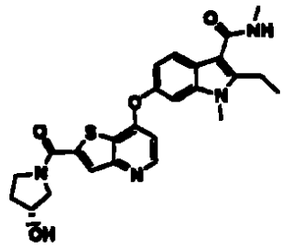
Se añadió cloruro de tionilo (0,383 ml, 4,45 mmol) a una disolución del ácido 2-etil-6-metoxi-1-metil-1H-indol-3-carboxílico 73 e (0,347 g, 1,48 mmol). La mezcla de reacción se calentó a reflujo durante 30 min y se concentró. El residuo se disolvió en 5 ml de CH_2Cl_2 y se añadió metilamina (2,0 M en THF, 2,22 ml, 4,44 mmol). la mezcla de reacción se agitó a temperatura ambiente durante 1 h, a continuación se concentró. El residuo se purificó por cromatografía en columna (CH_3OH al 2-5% en CH_2Cl_2) para dar un sólido de color amarillo (0,267 g, 73%). ^1H RMN ($CDCl_3$) δ 7,47 (1H, d, J=8,7 Hz), 6,80 (1H, s), 6,69 (1H, d, J=8,7 Hz), 3,47 (3H, s), 3,58 (3H, s), 3,00 (2H, q, J=7,4 Hz), 2,83 (3H, s), 1,14 (3H, t, J=7,4Hz). ESIMS (MH^+): 247,10.

Ejemplo 73(g): metilamida del ácido 2-etil-6-hidroxi-1-metil-1H-indol-3-carboxílico.



A una disolución de metilamida del ácido 2-etil-6-metoxi-1-metil-1H-indol-3-carboxílico 73 f (0,267 g, 1,08 mmol) en 15 ml de CH_2Cl_2 a 0°C se añadió BBr_3 (1,0 M en CH_2Cl_2, 3,25 ml, 3,25 mmol). La mezcla de reacción se agitó a temperatura ambiente durante 2 h, se enfrió rápidamente con NH_4OH saturado para conseguir pH 10. La mezcla se diluyó con H_2O y se extrajo con CH_3OH al 10% en CH_2Cl_2. La capa orgánica se secó sobre $MgSO_4$ y se concentró. El residuo se purificó por cromatografía flash en columna (CH_3OH al 3-5% en CH_2Cl_2) para dar un sólido de color amarillo pálido (0,170 g, 68%). ^1H RMN ($CDCl_3$) δ 7,40 (1H, d, J=8,5 Hz), 6,65 (1H, s), 6,59 (1H, d, J=8,5 Hz), 3,53 (3H, s), 3,28 (2H, q, J=7,5 Hz), 2,82 (3H, s), 1,13 (3H, t, J=7,5Hz). ESIMS (MH^+): 233,15.

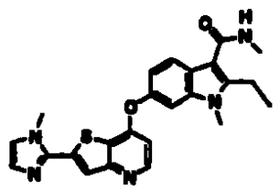
Ejemplo 73: metilamida del ácido 2-etil-6-[2-(3-hidroxi-pirrolidina-1-carbonil)-tieno[3,2-b]piridin-7-iloxi]-1-metil-1H-indol-3-carboxílico.



El material se preparó por la reacción de (7-cloro-tieno[3,2-b]piridin-2-il)-(3-hidroxi-pirrolidin-1-il)metanona 4 a (0,146 g, 0,517 mmol) con metilamida del ácido 2-etil-6-hidroxi-1-metil-1H-indol-3-carboxílico 73 g (0,080 g, 0,344 mmol) y Cs_2CO_3 (0,112 g, 0,344 mmol) de una manera como se describe previamente para el ejemplo 1 para dar 30 mg (rendimiento del 18%) de un sólido amarillo pálido. ^1H RMN (CD_3OD) δ 8,34 (1H, d, J=5,5 Hz), 7,69-7,70 (2H, m), 7,26 (1H, s), 6,91 (1H, d, J=6,8 Hz), 6,65 (1H, d, J=5,5 Hz), 4,39 (1H, m), 3,90 (2H, m), 3,67-3,61 (5H, m), 2,99 (2H, m), 2,86 (3H, m), 2,00 (2H, m), 1,14-1,19 (3H, m). ESIMS (MH^+): 479,10.

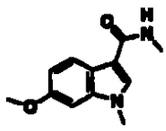
Análisis Calculado para $C_{25}H_{28}N_4O_4S$. 0,55 CH_2Cl_2: C, 58,42; H, 5,20; N, 10,67. Encontrado: C, 58,47; H, 5,43; N, 11,31.

Ejemplo 74: metilamida del ácido 2-etil-1-metil-6-[2-(1-metil-1H-imidazol-2-il)-tieno[3,2-b]piridin-7-iloxi]-1H-indol-3-carboxílico.



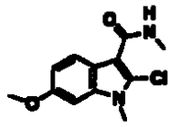
Este material se preparó por la reacción de 7-cloro-2-(1-metil-1H-imidazol-2-il)tieno[3,2-b]piridina 1 e (0,084 g, 0,34 mmol) con 2-etil-6-hidroxi-N,1-dimetil-1H-indol-3-carboxamida 73 g (0,078 g, 0,33 mmol) y Cs_2CO_3 (0,111 g, 0,34 mmol) de una manera como se describe previamente para el ejemplo 1 para dar un sólido blancuzco (0,058 g, 40%). ^{1}H RMN (300 MHz, CD_3OD) δ 8,27 (1H, d, J=5,4 Hz), 7,68 (1H, d, J=8,6 Hz), 7,59 (1H, s), 7,24 (1H, d, J=1,9 Hz), 7,17 (1H, s), 6,96 (1H, s), 6,90 (1H, dd, J=1,9, 8,6 Hz), 6,50 (1H, d, J=5,4 Hz), 3,87 (3H, s), 3,58 (3H, s), 3,01 (2H, m), 2,85 (3H, s), 1,14 (3H, m). HRMS (MH^+): Calculado: 446,1655; Encontrado: 446.1651.

Ejemplo 75(a): metilamida del ácido 6-metoxi-1-metil-1H-indol-3-carboxílico.



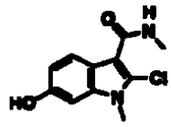
Este material se preparó a partir de ácido 6-metoxi-1-metil-1H-indol-3-carboxílico 16 b (2,39 g, 10,9 mmol), cloruro de oxalilo y metilamina de una manera como se describe previamente para el ejemplo 16 d para dar un sólido marrón (1,08 g, 45%). ^{1}H RMN (300 MHz, DMSO-d_6) δ 7,97 (1H, d, J=8,7 Hz), 7,76 (2H, m), 6,99 (1H, d, J=2,3 Hz), 6,77 (1H, dd, J=2,3, 8,7 Hz), 3,80 (3H, s), 3,76 (3H, s), 2,74 (3H, s); ESIMS (MH^+): 219,05.

Ejemplo 75(b): metilamida del ácido 2-cloro-6-metoxi-1-metil-1H-indol-3-carboxílico.



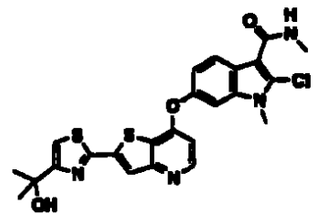
Se añadió N-clorosuccinimida (0,150 g, 1,12 mmol) a una disolución de 6-metoxi-N,1-dimetil-1H-indol-3-carboxamida 75 a (0,243 g, 1,11 mmol) en CCl_4 (10 ml) y DMF (3 ml). La mezcla de reacción se calentó a 60°C durante 3 h y se concentró. El residuo se purificó por cromatografía en fase inversa eluyendo con CH_3OH al 0-1% en EtOAc y CH_2Cl_2 1:1 para dar un aceite de color marrón (0,243 g, rendimiento del 87%); ^1H RMN (300 MHz, $CDCl_3$) δ 7,61 (1H, d, J=8,6 Hz), 6,38 (1H, d, J=8,6 Hz), 6,19 (1H, s), 3,35 (3H, s), 2,96 (3H, s), 2,52 (3H, s); ESIMS (MH^+): 253,05.

Ejemplo 75(c): metilamida del ácido 2-cloro-6-hidroxi-1-metil-1H-indol-3-carboxílico.



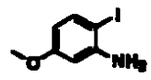
Este material se preparó por reacción de 2-cloro-6-metoxi-N,1-dimetil-1H-indol-3-carboxamida 75 b (0,38 g, 1,4 mmol) con BBr_3 1,0 M en CH_2Cl_2 (4,19 ml, 4,19 mmol) de una manera como se describe previamente para el ejemplo 1 d para dar un sólido blancuzco (0,195 g, 85%). ^1H RMN (300 MHz, CD_3OD) δ 7,61 (1H, d, J=8,3 Hz), 6,55 (1H, s), 6,62 (1H, d, J=2,1 Hz), 3,56 (3H, s), 2,85 (3H, s); ESIMS (MH^+): 239,00.

Ejemplo 75: metilamida del ácido 2-cloro-6-{2-[4-(1-hidroxi-1-metil-etil)tiazol-2-il]tieno[3,2-b]piridin-7-iloxi}-1-metil-1H-indol-3-carboxílico.



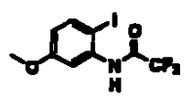
Este material se preparó por la reacción de 2-[2-(7-clorotieno[3,2-b]piridin-2-il)-1,3-tiazol-4-il]propan-2-ol **40 a** (0,102 g, 0,33 mmol) con 2-cloro-6-hidroxi-N,1-dimetil-1H-indol-3-carboxamida **75 c** (0,085 g, 0,33 mmol) y Cs_2CO_3 (0,108g, 0,33 mmol) de una manera como se describe previamente para el ejemplo 1 para dar un sólido blancuzco (0,039 g, 21%). ^{1}H RMN (300 MHz, $CDCl_3$) δ 8,40 (1H, d, J=5,5 Hz), 8,31 (1H, d, J=8,3 Hz), 7,82 (1H, m), 7,20 (1H,s), 7,14 (1H, s), 7,07 (2H, m), 6,47 (1H, d, J=5,5 Hz), 6,34 (1H, m), 3,69 (3H, s), 3,01 (3H, d, J=4,7 Hz), 1,60 (6H, s).
Análisis Calculado para $C_{24}H_{21}N_4O_3S_2Cl$. 0,6 H_2O. CH_3OH: C 54,71; H, 4,53; N, 10,36; Encontrado: C, 54,56; H, 4,45; N, 10,17.

Ejemplo 76(a): 2-yodo-5-metoxi-fenilamina



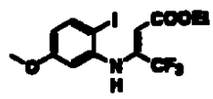
A una disolución de 4-yodo-3-nitroanisol (5 g, 17,9 mmol) en 100 ml de metanol se añadió $FeCl_3$ (50 mg, 0,3 mmol) y carbón activado (40 mg). La mezcla se calentó a reflujo y se añadió gota a gota hidracina hidrato (1,75 g, 35 mmol). La mezcla se calentó a reflujo durante unas 8 horas adicionales y se enfrió hasta temperatura ambiente, se filtró a través de Celite. El filtrado se concentró y purificó por cromatografía en columna (eluyendo con EtOAc al 10% en hexanos) para dar 4,05 g de producto en forma de aceite amarillo pálido (rendimiento del 91%). ^{1}H RMN (300 MHz, $CDCl_3$) δ 7,47 (1H, d, J=8,7 Hz), 6,31 (1H, d, J=2,8 Hz), 6,13 (1H, dd, J=2,8, 8,7 Hz), 3,73 (3H, s).

Ejemplo 76(b): 2,2,2-trifluoro-N-(2-yodo-5-metoxi-fenil)acetamida



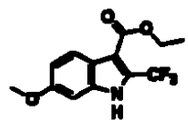
A una disolución de 2-yodo-5-metoxi-fenilamina 76 a (4,05 g, 16,3 mmol) en 10 ml de CH_2Cl_2 anhidro se añadió TFAA (4,1 g, 19,5 mmol). La mezcla se agitó a 36ºC durante la noche, la TLC indicó que quedaba algo del material de partida. Se añadió TFAA adicional (4,1 g, 19,5 mmol) y se agitó a 36ºC durante otras 24 horas. La mezcla se concentró en rotovapor y se purificó por cromatografía en columna (eluyendo con EtOAc al 5-10% en hexanos) para dar 4,6 g de producto (rendimiento del 81%). ^{1}H RMN (300 MHz, $CDCl_3$) δ 7,92 (1H, d, J=2,8 Hz), 7,66 (1H, d, J=8,9 Hz), 6,59 (1H, dd, J=2,8, 8,9 Hz), 3,82 (3H, s).

Ejemplo 76(c): éster etílico del ácido 4,4,4-trifluoro-3-(2-yodo-5-metoxi-fenilamino)-but-2-enoico.



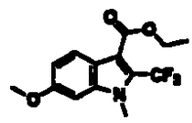
Una disolución de 2,2,2-trifluoro-N-(2-yodo-5-metoxi-fenil)acetamida 76 b (4,6 g, 13,3 mmol) y (trifenilfosforanilideno)acetato de metilo (8,7 g, 25 mmol) en 50 ml de tolueno se llevó a reflujo durante 5 horas y se enfrió a temperatura ambiente. La disolución se concentró a vacío y se purificó por cromatografía en columna (eluyendo con EtOAc al 2-6% en hexanos) para dar 4,8 g de producto (rendimiento del 87%). ^{1}H RMN (300 MHz, $CDCl_3$) δ 9,57 (1H, s), 7,68 (1H, d, J=8,8 Hz), 6,83 (1H, d, J=2,8 Hz), 6,57 (1H, dd, J=2,8, 8,8 Hz), 5,43 (1H, s), 4,23 (2H, m), 3,76 (3H, s), 1,55 (3H, s), 1,31 (3H, m).

Ejemplo 76(d): éster etílico del ácido 6-metoxi-2-trifluorometil-1H-indol-3-carboxílico



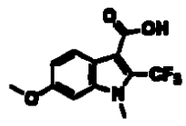
Una mezcla de éster etílico del ácido 4,4,4-trifluoro-3-(2-yodo-5-metoxi-fenilamino)but-2-enoico 76 c (0,5 g, 1,2 mmol), $PD(OAc)_2$ (22,4 mg, 0,1 mmol), PPh_3 (52,5 mg, 0,2 mmol) y $NaHCO_3$ (505 mg, 6 mmol) en 5 ml de DMF se calentó a 120°C en argón durante 24 horas y se enfrió hasta temperatura ambiente La mezcla se vertió en EtOAc/agua y se lavó con salmuera. La capa orgánica se secó sobre Na_2SO_4 y se concentró en rotovapor. El residuo se purificó por cromatografía en columna para dar 217 mg de producto (rendimiento del 63%). ^1H RMN (300 MHz, CD_3OD) δ 8.00 (1H, d, J=9,0 Hz), 6,96 (1H, d, J=2,0 Hz), 6,90 (1H, dd, J=2,0, 9,0 Hz), 4,37 (2H, m), 3,84 (3H, s), 1,40 (3H, m).

Ejemplo 76(e): éster etílico del ácido 6-metoxi-1-metil-2-trifluorometil-1H-indol-3-carboxílico.



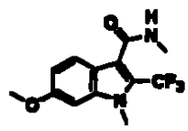
Este material se preparó a partir de éster etílico del ácido 6-metoxi-2-trifluorometil-1h-indol-3-carboxílico 76 d (1,64 g, 5,7 mmol) por tratamiento con NaH (274 mg, al 60% en aceite mineral, 6,84 mmol) y yoduro de metilo (1,21 g, 8,55 mmol) y NaH de una manera como se describe previamente para el ejemplo 16 b para dar 1,5 g de producto (rendimiento del 87%). ^1H RMN (300 MHz, $CDCl_3$) δ 7,96 (1H, dd, J=3,7, 8,8 Hz), 6,94 (1H, dd, J=2,3, 9,1 Hz), 6,77 (1H, d, J=2,1 Hz), 4,40 (2H, m), 3,89 (3H, s), 3,86 (3H, s), 1,41 (3H, m).

Ejemplo 76(f): ácido 6-metoxi-1-metil-2-trifluorometil-1H-indol-3-carboxílico.



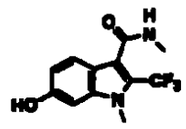
A una disolución de éster etílico del ácido 6-metoxi-1-metil-2-trifluorometil-1H-indol-3-carboxílico **76 e** (1,5 g, 4,98 mmol) en 10 ml de THF y 5 ml de MeOH se añadió una disolución de KOH (2,8 g, 50 mmol) en 5 ml de agua con enfriamiento en un baño de hielo. La mezcla se calentó hasta temperatura ambiente y se agitó durante la noche. Se añadió disolución de HCl acuoso concentrado para ajustar el pH a 1. La mezcla se extrajo con EtOAc y la capa orgánica combinada se secó sobre Na_2SO_4, se filtró y se concentró. El residuo se purificó adicionalmente por cromatografía en columna (eluyendo con MeOH al 1-5% en CH_2Cl_2) para dar 880 mg de producto (rendimiento del 65%). ^{1}H RMN (300 MHz, CD_3OD) δ 7,90 (1H, d, J=9,0 Hz), 7,01 (1H, d, J=2,1 Hz), 6,91 (1H, dd, J=2,1, 9,0 Hz), 3,90 (3H, s), 3,88 (3H, s).

Ejemplo 76(g): metilamida del ácido 6-metoxi-1-metil-2-trifluorometil-1H-indol-3-carboxílico.



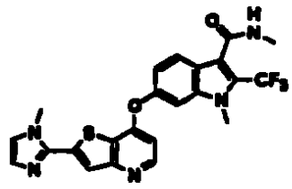
Este material se preparó a partir de ácido 6-metoxi-1-metil-2-trifluorometil-1H-indol-3-carboxílico **76 f** (880 mg, 3,22 mmol), cloruro de oxalilo (3 ml, disolución 2,0 M) y metilamina (5 ml, disolución 2,0 M) de una manera como se describe previamente para el ejemplo **16 d** para dar 900 mg de producto en forma de sólido blanco (rendimiento del 98%). ^{1}H RMN (300 MHz, $CDCl_3$) δ 7,62 (1H, d, J=8,9 Hz), 6,88 (1H, dd, J=2,1, 8,9 Hz), 6,73 (1H, d, J=2,1 Hz), 5,80 (1H, s ancho), 3,88 (3H, s), 3,79 (3H, s), 3,04 (3H, d, J=4,9 Hz).

Ejemplo 76(h): metilamida del ácido 6-hidroxi-1-metil-2-trifluorometil-1H-indol-3-carboxílico.



Este material se preparó a partir de metilamida del ácido 6-metoxi-1-metil-2-trifluorometil-1H-indol-3-carboxílico **76 g** (900 mg, 3.14 mmol) por tratamiento con BBr_3 de una manera como se describe previamente para el ejemplo 1 d para dar 780 mg de producto en forma de sólido blanco (rendimiento del 89%). ^1H RMN (300 MHz, CD_3OD) δ 7,44 (1H, d, J=8,7 Hz), 6,76-6,81 (2H, m), 3,77 (1H, s), 2,93 (3H, s).

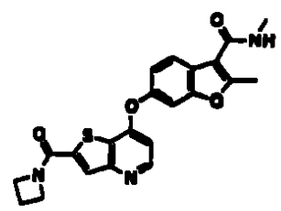
Ejemplo 76: metilamida del ácido 1-metil-6-[2-(1-metil-1H-imidazol-2-il)tieno[3,2-b]piridin-7-iloxi]-2-trifluorometil-1H-indol-3-carboxílico.



Este material se preparó por la reacción de 7-cloro-2-(1-metil-1H-imidazol-2-il)tieno[3,2-b]piridina **1 e** con metilamida del ácido 6-hidroxi-1-metil-2-trifluorometil-1H-indol-3-carboxílico **76 h** y Cs_2CO_3 de una manera como se describe para el ejemplo 1. ^1H RMN (300 MHz, DMSO-d_6) δ 8,51 (1H, d, J=5,5 Hz), 7,89 (1H, s), 7,78 (1H, s), 7,72 (1H, d, J=8,6 Hz), 7,41 (1H, s), 7,18 (1H, d, J=9,8 Hz), 7,03 (1H, s), 6,66 (1H, d, J=5,4 Hz), 3,99 (3H, s), 3,86 (3H, s), 2,81 (3H, s). LCMS (ESI+) [M+H]/z Calculado 486, encontrado 486.

Análisis ($C_{23}H_{16}F_3N_5O_2S$. 1,3 H_2O) C, H, N.

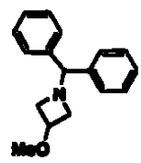
Ejemplo 77: metilamida del ácido 6-[2-(azetidina-1-carbonil)-tieno[3,2-b]piridin-7-iloxi]-2-metil-benzofuran-3-carboxílico.



Este material se preparó por la reacción de 2-(azetidin-1-il-carbonil)-7-clorotieno[3,2-b]piridina **25 a** (100 mg, 0,40 mmol) con metilamida del ácido 6-hidroxi-2-metilbenzofuran-3-carboxílico (100 mg, 0,49 mmol) y Cs_2CO_3 (257 mg, 0,79 mmol) de una manera como se describe previamente para el ejemplo 1 para dar 124 mg (74%) de un sólido marrón. ^{1}H RMN (DMSO-d_6) δ 8,56 (1H, d, J=5,6 Hz), 7,99 (1H, d, J=4,6 Hz), 7,89 (1H, s), 7,83 (1H, d, J=8,6 Hz), 7,66 (1H, d, J=2,0 Hz), 7,24 (1H, dd, J=8,6, 2,3 Hz), 6,70 (1H, d, J=5,3 Hz), 4,61 (2H, t, J=7,6 Hz), 4,10 (2H, t, J=7,3 Hz), 2,81 (3H, d, J=4,6 Hz), 2,63 (3H, s), 2,35 (2H, p, J=7,7 Hz).

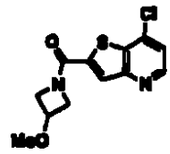
Análisis Calculado para $C_{22}H_{19}N_3O_4S$. 0,5 H_2O: C, 62,03; H, 4,61; N, 9,86; S, 7,53. Encontrado: C, 62,31; H, 4,65; N, 9,60; S, 7,34.

Ejemplo 78(a): 1-bencidril-3-metoxi-azetidina



A una disolución enfriada con hielo de 1-bencidrilazetidin-3-ol **9a** (1,0 g, 4,2 mmol) en DMF (10 ml) se añadió una dispersión de NaH al 60% en aceite mineral (0,25 g, 6,3 mmol). Después de 30 min a 0°C, se añadieron 5 ml más de DMF junto con yoduro de metilo (0,39 ml, 6,3 mmol). Se retiró el baño de hielo, y la reacción se agitó a temperatura ambiente (ta.). Después de 1,5 h, la reacción se vertió sobre salmuera y se extrajo con Et_2O (2x). Las capas orgánicas combinadas se lavaron con salmuera, se secaron ($MgSO_4$) y se concentraron a presión reducida. El residuo se sometió a cromatografía flash en gel de sílice eluyendo con Hexanos/EtOAc (1:1) para dar 919 mg (92%) de un aceite incoloro que cristalizó al reposar. ^{1}H RMN (DMSO-d_6) δ

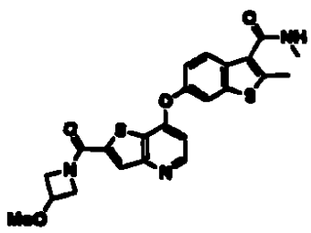
7,42 (4H, d, J=7,3 Hz), 7,27 (4H, t, J=7,3 Hz), 7,13 (2H, t, J=7,3 Hz), 4,39 (1H, s), 3,95 (1H, p, J=5,8 Hz), 3,35 (2H, t, J=6,3 Hz), 3,11 (3H, s), 2,75 (2H, t, J=5,6 Hz).



Ejemplo 78(b): (7-cloro-tieno[3,2-b]piridin-2-il)-(3-metoxi-azetidin-1-il)metanona

Se cargó un matraz de fondo redondo de 100 ml con 1-benzhidril-3-metoxi-azetidina **78 a** (447 mg, 1,77 mmol), 10% P/C (300 mg), ácido trifluoroacético (0,15 ml, 1,94 mmol) y EtOH (30 ml) y se colocó en 1 atm de H_2 y se agitó vigorosamente a ta. Después de 2 h, se retiró el catalizador y se lavó con MeOH. El filtrado se concentró a presión reducida para dar la azetidina en bruto que se disolvió en CH_2Cl_2. A esta disolución se añadieron trietilamina (0,6 ml, 4,41 mmol) y cloruro de 7-cloro-tieno[3,2-b]piridina-2-carbonilo, preparado como se describe previamente en el ejemplo **25 a**. Después de agitar a temperatura ambiente durante la noche, la mezcla de reacción se diluyó con más CH_2Cl_2, a continuación se lavó secuencialmente con HCl 0,5 N, $NaHCO_3$ acuoso saturado, y salmuera. La capa orgánica se secó ($MgSO_4$) y se concentró casi a sequedad a presión reducida, a continuación se trituró con hexanos para dar 278 mg (56%) del producto deseado en forma de sólido amarillo claro. ^1H RMN (DMSO-d_6) δ 8,73 (1H, d, J=5,1 Hz), 8,00 (1H, s), 7,70 (1H, d, J=5,1 Hz), 4,77 (1H, m), 4,49 (1H, m), 4,31 (2H, m), 3,90 (1H, m), 3,24 (3H, s). APCI *m/z* 283/285 $(M+H)^+$.

Ejemplo 78: metilamida del ácido [(metoxi-azetidina-1-carbonil)-tieno[3,2-b]piridin-7-iloxi]-2-metil-benzofuran-3-carboxílico.

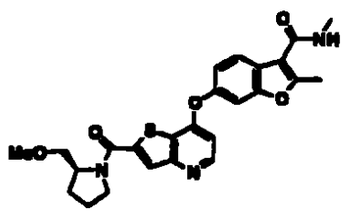


Este material se preparó por la reacción de (7-cloro-tieno[3,2-b]piridin-2-il)-(3-metoxi-azetidin-1-il)metanona **78 b** (241 mg, 0,85 mmol) con metilamida del ácido 6-hidroxi-2-metilbenzo[b]furan-3-carboxílico **12 c** (210 mg, 1,02 mmol) y Cs_2CO_3 (833

mg, 2,56 mmol) de una manera como se describe previamente en el ejemplo 1 para dar 298 mg (77%) de un sólido amarillo. ^{1}H RMN (DMSO-d_6) δ 8,57 (1H, d, J=5,3 Hz), 7,99 (1H, d, J=4,7 Hz), 7,94 (1H, s), 7,82 (1H, d, J=8,5 Hz), 7,66 (1H, d, J=2,3 Hz), 7,24 (1H, dd, J=8,5, 2,3 Hz), 6,72 (1H, d, J=5,5 Hz), 4,76 (1H, m), 4,47 (1H, m), 4,30 (2H, m), 3,90 (1H, m), 3,25 (3H, s), 2,82 (3H, d, J=4,5 Hz), 2,63 (3H, s).

Análisis Calculado para $C_{23}H_{21}N_3O_5S$. 0,4 H_2O: C, 60,22; H, 4,79; N, 9,16; S, 6,99. Encontrado: C, 60,33; H, 4,78; N, 9,13; S, 6,79.

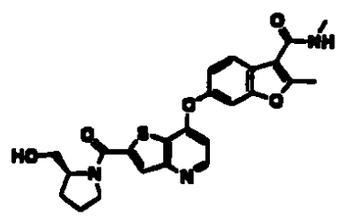
Ejemplo 79: metilamida del ácido 6-(2-[(S)-2-(metoximetil)pirrolidina-1-carbonil]tieno[3,2-b]piridin-7-iloxi)-2-metilbenzofuran-3-carboxílico.



Este material se preparó por la reacción de 7-cloro-2-[(R)-2-metoximetilpirrolidina-1-carbonil]tieno[3,2-b]piridina 2 a con metilamida del ácido 6-hidroxi-2-metil-benzofuran-3-carboxílico 12 c y Cs_2CO_3 de una manera como se describe previamente para el ejemplo 1. ^{1}H RMN (DMSO-d_6) δ 8,57 (1H, d, J=5,3 Hz), 8,02 (1H, s), 7,98 (1H, m), 7,83 (1H, d, J=8,6 Hz), 7,66 (1H, d, J=2,0 Hz), 7,25 (1H, dd, J=8,6, 2,0 Hz), 6,72 (1H, d, J=5,3 Hz), 4,31 (1H, m), 3,94-3,80 (2H, m), 3,60-3,39 (2H, m), 3,28 (3H, s), 2,82 (3H, d, J=4,6 Hz), 2,63 (3H, s), 2,06-1,85 (4H, m).

Análisis Calculado para $C_{25}H_{25}N_3O_5S$. 0,6 H_2O. 0,2 hexanos: C, 61,99; H, 5,76; N, 8,28; S, 6,32. Encontrado: C, 61,94; H, 5,74; N, 8,12; S, 6,32.

Ejemplo 80: metilamida del ácido 6-(2-[(S)-2-(hidroximetil)pirrolidina-1-carbonil]tieno[3,2-b]piridin-7-iloxi)-2-metil-benzofuran-3-carboxílico.

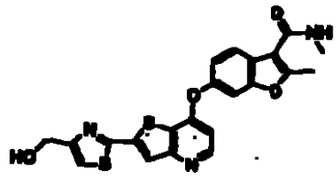


Este material se preparó a partir de metilamida del ácido 2-metil-6-[2-(2-metoximetil-pirrolidina-1-carbonil)-tieno[3,2-b]piridin-7-iloxi]benzofuran-3-carboxílico 79

por tratamiento con BBr_3 de una manera como se describe previamente para el ejemplo 1 d. ^{1}H RMN (DMSO-d_6) δ 8,56 (1H, d, J=5,1 Hz), 8,00-7,98 (2H, m), 7,83 (1H, d, J=8,6 Hz), 7,66 (1H, d, J=2,0 Hz), 7,25 (1H, dd, J=8,6, 2,0 Hz), 6,73 (1H, d, J=5,1 Hz), 4,81 (1H, m), 4,18 (1H, m), 3,91-3,32 (4H, m), 2,81 (3H, d, J=4,5 Hz), 2,63 (3H, s), 2,05-1,83 (4H, m).

Análisis Calculado para $C_{24}H_{23}N_3O_5S$. 2 H_2O. 0,2 EtOAc. C, 57,37; H, 5,55; N, 8,09; S, 6,18. Encontrado: C, 57,15; H, 5,24; N, 7,71; S, 6,01.

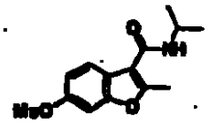
Ejemplo 81: metilamida del ácido 6-[2-(4-hidroximetil-tiazol-2-il)tieno[3,2-b]piridin-7-iloxi]-2-metil-benzofuran-3-carboxílico.



Este material se preparó por la reacción de [2-(7-clorotieno[3,2-b]piridin-2-il)-tiazol-4-il]-metanol con metilamida del ácido 6-hidroxi-2-metil-benzofuran-3-carboxílico 12 c y Cs_2CO_3 de una manera como se describe previamente para el ejemplo 1. ^{1}H RMN (DMSO-d_6) δ 8,55 (1H, d, J=5,6 Hz), 8,16 (1H, s), 7,98 (1H, m), 7,84 (1H, d, J=8,6 Hz), 7,67 (1H, d, J=2,0 Hz), 7,63 (1H, s), 7,26 (1H, dd, J=8,6, 2,0 Hz), 6,73 (1H, d, J=5,6 Hz), 5,43 (1H, m), 4,61 (2H, s), 2,82 (3H, d, J=4,6 Hz), 2,64 (3H, s)

Análisis Calculado para $C_{22}H_{17}N_3O_4S_2$. 0,6 H_2O. C, 57,15; H, 3,97; N, 9,09; S, 13,87. Encontrado: C, 57,13; H, 4,07; N, 8,95; S, 13,87.

Ejemplo 82(a): isopropilamida del ácido 6-metoxi-2-metil-benzofuran-3-carboxílico.

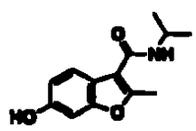


Este material se preparó a partir de 6-metoxi-2-metilbenzofurano 12 a (500 mg, 3,1 mmol) por acilación con cloruro de oxalilo en presencia de $AlCl_3$, seguido de tratamiento con isopropilamina de una manera como se describe para el ejemplo 1 c para dar 540 mg (71%) de un sólido blancuzco. ^{1}H RMN (DMSO-d_6) δ 7,80 (1H, d,

J=7,8 Hz), 7,50 (1H, d, J=8,6 Hz), 7,14 (1H, d, J=2,2 Hz), 6,89 (1H, dd, J=8,6, 2,2 Hz), 4,09 (1H, m), 3,76 (3H, s), 2,56 (3H, s), 1,16 (6H, d, J=6,6 Hz).

Análisis. Calculado para $C_{14}H_{17}NO_3$: C, 67,99; H, 6,93; N, 5,66. Encontrado: C, 67,86; H, 6,87; N, 5,60.

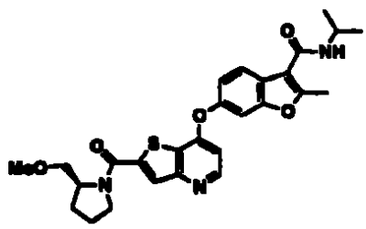
Ejemplo 82(b): isopropilamida del ácido 6-hidroxi-2-metil-benzofuran-3-carboxílico.



Este material se preparó a partir de isopropilamida del ácido 6-metoxi-2-metilbenzofuran-3-carboxílico **82 a** (507 mg, 2,05 mmol) por tratamiento con BBr_3 de una manera como se describe previamente para el ejemplo 1 d para dar 425 mg (89%) de un sólido marrón. ^{1}H RMN (DMSO-d_6) δ 9,54 (1H, s), 7,71 (1H, d, J=8,1 Hz), 7,38 (1H, d, J=8,6 Hz), 6,87 (1H, s), 6,70 (1H, d, J=8,6 Hz), 4,07 (1H, m), 2,51 (3H, s), 1,17 (6H, d, J=6,8 Hz).

Análisis. Calculado para $C_{13}H_{15}NO_3$. 0,1 MeOH: C, 66,54; H, 6,56; N, 5,92. Encontrado: C, 66,38; H, 6,48; N, 5,93.

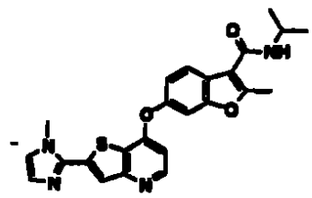
Ejemplo 82: isopropilamida del ácido 6-(2-[(S)-2-(metoximetil)pirrolidina-1-carbonil]tieno[3,2-b]piridin-7-iloxi)-2-metil-benzofuran-3-carboxílico.



Este material se preparó por la reacción de 7-cloro-2-[(S)-2-(metoximetil)pirrolidina-1-carbonil]tieno[3,2-b]piridina **2 a** (133 mg, 0,43 mmol), isopropilamida del ácido 6-hidroxi-2-metil-benzofuran-3-carboxílico **82 b** (120 mg, 0,51 mmol) y Cs_2CO_3 (279 mg, 0,86 mmol) de una manera como se describe previamente para dar 150 mg (69%) de una espuma frágil blancuzca. ^{1}H RMN (DMSO-d_6) δ 8,56 (1H, d, J=5,3 Hz), 8,03 (1H, s), 7,96 (1H, d, J=8,1 Hz), 7,75 (1H, d, J=8,3 Hz), 7,65 (1H, d, J=2,3 Hz), 7,24 (1H, dd, J=8,6, 2,3 Hz), 6,72 (1H, d, J=5,3 Hz), 4,30 (1H, m),

4,12 (1H, m), 3,85 (2H, m), 3,56 (1H, m), 3,42 (1H, m), 3,25 (3H, s), 2,59 (3H, s), 2,08-1,81 (4H, m), 1,20 (6H, d, J=6,6 Hz). Análisis. Calculado para $C_{27}H_{29}N_3O_5S$. 0,3 EtOAc: C, 63,42; H, 5,93; N, 7,87; S, 6,00. Encontrado: C, 63,20; H, 5,90; N, 7,85; S, 6,03.

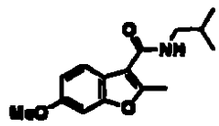
Ejemplo 83: isopropilamida del ácido 2-metil-6-[2-(1-metil-1H-imidazol-2-il)tieno[3,2-b]piridin-7-iloxi]-benzofuran-3-carboxílico.



Este material se preparó por la reacción de 7-cloro-2-(1-metil-1H-imidazol-2-il)tieno[3,2-b]piridina 1 e (89 mg, 0,36 mmol) con isopropilamida del ácido 6-hidroxi-2-metilbenzo[b]furan-3-carboxílico 82 a (100 mg, 0,43 mmol) y Cs_2CO_3 (233 mg, 0,72 mmol) de una manera como se describe previamente para el ejemplo 1 para dar un 37% de rendimiento de un sólido amarillo claro. ^{1}H RMN (DMSO-d_6) δ 8,51 (1H, d, J=5,3 Hz), 7,97 (1H, d, J=7,8 Hz), 7,88 (1H, s), 7,74 (1H, d, J=8,6 Hz), 7,65 (1H, d, J=2,3 Hz), 7,40 (1H, s), 7,24 (1H, dd, J=8,3, 2,0 Hz), 7,01 (1H, s), 6,65 (1H, d, J=5,6 Hz), 4,12 (1H, m), 3,98 (3H, s), 2,60 (3H, s), 1,20 (6H, d, J=6,6 Hz).

Análisis. Calculado para $C_{24}H_{22}N_4O_3S$. 0,9 EtOAc: C, 63,04; H, 5,60; N, 10,66. Encontrado: C, 62,85; H, 5,52; N, 10,76; S, 6,24.

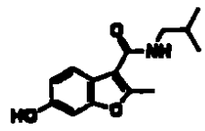
Ejemplo 84(a): Isobutilamida del ácido 6-metoxi-2-metil-benzofuran-3-carboxílico.



Este material se preparó a partir de 6-metoxi-2-metilbenzofurano 12 a (500 mg, 3,1 mmol) por acilación con cloruro de oxalilo en presencia de $AlCl_3$, seguido de tratamiento con isobutilamina de una manera como se describe previamente para el ejemplo 1 c para dar 585 mg (73%) de un sólido blancuzco. ^{1}H RMN (DMSO-d_6) δ 7,95 (1H, t, J=5,8 Hz), 7,56 (1H, d, J=8,6 Hz), 7,15 (1H, d, J=2,3 Hz), 6,91 (1H, dd, J=8,6, 2,3 Hz), 3,76 (3H, s), 3,07 (2H, m), 2,57 (3H, s), 1,83 (1H, m), 0,88 (6H, d, J=6,8 Hz). Análisis. Calculado para $C_{15}H_{19}NO_3$: C, 68,94; H, 7,33; N, 5,36. Encontrado: C, 68,75; H, 7,27; N, 5,38

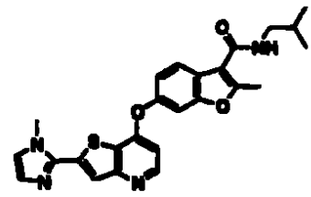
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Ejemplo 84(b): isobutilamida del ácido 6-hidroxi-2-metil-benzofuran-3-carboxílico



Este material se preparó a partir de isobutilamida del ácido 6-metoxi-2-metil-benzofuran-3-carboxílico **84 a** por tratamiento con BBr_3 de una manera como se describe previamente para el ejemplo 1 d. ^1H RMN (DMSO-d_6) δ 9,53 (1H, s), 7,90 (1H, t, J=6,1 Hz), 7,44 (1H, d, J=8,3 Hz), 6,86 (1H, s), 6,74 (1H, dd, J=8,6, 1,8 Hz), 3,07 (2H, t, J=6,1 Hz), 2,52 (3H, s), 1,81 (1H, m), 0,90 (6H, d, J=6,8 Hz).

Ejemplo 84: isobutilamida del ácido 2-metil-6-[2-(1-metil-1H-imidazol-2-il)tieno[3,2-b]piridin-7-iloxi]benzofuran-3-carboxílico.

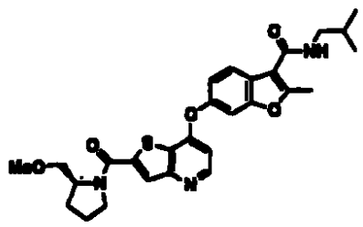


Este material se preparó por la reacción de 7-cloro-2-(1-metil-1H-imidazol-2-il)tieno[3,2-b]piridina **1 e** con isobutilamida del ácido 6-hidroxi-2-metil-benzofuran-3-carboxílico **84 b** y Cs_2CO_3 de una manera como se describe previamente para el ejemplo 1. ^1H RMN (CD_3CN) δ 8,48 (1H, d, J=5,6 Hz), 7,81 (1H, d, J=8,3 Hz), 7,74 (1H, s), 7,43 (1H, d, J=2,0 Hz), 7,21 (1H, dd, J=8,6, 2,3 Hz), 7,17 (1H, s), 7,04 (1H, s), 6,70 (1H, m), 6,67 (1H, d, J=5,6 Hz), 3,97 (3H, s), 3,23 (2H, t, J=6,6 Hz), 2,66 (3H, s), 1,78 (1H, m), 0,98 (6H, d, J=6,6 Hz).

Análisis. Calculado para $C_{25}H_{24}N_4O_3S$. 0,3 H_2O: C, 64,44; H, 5,32; N, 12,02; S, 6,88. Encontrado: C, 64,40; H, 5,38; N, 11,76; S, 6,72.

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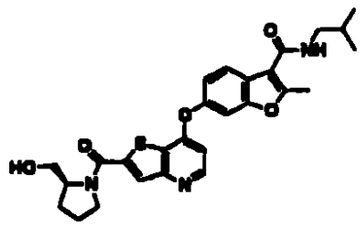
Ejemplo 85: isobutilamida del ácido 6-[2-(2-metoximetil-pirrolidina-1-carbonil)-tieno[3,2-b]piridin-7-iloxi]-2-metilbenzofuran-3-carboxílico.



Este material se preparó por la reacción de 7-cloro-2-[(R)-2-metoximetilpirrolidina-1-carbonil]tieno[3,2-b]piridina **2 a** con isobutilamida del ácido 6-hidroxi-2-metil-benzofuran-3-carboxílico **84 b** y Cs_2CO_3 de una manera como se describe previamente para el ejemplo 1. ^1H RMN (CD_3CN) δ 8,53 (1H, d, J=5,3 Hz), 7,87 (1H, s), 7,82 (1H, d, J=8,5 Hz), 7,41 (1H, d, J=1,9 Hz), 7,20 (1H, dd, J=8,5, 1,9 Hz), 6,70 (1H, d, J=5,5 Hz), 4,38 (1H, m), 3,85 (2H, m), 3,65-3,41 (2H, m), 3,32 (3H, s), 3,23 (2H, t, J=6,4 Hz), 2,65 (3H, s), 2,15-1,94 (4H, m, parcialmente oscurecido por el CD_3CN), 1,73 (1H, m).

Análisis. Calculado para $C_{28}H_{31}N_3O_5S$. 0,2 H_2O: C, 64,03; H, 6,03; N, 8,00; S, 6,10. Encontrado: C, 64,02; H, 6,11; N, 7,79; S, 5,89.

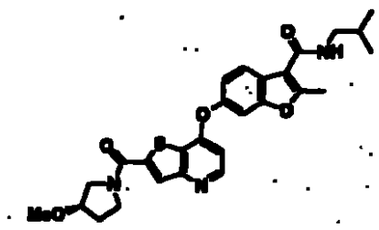
Ejemplo 86: isobutilamida del ácido 2-metil-6-[2-(2-hidroximetil-pirrolidina-1-carbonil)-tieno[3,2-b]piridin-7-iloxi]-benzofuran-3-carboxílico.



Este material se preparó a partir de isobutilamida del ácido 2-metil-6-[2-(2-metoximetil-pirrolidina-1-carbonil)tieno[3,2-b]piridin-7-iloxi]-benzofuran-3-carboxílico **85** por tratamiento con BBr_3 de una manera como se describe previamente para el ejemplo 1 d. ^1H RMN (CD_3CN) δ 8,52 (1H, d, J=5,5 Hz), 7,89 (1H, s), 7,81 (1H, d, J=8,5 Hz), 7,42 (1H, d, J=2,1 Hz), 7,20 (1H, dd, J=8,5, 2,1 Hz), 6,78 (1H, m), 6,71 (1H, d, J=5,3 Hz), 4,29 (1H, m), 3,94-3,63 (4H, m), 3,22 (2H, t, J=6,4 Hz), 2,65 (3H, s), 2,22-1,95 (4H, m), 0,98 (6H, d, J=6,8 Hz).

Análisis. Calculado para $C_{27}H_{29}N_3O_5S$: C, 63,89; H, 5,76; N, 8,28; S, 6,32. Encontrado: C, 63,56; H, 5,95; N, 8,01; S, 6,07.

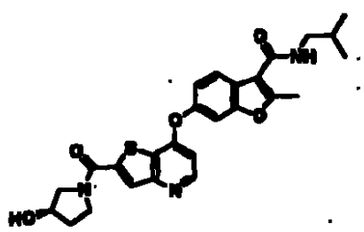
Ejemplo 87: isobutilamida del ácido 6-[2-(3-metoxi-pirrolidina-1-carbonil)-tieno[3,2-b]piridin-7-iloxi]-2-metil-benzofuran-3-carboxílico.



Este material se preparó por la reacción de 7-cloro-2-[(R)-3-metoxipirrolidina-1-carbonil]tieno[3,2-b]piridina 4 b con isobutilamida del ácido 6-hidroxi-2-metil-benzofuran-3-carboxílico 83 b y Cs_2CO_3 de una manera como se describe previamente para el ejemplo 1. ^{1}H RMN (CD_3CN) δ 8,53 (1H, d, J=5,5 Hz), 7,88 (1H, d, J=3,0 Hz), 7,82 (1H, d, J=8,5 Hz), 7,41 (1H, d, J=2,3 Hz), 7,20 (1H, dd, J=8,5, 2,3 Hz), 6,70 (2H, d, J=5,5 Hz), 4,10-3,83 (3H, m), 3,73-3,58 (2H, m), 3,33-3,29 (3H, 2s), 3,23 (2H, t, J=6,8 Hz), 2,65 (3H, s), 2,10-1,95 (2H, m), 0,98 (6H, d, J=6,6 Hz).

Análisis. Calculado para $C_{27}H_{29}N_3O_5S$: C, 63,89; H, 5,76; N, 8,28; S, 6,32. Encontrado: C, 63,83; H, 5,95; N, 8,08; S, 6,10.

Ejemplo 88: isobutilamida del ácido 2-metil-6-[2-(3-hidroxi-pirrolidina-1-carbonil)-tieno[3,2-b]piridin-7-iloxi]-benzofuran-3-carboxílico.

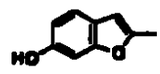


Este material se preparó a partir de isobutilamida del ácido 2-metil-6-[2-(3-metoxi-pirrolidina-1-carbonil)tieno[3,2-b]piridin-7-iloxi]benzofuran-3-carboxílico 87 por tratamiento con BBr_3 de una manera como se describe previamente para el ejemplo 1 d. ^{1}H RMN (CD_3CN/DMSO-d_6) δ 8,55 (1H, d, J=5,6 Hz), 7,94-7,88 (1H, 2s), 7,81 (1H, d, J=8,5 Hz), 7,46 (1H, d, J=2,1 Hz), 7,38 (1H, m), 7,20 (1H, dd, J=8,5, 2,1 Hz), 6,76 (1H, d, J=5,7 Hz), 4,39 (1H, m), 3,94 (1H, m), 3,74-3,51 (3H, m), 3,18 (2H, t, J=6,5 Hz),

2,63 (3H, s), 2,07-1,86 (2H, m, parcialmente oscurecido por el CD_3CN), 0,96 (6H, d, J=6,6 Hz).

Análisis. Calculado para $C_{28}H_{27}N_3O_5S$. 0,5 CH_2Cl_2: C, 59,37; H, 5,27; N, 7,84; S, 5,96. Encontrado: C, 59,42; H, 5,44; N, 7,86; S, 5,99.

Ejemplo 89(a): 6-hidroxi-2-metilbenzofurano

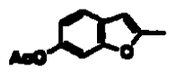


Este material se preparó a partir de 6-metoxi-2-metilbenzofurano (1,00 g, 6,17 mmol) por tratamiento con BBr_3 de una manera como se describe previamente para **1 d** para dar un aceite incoloro (690 mg, 75%) que se solidificó al reposar.

^1H RMN (DMSO-d_6) δ 9,32 (1H, s), 7,23 (1H, d, J=8,3 Hz), 6,80 (1H, s), 6,64 (1H, d, J=8,3 Hz), 6,37 (1H, s), 2,35 (3H, s).

Análisis. Calculado para $C_9H_8O_2$: C, 72,96; H, 5,44. Encontrado: C, 72,72; H, 5,43.

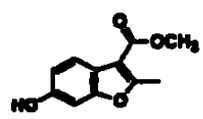
Ejemplo 89(b): 6-acetoxi-2-metilbenzofurano.



Este material se preparó a partir de 6-hidroxi-2-metilbenzofurano (6,54 mg, 4,41 mmol) por tratamiento con cloruro de acetilo (0,41 ml, 5,74 mmol) y trietilamina (0,74 ml, 5,30 mmol) de una manera como se describe previamente para **8 b** para dar el producto deseado en forma de un aceite (850 mg, ~cuantitativo). ^1H RMN ($CDCl_3$) δ 7,41 (1H, d, J=8,3 Hz), 7,13 (1H, s), 6,88 (1H, dd, J=8,3, 1,9 Hz), 6,32 (1H, s), 2,42(3H, s), 2,30 (3H, s)

Análisis. Calculado para $C_{11}H_{10}O_3$: C, 69,46; H, 5,30. Encontrado: C, 69,02; H, 5,44.

Ejemplo 89(c): 6-hidroxi-2-metilbenzofurano-3-carboxilato de metilo

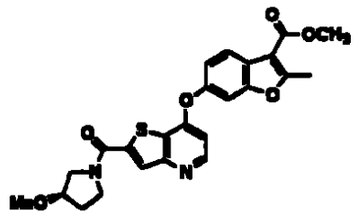


Este material se preparó a partir de 6-acetoxi-2-metilbenzofurano **89 b** (0,81 g, 4,3 mmol) por acilación con cloruro de oxalilo en presencia de $AlCl_3$, seguido de tratamiento con metanol y K_2CO_3 de una manera como se describe previamente para

el ejemplo 11 a para dar un sólido beis (607 mg, 69%). ^{1}H RMN (DMSO-d_6) δ 9,64 (1H, s), 7,62 (1H, d, J=8,5 Hz), 6,93 (1H, d, J=1,9 Hz), 6,78 (1H, dd, J=8,5, 2,0 Hz), 3,79 (3H, s), 2,66 (3H, s).

Análisis. Calculado para $C_{11}H_{10}O_4$: C, 64,07; H, 4,89. Encontrado: C, 64,06; H, 4,89.

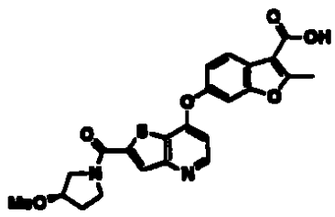
Ejemplo 89(d): 6-[2-(3-metoxipirrolidina-1-carbonil)tieno[3,2-b]piridin-7-iloxi]-2-metil-benzofuran-3-carboxilato de metilo.



Este material se preparó por la reacción de 7-cloro-2-[(R)-3-metoxipirrolidina-1-carbonil]tieno[3,2-b]piridina 4 b (707 mg, 2,38 mmol) con 6-hidroxi-2-metil-benzofuran-3-carboxilato de metilo 89 c (565 mg, 2,74 mmol) y Cs_2CO_3 (3,10 g, 9,53 mmol) de una manera como se describe previamente para el ejemplo para dar 650 mg (58%) de un sólido blancuzco. ^{1}H RMN (DMSO-d_6) δ 8,57 (1H, d, J=5,3 Hz), 8,07 (1H, s), 7,96 (1H, d, J=8,6 Hz), 7,75 (1H, d, J=2,0 Hz), 7,31 (1H, dd, J=8,6, 2,0 Hz), 6,74 (1H, d, J=5,6 Hz), 4,10-3,85 (3H, m), 3,90 (3H, s), 3,65-3,45 (2H, m), 3,25 (3H, d, J=12,6 Hz), 2,77 (3H, s), 2,15-1,95 (2H, m).

Análisis. Calculado por $C_{24}H_{22}N_2O_6S$. 0,2 H_2O: C. 61,31; H, 4,80; N, 5,96; S, 6,82. Encontrado: C, 61,21; H, 4,99; N, 5,90; S, 6,68.

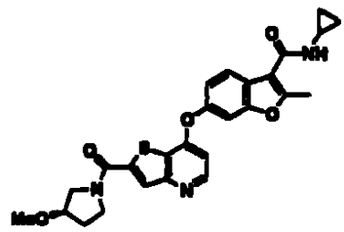
Ejemplo 89(e): ácido 6-[2-(3-metoxipirrolidina-1-carbonil)tieno[3,2-b]piridin-7-iloxi]-2-metil-benzofuran-3-carboxílico.



A una disolución agitada de 6-[2-(3-metoxipirrolidina-1-carbonil)-tieno[3,2-b]piridin-7-iloxi]-2-metil-benzofuran-3-carboxilato de metilo 89 d (540 mg, 1,16 mmol) en THF/MeOH/MeOH (6 ml, 1:1:1) se añadió hidróxido de litio monohidrato (54 mg,

1,29 mmol). Cuando el éster desapareció por cromatografía en capa fina (tlc), se retiraron los disolventes orgánicos a presión reducida, y el residuo acuoso se neutralizó con HCl 2 N. El sólido blanco que precipitó se recogió por filtración y se secó a vacío para dar el ácido deseado (411 mg, 83%). ^{1}H RMN (DMSO-d_6) δ13,02 (1H, s ancho), 8,57 (1H, d, J=5,3 Hz), 8,05 (1H, s), 7,94 (1H, d, J=8,5 Hz), 7,68 (1H, s), 7,25 (1H, d, J=8,5 Hz), 6,75 (1H, d, J=5,5 Hz), 4,10-3,85 (3H, m), 3,65-3,45 (2H, m), 3,25 (3H, d, J=9,4 Hz), 2,74 (3H, s), 2,15-1,95 (2H, m).

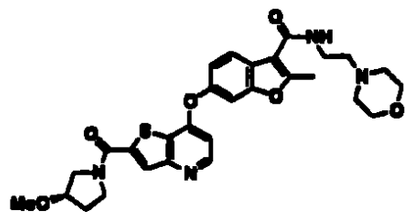
Ejemplo 89: ciclopropilamida del ácido 6-[2-(3-metoxipirrolidina-1-carbonil)tieno[3,2-b]piridin-7-iloxi]-2-metil-benzofuran-3-carboxílico.



Este material se preparó a partir de ácido 6-[2-(3-metoxipirrolidina-1-carbonil)-tieno[3,2-b]piridin-7-iloxi]-2-metil-benzofuran-3-carboxílico **89 e** (37 mg, 0,08 mmol) por tratamiento con cloruro de oxalilo (15 µl, 0,17 mmol) y ciclopropilamina (56 µl, 0,81 mmol) de una manera como se describe previamente para el ejemplo **16 d** para dar un sólido blanco (13 mg, 33%). ^{1}H RMN (DMSO-d_6) δ 8,57 (1H, d, J=5,1 Hz), 8,19 (1H, s), 8,06 (1H, s ancho), 7,74 (1H, d, J=6,1 Hz), 7,65 (1H, s), 7,24 (1H, d, J=6,1 Hz), 6,71 (1H, d, J=1,8 Hz), 4,10-3,80 (3H, m), 3,70-3,35 (2H, m), 3,25 (3H, d, J=13,1 Hz), 2,86 (1H, m), 2,59 (3H, s), 2,25-1,95 (2H, m), 0,71 (2H, m), 0,60 (2H, m).

Análisis. Calculado para $C_{28}H_{25}N_3O_5S$. 0,1 hexanos: C, 63,87; H, 5,32; N, 8,40; S, 6,41. Encontrado: C, 63,61; H, 5,51; N, 8,31; S, 6,23.

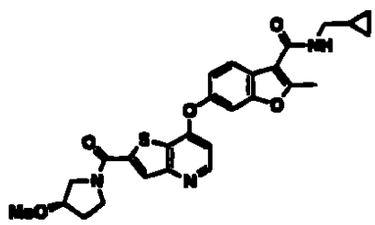
Ejemplo 90: (2-morfolin-4-il-etil)amida del ácido 6-[2-(3-metoxi-pirrolidina-1-carbonil)tieno[3,2-b]piridin-7-iloxi]-2-metil-benzofuran-3-carboxílico.



Este material se preparó a partir de ácido 6-[2-(3-metoxipirrolidina-1-carbonil)-tieno[3,2-b]piridin-7-iloxi]-2-metil-benzofuran-3-carboxílico **89** e por tratamiento con cloruro de oxalilo y 2-(morfolin-4-il)etilamina de una manera como se describe previamente para el ejemplo **16 d**. ^{1}H RMN (DMSO-d_6) δ 8,57 (1H, d, J=5,1 Hz), 8,06 (1H, s), 8,97 (1H, s ancho), 7,83 (1H, d, J=8,6 Hz), 7,66 (1H, s), 7,27 (1H, d, J=8,3 Hz), 6,71 (1H, d, J=5,3 Hz), 4,20-3,95 (4H, m), 3,70-3,35 (10H, m), 3,25 (3H, d, J=12,6 Hz), 2,64 (3H, s), 2,41 (3H, s), 2,06 (2H, m).

Análisis. Calculado para $C_{29}H_{32}N_4O_6S$. 0,7 H_2O: C, 60,34; H, 5,83; N, 9,71; S, 5,55. Encontrado: C, 60,76; H, 5,92; N, 9,71; S, 5,39.

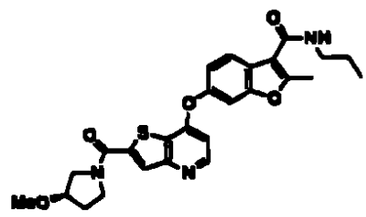
Ejemplo 91: ciclopropilmetilamida del ácido 6-[2-(3-metoxi-pirrolidina-1-carbonil)-tieno[3,2-b]piridin-7-iloxi]-2-metil-benzofuran-3-carboxílico.



Este material se preparó a partir de ácido 6-[2-(3-metoxipirrolidina-1-carbonil)-tieno[3,2-b]piridin-7-iloxi]2-metilbenzofuran-3-carboxílico 89 e por tratamiento con cloruro de oxalilo y (aminometil)ciclopropano de una manera como se describe previamente para el ejemplo 16 d. ^{1}H RMN (DMSO-d_6) δ 8,55 (1H, d, J=5,1 Hz), 8,20 (1H, s), 8,05 (1H, s), 7,80 (1H, d, J=8,6 Hz), 7,64 (1H, s), 7,22(1H, d, J=8,3 Hz), 6,69 (1H, d, J=5,3 Hz), 4,10-3,80 (3H, m), 3,70-3,50 (2H, m), 3,26 (3H, d, J=12,6), 3,15 (2H, m), 2,63 (3H, s), 2,20-1,95 (2H, m), 1,08 (1H, m), 0,45 (2H, d, J=7,1 Hz), 0,25 (2H, d, J=4,3 Hz).

Análisis. Calculado para $C_{27}H_{27}N_3O_5S$. 0,2 hexanos. 0,6 H_2O: C, 63,47; H, 5,86; N, 8,87; S, 6,01. Calculado: C, 63,54; H, 5,88; N, 7,74; S, 5,91.

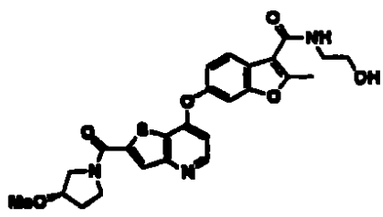
Ejemplo 92: propilamida del ácido 6-[2-(3-metoxi-pirrolidina-1-carbonil)-tieno[3,2-b]piridin-7-iloxi]-2-metil-benzofuran-3-carboxílico.



Este material se preparó a partir de ácido 6-[2-(3-metoxipirrolidina-1-carbonil)-tieno[3,2-b]piridin-7-iloxi]-2-metilbenzofuran-3-carboxílico 89 e por tratamiento con cloruro de oxalilo y 1-aminopropano de una manera como se describe previamente para el ejemplo 16 d. ^{1}H RMN (DMSO-d_6) δ 8,57 (1H, dd, J=5,6, 1,3 Hz), 8,09 (1H, m), 8,06 (1H, s), 7,79 (1H, d, J=8,6 Hz), 7,66 (1H, d, J=2,0 Hz), 7,26(1H, dd, J=8,6, 2,0 Hz), 6,72 (1H, d, J=5,6 Hz), 4,08-3,82 (3H, m), 3,70-3,44 (2H, m), 3,27-3,22 (5H, m), 2,62 (3H, s), 2,15-1,92 (2H, m), 1,56-1,54 (2H, m), 0,92 (3H, t, J=7,3 Hz).

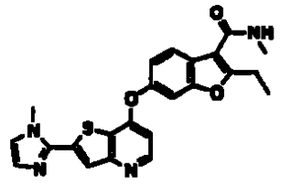
Análisis. Calculado para $C_{28}H_{27}N_3O_5S$. 0,7 H_2O. 0,3 MTBE: C, 62,01; H, 6,06; N, 7,89; S, 6,02. Calculado: C, 61,82; H, 6,07; N, 7,87; S, 5,97.

Ejemplo 93: 2-hidroxietilamida del ácido 6-[2-(3-metoxi-pirrolidina-1-carbonil)-tieno[3,2-b]piridin-7-iloxi]-2-metil-benzofuran-3-carboxílico.



Este material se preparó a partir de ácido 6-[2-(3-metoxipirrolidina-1-carbonil)-tieno[3,2-b]piridin-7-iloxi]-2-metilbenzofuran-3-carboxílico 89 e por tratamiento con cloruro de oxalilo y 2-aminoetanol de una manera como se describe previamente para el ejemplo 16 d. ^{1}H RMN (DMSO-d_6) δ 8,57 (1H, d, J=5,6 Hz), 8,06 (1H, s), 8,00 (1H, t, J=5,3 Hz), 7,82 (1H, d, J=8,6 Hz), 7,66 (1H, d, J=2,3 Hz), 7,26 (1H, dd, J=8,3, 2,3 Hz), 6,72 (1H, d, J=5,3 Hz), 4,76 (1H, m), 4,10-3,82 (3H, m), 3,67-3,59 (2H, m), 3,55 (2H, t, J=6,1 Hz), 3,37 (2H, t, J=6,1 Hz), 3,27, 3,24 (3H, 2s), 2,63 (3H, s), 2,06 (2H, m).

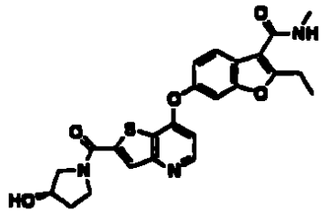
Ejemplo 94: metilamida del ácido 2-etil-6-[2-1(metil-1H-imidazol-2-il)tieno[3,2-b]piridin-7-iloxi]-benzofuran-3-carboxílico.



Este material se preparó por la reacción de 7-cloro-2-(1-metil-1H-imidazol-2-il)tieno[3,2-b]piridina 1 e (114 mg, 0,46 mmol) con metilamida del ácido 6-hidroxi-2-etilbenzofuran-3-carboxílico 14 c (120 mg, 0,55 mmol) y Cs_2CO_3 (594 mg, 1,82 mmol) de una manera como se describe previamente para el ejemplo 1 para dar 60 mg (30%) de un sólido marrón. ^{1}H RMN (DMSO-d_6) δ 8,49 (1H, d, J=5,6 Hz), 8,00 (1H, d, J=4,6 Hz), 7,89 (1H, s), 7,82 (1H, d, J=8,6 Hz), 7,67 (1H, s), 7,41 (1H, s), 7,26 (1H, d, J=8,6 Hz), 7,03 (1H, s), 6,68 (1H, d, J=5,6 Hz), 3,99 (3H, s), 3,04 (2H, q, J=7,6 Hz), 2,81 (3H, d, J=4,6 Hz), 1,28 (3H, t, J=7,3 Hz).

Análisis. Calculado para $C_{23}H_{20}N_4O_3S$. 0,1 hexanos. 0,3 H_2O: C, 63,48; H, 4,97; N, 12,55; S, 7,18. Encontrado: C, 63,40; H, 5,07; N, 12,88; S, 7,15.

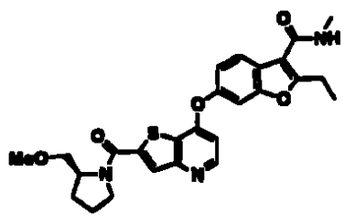
Ejemplo 95: metilamida del ácido 2-etil-6-[2-(3-hidroxi-pirrolidina-1-carbonil)tieno[3,2-b]piridin-7-iloxi]benzofuran-3-carboxílico.



Este material se preparó a partir de metilamida del ácido 2-etil-6-[2-(3-metoxipirrolidina-1-carbonil)-tieno[3,2-b]piridin-7-iloxi]benzofuran-3-carboxílico 14 por tratamiento con BBr_3 de una manera como se describe previamente para 1 d. ^{1}H RMN (DMSO-d_6) δ 8,56 (1H, d, J=5,3 Hz), 8,07 (1H, s), 8,00 (1H, d, J=4,1 Hz), 7,82 (1H, d, J=8,6 Hz), 7,68 (1H, d, J=2,0 Hz), 7,25 (1H, dd, J=8,6, 2,0 Hz), 6,73 (1H, d, J=5,3 Hz), 5,07 (1H, t, J=3,5 Hz), 4,35 (1H, m), 3,97 (1H, m), 3,86-3,46 (3H, m), 3,03 (2H, q, J=7,6 Hz), 2,80 (3H, d, J=4,5 Hz), 2,10-1,80 (2H, m), 1,27 (3H, t, J=7,6 Hz).

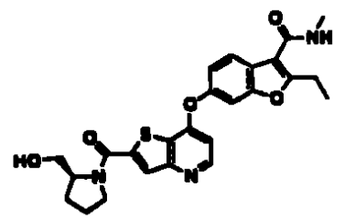
Análisis. Calculado para $C_{24}H_{23}N_3O_5S$. 0,5 H_2O: C, 60,74; H, 5,10; N, 8,86; S, 6,76. Encontrado: C, 60,79; H, 5,24; N, 8,61; S, 6,69.

Ejemplo 96: metilamida del ácido 2-etil-6-(2-[(S)-2-(metoximetil)pirrolidina-1-carbonil]tieno[3,2-b]piridin-7-iloxi)benzofuran-3-carboxílico.



Este material se preparó por la reacción de 7-cloro-2-[(R)-2-metoximetilpirrolidina-1-carbonil]tieno[3,2-b]piridina 2 a con metilamida del ácido 6-hidroxi-2-etilbenzofuran-3-carboxílico 14 c y Cs_2CO_3 de una manera como se describe previamente. ^{1}H RMN (DMSO-d_6) δ 8,57 (1H, d, J=5,5 Hz), 8,03 (1H, s), 8,01 (1H, m), 7,83 (1H, d, J=8,6 Hz), 7,67 (1H, d, J=2,1 Hz), 7,25 (1H, dd, J=8,7, 2,1 Hz), 6,73 (1H, d, J=5,5 Hz), 4,31 (1H, m), 3,92-3,77 (2H, m), 3,58-3,45 (2H, m), 3,27 (3H, s), 3,04 (2H, q, J=7,5 Hz), 2,82 (3H, d, J=4,5 Hz), 2.06-1,85 (4H, m), 1,26 (3H, t, J=7,5 Hz). Análisis. Calculado para $C_{28}H_{27}N_3O_5S$. 0,5 H_2O. 0,2 MTBE C, 62,34; H, 5,89; N, 8,08; S, 6,16. Encontrado: C, 62,38; H, 5,86; N, 7,97; S, 6,15.

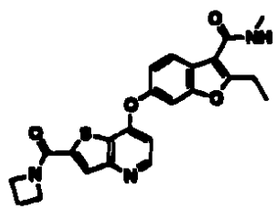
Ejemplo 97: metilamida del ácido 2-etil-6-(2-[(S)-2-(hidroximetil)pirrolidina-1-carbonil]tieno[3,2-b]piridin-7-iloxi]-benzofuran-3-carboxílico.



Este material se preparó a partir de metilamida del ácido 2-etil-6-[2-(2-metoximetil-pirrolidina-1-carbonil)-tieno[3,2-b]piridin-7-iloxi]benzofuran-3-carboxilico 95 por tratamiento con BBr_3 de una manera como se describe previamente para 1 d. ^{1}H RMN (DMSO-d_6) δ 8,56 (1H, d, J=5,3 Hz), 8,01 (2H, s), 7,82 (1H, d, J=8,6 Hz), 7,68 (1H, s), 7,25 (1H, dd, J=8,3, 2,0 Hz), 6,73 (1H, d, J=5,1 Hz), 4,82 (1H, m), 4,20 (1H, m), 3,92-3,47 (4H, m), 3,04 (2H, q, J=7,6 Hz), 2,81 (3H, d, J=4,5 Hz), 2,08-1,83 (4H, m), 1,26 (3H, t, J=7,6 Hz).

Análisis. Calculado para $C_{25}H_{25}N_3O_5S$. 1 H_2O: C, 60,35; H, 5,47; N, 8,45; S, 6,44. Encontrado: C, 60,59; H, 5,47; N, 8,28; S, 6,20.

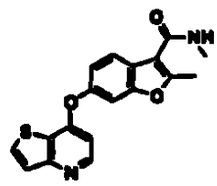
Ejemplo 98: metilamida del ácido 6-[2-(azetidina-1-carbonil)-tieno[3,2-b]piridin-7-iloxi]-2-etil-benzofuran-3-carboxílico.



Este material se preparó por la reacción de 2-(azetidin-1-il-carbonil)-7-clorotieno[3,2-b]piridina 25 a con metilamida del ácido 6-hidroxi-2-etilbenzofuran-3-carboxílico 14 c y Cs_2CO_3 de una manera como se describe previamente para el ejemplo 1. ^{1}H RMN (DMSO-d_6) δ 8,56 (1H, d, J=5,6 Hz), 7,99 (1H, m), 7,89 (1H, s), 7,82 (1H, d, J=8,6 Hz), 7,67 (1H, d, J=2,0 Hz), 7,25 (1H, dd, J=8,6, 2,3 Hz), 6,72 (1H, d, J=5,3 Hz), 4,62 (2H, t, J=7,8 Hz), 4,11 (2H, t, J=7,8 Hz), 3,04 (2H, q, J=7,6 Hz), 2,81 (3H, d, J=4,6 Hz), 2,35 (2H, p, J=7,7 Hz), 1,26 (3H, t, J=7,6 Hz).

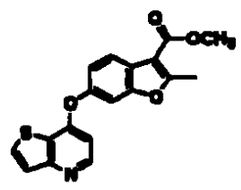
Análisis. Calculado para $C_{23}H_{21}N_3O_4S$. 0,3 H_2O: 62,65; H, 4,94; N, 9,53; S, 7,27. Encontrado: C, 62,66; H, 4,84; N, 9,47; S, 7.52.

Ejemplo 99: metilamida del ácido 6-[tieno[3,2-b]piridin-7-iloxi]-2-metilbenzofuran-3-carboxílico.



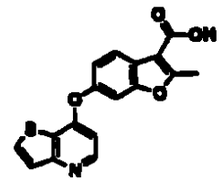
Este material se preparó por la reacción de 7-cloro-tieno[3,2-b]piridina con metilamida del ácido 6-hidroxi-2-metilbenzofuran-3-carboxílico 12 c y Cs_2CO_3 de una manera como se describe previamente para el ejemplo 1. ^{1}H RMN (CD_3CN) δ 8,48 (1H, d, J=5,3 Hz), 7,91 (1H, d, J=5,6 Hz), 7,84 (1H, d, J=8,6 Hz), 7,53 (1H, d, J=5,6 Hz), 7,41 (1H, d, J=2,0 Hz), 7,20 (1H, dd, J=8,6, 2,0 Hz), 6,62 (1H, d, J=5,3 Hz), 6,60 (1H, m ancho), 2,91 (3H, d, J=4,6 Hz), 2,66 (3H, s).

Ejemplo 100(a): 2-metil-6-[tieno[3,2-b]piridin-7-iloxi]benzofuran-3-carboxilato de metilo.



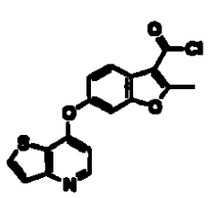
Este material se preparó por la reacción de 7-cloro-tieno[3,2-b]piridina con 6-hidroxi-2-metilbenzofuran-3-carboxilato de metilo 89 c y Cs_2CO_3 de una manera como se describe previamente. ^{1}H RMN ($CDCl_3$) δ 8,48 (1H, d, J=5,3 Hz), 7,99 (1H, d, J=8,3 Hz), 7,74 (1H, d, J=5,6 Hz), 7,56 (1H, d, J=5,3 Hz), 7,29 (1H, d, J=2,0 Hz), 7,16 (1H, dd, J=8,6, 2,3 Hz), 6,53 (1H, d, J=5,3 Hz), 3,96 (3H, s), 2,79 (3H, s).

Ejemplo 100: ácido 2-metil-6-[tieno[3,2-b]piridin-7-iloxi]benzofuran-3-carboxílico.



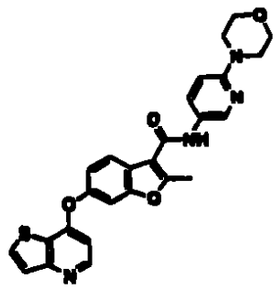
Este material se preparó a partir de 2-metil-6-[tieno[3,2-b]piridin-7-iloxi]benzofuran-3-carboxilato de metilo **100 a** de una manera como se describe previamente para el ejemplo **89 e**. ^{1}H RMN (DMSO-d_6) δ 12,95 (1H, s ancho), 8,50 (1H, d, J=5,3 Hz), 8,15 (1H, d, J=5,5 Hz), 7,97 (1H, d, J=8,3 Hz), 7,69 (1H, d, J=2,1 Hz), 7,59 (1H, d, J=5,5 Hz), 7,26 (1H, dd, J=8,5, 2,1 Hz), 6,64 (1H, d, J=5,5 Hz), 2,74 (3H, s).

Ejemplo 101: cloruro de 2-metil-6-[tieno[3,2-b]piridin-7-iloxi]benzofuran-3-carbonilo.



A una suspensión de ácido 2-metil-6-[tieno[3,2-b]piridin-7-iloxi]benzofuran-3-carboxílico **100** (800 mg, 2,33 mmol) en $CHCl_3$ (20 ml) se añadió cloruro de tionilo (850 µl, 11,6 mmol) y una cantidad catalítica de DMF. La reacción se dejó agitando a 50°C durante 3 h antes de retirar los compuestos volátiles a presión reducida. El residuo en bruto se trituró con MTBE para dar el cloruro de ácido en forma de sólido pálido. ^{1}H RMN (DMSO-d_6) δ 8,81 (1H, d, J=6,6 Hz), 8,57 (1H, d, J=5,6 Hz), 8,03 (1H, d, J=8,6 Hz), 7,86 (1H, d, J=2,0 Hz), 7,82 (1H, d, J=5,6 Hz), 7,39 (1H, dd, J=8,6, 2,0 Hz), 7,06 (1H, d, J=6,3 Hz), 2,76 (3H, s).

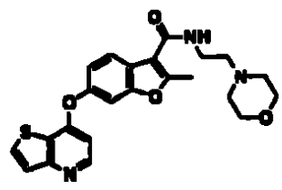
Ejemplo 102: (6-morfolin-4-il-piridin-3-il)amida del ácido 2-metil-6-(tieno[3,2-b]piridin-7-iloxi)benzofuran-3-carboxílico.



Una disolución de ácido 2-metil-6-[tieno[3,2-b]piridin-7-iloxi]benzofuran-3-carboxílico 100 (70 mg, 0,215 mmol), 6-morfolin-4-il-piridin-3-ilamina (77 mg, 0,43 mmol), HATU (163 mg, 0,43 mmol), y diisopropiletilamina (75 µl, 0,43 mmol) se agitó en DMF (2 ml) a temperatura ambiente durante 17 h. La mezcla se añadió a continuación gota a gota a una disolución de $NaHCO_3$ acuoso frío dando como resultado un precipitado que se recogió por filtración. Este material se purificó en gel de sílice usando un gradiente de 0 a 5% de metanol en una mezcla 1:1 acetato de etilo y diclorometano como eluyente para dar 77 mg (74%) de un sólido color lavanda. ^{1}H RMN (CD_3CN) δ 8,50 (1H, d, J=5,3 Hz), 8,37 (1H, d, J=2,5 Hz), 8,29 (1H, s), 7,92-7,88 (3H, m), 7,54 (1H, d, J=5,3 Hz), 7,45 (1H, d, J=2,0 Hz), 7,23 (1H, dd, J=8,6, 2,0 Hz), 6,78 (1H, d, J=9,1 Hz), 6,64 (1H, d, J=5,3 Hz), 3,76 (4H, t, J=4,9 Hz), 3,44 (4H, t, J=4,9 Hz), 2,72 (3H, s).

Análisis. Calculado para $C_{26}H_{22}N_4O_4S$: C, 64,18; H, 4,56; N, 11,52; S, 6,59. Encontrado: C, 64,42; H, 4,47; N, 11,32; S, 6,50.

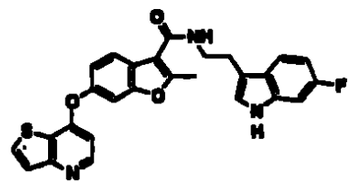
Ejemplo 103: (2-morfolin-4-il-etil)amida del ácido 2-metil-6-[tieno[3,2-b]piridin-7-iloxi]benzofuran-3-carboxílico.



Este material se preparó a partir de ácido 2-metil-6-[tieno[3,2-b]piridin-7-iloxi]benzofuran-3-carboxílico **100** y 2-(morfolin-4-il)etilamina de una manera similar a la descrita para el ejemplo **102**. ^{1}H RMN (CD_3CN) δ 8,50 (1H, d, J=5,3 Hz), 7,92 (1H, d, J=5,6 Hz), 7,89 (1H, d, J=8,6 Hz), 7,54 (1H, d, J=5,6 Hz), 7,42 (1H, d, J=2,3 Hz), 7,23 (1H, dd, J=8,6, 2,3 Hz), 6,83 (1H, m ancho), 6,63 (1H, d, J=5,6 Hz), 3,65 (4H, t, J=4,6 Hz), 3,51 (2H, q, J=6,1 Hz), 2,69 (3H, s), 2,59 (2H, t, J=6,1 Hz), 2,50 (4H, m ancho).

Análisis. Calculado para $C_{23}H_{23}N_3O_4S$. 1,4 H_2O. 0,05 CH_2Cl_2: C, 59,28; H, 5,59; N, 9,00; S, 6,87. Encontrado: C, 59,18; H, 5,23; N, 8,99; S, 6,74.

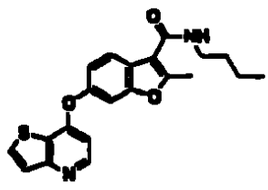
Ejemplo 104: [2-(6-fluoro-1H-indol-3-il)-etil]amida del ácido 2-metil-6-(tieno[3,2-b]piridin-7-iloxi)benzofuran-3-carboxílico.



Este material se preparó a partir de ácido 2-metil-6-[tieno[3,2-b]piridin-7-iloxi]benzofuran-3-carboxílico **100** y 2-(6-fluoro-1H-indol-3-il)etilamina de una manera similar a la descrita para el ejemplo **102**. ^{1}H RMN (CD_3CN) δ 8,48 (1H, d, J=5,6 Hz), 7,91 (1H, d, J=5,6 Hz), 7,63-7,59 (2H, m), 7,54 (1H, d, J=5,6 Hz), 7,38 (1H, d, J=2,3 Hz), 7,17 (1H, d, J=2,3 Hz), 7,14 (1H, t, J=2,3 Hz), 7,11 (1H, d, J=2,3 Hz), 6,85 (1H, m), 6,65 (1H, m ancho), 6,61 (1H, d, J=5,6 Hz), 3,69 (2H, q, J=7,1 Hz), 3,06 (2H, t, J=7,1 Hz), 2,57 (3H, s).

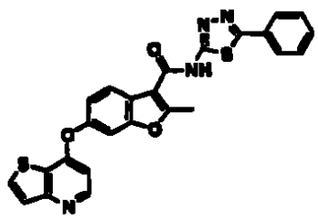
Análisis. Calculado para $C_{27}H_{20}N_3O_3SF$. 0,7 H_2O: C, 65,10; H, 4,33; N, 8,44; S, 6,44. Encontrado: C, 65,04; H, 4,42; N, 8,34; S, 6,40.

Ejemplo 105: butilamida del ácido 2-metil-6-[tieno[3,2-b]piridin-7-iloxi]benzofuran-3-carboxílico.



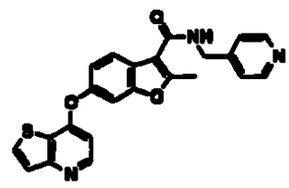
Este material se preparó a partir de ácido 2-metil-6-[tieno[3,2-b]piridin-7-iloxi]benzofuran-3-carboxílico **100** y butilamina de una manera similar a la descrita para el ejemplo **102**. ^{1}H RMN (CD_3CN) δ 8,48 (1H, d, J=5,3 Hz), 7,91 (1H, d, J=5,6 Hz), 7,81 (1H, d, J=8,6 Hz), 7,53 (1H, d, J=5,6 Hz), 7,41 (1H, d, J=2,3 Hz), 7,20 (1H, dd, J=8,6, 2,3 Hz), 6,62 (1H, d, J=5,3 Hz), 6,62 (1H, m ancho), 3,40 (2H, q, J=6,9 Hz), 2,65 (3H, s), 1,60 (2H, m), 1,42 (2H, m), 0,97 (3H, t, J=7,3 Hz).

Ejemplo 106: (5-fenil-[1,3,4]tiadiazol-2-il)amida del ácido 2-metil-6-(tieno[3,2-b]piridin-7-iloxi)benzofuran-3-carboxílico.



Este material se preparó a partir de ácido 2-metil-6-[tieno[3,2-b]piridin-7-iloxi]benzofuran-3-carboxílico **100** y 5-fenil-[2,3,4]tiadiazol-2-il-amina de una manera similar a la descrita para el ejemplo **102**. ^{1}H RMN (CD_3CN/CD_3OD) δ 8,45 (1H, d, J=5,6 Hz), 8,00-7,95 (4H, m), 7,52-7,50 (4H, m), 7,48 (1H, d, J=2,3 Hz), 7,25 (1H, dd, J=8,6, 2,3 Hz), 6,66 (1H, d, J=5,3 Hz), 2,76 (3H, s).

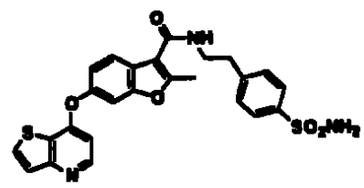
Ejemplo 107: 2-[(4-piridil)-metil]amida del ácido 2-metil-6-[tieno[3,2-b]piridin-7-iloxi]benzofuran-3-carboxílico.



Este material se preparó a partir de ácido 2-metil-6-[tieno[3,2-b]piridin-7-iloxi]benzofuran-3-carboxílico **100** y 4-(aminometil)piridina de una manera similar a la descrita para el ejemplo **102**. ^{1}H RMN (DMSO-d_6) δ 8,68 (1H, t, J=5,6 Hz), 8,53 (2H, d, J=5,3 Hz), 8,50 (1H, d, J=5,3 Hz), 8,15 (1H, d, J=5,3 Hz), 7,88 (1H, d, J=8,3 Hz), 7,68 (1H, d, J=2,0 Hz), 7,60 (1H, d, J=5,6 Hz), 7,36 (2H, d, J=5,6 Hz), 7,27 (1H, dd, J=8,6, 2,3 Hz), 6,62 (1H, d, J=5,3 Hz), 4,53 (2H, d, J=6,1 Hz), 2,67 (3H, s).

Análisis. Calculado para $C_{23}H_{17}N_3O_3S$. 0,40 H_2O: C, 65,36; H, 4,25; N, 9,94; S, 7,59. Encontrado: C, 65,23; H, 4,21; N, 9,92; S, 7,49.

Ejemplo 108: [2-(4-sulfamoil-fenil)-etil]-amida del ácido 2-metil-6-[tieno[3,2-b]piridin-7-iloxi]benzofuran-3-carboxílico.

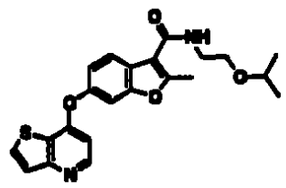


Se añadió gota a gota una suspensión de cloruro de 2-metil-6-[tieno[2,3-b]piridin-7-iloxi]benzofuran-3-carbonilo **101** (100 mg, 0,29 mmol) en DMF (1 ml) a una disolución de [2-(4-sulfamoil-fenil)-etil]-amina (116 mg, 0,58 mmol), trietilamina (80 µl, 0,58 mmol) y dimetilaminopiridina (5 mg) en DMF (2 ml) a 50°C. La disolución amarilla resultante se agitó a 50°C durante 2 h y a continuación se añadió a una disolución acuosa de bicarbonato de sodio enfriada con hielo. El precipitado resultante se recogió por filtración, se lavó con agua y se secó al aire. El filtrado se extrajo dos veces con acetato de etilo. Los extractos se lavaron con NaOH 1 N, a continuación se combinaron con el sólido anterior y se secaron sobre $MgSO_4$, y se concentraron a sequedad. El residuo se trituró con MTBE y a continuación con EtOAc para obtener 49 mg (33%) de un sólido blancuzco. ^{1}H RMN (CD_3CN) δ 8,48 (1H, d, J=5,3 Hz), 7,91

(1H, d, J=5,6 Hz), 7,81 (1H, d, J=8,3 Hz), 7,64 (1H, d, J=8,6 Hz), 7,54 (1H, d, J=5,3 Hz), 7,48 (1H, d, J=8,3 Hz), 7,39 (1H, d, J=2,0 Hz), 7,16 (1H, dd, J=8,6, 2,0 Hz), 6,68 (1H, m ancho), 6,62 (1H, d, J=5,6 Hz), 5,62 (2H, s ancho), 3,69 (2H, q, J=6,8 Hz), 3,04 (2H, t, J=6,8 Hz), 2,57 (3H, s).

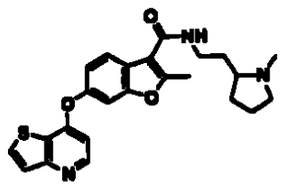
Análisis. Calculado para $C_{25}H_{21}N_3O_5S_2$. 0,9 H_2O. 0,4 EtOAc: C, 57,15; H, 4,69; N, 7,52; S, 11,47. Encontrado: C, 57,15; H, 4,42; N, 7,60; S, 11,55.

Ejemplo 109: (2-isopropil-etil)amida del ácido 2-metil-6-(tieno[3,2-b]piridin-7-iloxi)-benzofuran-3-carboxílico.



Este material se preparó a partir de cloruro de 2-metil-6-[tieno[3,2-b]piridin-7-iloxi]benzofuran-3-carbonilo **101** y 2-(isopropoxi)etilamina de una manera similar a la descrita para el ejemplo **108**. ^{1}H RMN (CD_3CN) δ 8,49 (1H, d, J=5,6 Hz), 7,91 (1H, d, J=5,6 Hz), 7,82 (1H, d, J=8,6 Hz), 7,54 (1H, d, J=5,6 Hz), 7,41 (1H, d, J=2,3 Hz), 7,20 (1H, dd, J=8,6, 2,3 Hz), 6,67 (1H, m ancho), 6,63 (1H, d, J=5,3 Hz), 3,8-3,51 (5H, m), 2,66 (3H, s), 1,15 (6H, d, J=6,1 Hz). Análisis Calculado para $C_{22}H_{22}N_2O_4S$: C, 64,37; H, 5,40; N, 6,82; S, 7,81. Encontrado: C, 64,35; H, 5,51; N, 6,76; S, 7,74.

Ejemplo 110: [2-(1-metil-pirrolidin-2-il)-etil]-amida del ácido 2-metil-6-(tieno[3,2-b]piridin-7-iloxi)-benzofuran-3-carboxílico.

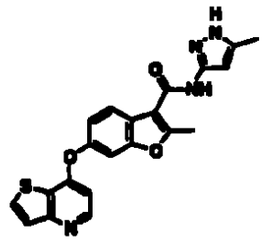


Este material se preparó a partir de cloruro de 2-metil-6-[tieno[3,2-b]piridin-7-iloxi]benzofuran-3-carbonilo **101** y 2-(1-metilpirrolidin-2-il)etilamina de una manera similar a la descrita para el ejemplo **108**. ^{1}H RMN (CD_3CN) δ 8,49 (1H, d, J=5,6 Hz), 7,91 (1H, d, J=5,3 Hz), 7,85 (1H, d, J=8,3 Hz), 7,61 (1H, m ancho), 7,53 (1H, d, J=5,6 Hz), 7,40 (1H, d, J=2,0 Hz), 7,20 (1H, dd, J=8,6, 2,3 Hz), 6,63 (1H, d, J=5,6 Hz), 3,61-3,53 (1H, m), 3,45-3,40 (1H, m), 3,05-3,00 (1H, m), 2,67 (3H, s), 2,42-2,36 (1H, m),

2,29 (3H, s), 2,18 (1H, q, J=8,8 Hz), 2,05-1,95 (1H, m, parcialmente oscurecido por el CD_3CN), 1,87-1,66 (5H, m).

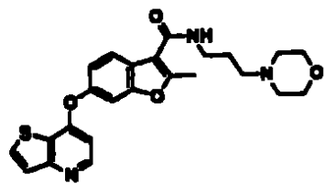
Análisis Calculado para $C_{24}H_{25}N_3O_3S$. 0,5 H_2O: C, 64,84; H, 5,90; N, 9,45; S, 7,21. Encontrado: C, 64,73; H, 5,94; N, 9,41; S, 6,98.

Ejemplo 111: (5-metil-1H-pirazol-3-il)-amida del ácido 2-metil-6-(tieno[3,2-b]piridin-7-iloxi)-benzofuran-3-carboxílico.



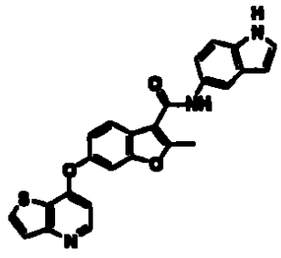
Este material se preparó a partir de cloruro de 2-metil-6-[tieno[3,2-b]piridin-7-iloxi]benzofuran-3-carbonilo **101** y (5-metil-1H-pirazol-3-il)amina de una manera similar a la descrita para el ejemplo **108**. ^{1}H RMN (DMSO-d_6) δ 12, 09 (1H, s ancho), 10,45 (1H, s), 8,50 (1H, d, J=5,6 Hz), 8,14 (1H, d, J=5,6 Hz), 7,77 (1H, d, J=8,6 Hz), 7,65 (1H, d, J=2,3 Hz), 7,59 (1H, d, J=5,3 Hz), 7,24 (1H, dd, J=8,3, 2,0 Hz), 6,64 (1H, d, J=5,6 Hz), 6,39 (1H, s ancho), 2,64 (3H, s), 2,23 (3H, s).

Ejemplo 112: (3-morfolin-4-il-propil)-amida del ácido 2-metil-6-(tieno[3,2-b]piridin-7-iloxi)-benzofuran-3-carboxílico.



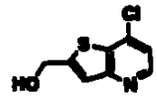
Este material se preparó a partir de cloruro de 2-metil-6-[tieno[3,2-b]piridin-7-iloxi]benzofuran-3-carbonilo **101** y 3-(morfolin-4-il)propilamina de una manera similar a la descrita para el ejemplo **108**. ^{1}H RMN (DMSO-d_6) δ 8,50 (1H, d, J=5,6 Hz), 8,14 (1H, d, J=5,6 Hz), 8,07 (1H, m ancho), 7,80 (1H, d, J=8,6 Hz), 7,64 (1H, d, J=2,0 Hz), 7,59 (1H, d, J=5,6 Hz), 7,24 (1H, dd, J=8,3, 2,0 Hz), 6,61 (1H, d, J=5,6 Hz), 3,56 (4H, m ancho), 3,35-3,27 (4H, m), 2,63 (3H, s), 2,36 (4H, m ancho), 1,73 (2H, m ancho).

Ejemplo 113: (1H-indol-5-il)-amida del ácido 2-metil-6-(tieno[3,2-b]piridin-7-iloxi)-benzofuran-3-carboxílico..



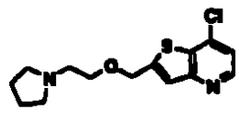
Este material se preparó a partir de cloruro de 2-metil-6-[tieno[3,2-b]piridin-7-iloxi]benzofuran-3-carbonilo **101** y 5-aminoindol de una manera similar a la descrita para el ejemplo **108**. ^{1}H RMN (DMSO-d_6) δ 11, 04 (1H, s), 9,96 (1H, s), 8,52 (1H, d, J=5,6 Hz), 8,15 (1H, d, J=5,3 Hz), 7,97 (1H, s), 7,83 (1H, d, J=8,3 Hz), 7,69 (1H, d, J=2,3 Hz), 7,60 (1H, d, J=5,6 Hz), 7,36 (2H, s), 7,33 (1H, t, J=2,8 Hz), 7,27 (1H, dd, J=8,6, 2,3 Hz), 6,64 (1H, d, J=5,3 Hz), 6,41 (1H, t, J=2,5 Hz), 2,69 (3H, s).

Ejemplo 114(a): 2-(hidroximetil)-7-clorotieno[3,2-b]piridina.



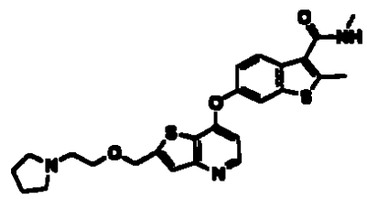
La sal de litio del ácido 7-cloro-tieno[3,2-b]piridina-2-carboxílico (2,0 g, 9,1 mmol) se disolvió en una disolución de DMF (10 ml) y cloroformo (50 ml). El carboxilato se trató con cloruro de tionilo (2,0 ml, 27,3 mmol) y se calentó a reflujo durante una hora. El cloruro de ácido resultante se enfrió hasta temperatura ambiente y se añadió gota a gota a una disolución de borohidruro de sodio (0,7 g, 18,2 mmol) en DMF (10 ml) a 0°C. La temperatura se dejó que llegara hasta temperatura ambiente durante 2 horas y la reacción se enfrió rápidamente con HCl concentrado. La mezcla de reacción se neutralizó con NaOH y se realizó el tratamiento con MTBE, salmuera y $MgSO_4$. El producto en bruto se trituró con MTBE, lo que proporcionó el compuesto del título en forma de sólido beis (0,7 g, 40%). ^{1}H RMN (DMSO-d_6, 400 MHz) δ 8,58 (1H, d, J=5,1 Hz), 7,51 (1H, d, J=5,1 Hz), 7,47 (1H, s), 5,94 (1H, t, J=5,8 Hz), 4,84-4,82 (2H, m), EM m/z 200 $(M+H)^+$.

Ejemplo 114(b): 7-cloro-2-[2-(pirrolidin-1-il]etoximetil)tieno[3,2-b]piridina.



Una mezcla de 2-(hidroximetil)-7-clorotieno[3,2-b]piridina **114** a (0,35 g, 1,8 mmol), hidrocloruro de 1-(2-cloro-etil)pirrolidina (31 g, 18 mmol), bromuro de benciltrietilamonio (0,2 g, 0,7 mmol) e hidróxido de sodio 19 M (10 ml) en tolueno se calentó a reflujo durante 3 horas. La mezcla de reacción se tamponó con bicarbonato de sodio saturado al 50% y el tratamiento se realizó con acetato de etilo, salmuera y sulfato de magnesio. El producto en bruto se purificó sobre gel de sílice (100 g) usando 2-7% de metanol-cloroformo con hidróxido de amonio al 0,1%, lo que proporcionó el compuesto del título en forma de un aceite ámbar (0,38 g, 62%): ^{1}H RMN (DMSO-d_6, 400 MHz) δ 8,62 (1H, d, J=5,0 Hz), 7,58 (1H, s), 7,54 (1H, d, J=5,1 Hz), 4,86 (2H, s), 3,62 (2H, t, J=6,0 Hz), 2,64 (2H, t, J=5,8 Hz), 2,49-2,47 (4H, m), 1,67-1,63 (4H, m); EM m/z $(M+H)^+$.

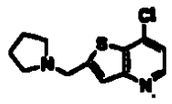
Ejemplo 114: metilamida del ácido 2-metil-6-(2-[2-(pirrolidin-1-il)etoximetil]tieno[3,2-b]piridin-7-iloxi)benzo[b]tiofeno-3-carboxílico.



Este material se preparó a partir de 7-cloro-2-(2-pirrolidin-1-il-etoximetil)-tieno[3,2-b]piridina **114 b** (150 mg, 0,51 mmol), metilamida del ácido 6-hidroxi-2-metil-benzo[b]tiofeno-3-carboxílico 1 d (123 mg, 0,56 mmol) y carbonato de cesio (497 mg, 1,53 mmol) de una manera similar a como se describe para el ejemplo 1 para dar un sólido beis (0,1 g, 41%): ^{1}H RMN (DMSO-d_6, 400 MHz) δ 8,48 (1H, d, J=5,3 Hz), 8,28 (1H, q, J=4,5 Hz), 7,92 (1H, d, J=2,3 Hz), 7,84 (1H, d, J=8,9 Hz), 7,51 (1H, s), 7,30 (1H, dd, J=2,3, 8,9 Hz), 6,63 (1H, d, J=5,6 Hz), 4,82 (2H, s), 3,60 (2H, t, J=6,0 Hz), 2,82 (3H, d, J=4,5 Hz), 2,64-2,60 (5H, m), 2,47 (4H, s ancho), 1,66-1,63 (4H, m); EM m/z 482 $(M+H)^+$:

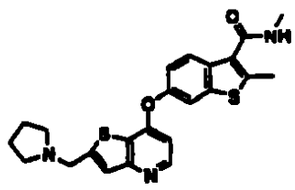
Análisis Calculado para $C_{25}H_{27}N_3O_3S_2$. 0,3 H_2O: C, 61,65; H, 5,71; N, 8,63; S, 13,17. Encontrado: C, 61,55; H, 5,71; N, 8,47; S, 12,97.

Ejemplo 115(a): 7-cloro-2-(pirrolidin-1-il-metil)tieno[3,2-b]piridina.



Una disolución de 2-(hidroximetil)-7-clorotieno[3,2-b]piridina 114 a (100 mg, 0,5 mmol) en dicloroetano se trató con trietilamina (0,08 ml, 0,55 mmol) y cloruro de mesilo (0,04 ml, 0,55 mmol). La disolución transparente se agitó durante 30 minutos y se trató con pirrolidina (0,12 ml, 1,5 mmol). Después de una hora, la mezcla de reacción se vertió en bicarbonato de sodio al 5% y el tratamiento se realizó con diclorometano, salmuera y sulfato de magnesio. El producto en bruto (167 mg de aceite verdoso) se purificó sobre gel de sílice (placa de 1 mm) usando 2% de metanol-cloroformo con hidróxido de amonio al 0,1%, lo que proporcionó el compuesto del título en forma de un aceite transparente (71 mg, 56%): ^{1}H RMN (DMSO-d_6, 400 MHz) δ 8,58 (1H, d, J=5,1 Hz), 7,51-7,49 (2H, m), 3,96 (2H, s), 2,56 (4H, s ancho), 1,75-1,72 (4H, m); EM m/z 253 $(M+H)^+$.

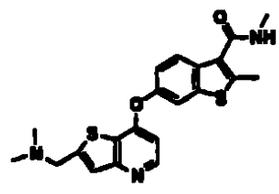
Ejemplo 115: metilamida del ácido 2-metil-6-(2-[pirrolidin-1-ilmetil]tieno[3,2-b]piridin-7-iloxi)benzo[b]tiofeno-3-carboxílico.



Este material se preparó a partir de 7-cloro-2-(pirrolidin-1-ilmetil)tieno[3,2-b]piridina 115 a, metilamida del ácido 6-hidroxi-2-metil-benzo[b]tiofeno-3-carboxílico 1 d y carbonato de cesio de una manera similar a como se describe en el ejemplo 1. ^{1}H RMN (DMSO-d_6, 400 MHz) δ 8,44 (1H, d, J=5,3 Hz), 8,27 (1H, q, J=4,6 Hz), 7,91 (1H, d, J=2,3 Hz), 7,83 (1H, d, J=8,6 Hz), 7,43 (1H, s), 7,28 (1H, dd, J=2,3, 8,6 Hz), 6,60 (1H, d, J=5,6 Hz), 3,93 (2H, s), 2,82 (3H, d, J=4,8 Hz), 2,60 (3H, s), 2,54 (4H, s ancho), 1,72 (4H, s); EM m/z 438 $(M+H)^+$;

Análisis Calculado para $C_{23}H_{23}N_3O_2S_2$: C, 63,13; H, 5,30; N, 9,60; S, 14,66: Encontrado: C, 62,75; H, 5,38; N, 9,35; S, 14,39.

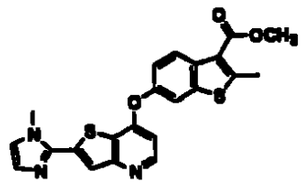
Ejemplo 116: metilamida del ácido 6-(2-[dimetilaminometil]tieno[3,2-b]piridin-7-iloxi)-2-metilbenzo[b]tiofeno-3-carboxílico.



Este material se preparó a partir de 7-cloro-2-(dimetilaminometil)tieno[3,2-b]piridina, metilamida del ácido 6-hidroxi-2-metil-benzo[b]tiofeno-3-carboxílico 1 d y carbonato de cesio de una manera similar a como se describe para el ejemplo 1. ^{1}H RMN (DMSO-d_6, 400 MHz) δ 8,45 (1H, d, J=5,3 Hz), 8,27 (1H, q, J=4,5 Hz), 7,92 (1H, d, J=2,3 Hz), 7,83 (1H, d, J=8,8 Hz), 7,44 (1H, s), 7,28 (1H, dd, J=2,3, 8,9 Hz), 6,62 (1H, d, J=5,3 Hz), 3,75 (2H, s ancho), 2,82 (3H, d, J=4,5 Hz), 2,60 (3H, s), 2,24 (6H, s); EM m/z 412 $(M+H)^+$;

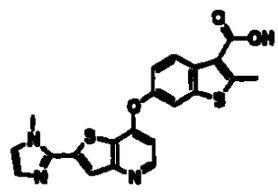
Análisis Calculado para $C_{21}H_{21}N_3O_2S_2$. 0,3 H_2O: C, 60,49; H, 5,22; N, 10,08; S, 15,38: Encontrado: C, 60,47; H, 5,01; N, 9,76; S, 15,09.

Ejemplo 117(a): 2-metil-6-{[2-(1-metil-1H-imidazol-2-il)tieno[3,2-b]piridin-7-il]oxi}benzo[b]tiofeno-3-carboxilato de metilo



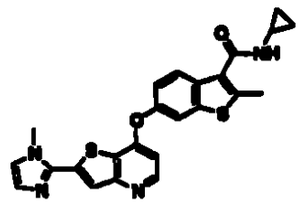
Este material se preparó por la reacción de 6-hidroxi-2-metilbenzo[b]tiofeno-3-carboxilato de metilo 11 a (200 mg, 0,90 mmol) con 7-cloro-2-(1-metil-1H-imidazol-2-il)tieno[3,2-b]piridina 1 e (188 mg, 0,75 mmol) y Cs_2CO_3 (1,22 g, 3,75 mmol) de una manera como se describe previamente para el ejemplo 1 para dar un sólido amarillo (200 mg, 51%). ^{1}H RMN (DMSO-d_6, 300 MHz) δ 8,52 (1H, d, J=5,46 Hz), 8,38 (1H, d, J=9,04 Hz), 8,02 (1H, d, J=2,26 Hz), 7,89 (1H, s), 7,40 (2H, s), 7,02 (1H, s), 6,73 (1H, d, J=5,46 Hz), 3,98 (3H, s), 3,91 (3H, s), 2,82 (3H, s).

Ejemplo 117(b): ácido 2-metil-6-{[2-(1-metil-1H-imidazol-2-il)tieno[3,2-b]piridin-7-il]oxi}benzo[b]tiofeno-3-carboxílico.



Este material se preparó por la reacción de 2-metil-6-{[2-(1-metil-1H-imidazol-2-il)tieno[3,2-b]piridin-7-il]oxi}benzo[b]tiofeno-3-carboxilato de metilo 117 a (200 mg, 0,46 mmol) con LiOH. H_2O (192 mg, 4,6 mmol) de una manera como se describe previamente para el ejemplo 11 c para dar un sólido amarillo (165 mg, 85%). ^{1}H RMN (DMSO-d_6, 300 MHz): δ 8,57 (1H, d, J=5,46 Hz), 8,45 (1H, d, J=8,85 Hz), 8,00 (2H, s), 7,53 (1H, s), 7,40 (1H, dd, J=2,35, 8,95 Hz), 7,22 (1H, s), 6,79 (1H, d, J=5,46 Hz), 4,00 (3H, s), 2,82 (3H, s).

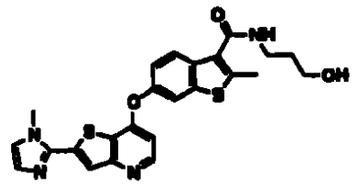
Ejemplo 117: ciclopropilamida del ácido 2-metil-6-{[2-(1-metil-1H-imidazol-2-il)tieno[3,2-b]piridin-7-il]oxi}benzo[b]tiofeno-3-carboxílico.



A una disolución de ácido 2-metil-6-{[2-(1-metil-1H-imidazol-2-il)tieno[3,2-b]piridin-7-il]oxi}benzo[b]tiofeno-3-carboxílico 117 b (75 mg, 0,18 mmol) en DMF (1,5 ml) a 0°C se añadió N,N-diisopropiletilamina (68 µl, 0,39 mmol) y HBTU (100 mg, 0,27 mmol). La mezcla de reacción se agitó 30 min a 0°C y a continuación se calentó hasta temperatura ambiente y se agitó 18 h. La mezcla se vertió sobre H_2O (25 ml) y el precipitado se recogió por filtración a vacío. El papel de filtro se extrajo con una mezcla de CH_2Cl_2 (10 ml) y MeOH (10 ml). La disolución se concentró y la mezcla en bruto se purificó por cromatografía en gel de sílice (5% MeOH/EtOAc) para dar un sólido amarillo pálido (58 mg, 71%). ^{1}H RMN (DMSO-d_6, 300 MHz) δ 8,52 (1H, d, J=5,46 Hz), 8,46 (1H, d, J=4,33 Hz), 7,95 (1H, d, J=2,26 Hz), 7,88 (1H, s), 7,80 (1H, d, J=8,67 Hz), 7,40 (1H, s), 7,32 (1H, dd, J=2,26, 8,85 Hz), 7,02 (1H, s), 6,70 (1H, d, J=5,46 Hz), 3,98 (3H, s), 2,90 (1H, m), 2,57 (3H, s), 0,73 (2H, m), 0,57 (2H, m).

Análisis Calculado para $C_{24}H_{20}N_4O_2S_2$: C, 62,59; H, 4,38; N, 12,17; S, 13,92. Encontrado: C, 62,04; H, 4,22; N, 11,91; S, 13,49.

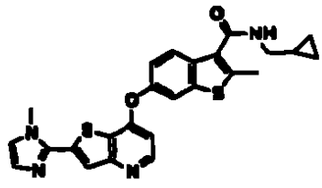
Ejemplo 118: 3-hidroxipropilamida del ácido 2-metil-6-{[2-(1-metil-1H-imidazol-2-il)tieno[3,2-b]piridin-7-il]oxi}benzo[b]tiofeno-3-carboxílico.



Este material se preparó por la reacción de ácido 2-metil-6-{[2-(1-metil-1H-imidazol-2-il)tieno[3,2-b]piridin-7-il]oxi}benzo[b]tiofeno-3-carboxílico 117 b (85 mg, 0,20 mmol) con 3-amino-1-propanol (46 µl, 0,44 mmol), N,N-diisopropiletilamina (77 µl, 0,30 mmol) y HBTU (115 mg, 0,303 mmol) de una manera como se describe previamente para el ejemplo 117. El material en bruto se purificó por cromatografía en gel de sílice (10:30:60% MeOH/CH_2Cl_2/EtOAc) para dar un sólido amarillo (57 mg, 59%). ^{1}H RMN (DMSO-d_6, 300 MHz) δ 8,52 (1H, d, J=5,27 Hz), 8,37 (1H, t, J=5,56 Hz), 7,95 (1H, d, J=2,26 Hz), 7,88 (1H, s), 7,82 (1H, d, J=8,85 Hz), 7,40 (1H, s), 7,33 (1H, dd, J=2,35, 8,76 Hz), 7,02 (1H, d, J=0,94 Hz), 6,70 (1H, d, J=5,46 Hz), 4,51 (1H, t, J=5,09 Hz), 3,98 (3H, s), 3,50 (2H, q, J=6,22 Hz), 3,35 (2H, m), 2,60 (3H, s), 1,71 (2H, m).

Análisis Calculado para $C_{24}H_{22}N_4O_3S_2$: C, 60,23; H, 4,63; N, 11,71, S, 13,40. Encontrado: C, 59,01; H, 4,70; N, 11,13; S, 12,89.

Ejemplo 119: (ciclopropilmetil)amida del ácido 2-metil-6-{[2-(1-metil-1H-imidazol-2-il)tieno[3,2-b]piridin-7-il]oxi}benzo[b]tiofeno-3-carboxílico.

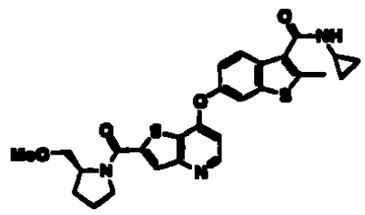


Este material se preparó por la reacción de ácido 2-metil-6-{[2-(1-metil-1H-imidazol-2-il)tieno[3,2-b]piridin-7-il]oxi}benzo[b]tiofeno-3-carboxílico 117 b (70 mg, 0,166 mmol), (aminometil)ciclopropano (43 µl, 0,50 mmol) y diisopropiletilamina (58 µl, 0,33 mmol) y HBTU (94 mg, 0,25 mmol) de una manera similar a la previamente descrita para el ejemplo 117 para dar un sólido amarillo pálido (64 mg, 53%). ^{1}H RMN (DMSO-d_6, 300 MHz) δ 8,61 (1H, d, J=5,46 Hz), 8,49 (1H, t, J=5,65 Hz), 8,07 (1H, s), 7,99 (1H, d, J=2,26 Hz), 7,85 (1H, d, J=8,67 Hz), 7,63 (1H, s), 7,37 (1H, s), 7,36 (1H,

dd, J=2,4, 8,67 Hz), 6,81 (1H, d, J=5,65 Hz), 4,01 (3H, s), 3,20 (2H, t, J=6,31 Hz), 2,62 (3H, s), 1,08 (1H, m), 0,47 (2H, m), 0,27 (2H, m).

Análisis Calculado para $C_{25}H_{22}N_4O_2S_2$. $2(CF_2CO_2H)$; C, 49,57; H, 3,44; N, 7,97, S, 9,13. Encontrado: C, 48,25; H, 3,48; N, 7,64; S, 8,77.

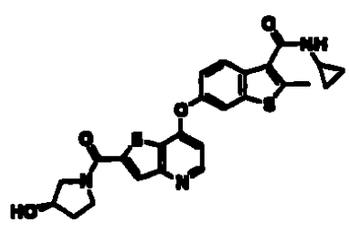
Ejemplo 120: ciclopropilamida del ácido 6-{(2-{[(2S)-2-(metoximetil)pirrolidin-1-il]carbonil}tieno[3,2-b]piridin-7-il)oxi]-2-metilbenzo[b]tiofeno-3-carboxílico.



Este material se preparó por la reacción de 7-cloro-2-{[(2S)-2-(metoximetil)pirrolidin-1-il]carbonil}tieno[3,2-b]piridina **2 a** (124 mg, 0,40 mmol) con ciclopropilamida del ácido 6-hidroxi-2-metilbenzo[b]tiofeno-3-carboxílico **8 c** (119 mg, 0,48 mmol) y Cs_2CO_3 (391 mg, 1,2 mmol) de una manera como se describe previamente para el ejemplo 1 para dar un sólido amarillo (146 mg, 70%). ^{1}H RMN (DMSO-d_6, 300 MHz) δ 8,58 (1H, d, J=5,27 Hz), 8,46 (1H, d, J=4,33 Hz), 8,03 (1H, s), 7,96 (1H, d, J=2,26 Hz), 7,80 (1H, d, J=8,67 Hz), 7,32 (1H, dd, J=2,17, 8,76 Hz), 6,75 (1H, d, J=5,27 Hz), 4,30 (1H, m), 3,84 (2H, m), 3,53 (1H, m), 3,42 (1H, m), 3,27 (3H, s), 2,89 (1H, m), 2,57 (3H, s), 2,09-1,81 (4H, m), 0,72 (2H, m), 0,59 (2H, m).

Análisis Calculado para $C_{27}H_{27}N_3O_4S_2$: C, 62,17; H, 5,22; N, 8,06; S, 12,19. Encontrado: C, 60,94; H, 5,34; N, 7,71; S, 11,71.

Ejemplo 121: ciclopropilamida del ácido 6-{(2-{[(3R)-3-hidroxipirrolidin-il]carbonil}tieno[3,2-b]piridin-7-il)oxi]-2-metilbenzo[b]tiofeno-3-carboxílico.

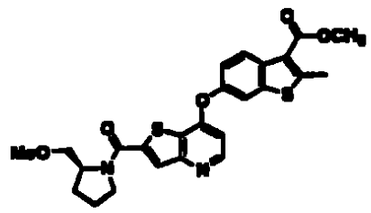


Este material se preparó por la reacción de 7-cloro-2-[(R)-3-hidroxipirrolidina-1-carbonil]tieno[3,2-b]piridina **4 a** (113 mg, 0,40 mmol) con ciclopropilamida del ácido 6-hidroxi-2-metilbenzo[b]tiofeno-3-carboxílico **8 c** (119 mg, 0,48 mmol) y Cs_2CO_3 (391

mg, 1,2 mmol) de una manera como se describe previamente para el ejemplo 1 para dar un sólido amarillo (130 mg, 66%). ^{1}H RMN (DMSO-d_6, 300 MHz) δ 8,58 (1H, d, J=5,46 Hz), 8,46 (1H, d, J=4,33 Hz), 8,06, 8,00 (1H, s), 7,96 (1H, d, J=2,26 Hz), 7,80 (1H, d, J=8,85 Hz), 7,33 (1H, dd, J=2,35, 8,76 Hz), 6,75 (1H, d, J=5,27 Hz), 5,07 (1H, m), 4,38, 4,33 (1H, s ancho), 4,02-3,92 (2H, m), 3,67-3,44 (2H, m), 2,93-2,87 (1H, m), 2,57 (3H, s), 2,08-1,79 (2H, m), 0,76-0,70 (2H, m), 0,60-0,55 (2H, m).

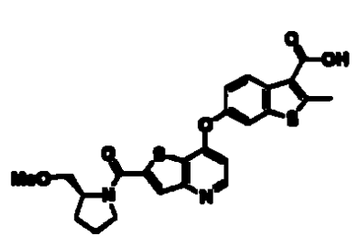
Análisis Calculado para $C_{29}H_{23}N_3O_4S$: C, 60,83; H, 4,70; N, 8,51; S, 12,99. Encontrado: C, 57,46; H, 4,80; N, 7,81; S, 13,85.

Ejemplo 122(a): 6-[(2-{[(2S)-2-(metoximetil)pirrolidin-1-il]carbonil}tieno[3,2-b]piridin-7-il)oxi]-2-metilbenzo[b]tiofeno-3-carboxilato de metilo



Este material se preparó por la reacción de 6-hidroxi-2-metilbenzo[b]tiofeno-3-carboxilato de metilo **11 a** (85,8 mg, 0,386 mmol) con 7-cloro-2-{[(2S)-2-(metoximetil)pirrolidin-1-il]carbonil}tieno[3,2-b]piridina **2 a** (100 mg, 0,322 mmol) y Cs_2CO_3 (524 mg, 1,61 mmol) de una manera similar a la descrita previamente para el ejemplo 1 para dar un sólido marrón (64 mg, 40%). ^{1}H RMN (DMSO-d_6, 300 MHz), δ 8,70 (1H, d, J=4,90 Hz), 8,51 (1H, d, J=9,04 Hz), 8,15 (1H, s), 8,14 (1H, s), 7,54 (1H, dd, J=2,17, 8,95 Hz), 6,91 (1H, d, J=5,46 Hz), 4,47-4,38 (1H, m), 4,07-3,90 (2H, m), 4,03 (3H, s), 3,72-3,50 (2H, m), 3,42, 3,39 (3H, s), 2,94 (3H, s), 2,21-1,93 (4H, m).

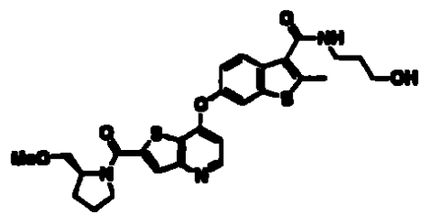
Ejemplo 122(b): ácido 6-[(2-{[(2S)-2-(metoximetil)pirrolidin-1-il]carbonil}tieno[3,2-b]piridin-7-il)oxi]-2-metilbenzo[b]tiofeno-3-carboxílico.



Este material se preparó por la hidrólisis de 6-[(2-{[(2S)-2-(metoximetil)pirrolidin-1-il]carbonil}tieno[3,2-b]piridin-7-il)oxi]-2-metilbenzo[b]tiofeno-3-

carboxilato de metilo **122 a** (63 mg, 0,13 mmol) con LiOH. H_2O (54 mg, 13 mmol) de una manera como se describe previamente para el ejemplo **11 c** para dar un sólido blanco (46 mg, 75%). ^{1}H RMN (DMSO-d_6, 300 MHz) δ 8,58 (1H, d, J=5,46 Hz), 8,44 (1H, d, J=8,85 Hz), 8,03 (1H, s), 8,00 (1H, d, J=2,26 Hz), 7,38 (1H, dd, J=2,45, 9,04 Hz), 6,78 (1H, d, J=5,84 Hz), 4,35-4,25 (1H, m), 3,93-3,76 (2H, m), 3,59-3,50 (2H, m), 3,27, 3,15 (3H, s), 2,81 (3H, s), 2,11-1,83 (4H, m).

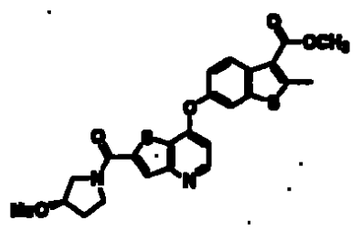
Ejemplo 122: 3-hidroxipropilamida del ácido 6-[(2-{[(2S)-2-(metoximetil)pirrolidin-1-il]carbonil}tieno[3,2-b]piridin-7-il)oxi]-2-metilbenzo[b]tiofeno-3-carboxílico.



Este material se preparó por la reacción del ácido 6-[(2-{[(2S)-2-(metoximetil)pirrolidin-1-il]carbonil}tieno[3,2-b]piridin-7-il)oxi]-2-metilbenzo[b]tiofeno-3-carboxílico **121 b** (45 mg, 0,093 mmol) con 3-amino-1-propanol (21 µl, 0,28 mmol), HBTU (53 mg, 0,14 mmol), y diisopropiletilamina (36 µl, 0,21 mmol) de una manera como se describe previamente para el ejemplo **117** para dar un sólido amarillo (44 mg, 88%). ^{1}H RMN (DMSO-d_6, 300 MHz) δ 8,58 (1H, d, J=5,27 Hz), 8,36 (1H, t, J=5,46 Hz), 8,03 (1H, s), 7,96 (1H, d, J=2.26 Hz), 7,82 (1H, d, J=8,85 Hz), 7,33 (1H, dd, J=1,70, 8,67 Hz), 6,75 (1H, d, J=5,27 Hz), 4,51 (1H, t, J=5,18 Hz), 4,30 (1H, m), 3,85 (2H, m), 3,27 (3H, s), 2,60 (3H, s), 2,09-1,83 (4H, m), 1,71 (2H, m).

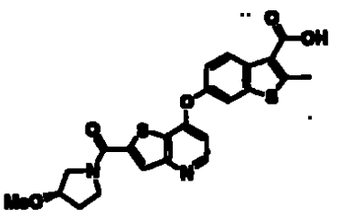
Análisis Calculado para $C_{27}H_{29}N_3O_5S_2$: C, 60,09; H, 5,42; N, 7,79; S, 11,88. Encontrado: C, 57,22; H, 5,72; N, 7,22; S, 11,16.

Ejemplo 123(a): 6-[(2-{[(3R)-3-metoxipirrolidin-1-il]carbonil}tieno[3,2-b]piridin-7-il)oxi]-2-metilbenzo[b]tiofeno-3-carboxilato de metilo.



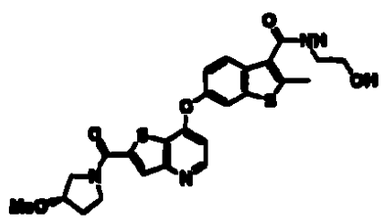
Este material se preparó por la reacción de 6-hidroxi-2-metilbenzo[b]tiofeno-3-carboxilato de metilo **11 a** (267 mg, 1,20 mmol) con 7-cloro-2-{[(3R)-3-metoxipirrolidin-1-il]carbonil}tieno[3,2-b]piridina **4 b** (297 mg, 1,00 mmol) y Cs_2CO_3 (977 mg, 3,00 mmol) de una manera similar a la descrita previamente para el ejemplo 1 para dar un sólido marrón (480 mg, 100%). ^1H RMN (DMSO-d_6, 300 MHz), δ 8,58 (1H, d, J=5,46 Hz), 8,39 (1H, d, J=8,85 Hz), 8,07 (1H, s), 8,02 (1H, d, J=2,26 Hz), 7,42 (1H, dd, J=2,35, 8,95 Hz), 6,79 (1H, d, J=5,46 Hz), 4,12-3,80 (3H, m), 3,91 (3H, s), 3,68-3,46 (2H, m), 3,27, 3,24 (3H, s), 2,82 (3H, s), 2,17-1,92 (2H, m).

Ejemplo 123(b): ácido 6-[(2-{[(3R)-3-metoxipirrolidin-1-il]carbonil}tieno[3,2-b]piridin-7-il)oxi]-2-metilbenzo[b]tiofeno-3-carboxílico.



Este material se preparó por la reacción de 6-[(2-{[(3R)-3-metoxipirrolidin-1-il]carbonil}tieno[3,2-b]piridin-7-il)oxi]-2-metilbenzo[b]tiofeno-3-carboxilato de metilo **122 a** (483 mg, 1,00 mmol) con LiOH. H_2O (420 mg, 10,0 mmol) de una manera análoga a al descrita para el ejemplo 11 c. El material en bruto se dejó fluir a través de un relleno de gel de sílice con 10% MeOH/CH_2Cl_2 y la mezcla de productos resultante se usó en la reacción subsecuente sin purificación adicional.

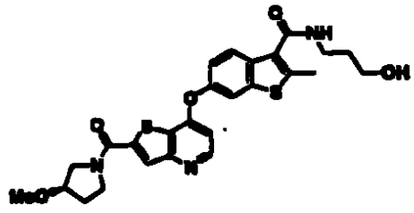
Ejemplo 123: 2-hidroxietilamida del ácido 6-[(2-{[(3R)-3-metoxipirrolidin-1-il]carbonil}tieno[3,2-b]piridin-7-il)oxi]-2-metilbenzo[b]tiofeno-3-carboxílico.



Este material se preparó por la reacción del ácido 6-[(2-{[(3R)-3-metoxipirrolidin-1-il]carbonil}tieno[3,2-b]piridin-7-il)oxi]-2-metilbenzo[b]tiofeno-3-carboxílico **123 b** (130 mg, 0,278 mmol) con etanolamina (84 µl, 1,39 mmol), N,N-diisopropiletilamina (0,15 ml, 0,83 mmol), y HBTU (263 mg, 0,694 mmol) de una manera similar a la descrita previamente para el ejemplo 117 para dar un sólido amarillo (40 mg, 28%). ^{1}H RMN (DMSO-d_6, 300 MHz) δ 8,58 (1H, d, J=5,27 Hz), 8,33 (1H, t, J=5,56 Hz), 8,06 (1H, s), 7,96 (1H, d, J=2,26 Hz), 7,86 (1H, d, J=8,85 Hz), 7,32 (1H, dd, J=2,26, 8,85 Hz), 6,75 (1H, d, J=5,46 Hz), 4,76 (1H, s ancho), 4,13-3,81 (3H, m), 3,67-3,50 (4H, m), 3,43-3,32 (2H, m), 3,27, 3,24 (3H, s), 2,61 (3H, s), 2,18-1,94 (2H, m).

Análisis Calculado para $C_{25}H_{25}N_3O_6S_2$: C, 58,69; H, 4,93; N, 8,21; S, 12,54. Encontrado: C, 56,56; H, 5,01; N, 7,62; S, 11,67.

Ejemplo 124: 3-hidroxipropilamida del ácido 6-[(2-{[(3R)-3-metoxipirrolidin-1-il]carbonil}tieno[3,2-b]piridin-7-il)oxi]-2-metilbenzo[b]tiofeno-3-carboxílico.

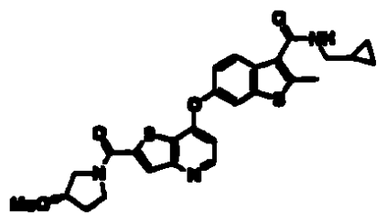


Este material se preparó por la reacción del ácido 6-[(2-{[(3R)-3-metoxipirrolidin-1-il]carbonil}tieno[3,2-b]piridin-7-il)oxi]-2-metilbenzo[b]tiofeno-3-carboxílico **123 b** (130 mg, 0,278 mmol) con 3-amino-1-propanol (106 µl, 1,39 mmol), N,N-diisopropiletilamina (0,15 ml, 0,83 mmol), y HBTU (263 mg, 0,694 mmol) de una manera similar a la descrita previamente para el ejemplo 117 para dar un sólido amarillo (34 mg, 23%). ^{1}H RMN (DMSO-d_6, 300 MHz) δ 8,58 (1H, d, J=5,27 Hz), 8,36 (1H, t, J=5,65 Hz), 8,06 (1H, s), 7,96 (1H, d, J=2,07 Hz), 7,83 (1H, d, J=8,85 Hz), 7,33 (1H, dd, J=2,07, 8,85 Hz), 6,75 (1H, d, J=5,27 Hz), 4,51 (1H, t, J=5,18 Hz), 4,13-3,82

(3H, m), 3,62 (2H, m), 3,50 (2H, m), 3,39-3,30 (2H, m), 3,27, 3,24 (3H, s), 2,60 (3H, s), 2,18-1,93 (2H, m), 1,71 (2H, quintete, J=6,6 Hz).

Análisis Calculado para $C_{28}H_{27}N_3O_5S_2$. HCl: C, 55,56; H, 5,02; N, 7,48; S, 11,41. Encontrado: C, 53,38; H, 4,96; N, 7,09; S, 10,83.

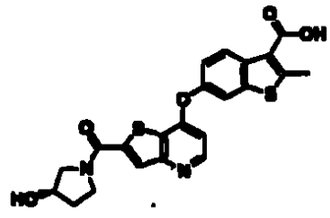
Ejemplo 125: (ciclopropilmetil)amida del ácido 6-[(2-{[(3R)-3-metoxipirrolidin-1-il]carbonil}tieno[3,2-b]piridin-7-il)oxi]-2-metilbenzo[b]tiofeno-3-carboxílico.



Este material se preparó por la reacción del ácido 6-[(2-{[(3R)-3-metoxipirrolidin-1-il]carbonil}tieno[3,2-b]piridin-7-il)oxi]-2-metilbenzo[b]tiofeno-3-carboxílico 123 b (130 mg, 0,278 mmol) con (aminometil)ciclopropano (120 µl, 1,39 mmol), diisopropiletilamina (0,15 ml, 0,83 mmol), y HBTU (263 mg, 0,694 mmol) de una manera similar a la descrita previamente para el ejemplo 117 para dar un sólido amarillo (42 mg, 24%). ^{1}H RMN (DMSO-d_6, 300 MHz) δ 8,61 (1H, d, J=5,56 Hz), 8,49 (1H, t, J=5,56 Hz), 8,06 (1H, s), 7,97 (1H, s), 7,84 (1H, d, J=8,59 Hz), 7,34 (1H, dd, J=2,27, 8,84 Hz), 6,79 (1H, d, J=5,56 Hz), 4,11-3,80 (3H, m), 3,70-3,46 (2H, m), 3,27, 3,24 (3H, s), 3,20 (2H, t, J=6,19 Hz), 2,62 (3H, s), 2,18-1,91 (2H, m), 1,08 (1H, m), 0,47 (2H, m), 0,26 (2H, m)

Análisis Calculado para $C_{27}H_{27}N_3O_4S_2$. 2(CF_2CO_2H): C, 49,66; H, 3,90; N, 5,60; S, 8,55. Encontrado: C, 49,29; H, 4,03; N, 5,64; S, 8,59

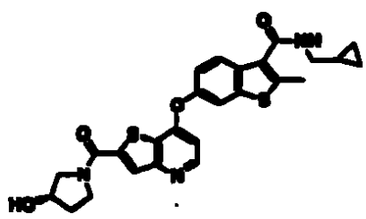
Ejemplo 126(a): ácido 6-[(2-{[(3R)-3-hidroxipirrolidin-1-il]carbonil}tieno[3,2-b]piridin-7-il)oxi]-2-metilbenzo[b]tiofeno-3-carboxílico



Este material se preparó a partir de la reacción de 6-hidroxi-2-metilbenzo[b]tiofeno-3-carboxilato de metilo 11 a (283 mg, 1,00 mmol) con 7-cloro-2-

[(R)-3-hidroxipirrolidina-1-carbonil]tieno[3,2-b]piridina 4 a y Cs_2CO_3 (977 mg, 3,00 mmol) de una manera como se describe previamente para el ejemplo 1. El producto en bruto se hizo reaccionar a continuación con LiOH. H_2O (227 mg, 5,4 mmol) de una manera similar a la descrita para el ejemplo 11 c para dar un sólido amarillo (202 mg, 45%). ^{1}H RMN (DMSO-d_6, 300 MHz) δ 8,58 (1H, d, J=5,31 Hz), 8,44 (1H, d, J=8,84 Hz), 8,14, 8,07 (1H, s), 8,00 (1H, s), 7,39 (1H, dd, J=2,40, 8,97 Hz), 6,78 (1H, d, J=5,56 Hz), 4,38, 4,33 (1H, s ancho), 4,01-3,91 (1H, m), 3,68-3,56 (2H, m), 3,49-3,22 (2H, m), 2,81 (3H, s), 2,07-1,79 (2H, m).

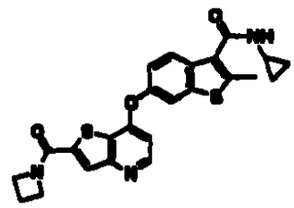
Ejemplo 126: (ciclopropilmetil)amida del ácido 6-[(2-{[(3R)-3-hidroxipirrolidin-1-il]carbonil}tieno[3,2-b]piridin-7-il)oxi]-2-metilbenzo[b]tiofeno-3-carboxílico



Este material se preparó por la reacción del ácido 6-[(2-{[(3R)-3-hidroxipirrolidin-1-il]carbonil}tieno[3,2-b]piridin-7-il)oxi]-2-metilbenzo[b]tiofeno-3-carboxílico 126 a (65 mg, 0,14 mmol) con (aminometil)ciclopropano (37 µl, 0,43 mmol), diisopropiletilamina (50 µl, 0,29 mmol), y HBTU (81 mg, 0,22 mmol) de una manera similar previamente descrita para el ejemplo 117 para dar un sólido amarillo pálido (47 mg, 46%). ^{1}H RMN (DMSO-d_6, 300 MHz) δ 8,60 (1H, d, J=5,56 Hz), 8,49 (1H, t, J=5,68 Hz), 8,07, 8,01 (1H, s), 7,97 (1H, d, J=2,27 Hz), 7,84 (1H, d, J=8,59 Hz), 7,34 (1H, dd, J=2,27, 8,84 Hz), 6,78 (1H, d, J=5,31 Hz), 4,38, 4,33 (0,5H, s ancho), 4,01-3,93 (3H, m), 3,67-3,47 (2H, m), 3,20 (2H, t, J=6,19 Hz), 2,62 (3H, s), 2,07-1,81 (2H, m), 1,08 (1H, m), 0,46 (2H, m), 0,26 (2H, m),

Análisis Calculado para $C_{28}H_{28}N_3O_4S_2$. 2(CF_2CO_2H): C, 49,72; H, 3,77; N, 5,86; S, 8,95. Encontrado: C, 49,52; H, 3,71; N, 5,83; S, 8,92.

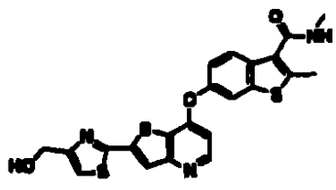
Ejemplo 127: ciclopropilamida del ácido 6-{[2-(azetidin-1-il-carbonil)tieno[3,2-b]piridin-7-il]oxi}2-metilbenzo[b]tiofeno-3-carboxílico.



Este material se preparó haciendo reaccionar 2-(azetidin-1-il-carbonil)-7-clorotieno[3,2-b]piridina 25 a (90 mg, 0,36 mmol) con ciclopropilamida del ácido 6-hidroxi-2-metilbenzo[b]tiofeno-3-carboxílico 8 c (106 mg, 0,43 mmol) y Cs_2CO_3 (349 mg, 1,07 mmol) de una manera análoga a la descrita para el ejemplo 1 para dar un sólido amarillo (106 mg, 47%). ^1H RMN (DMSO-d_6, 300 MHz), δ 8,58 (1H, d, J=5,27 Hz), 8,45 (1H, d, J=3,77 Hz), 7,95 (1H, d, J=2,07 Hz), 7,89 (1H, s), 7,80 (1H, d, J=8,67 Hz), 7,32 (1H, dd, J=2,17, 8,95 Hz), 6,75 (1H, d, J=5,46 Hz), 4,62 (2H, t, J=7,35 Hz), 4,10 (2H, t, J=7,72 Hz), 2,90 (1H, m), 2,57 (3H, s), 2,34 (2H, m), 0,73 (2H, m), 0,58 (2H, m).

Análisis Calculado para $C_{24}H_{21}N_3O_3S_2$. 1,5 (CF_3CO_2H): C, 51,10; H, 3,57; N, 6,62; S, 10,11: Encontrado: C, 51,40; H, 3,95; N, 6,85; S, 10,29.

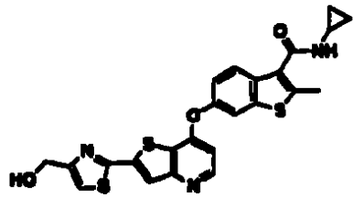
Ejemplo 128: metilamida del ácido (6-{(2-[4-(hidroximetil)-1,3-tiazol-2-il]tieno[3,2-b]piridin-7-il}oxi)-2-metilbenzo[b]tiofeno-3-carboxílico.



Este material se preparó haciendo reaccionar 7-cloro-2-[4-(hidroximetil)-1,3-tiazol-2-il]tieno[3,2-b]piridina (113 mg, 0,4 mmol) con metilamida del ácido 6-hidroxi-2-metilbenzo[b]tiofeno-3-carboxílico 1 d (111 mg, 0,5 mmol) y Cs_2CO_3 (6511 mg, 2 mmol) de una manera similar a la previamente descrita para el ejemplo 1 para dar un sólido amarillo (99 mg, 53%). ^1H RMN (DMSO-d_6, 300 MHz) δ 8,56 (1H, d, J=5,4 Hz), 8,29 (1H, q, J=4,5 Hz), 8,17 (1H, s), 7,96 (1H, d, J=2,2 Hz), 7,85 (1H, d, J=8,7 Hz), 7,63 (1H, s), 7,33 (1H, dd, J=2,2, 8,7 Hz), 6,75 (1H, d, J=5,4 Hz), 5,45 (1H, s ancho), 4,60 (2H, s), 2,83 (3H, d, J=4,5 Hz), 2,60 (3H, s).

Análisis Calculado para $C_{22}H_{17}N_3O_3S_3$. 0,3 CH_3OH. 0,2 EtOAc: C, 56,07; H, 4,03; N, 8,49; S, 19,44. Encontrado: C, 56,05; H, 4,08; N, 8,43; S, 19,47.

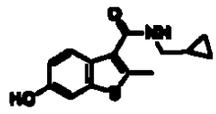
Ejemplo 129: ciclopropilamida del ácido (6-({2-[4-(hidroximetil)-1,3-tiazol-2-il]tieno[3,2-b]piridin-7-il}oxi)-2-metilbenzo[b]tiofeno-3-carboxílico.



Este material se preparó haciendo reaccionar [2-(7-clorotieno[3,2-b]piridin-2-il)-1,3-tiazol-4-il]metanol (124 mg, 0,5 mmol) con ciclopropilamida del ácido 6-hidroxi-2-metilbenzo[b]tiofeno-3-carboxílico 8 c (113 mg, 0,4 mmol) y Cs_2CO_3 (391 mg, 1,2 mmol) de una manera similar a la previamente descrita para el ejemplo 1 para dar un sólido amarillo (86 mg, 44%). ^{1}H RMN (DMSO-d_6, 300 MHz) δ 8,56 (1H, d, J=5,4 Hz), 8,46 (1H, d, J=4,3 Hz), 8,17 (1H, s), 7,96 (1H, d, J=2,2 Hz), 7,81 (1H, d, J=8,8 Hz), 7,63 (1H, s), 7,34 (1H, dd, J=2,2 Hz, 8,8 Hz), 6,75 (1H, d, J=5,4 Hz), 4,60 (2H, d, J=4,9 Hz), 2,96-2,85 (1H, m), 2,57 (3H, s), 0,78-0,67 (2H, m), 0,62-0,53 (2H, m).

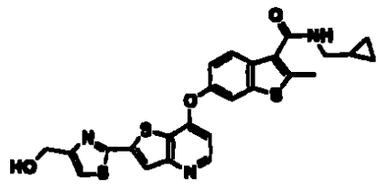
Análisis Calculado para $C_{24}H_{19}N_3O_3S_3$. 1,2 H_2O: C, 55,94; H, 4,19; N, 8,16; S, 18,67: Encontrado: C, 55,85; H, 4,19; N, 7,95; S, 19,01.

Ejemplo 130(a): (ciclopropilmetil)amina del ácido 6-hidroxi-2-metil-1-benzo[b]tiofeno-3-carboxílico.



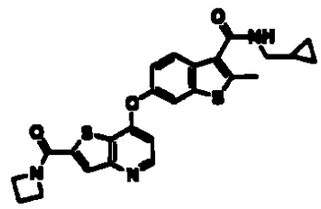
Este material se preparó por la reacción de acetato de 3-(clorocarbonil)-2-metil-1-benzotien-6-ilo en bruto (650 mg, 2,42 mmol (teórico)) con (aminometil)ciclopropano (1,2 ml, 13,8 mmol) y N,N-diisopropiletilamina (0,5 ml, 2,9 mmol) de una manera similar a la previamente descrita para el ejemplo 8 c. El producto en bruto se purificó por cromatografía en gel de sílice (25-50% EtOAc/hexanos) para dar un vidrio amarillo (475 mg, 72%). ^{1}H RMN δ 9,56 (1H, s), 8,31 (1H, t, J=5,56 Hz), 7,52 (1H, d, J=8,67 Hz), 7,18 (1H, d, J=2,07 Hz), 6,84 (1H, dd, J=2,26, 8,67 Hz), 3,16 (2H, m), 2,51 (3H, s), 1,05 (1H, m), 0,44 (2H, m), 0,24 (2H, m).

Ejemplo 130: (ciclopropilmetil)amida del ácido (6-({2-[4-(hidroximetil)-1,3-tiazol-2-il]tieno[3,2-b]piridin-7-il}oxi)-2-metilbenzo[b]tiofeno-3-carboxílico.



Este material se preparó haciendo reaccionar [2-(7-clorotieno[3,2-b]piridin-2-il)-1,3-tiazol-4-il]metanol (85 mg, 0,30 mmol) con (ciclopropilmetil)amida del ácido 6-hidroxi-2-metilbenzo[b]tiofeno-3-carboxílico 130 a (94 mg, 0,36 mmol) y Cs_2CO_3 (195 mg, 0,60 mmol) de una manera similar a la previamente descrita para el ejemplo 1 para dar un sólido amarillo (57 mg, 25%). ^{1}H RMN (DMSO-d_6, 300 MHz) δ 8,56 (1H, d, J=5,46 Hz), 8,49 (1H, t, J=5,75 Hz), 8,17 (1H, s), 7,98 (1H, d, J=2,26 Hz), 7,84 (1H, d, J=8,67 Hz), 7,65 (1H, s), 7,36 (1H, dd, J=2,35, 8,76 Hz), 6,80 (1H, d, J=5,46 Hz), 4,60 (2H, s), 3,20 (2H, t, J=6,22 Hz), 2,62 (3H, s), 1,07 (1H, m), 0,47 (2H, m), 0,26 (2H, m). Análisis Calculado para $C_{25}H_{21}N_3O_3S_3$: 2(CF_3CO_2H): C, 47,34; H, 3,15; N, 5,71; S, 13,08. Encontrado: C, 46,72; H, 3,15; N, 5,71; S, 12,92.

Ejemplo 131: (ciclopropilmetil)amida del ácido 6-{[2-(azetidin-1-il-carbonil)tieno[3,2-b]piridin-7-il]oxi}-2-metilbenzo[b]tiofeno-3-carboxílico.

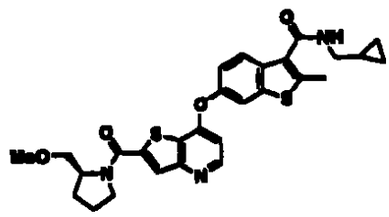


Este material se preparó haciendo reaccionar 2-(azetidin-1-il-carbonil)-7-clorotieno[3,2-b]piridina 25 a (88 mg, 0,35 mmol) con (ciclopropilmetil)amida del ácido 6-hidroxi-2-metil-1-benzo[b]tiofeno-3-carboxílico 130 a (110 mg, 0,42 mmol) y Cs_2CO_3 (228 mg, 0,70 mmol) de una manera similar a la previamente descrita para el ejemplo 1 para dar un sólido amarillo (90 mg, 54%). ^{1}H RMN (DMSO-d_6, 300 MHz) δ 8,58 (1H, d, J=5,46 Hz), 8,49 (1H, t, J=5,46 Hz), 7,96 (1H, d, J=2,26 Hz), 7,89 (1H, s), 7,83 (1H, d, J=8,85 Hz), 7,33 (1H, dd, J=2,35, 8,76 Hz), 6,75 (1H, d, J=5,46 Hz), 4,62 (2H, t,

J=7,72 Hz), 4,10 (2H, t, J=7,82 Hz), 3,20 (2H, t, J=6,31 Hz), 2,62 (3H, s), 2,35 (2H, m), 1,07 (1H, m), 0,46 (2H, m), 0,26 (2H, m).

Análisis Calculado para $C_{25}H_{23}N_3O_3S_2$: C, 62,87; H, 4,85; N, 8,80; S, 13,43. Encontrado: C, 62,58; H, 4,90; N, 8,66; S, 13,33.

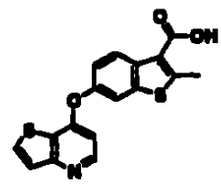
Ejemplo 132: (ciclopropilmetil)amida del ácido 6-[(2-{[(2S)-2-(metoximetil)pirrolidin-1-il]carbonil}tieno[3,2-b]piridin-7-il)oxi]-2-metilbenzo[b]tiofeno-3-carboxílico.



Este material se preparó a partir de 7-cloro-2-{[(3R)-3-metoxipirrolidin-1-il]carbonil}tieno[3,2-b]piridina 2 a (93 mg, 0,30 mmol), (ciclopropilmetil)amida del ácido 6-hidroxi-2-metilbenzo[b]tiofeno-3-carboxílico 130 a (94 mg, 0,36 mmol) y Cs_2CO_3 (195 mg, 0,60 mmol) de una manera similar a la previamente descrita para el ejemplo 1 para dar un sólido amarillo (33 mg, 18%). ^{1}H RMN (DMSO-d_6, 300 MHz) δ 8,64 (1H, d, J=5,46 Hz), 8,51 (1H, t, J=5,65 Hz), 8,05 (1H, s), 7,99 (1H, d, J=2,26 Hz), 7,85 (1H, d, J=8,85 Hz), 7,36 (1H, dd, J=2,26, 8,85 Hz), 6,83 (1H, d, J=5,46 Hz), 4,30 (1H, m), 3,85 (2H, m), 3,53 (1H, m), 3,42 (1H, m), 3,27 (3H, s), 3,20 (2H, m), 2,63 (3H, s), 1,97 (2H, m), 1,90 (2H, m), 1,07 (1H, m), 0,46 (2H, m), 0,26 (2H, m).

Análisis Calculado para $C_{28}H_{29}N_3O_4S_2$. 1,5 (HCl): C, 56,96; H, 5,21; N, 7,12; S, 10,86. Encontrado: C, 56,05; H, 5,44; N, 7,09; S, 10,68.

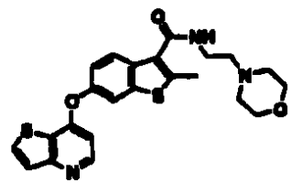
Ejemplo 133(a): ácido 2-metil-6-(tieno[3,2-b]piridin-7-iloxi)benzo[3,2-b]tiofeno-3-carboxílico.



Este material se preparó haciendo reaccionar 7-clorotieno[3,2-b]piridina (170 mg, 1,0 mmol) con 6-hidroxi-2-metilbenzo[b]tiofeno-3-carboxilato de metilo 11 a (267 mg, 1,2 mmol) y Cs_2CO_3 (488 mg, 1,5 mmol) de una manera similar a la previamente

descrita para el ejemplo 1. La cromatografía en gel de silice (10% MeOH/CH_2Cl_2) proporcionó el compuesto del título en forma de aceite marrón viscoso (39 mg, 27%). ^{1}H RMN (DMSO-d_6, 300 MHz) δ 8,47 (1H, d, J=5,27 Hz), 8,41 (1H, d, J=8,85 Hz), 8,11 (1H, d, J=5,46 Hz), 7,93 (1H, d, J=2,07 Hz), 7,55 (1H, d, J=7,55 Hz), 7,32 (1H, dd, J=2,26, 8,85 Hz); 6,64 (1H, d, J=5,27 Hz), 2,77 (3H, s).

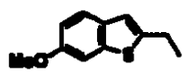
Ejemplo 133: (2-morfolin-4-il)etilamida del ácido 2-metil-6-(tieno[3,2-b]piridin-7-iloxi)benzo[b]tiofeno-3-carboxílico.



Este material se preparó a partir de la reacción del ácido 2-metil-6-(tieno[3,2-b]piridin-7-iloxi)benzo[b]tiofeno-3-carboxílico 133 a (93 mg, 0,27 mmol) con 4-(2-aminoetil)morfolina (0,12 ml, 0,82 mmol), diisopropiletilamina (0,10 ml, 0,55 mmol), y HBTU (155 mg, 0,41 mmol) de una manera similar a la previamente descrita para el ejemplo 117 para dar un sólido blanco cristalino (35 mg, 28%). ^{1}H RMN (DMSO-d_6, 300 MHz) δ 8,51 (1H, d, J=5,27 Hz), 8,28 (1H, t, J=5,37 Hz), 8,15 (1H, d, J=5,46 Hz), 7,94 (1H, dd, J=2,26 Hz), 7,94 (1H, d, J=8,48 Hz), 7,59 (1H, d, J=5,46 Hz), 7,33 (1H, dd, J=2,26, 8,85 Hz), 6,64 (1H, d, J=5,27 Hz), 3,58 (4H, t, J=4,33 Hz), 3,42 (2H, q, J=6,09 Hz), 3,32 (2H, m), 2,63 (3H, s), 2,52-2,39 (4H, m).

Análisis Calculado para $C_{23}H_{23}N_3O_3S_2$: C, 60,90; H, 5,11; N, 9,26; S, 14,4. Encontrado: C, 61,12; H, 5,16; N, 9,16; S, 14,02.

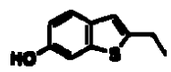
Ejemplo 134(a): 2-etil-6-hidroxibenzo[b]tiofeno.



Este material se preparó a partir de 6-metoxibenzo[b]tiofeno 1 a (2,63 g, 16 mmol) por tratamiento con n-BuLi y yoduro de etilo (7,80 g, 50 mmol) de una manera como se describe previamente para el ejemplo 1 b para dar un sólido blanco (2,78 g, 90%). ^{1}H RMN (DMSO-d_6) δ 7,58 (1H, d, J=8,7 Hz), 7,44 (1H, d, J=2,3 Hz), 7,02 (1H, s), 6,92 (1H, dd, J=2,3, 8,7 Hz), 2,84 (2H, q, J=7,5 Hz), 1,27 (3H, t, J=7,5 Hz).

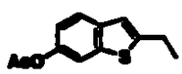
Análisis Calculado para $C_{11}H_{12}OS$: C, 68,71; H, 6.29; S, 16,68. Encontrado: C, 68,50; H, 6,21; S, 16,93.

Ejemplo 134(b): 2-etil-6-hidroxibenzo[b]tiofeno



Este material se preparó a partir de 2-etil-6-metoxibenzo[b]tiofeno 134 a (2,30 g, 12 mmol) por tratamiento con BBr_3 de una manera como se describe previamente para el ejemplo 1 d para dar un sólido blanco (1,75 g, 82%). ^{1}H RMN (DMSO-d_6) δ 9,43 (1H, s), 7,48 (1H, d, J=8,5 Hz), 7,16 (1H, d, J=2,2 Hz), 6,95 (1H, s), 6,78 (1H, dd, J=2,2, 8,5 Hz), 2,81 (2H, q, J=7,5 Hz), 1,26 (3H, t, J=7,5 Hz).

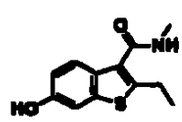
Ejemplo 134(c): 6-acetoxi-2-etilbenzo[b]tiofeno.



Este material se preparó por tratamiento de 2-etil-6-hidroxibenzo[b]tiofeno 134 b (1,60 g, 9 mmol) con cloruro de acetilo (1 ml, 1,10 g, 14 mmol) y Et_3N (2 ml, 1,45 g, 14 mmol) de una manera como se describe previamente para el ejemplo 8 b para dar un sólido blanco (2,93 g, 93%). ^{1}H RMN (DMSO-d_6) δ 7,72 (1H, d, J=8,5 Hz), 7,68 (1H, d, J=2,2 Hz), 7,15 (1H, s), 7,08 (1H, dd, J=2,2, 8,5 Hz), 2,89 (2H, q, J=7,5 Hz), 2,28 (3H, s), 1,29 (3H, t, J=7,5 Hz),

Análisis Calculado para $C_{12}H_{12}O_2S$: C, 65,43; H, 5,49; S, 14,56. Encontrado: C, 65,64; H, 5,61; S, 14,49.

Ejemplo 134(d): metilamida del ácido 2-etil-6-hidroxibenzo[b]tiofeno-3-carboxílico

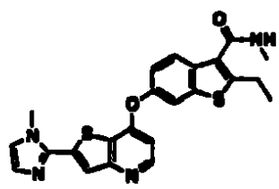


Este material se preparó a partir de 6-acetoxi-2-etilbenzo[b]tiofeno 134 c (1,77 g, 8 mmol) por acilación con cloruro de oxalilo en presencia de $AlCl_3$ seguido de tratamiento con metilamina de una manera como se describe previamente para el

ejemplo 1 d para dar un sólido amarillo pálido (1,55 g, 82%). ^{1}H RMN (DMSO-d_6) δ 9.57 (1H. s), 8,15 (1H, q, J=4,5 Hz), 7,48 (1H, d, J=8,6 Hz), 7,19 (1H, d, J=2,3 Hz), 6,84 (1H, dd, J=2,3, 8,6 Hz), 2,90 (2H, q, J=7,5 Hz), 2,78 (3H, d, J=4,5 Hz), 1,22 (3H, t, J=7,5 Hz).

Análisis Calculado para $C_{12}H_{13}NO_2S$: C, 61,25; H, 5,57; N, 5,95; S, 13,63. Encontrado: C, 61,11; H, 5,68; N, 5,88; S, 13,41.

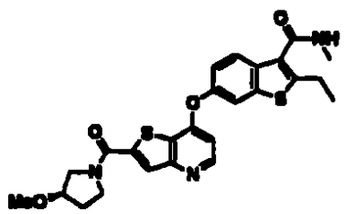
Ejemplo 134: metilamida del ácido 2-etil-6-{[2-(1-metil-1H-imidazol-2-il)tieno[3,2-b]piridin-7-il]oxi}benzo[b]tiofeno-3-carboxílico.



Este material se preparó haciendo reaccionar 7-cloro-2-(1-metil-1H-imidazol-2-il)tieno[3,2-b]piridina 1 e (87 mg, 0,35 mmol) con metilamida del ácido 2-etil-6-hidroxibenzo[b]tiofeno-3-carboxílico 134 d (99 mg, 0,42 mmol) y Cs_2CO_3 (342 mg, 1,05 mmol) de una manera análoga a la descrita para el ejemplo 1 para dar un sólido amarillo (89 mg, 37%). ^{1}H RMN (DMSO-d_6, 300 MHz) δ 8,52 (1H, d, J=5,56 Hz), 8,33 (1H, m), 7,98 (1H, d, J=2,27 Hz), 7,89 (1H, s), 7,81 (1H, d, J=8,59 Hz), 7,40 (1H, s), 7,33 (1H, dd, J=2,27, 8,84 Hz), 7,02 (1H, s), 6,97 (1H, d, J=5,31 Hz), 3,98 (3H, s), 3,00 (2H, q, J=7,58 Hz), 2,83 (3H, d, J=4,80 Hz), 1,28 (3H, t, J=7,58 Hz).

Análisis Calculado para $C_{23}H_{20}N_4O_2S_2$. 2(CF_2CO_2H): C, 47,93; H, 3,28; N, 8,28; S, 9,48. Encontrado: C, 47,63; H, 3,24; N, 8,14; S, 9,29.

Ejemplo 135: metilamida del ácido 2-etil-6-[(2-{[(3R)-3-metoxipirrolidin-1-



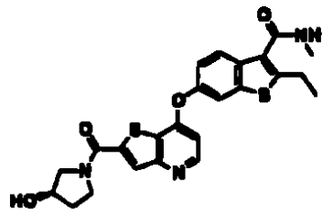
il]carbonil}tieno[3,2-b]piridin-7-il)oxi]benzo[b]tiofeno-3-carboxílico.

Este material se preparó haciendo reaccionar 7-cloro-2-{[(3R)-3-metoxipirrolidin-1-il]carbonil}tieno[3,2-b]piridina 4 b (74 mg, 0,25 mmol) con metilamida del ácido 2-etil-6-hidroxibenzo[b]tiofeno-3-carboxílico 134 d (71 mg, 0,30 mmol) y

Cs_2CO_3 (244 mg, 0,75 mmol) de una manera análoga a la descrita para el ejemplo 1 para dar un sólido amarillo (34 mg, 19%). ^1H RMN (DMSO-d_6, 300 MHz), δ 8,59 (1H, d, J=5,31 Hz), 8,33 (1H, q, J=4,46 Hz), 8,06 (1H, s), 7,99 (1H, d, J=2,27 Hz), 7,81 (1H, d, J=8,84 Hz), 7,34 (1H, dd, J=2,27, 8,84 Hz), 6,76 (1H, d, J=5,56 Hz), 4,08-3,83 (3H, m), 3,67-3,48 (2H, m), 3,27, 3,24 (3H, s), 3,00 (2H, t, J=7,49 Hz), 2,83 (3H, d, J=4,55 Hz), 2,16-1,95 (2H, m), 1,28 (3H, t, J=7,58 Hz).

Análisis Calculado para $C_{25}H_{25}N_3O_4S_2$. 1,25 (CH_3CO_2H): C, 51,76; H, 4,15; N, 6,58; S, 10,05. Encontrado: C, 51,24; H, 4,23; N, 6,55; S, 10,05.

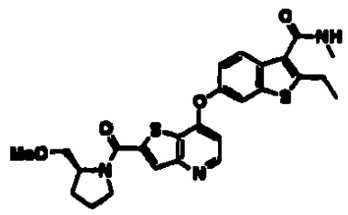
Ejemplo 136: metilamida del ácido 2-etil-6-[(2-{[(3R)-3-hidroxipirrolidin-1-il]carbonil}tieno[3,2-b]piridin-7-il)oxi]benzo[b]tiofeno-3-carboxílico.



Este material se preparó haciendo reaccionar 7-cloro-2-{[(3R)-3-hidroxipirrolidin-1-il]carbonil}tieno[3,2-b]piridina 4 a (71 mg, 0,25 mmol) con metilamida del ácido 2-etil-6-hidroxibenzo[b]tiofeno-3-carboxílico 134 d (71 mg, 0,30 mmol) y Cs_2CO_3 (244 mg, 0,75 mmol) de una manera análoga a la descrita para el ejemplo 1 para dar un sólido marrón claro (76 mg, 63%). ^1H RMN (DMSO-d_6, 300 MHz), δ 8,58 (1H, d, J=5,56 Hz), 8,32 (1H, q, J=4,38 Hz), 8,07, 8,00 (1H, s), 7,98 (1H, d, J=2,27 Hz), 7,80 (1H, d, J=8,84 Hz), 7,33 (1H, dd, J=2,27, 8,59 Hz), 6,75 (1H, d, J=5,31 Hz), 4,38, 4,33 (1H, s ancho), 4,01-3,93 (2H, m), 3,67-3,45 (3H, m), 3,00 (2H, t, J=7,49 Hz), 2,83 (3H, d, J=4,55 Hz), 2,06-1,80 (2H, m), 1,28 (3H, t, J=7,58 Hz).

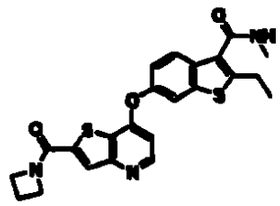
Análisis Calculado para $C_{24}H_{23}N_3O_4S_2$: C, 59,86; H, 4,81; N, 8,73; S, 13,32. Encontrado: C, 58,63; H, 4,78; N, 8,46; S, 13,33.

Ejemplo 137: metilamida del ácido 2-etil-6-{(2-{[(2S)-2-(metoximetil)pirrolidin-1-il]carbonil}tieno[3,2-b]piridin-7-il)oxi]benzo[b]tiofeno-3-carboxílico.



Este material se preparó haciendo reaccionar 7-cloro-2-{[(3R)-3-metoxipirrolidin-1-il]carbonil}tieno[3,2-b]piridina 2 a (155 mg, 0,5 mmol) con metilamida del ácido 2-etil-6-hidroxibenzo[b]tiofeno-3-carboxílico 134 d (141 mg, 0,60 mmol) y Cs_2CO_3 (488 mg, 1,5 mmol) de una manera análoga a la descrita para el ejemplo 1 para dar un sólido amarillo (25 mg, 10%). ^{1}H RMN (DMSO-d_6, 300 MHz), δ 8,59 (1H, d, J=5,56 Hz), 8,33 (1H, d, J=4,55 Hz), 8,03 (1H, s), 7,99 (1H, d, J=2,02 Hz), 7,81 (1H, d, J=8,59 Hz), 7,33 (1H, dd, J=2,27, 8,84 Hz), 6,77 (1H, d, J=5,56 Hz), 4,31 (1H, s ancho), 3,90-3,81 (2H, m), 3,37-3,15 (2H, s), 3,37 (3H, s), 3,00 (2H, q, J=7,41 Hz), 2,83 (3H, d, J=4,55 Hz), 2,09-1,84 (4H, m), 1,28 (3H, t, J=7,58 Hz).
Análisis Calculado para $C_{28}H_{27}N_3O_4S_2$. 1,75 (HCl): C, 54,46; H, 5,05; N, 7,33; S, 11,18. Encontrado: C, 54,50; H, 5,19; N, 7,30; S, 11,22.

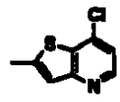
Ejemplo 138: metilamida del ácido 6-{[2-(azetidin-1-ilcarbonil)tieno[3,2-b]piridin-7-il]oxi}-2-etilbenzo[b]tiofeno-3-carboxílico.



Este material se preparó haciendo reaccionar 2-(azetidin-1-ilcarbonil)-7-clorotieno[3,2-b]piridina 25 a (97 mg, 0,40 mmol) con metilamida del ácido 2-etil-6-hidroxibenzo[b]tiofeno-3-carboxílico 134 d (113 mg, 0,48 mmol) y Cs_2CO_3 (391 mg, 1,2 mmol) de una manera similar a la descrita para el ejemplo 1 para dar un sólido amarillo (120 mg, 52%). ^{1}H RMN (DMSO-d_6, 300 MHz), δ 8,59 (1H, d, J=5,67 Hz), 8,31 (1H, m), 7,98 (1H, d, J=2,27 Hz), 7,89 (1H, s), 7,81 (1H, d, J=8,69 Hz), 7,33 (1H, dd, J=1,51,

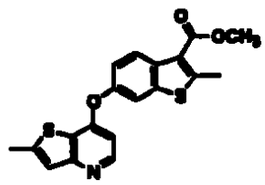
8,69 Hz), 6,76 (1H, d, J=5,29 Hz), 4,62 (1H, t, J=7,37 Hz), 4,11 (2H, t, J=7,37 Hz), 3,00 (2H, q, J=7,55 Hz), 2,83 (3H, d, J=4,53 Hz), 2,35 (2H, m), 1,28 (3H, t, J=7,55 Hz).
Análisis Calculado para $C_{24}H_{21}N_3O_3S_2$. CF_3CO_2H: C, 53,09; H, 3,92; N, 7,43; S, 11,34. Encontrado: C, 52,58; H, 3,80; N, 7,26; S, 11,12.

Ejemplo 139(a): 7-cloro-2-metiltieno[3,2-b]piridina



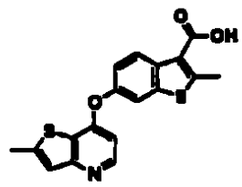
Este material se preparó a partir de 7-clorotieno[3,2-b]piridina (1,69 g, 10 mmol) por tratamiento con n-BuLi y yodometano (2 ml, 4,56 g, 32 mmol) de una manera como se describe previamente para el ejemplo 1 b para dar un sólido amarillo pálido de bajo punto de fusión (1,48 g, 81%). ^{1}H RMN (DMSO-d_6): δ 8,56 (1H, d, J=5,1 Hz), 7,48 (1H, d, J=5,1 Hz), 7,38 (1H, s), 2,65 (3H, s),
Análisis Calculado para C_8H_6NSCl: C, 52,32; H, 3,29; N, 7,63; S 17,46; Cl, 19,30. Encontrado: C, 52,13; H, 3,36; N, 7,86; S, 17,44; Cl, 19,20.

Ejemplo 139(b): 2-metil-6-(2-metiltieno[3,2-b]piridin-7-iloxi)-benzo[b]tiofeno-3-carboxilato de metilo.



Este material se preparó por la reacción de 7-cloro-2-metiltieno[3,2-b]piridina 139 a (1,29 g, 7 mmol) con 6-hidroxi-2-metilbenzo[b]tiofeno-3-carboxilato de metilo 11 a (2,18 g, 9,8 mmol) y Cs_2CO_3 (6,51 g, 20 mmol) de una manera como se describe previamente para el ejemplo 1 para dar un sólido amarillo (1,91 g, 74%). ^{1}H RMN ($CDCl_3$) δ 8,43 (1H, d, J=5,4 Hz), 8,37 (1H, d, J=9,0 Hz), 7,97 (1H, d, J=2,2 Hz), 7,37 (1H, dd, J=2,2, 9,0 Hz), 7,30 (1H, s), 6,63 (1H, d, J=5,4 Hz), 3,91 (3H, s), 2,81 (3H, s), 2,61 (3H, s).
Análisis Calculado para $C_{19}H_{15}N_3O_2S$. 0,1 CH_2Cl_2: C, 60,70; H, 4,05; N, 3,71; S; 16,97. Encontrado: C, 60,71; H, 4,17; N, 3,60; S, 17,11.

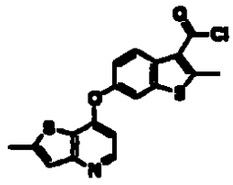
Ejemplo 139(c): ácido 2-metil-6-(2-metiltieno[3,2-b]piridin-7-iloxi)benzo[b]tiofeno-3-carboxílico.



Este material se preparó a partir de 2-metil-6-(2-metiltieno[3,2-b]piridin-7-iloxi)benzo[b]tiofeno-3-carboxilato de metilo 139 b (1,80 g, 4,8 mmol) de una manera como se describe previamente para el ejemplo 11 c para dar un sólido amarillo (1,41 g, 82%). ^{1}H RMN (DMSO-d_6) δ 13.08 (1H, s ancho), 8,45 (1H, d, J=5,5 Hz), 8,43 (1H, d, J=8,8 Hz), 7,96 (1H, d, J=2,4 Hz), 7,35 (1H, dd, J=2,4, 8,8 Hz), 7,32 (1H, s), 6,66 (1H, d, J=5,5 Hz), 2,81 (3H, s), 2,62 (3H, s).

Análisis Calculado para $C_{18}H_{13}NO_3S_2$. 0,5 H_2O: C, 59,32; H, 3,87; N, 3,84; S, 17,60. Encontrado: C, 59,31; H, 3,74; N, 3,79; S, 17,49.

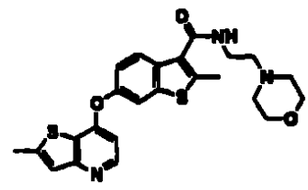
Ejemplo 139(d): cloruro de 2-metil-6-(2-metiltieno[3,2-b]piridin-7-iloxi)benzo[b]tiofeno-3-carbonilo.



Este material se preparó a partir de ácido 2-metil-6-(2-metiltieno[3,2-b]piridin-7-iloxi)benzo[b]tiofeno-3-carboxílico 139 c (1,34 g, 3,8 mmol) por tratamiento con cloruro de tionilo (1ml, 1,63 g, 13,7 mmol) de una manera como se describe previamente para el ejemplo 11 para dar un sólido naranja (1,37 g, 97%). ^{1}H RMN (DMSO-d_6) δ 8,74 (1H, d, J=6,6 Hz), 8,50 (1H, d, J=9,0 Hz), 8,12 (1H, d, J=2,4 Hz), 7,60 (1H, s), 7,48 (1H, dd, J=2,4, 9,0 Hz), 7,05 (1H, d, J=6,6 Hz), 2,83 (3H, s), 2,75 (3H, s).

Análisis Calculado para $C_{18}H_{12}NOS_2Cl$. 0,9 HCl: C, 50,69; H, 3,57; N, 3,28; S, 15,04; Cl, 15,79. Encontrado: C, 50,64; H, 3,56; N, 3,22; S, 14,98; Cl, 15,65.

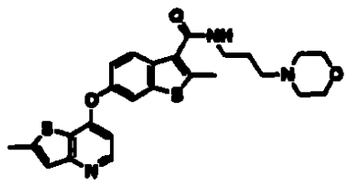
Ejemplo 139: (2-morfolin-4-il-etil)amida del ácido 2-metil-6-(2-metiltieno[3,2-b]piridin-7-iloxi)benzo[b]tiofeno-3-carboxílico.



Este material se preparó a partir de cloruro de 2-metil-6-(2-metiltieno[3,2-b]piridin-7-iloxi)benzo[b]tiofeno-3-carbonilo 139 d (112 mg, 0,3 mmol) y 2-(morfolin-4-il)etilamina (157 mg, 1,2 mmol) de una manera similar a la descrita para el ejemplo 108 para dar un sólido amarillo (105 mg, 75%). ^{1}H RMN (DMSO-d_6) δ 8,44 (1H, d, J=5,5 Hz), 8,29 (1H, t, J=4,8 Hz), 7,94 (1H, d, J=8,7 Hz), 7,92 (1H, d, J=2,3 Hz), 7,31 (1H, s), 7,30 (1H, dd, J=2,3, 8,7 Hz), 6,60 (1H, d, J=5,5 Hz), 3,60 (4H, t, J=4,2 Hz), 3,45 (2H, dt, J=4,8, 6,2 Hz), 2,64 (3H, s), 2,62 (3H, s), 2,55-2,41 (6H, m).

Análisis Calculado para $C_{24}H_{25}N_3O_3S_2$: C. 61,64; H, 5,39; N, 8,99; S, 13,71. Encontrado: C, 61,34; H, 5,49; N, 8,90; S, 13,68.

Ejemplo 140: (3-morfolin-4-il-propil)amida del ácido 2-metil-6-(2-metiltieno[3,2-b]piridin-7-iloxi)benzo[b]tiofeno-3-carboxílico.



Este material se preparó a partir de cloruro de 2-metil-6-(2-metiltieno[3,2-b]piridin-7-iloxi)benzo[b]tiofeno-3-carbonilo 139 d (112 mg, 0,3 mmol) y 3-(morfolin-4-il)propilamina (175 mg, 1,2 mmol) de una manera similar a la descrita para el ejemplo 108 para dar un sólido amarillo (64 mg, 44%). ^{1}H RMN (DMSO-d_6) δ 8,43 (1H, d, J=5,5 Hz), 8,38 (1H, t, J=5,3 Hz), 7,91 (1H, d, J=2,3 Hz), 7,81 (1H, d, J=8,6 Hz), 7,30 (1H, s), 7,28 (1H, dd, J=2,3, 8,6 Hz), 6,59 (1H, d, J=5,5 Hz), 3,56 (4H, t, J=4,3 Hz), 3,33 (2H, dt, J=5,3, 6,8 Hz), 2,61 (3H, s), 2,60 (3H, s), 2,42-2,31 (6H, m), 1,72 (2H, tt, J=6,8, 7,0 Hz).

Análisis Calculado para $C_{25}H_{27}N_3O_3S_2$. 0,1 CH_2Cl_2: C. 61,51; H, 5,59; N, 8,57; S, 13,08. Encontrado: C, 61,53; H, 5,55; N, 8,25; S, 13,08.

Los compuestos ejemplares descritos anteriormente se pueden ensayar para ver su actividad usando los ensayos descritos a continuación.

ENSAYO BIOLOGICO; ENSAYOS ENZIMATICOS

La estimulación de la proliferación celular por los factores de crecimiento tales como VEFG, FGF, y otros depende de su inducción de la autofosforilación de cada una de sus respectivas tirosina quinasas del receptor. Por lo tanto, la capacidad de un inhibidor de la proteína quinasa para bloquear la proliferación celular inducida por estos factores de crecimiento está directamente correlacionada con su capacidad de bloquear la autofosforilación del receptor. Para medir la actividad de inhibición de la proteína quinasa de los compuestos, se idearon las siguientes construcciones.

Construcción de VEGF-R2 para ensayo:

Esta construcción determina la capacidad de un compuesto de ensayo para inhibir la actividad de la tirosina quinasa. Una construcción (VEGF-R2Δ50) del dominio citosólico del receptor 2 del factor de crecimiento endotelial vascular humano (VEGF-R2) que carece de los 50 restos centrales de los 68 restos del dominio de inserción de la quinasa se expresó en un sistema celular de baculovirus/insecto. De los 1356 restos de la longitud total del VEGF-R2, el VEGF-R2Δ50 contiene los restos 806-939 y 990-1171, y también una mutación puntual (E990V) dentro del dominio de inserción de la quinasa con relación al VEGF-R2 de tipo natural. La autofosforilación de la construcción purificada se realizó por incubación de la enzima a una concentración 4 μM en presencia de ATP 3 mM y $MgCl_2$ 40 mM en HEPES 100 mM, pH 7,5, que contiene glicerol al 5% y DTT 5 mM, a 4°C durante 2 h. Después de la autofosforilación, se ha mostrado que esta construcción posee actividad catalítica esencialmente equivalente a la construcción del dominio de quinasa autofosforilada de tipo natural. Véase Parast et al., Biochemistry, 37, 16788-16801 (1998).

Construcción de FGF-R1 para ensayo:

El dominio de quinasa intracelular de FGF-R1 humano se expresó usando el sistema del vector de expresión de baculovirus comenzando en el resto de metionina endógena 456 hasta el glutamato 766, según el sistema de numeración de restos de Mohammadi et al., Mol. Cell. Biol., 16, 977-989 (1996). Además, la construcción tiene también las siguientes 3 substituciones de aminoácidos: L457V, C488A, y C584S.

Ensayo de VEGF-R2

Ensayo Espectrofotométrico acoplado (FLVK-P)

La producción de ADP a partir de ATP que acompaña a la transferencia de fosforilo se acopló a la oxidación de NADH usando fosfoenolpiruvato (PEP) y un sistema que tiene piruvato quinasa (PK) y deshidrogenasa láctica (LDH). La oxidación de NADH se controló siguiendo la disminución de absorbancia a 340 nm (e_{340}= 6,22 cm^{-1} mM^{-1}) usando un espectrofotómetro Beckman DU 650. Las condiciones de ensayo para el VEGF-R2Δ50 fosforilado (indicado como FLVK-P en las tablas a continuación) fueron las siguientes: PEP 1 mM; NADH 250 μM; 50 unidades de LDH/ml; 20 unidades de PK/ml; DTT 5 mM; poli(E_4Y_1) 5,1 mM; ATP 1 mM; y $MgCl_2$ 25 mM en HEPES 200 mM, pH 7,5. Las condiciones de ensayo para el VEGF-R2Δ50 sin fosforilar (indicado como FLVK en las tablas) fueron las siguientes: PEP 1 mM; NADH 250 μM; 50 unidades de LDH/ml; 20 unidades de PK/ml; DTT 5 mM; poli(E_4Y_1) 20 mM; ATP 3 Mm; y $MgCl_2$ 60 mM y $MnCl_2$ 2 mM en HEPES 200 mM, pH 7,5: Los ensayos se iniciaron con 5 a 40 nM de enzima. Los valores K_i se determinaron midiendo la actividad de la enzima en presencia de concentraciones variables de compuestos de ensayo. El porcentaje de inhibición a 50 nm (% de inhibición @ 50 nm) se determinó por análisis de regresión lineal por mínimos cuadrados de la absorbancia en función del tiempo. Las inhibiciones de unión se ajustaron a la ecuación descrita por Morrison. Los datos se analizaron usando el software Enzyme Kinetic y Kaleidagraph.

Ensayo de FGF-R

El ensayo espectrofotométrico se llevó a cabo como se describe anteriormente para VEGF-R2 excepto por los siguientes cambios en la concentración: FGF-R= 50 nM, ATP= 2 mM, y poli(E_4Y_1)= 15 mM.

Ensayo de la proliferación de HUVEC+VEGF

Este ensayo determina la capacidad de un compuesto de ensayo para inhibir la proliferación simulada del factor de crecimiento de células endoteliales de vena umbilical humana ("HUVEC"). Se descongelaron células HUVEC (pasaje 3-4, Clonetics, Corp) en medio de cultivo EGM2 (Clonetics Corp) en matraces T75. Se añadió medio EGM2 de nueva aportación a los matraces 24 horas más tarde. Cuatro o cinco días más tarde, las células se expusieron a otro medio de cultivo (medio F12K suplementado con suero fetal bovino al 10% (FBS), 60 μg/ml de suplemento de crecimiento celular endotelial (ECGS), y 0,1 mg/ml de heparina). Se usaron células HUVEC de crecimiento exponencial en los experimentos siguientes. Se colocaron de diez a doce mil células HUVEC en placas de 96 pocillos en 100 μl de rico medio de cultivo (descrito anteriormente). Se dejó que se agregaran las células durante 24 horas en este medio. A continuación se retiró el medio por aspiración y se añadió en cada

pocillo 105 µl de medio de inanición (F12K+ 1% FBS). Después de 24 horas, se añadió en cada pocillo de tratamiento 15 µl del agente de ensayo disuelto en DMSO al 1% en medio de inanición o este vehículo solo; la concentración final de DMSO fue 0,1%. Una hora más tarde, se añadieron 30 µl de VEGF (30 ng/ml) en medio de inanición a todos los pocillos excepto a los que contenían controles sin tratar; la concentración final de DMSO fue 6 ng/ml. La proliferación celular se cuantificó 72 horas más tarde por reducción del colorante MTT, momento en el que las células se expusieron durante 4 horas a MTT (Promega Corp). La reducción del colorante se paró por adición de una disolución de detención (Promega Corp.) y se determinó la absorbancia a 595 nm en un lector espectrofotométrico de placas de 96 pocillos.

Ensayo de PK de ratón

La farmacocinética (por ejemplo, absorción y eliminación) de fármacos en ratones se analizó usando el siguiente experimento. Los compuestos de ensayo se formularon en forma de suspensión en un vehículo 30:70 (PEG 400: H_2O acidificada). Esta disolución se administró oralmente (p.o.) e intraperitonealmente (i.p.) a 50 mg/kg a dos grupos (n=4) distintos de ratones hembra B6. Se recogieron muestras de sangre vía un sangrado orbital en los siguientes momentos: 0 horas (predosis); 0,5 h, 1,0 h, 2,0 h y 4,0 posdosis. Se obtuvo plasma de cada muestra por centrifugación a 2500 rpm durante 5 min. El compuesto de ensayo se extrajo del plasma por un método de precipitación de la proteína orgánica. Para cada tiempo de sangrado se combinaron 50 µl de plasma con 1,0 ml de acetonitrilo, se sometieron a vórtice durante 2 min, y a continuación se centrifugaron a 4000 rpm durante 15 min para precipitar la proteína y extraer el compuesto de ensayo. A continuación, el acetonitrilo sobrenadante (el extracto que contiene el compuesto de ensayo) se vertió en nuevos tubos de ensayo y se evaporó sobre una placa caliente (25ºC) bajo una corriente de N_2 gaseoso. A cada tubo que contiene el extracto de compuesto de ensayo seco se añadieron 125 µl de fase móvil (60:40, $NH_4H_2PO_4$ 0,025 M + 2,5 ml/l de TEA:acetonitrilo). El compuesto de ensayo se resuspendió en una fase móvil sometiéndolo a vórtice y se retiró más proteína por centrifugación a 4000 rpm durante 5 min. Cada muestra se vertió en un vial para HPLC para el análisis del compuesto de ensayo en un HPLC Hewlett Packard serie 1100 con detección de UV. De cada muestra, se inyectaron 95 µl en una columna de 150 x 3,2 mm C-18 de fase inversa Phenomenex-Prodigy y se eluyó con gradiente de acetonitrilo 45-50% durante 10 minutos. Las concentraciones (µg/ml) en plasma del compuesto de ensayo se determinaron por una comparación con la curva estándar (área de pico frente a concentración µg/ml) usando concentraciones

conocidas de compuesto de ensayo extraído de muestras de plasma de la manera descrita anteriormente. Junto con los estándares y los desconocidos, se realizaron tres grupos (n=4) de controles de calidad (0,25 µg/ml, 1,5 µg/ml, y 7,5 µg/ml) para asegurar la consistencia del análisis. La curva estándar tenía un R_2>0,99 y las controles de calidad estaban todos dentro del 10% de sus valores esperados. Las muestras de ensayo cuantificadas se representaron para la observación visual usando software Kalidagraph y sus parámetros farmacocinéticos se determinaron usando el software WIN NONLIN.

Ensayo de microsoma de hígado humano (HLM)

Se midió el metabolismo del compuesto en microsomas de hígado humano por procedimientos de ensayo analítico de LCMS (cromatografía de líquidos-espectrometría de masas) como sigue. Primero, se descongelaron los microsomas de hígado humano (HLM) y se diluyeron hasta 5 mg/ml con tampón de fosfato de potasio (KPO_4) 100 mM. Se preincubaron apropiadas cantidades de tampón de KPO_4, disolución regenerante de NADPH (que contiene B-NADP, glucosa-6-fosfato, deshidrogenasa de glucosa-6-fosfato, y $MgCl_2$), y HLM en tubos de vidrio de 13 x 100 mm a 37°C durante 10 min (3 tubos por cada compuesto de ensayo–triplicado). Se añadió compuesto de ensayo (5 µM final) a cada tubo para iniciar la reacción y se mezcló por suave vórtice, seguido de incubación a 37°C. A t=0, y 2 h, se retiró una muestra de 250 µl de cada tubo de incubación para separar los tubos de vidrio de 12 x 75 mm que contienen 1 ml de acetonitrilo enfriado con hielo con reserpina 0,05 µM. Las muestras se centrifugaron a 4000 rpm durante 20 min para precipitar proteínas y sal (Beckman Allegra 6KR, S/N ALK98D06, nº 634). Se transfirió el sobrenadante a nuevos tubos de vidrio de 12 x 75 mm y se evaporó por medio de un evaporador centrífugo a vacío Speed-Vac. Las muestras se reconstituyeron en 200 µl de 0,1% ácido fórmico/acetonitrilo (90/10) y se sometieron a vórtice vigorosamente para disolverlas. Las muestras se transfirieron a continuación a tubos de microcentrífuga separados y se centrifugaron a 14000x g durante 10 min (Fisher Micro 14, S/N M0017580). Para cada réplica (nº 1-3) en cada punto de tiempo (0 y 2 h), se combinó una muestra alícuota de cada compuesto de ensayo en un único vial para HPLC (6 muestras en total) para el análisis por LCMS, que se describe a continuación.

Las muestras de compuesto combinadas se inyectaron en el sistema de LCMS, compuesto de un HPLC Hewlett-Packard HP1100 con dispositivo de diodos y un espectrómetro cuadrupolar de masas triple Micromass Quattro II que funciona en el modo SIR de electroespray positivo (programado para barrer específicamente para ver

el ion molecular de cada compuesto de ensayo). Cada pico de compuesto de ensayo se integró para cada punto de tiempo. Para cada compuesto, se promedió el área del pico en cada punto de tiempo (n=3), y este área de pico media a las 2 h se dividió entre el área de pico promedio para el tiempo 0 horas, para obtener el porcentaje de compuesto de ensayo que quedaba a las 2 h.

Ensayo de la fosforilación de KDR(VEGFR2) en células PAE-KDR

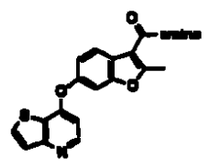
Este ensayo determina la capacidad de un compuesto de ensayo para inhibir la autofosforilación del KDR en células endoteliales de aorta porcina (PAE)-KDR. Se usaron en este ensayo células PAE que sobreexpresan el KDR humano. Las células se cultivaron en medio F12 de Ham suplementado con suero bovino fetal al 10% (FBS) y 400 µg/ml de G418. Se sembraron treinta mil células en cada pocillo de una placa de 96 pocillos en 75 µl de medio de cultivo y se dejó que se agregaran durante 6 horas a 37°C. Las células se expusieron a continuación al medio de inanición (medio F12 de Ham suplementado con FBS al 0,1%) durante 16 horas. Después de terminar el periodo de inanición, se añadieron 10 µl de un agente de ensayo en DMSO al 5% en medio de inanición a los pocillos de ensayo y se añadieron 10 µl del vehículo (DMSO al 5% en medio de inanición) a los pocillos de control. La concentración final de DMSO en cada pocillo fue 0,5%. Las placas se incubaron a 37°C durante 1 hora y a continuación se estimularon las células con 500 ng/ml de VEGF (comercialmente disponible del sistema de R&D) en presencia de Na_3VO_4 2 mM durante 8 minutos. Las células se lavaron una vez con Na_3VO_4 1 mM en HBSS y se sometieron a lisis añadiendo 50 µl por pocillo de tampón de lisis. Se añadieron a continuación a cada pocillo cien µl de tampón de dilución y el lisado de células diluidas se transfirió a una placa de 96 pocillos revestida de cabra anti-ratón (disponible comercialmente de Pierce) que estaba prerevestida con anticuerpo Anti-flk-1 C-20 anti-humano de ratón (disponible comercialmente de Santa Cruz). Las placas se incubaron a temperatura ambiente durante 2 horas y se lavaron siete veces con Tween 20 al 1% en PBS. Se diluyó HRP-PY20 (disponible comercialmente de Santa Cruz) y se añadió a la placa para una incubación de 30 minutos. Las placas se lavaron de nuevo y se añadió substrato de peroxidasa TMB (disponible comercialmente de Kirkegaard & Perry) para una incubación de 10 minutos. Se añadieron cien µl de H_2SO_4 0,09 N a cada pocillo de las placas de 96 pocillos para parar la reacción. Se verificó el estado de la fosforilación por lectura en el espectrofotómetro a 450 nm. Los valores IC_{50} se calcularon por ajuste de la curva usando un análisis de cuatro parámetros.

Ensayo de la fosforilación de PAE-PDGFRβ en células PAE-PDGFRB.

Este ensayo determina la capacidad de un compuesto de ensayo de inhibir la autofosforilación de PDGFRβ en células endoteliales de aorta porcina (PAE)-PDGFRβ. Se usaron en este ensayo células PAE que sobreexpresan el PDGFRβ humano. Las células se cultivaron en medio F12 de Ham suplementado con suero bovino fetal al 10% (FBS) y 400 µg/ml de G418. Se sembraron veinte mil células en cada pocillo de una placa de 96 pocillos en 50 µl de medio de cultivo y se dejó que se agregaran durante 6 horas a 37°C. Las células se expusieron a continuación al medio de inanición (medio F12 de Ham suplementado con FBS al 0,1%) durante 16 horas. Después de terminar el periodo de inanición, se añadieron 10 µl de un agente de ensayo en DMSO al 5% en medio de inanición a los pocillos de ensayo y se añadieron 10 µl del vehículo (DMSO al 5% en medio de inanición) a los pocillos de control. La concentración final de DMSO en cada pocillo fue 0,5%. Las placas se incubaron a 37°C durante 1 hora y a continuación se estimularon las células con 1 µg/ml de PDGF-BB (Sistema de R&D) en presencia de Na_3VO_4 2 mM durante 8 minutos. Las células se lavaron una vez con Na_3VO_4 1 mM en HBSS y se sometieron a lisis añadiendo 50 µl por pocillo de tampón de lisis. Se añadieron a continuación a cada pocillo cien µl de tampón de dilución y el lisado de células diluidas se transfirió a una placa de 96 pocillos revestida de cabra anti-ratón (disponible comercialmente de Pierce) que estaba prerevestida con anticuerpo PDGFRβ anti-humano de ratón (Santa Cruz). Las placas se incubaron a temperatura ambiente durante 2 horas y se lavaron siete veces con Tween 20 al 1% en PBS. Se diluyó HRP-PY20 (Santa Cruz) y se añadió a la placa para una incubación de 30 minutos. Las placas se lavaron de nuevo y se añadió substrato de peroxidasa TMB (Kirkegaard & Perry) para una incubación de 10 minutos. Se añadieron cien µl de H_2SO_4 0,09 N a cada pocillo de las placas de 96 pocillos para parar la reacción. Se verificó el estado de la fosforilación por lectura en el espectrofotómetro a 450 nm. Los valores IC_{50} se calcularon por ajuste de la curva usando un análisis de cuatro parámetros

Los resultados del ensayo de los compuestos usando varios ensayos se resumen en las Tablas 1 y 2 a continuación, en las que la notación "% @" indica el porcentaje de inhibición a la concentración dada.

Todas las aminas listadas en la Tabla 3 se hicieron reaccionar con el Ejemplo 101 y se denotan R_{101} en la Tabla 3 que tienen al siguiente estructura:



Las placas de la biblioteca para la Tabla 3 se prepararon de la siguiente manera general:

Procedimiento general para la formación del enlace de amida:

Se preparó una disolución 0,13 M de cada amina en la Tabla 3 en una mezcla 1:1 de piridina anhidra y DMF y se colocó en los pocillos apropiados de una placa de pocillos de profundidad de 1 ml. Se preparó la disolución 0,10 M del Ejemplo 101 en una disolución de DMF y se añadió a cada pocillo. Las reacciones se agitaron a 50°C durante 4 h. Los compuestos volátiles se retiraron usando el aparato Speedvac™, y las mezclas en bruto se reconstituyeron en DMSO para dar disoluciones con una concentración teórica final de 0,01 M.

En las tablas (abreviaturas no usadas en el resto del texto): autofos = autofosforilación; NT (not tested) = no ensayado; AVG (average) = promedio

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3441

TABLA 1						
Compuesto	FLVK (% Inh @ 50 nM)	FLVK Ki (nM)	HUVEC + VEGF IC50 (nM) AVG	PAE KDR autofos IC50 (nM) AVG	PAE PDGFR autofos IC50 (nM) AVG	bFGF Huvec IC50 (nM) Avg.
1	92%	1.02	0.68	0.31	164	122
2	75%	4.14	2.3	1.8	912	3333
3	59%	0.811	0.442	0.9	756	942
4	88%	2.58	0.404	0.47	284	NT
5	73%	1.91	1.55	NT	1000	235
6	94%	0.721	1.2	NT	255	145
7	95%	1.04	1.21	1.95	1000	2474
8	94%	0.403	1.37	NT	1000	504
9	83%	1.57	13	NT	313	135
10	74%	2.31	10	NT	461	99
11	93%	0.492	0.58	NT	103.5	40
12	100%	0.314	0.28	0.14	14.4	20
13	97%	0.322	0.082	0.21	41	27
14	81%	1.46	9.4	NT	NT	287
15	13%	48.3	NT	NT	NT	NT
16	46%	8.14	10	NT	NT	1000
17	77%	2.77	1.2	0.47	20	847
18	78%	2.373	0.64	0.62	32	1000
19	75%	2.83	2.7	1.7	172	10000
20	99%	0.082	0.19	0.217	43	1902
21	43%	13.11	NT	NT	NT	NT
22	38%	25.8	NT	NT	NT	NT
23	19%	78	NT	NT	NT	NT
24	69%	4.2	32	NT	NT	10000
25	70%	4.08	0.45	NT	12	7460
26	83%	3.66	0.74	NT	13	2233
27	13%	96	NT	NT	205	NT
28	78%	2.8	0.272	NT	15	462
29	6%	88.77	NT	NT	NT	NT
30	63%	6	33.6	NT	74	10000
31	25%	30.2	NT	NT	NT	NT

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TABLA 1						
Compuesto	FLVK (% inh @ 50 nM)	FLVK Ki (nM)	HUVEC + VEGF IC50 (nM) AVG	PAE KDR autofos IC50 (nM) AVG	PAE PDGFR autofos IC50 (nM) AVG	bFGF Huvec IC50 (nM) Avg.
32	22%	39.4	NT	NT	29.2	NT
33	61%	11.5	10	NT	63	10000
34	45%	11.4	NT	NT	31.3	NT
35	23%	35.166	NT	NT	70	NT
36	41%	11.513	NT	NT	NT	NT
37	66%	4.3	10	NT	1000	NT
38	60%	6.12	27	NT	12.3	10000
39	12%	47	8.7	NT	61	NT
40	77%	2.95	1.12	NT	24.2	7798
41	71%	3.3	3.7	NT	22.1	1224
42	76%	2.8	4.34	NT	8.9	NT
43	67%	3.21	10	NT	1000	NT
44	67%	1.2	1.78	NT	21.26	6036
45	64%	4.65	10	NT	26.9	NT
46	68%	6.49	3.13	NT	NT	NT
47	41%	19.7	NT	NT	NT	NT
48	91%	NT	0.94	NT	21	239
49	67%	16	7	NT	NT	NT
50	36%	36.5	NT	NT	NT	NT
51	34%	27.7	82	NT	NT	NT
52	41%	24.9	NT	NT	NT	NT
53	93%	1.07	1.8	NT	229	7233
54	89%	1.71	1.8	NT	133	10000
55	62%	4.86	5.8	NT	31	NT
56	60%	3.8	22	NT	109	10000
57	63%	9.8	NT	87	NT	
58	55%	7.59	3.65	NT	124	7830
59	81%	1.378	0.045	NT	115	1164
60	81%	2.17	1.34	NT	38.3	1703
61	89%	NT	0.605	0.4	17.8	3995
62	91%	0.57	2.15	0.24	16.7	619
63	67%	9.33	10	NT	84	10000
64	64%	11.8	10	NT	1000	10000

Not 399

TABLA 1						
Compuesto	FLVK (% Inh @ 50 nM)	FLVK Ki (nM)	HUVEC + VEGF IC50 (nM) AVG	PAE KDR autofos IC50 (nM) AVG	PAE PDGFR autofos IC50 (nM) AVG	bFGF Huvec IC50 (nM) Avg.
65	65%	7.97	10	NT	59	10000
66	76%	5.2	5.8	NT	90.7	NT
67	58%	12.51	NT	NT	NT	NT
68	37%	NT	NT	NT	NT	NT
69	95%	0.3	0.57	NT	6.52	4314
70	95%	0.43	0.537	NT	47.1	3975
71	5%	NT	NT	NT	NT	NT
72	2%	NT	NT	NT	NT	NT
73	48%	10.286	NT	NT	NT	NT
74	43%	12.721	NT	NT	312.5	NT
75	84%	2.62	1.4	NT	16.6	10000
76	36%	6.26	NT	NT	NT	NT
77	99%	0.2	0.2	NT	7.4	8
78	93%	0.221	0.507	NT	14.8	30
79	90%	0.276	0.223	NT	15.5	130
80	95%	0.438	0.239	NT	31	60
81	100%	0.2	0.09	NT	7	25.96
82	89%	0.884	2.28	NT	53.1	2058
83	98%	0.2	0.77	NT	28.8	142
84	94%	0.58	0.322	NT	12.4	429
85	83%	1.71	3.92	NT	27.3	6967
86	81%	1.44	3.07	NT	17.9	
87	98%	0.615	1.25	NT	17.8	6044
88	94%	0.574	0.46	NT	15.1	363
89	95%	0.419	NT	NT	250	5.2
90	93%	0.739	2.14	NT	33	745
91	94%	0.356	0.168	NT	16.5	250
92	100%	0.2	0.18	NT	4.4	13
93	84%	2.72	NT	NT	44	NT
94	81%	1.453	0.7	NT	112	251
95	89%	0.848	10	NT	235	98
96	51%	9.61	NT	NT	NT	NT
97	70%	4.84	10	NT	293	223

TABLA 1						
Compuesto	FLVK (% inh @ 50 nM)	FLVK Ki (nM)	HUVEC + VEGF IC50 (nM) AVG	PAE KDR autofos IC50 (nM) AVG	PAE PDGFR autofos IC50 (nM) AVG	bFGF Huvec IC50 (nM) Avg.
98	86%	0.38	9.4	NT	126.6	NT
99	68%	4.68	NT	NT	562.6	NT
100	0%	NT	NT	NT	NT	NT
102	96%	0.91	0.186	NT	49	1718
103	52%	7	NT	NT	203.4	NT
104	100%	NT	8.4	NT	163.9	227
105	61%	8.37	NT	NT	127	NT
106	98%	NT	10	NT	1000	638
107	17%	36.69	NT	NT	NT	NT
108	61%	NT	NT	NT	NT	NT
109	82%	NT	NT	NT	NT	NT
110	21%	NT	NT	NT	NT	NT
111	96%	NT	NT	NT	NT	NT
112	91%	NT	NT	NT	NT	NT
113	89%	NT	NT	NT	NT	NT
114	16%	116.86	NT	NT	1000	NT
115	4%	NT	NT	NT	1000	NT
116	4%	NT	NT	NT	NT	NT
117	87%	0.2	0.07	NT	189	86
118	84%	1.2	0.9	NT	1000	736
119	95%	0.375	1.46	NT	90.6	1827
120	93%	0.6	0.491	NT	405	489
121	94%	0.2	0.24	NT	220	100
122	58%	5.14	NT	NT	351	NT
123	74%	2.63	10	NT	229	NT
124	82%	2.19	1.6	NT	376	8243
125	95%	0.219	2	NT	179	969
126	96%	0.5896	10	NT	336	5656
127	100%	0.2	1	NT	102	41
128	91%	0.67	0.13	NT	148	100
129	88%	0.2	0.219	NT	166	100
130	95%	0.39	0.49	NT	335	100
131	96%	0.2	1.89	NT	97	260

TABLA 1

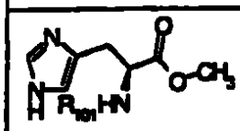
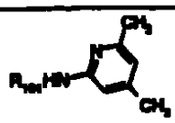
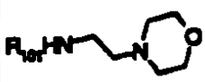
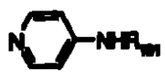
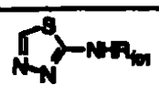
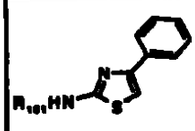
Compuesto	FLVK (% inh @ 50 nM)	FLVK KI (nM)	HUVEC + VEGF IC50 (nM) AVG	PAE KDR autofos IC50 (nM) AVG	PAE PDGFR autofos IC50 (nM) AVG	bFGF Huvec IC50 (nM) Avg.
132	80%	1.78	5.8	NT	467	NT
133	40%	5.9	NT	NT	467.9	NT
134	94%	1.44	0.858	NT	176.9	1070
135	87%	1.5411	1.02	NT	212	569
136	88%	1.1704	10	NT	609	NT
137	64%	5.1	2.1	NT	213	294
138	85%	0.78	9.9	NT	110	NT
139	40%	NT	NT	NT	NT	NT
140	90%	NT	NT	NT	NT	NT

TABLA 2

Compuesto	ratón PK AUC, po ng-h/mL**	ratón Cmax, po (ng/mL)	ratón Cmin, po (ng/mL)	%restante (HLM-UDPGA, 0.5 h)	%restante (HLM-NADPH, 0.5 h)
1	182608	124745	2793	NT	NT
2	NT	NT	NT	NT	NT
3	2450	956	66	NT	NT
4	7674	2340	200	NT	NT
5	12254	6743	258	NT	NT
6	586	356	20	NT	NT
7	NT	NT	NT	NT	NT
8	2348	686	106	NT	NT
9	NT	NT	NT	NT	NT
10	NT	NT	NT	NT	NT
11	NT	NT	NT	NT	NT
12	11970	5423	270	NT	NT
13	63000	24760	1700	NT	NT
14	NT	NT	NT	NT	NT
15	NT	NT	NT	NT	NT
16	NT	NT	NT	NT	NT
17	71580	28817	2334	NT	NT
18	8724	4120	342	NT	NT
19	120	51	4	NT	NT

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TABLA 3

Amina	% TIC	FLVK (% @ 100 nM)	FGF (%@100nM)	PAE PDGFR autofos IC50 (nM)
	58.552	52	NT	49
	53.7891	103	2	53
	0	26	NT	NT
	51.8111	79	20	60
	5.4277	20	NT	NT
	88.1771	75	35	>100
	0	16	NT	NT
	55.2161	17	NT	NT

1006
404

TABLA 3

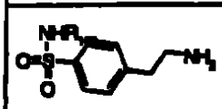
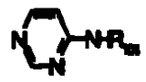
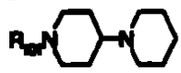
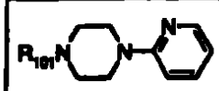
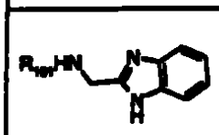
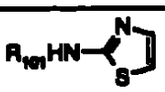
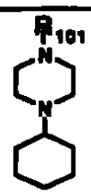
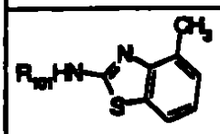
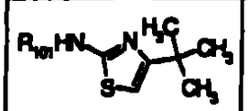
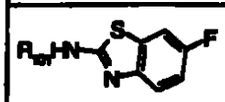
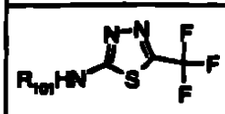
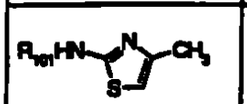
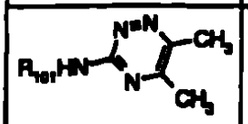
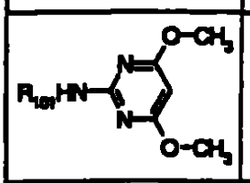
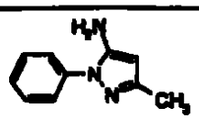
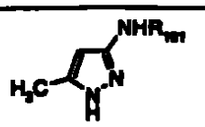
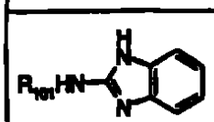
Amina	% TIC	FLVK (% @ 100 nM)	FGF (% @ 100nM)	PAE PDGFR autofos IC50 (nM)
	65.4679	68	0	>100
	95.752	38	NT	NT
	97.7442	24	NT	NT
	65.2303	20	NT	NT
	48.6673	22	NT	NT
	45.8972	24	NT	NT
	12.783	90	20	>100
	55.6	14	NT	NT
	0	20	NT	NT

TABLA 3				
Amina	% TIC	FLVK (% @ 100 nM)	FGF (%@100nM)	PAE PDGFR autofos IC50 (nM)
	0	27	NT	NT
	0	28	NT	NT
	0	14	NT	NT
	5.35845	62	7	>100
	0	14	NT	NT
	0	16	NT	NT
	0	30	NT	NT
	19.2675	100	4	46
	58.6779	16	NT	NT

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TABLA 3

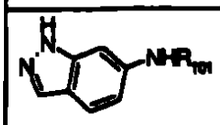
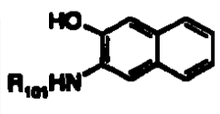
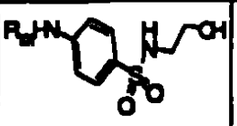
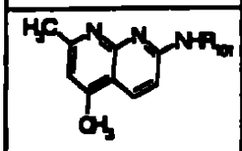
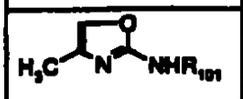
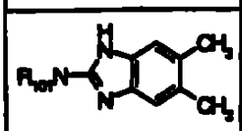
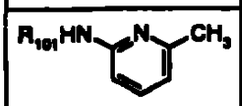
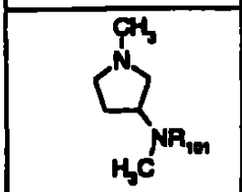
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	29.8321	87	0	57
	10.8303	29	NT	NT
	77.1177	16	NT	NT
	0	20	NT	NT
	0	13	NT	NT
	55.2356	14	NT	NT
	0	14	NT	NT
	49.6134	25	NT	NT
	43.8419	25	NT	NT

TABLA 3

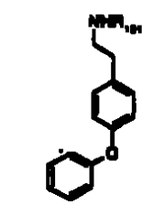
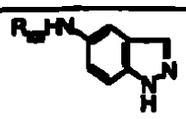
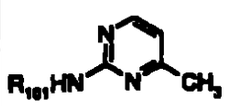
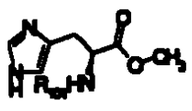
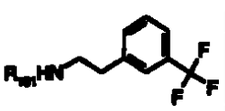
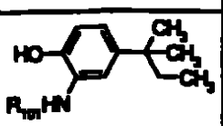
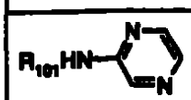
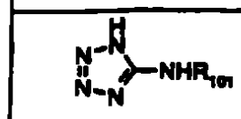
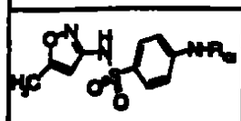
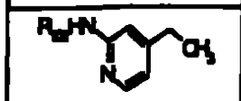
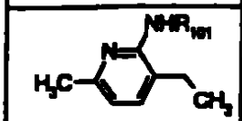
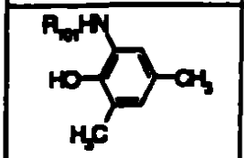
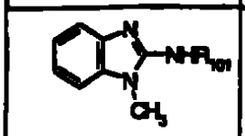
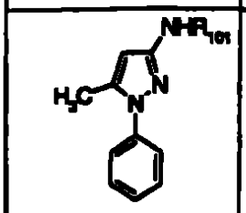
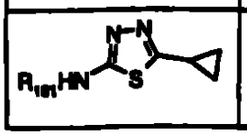
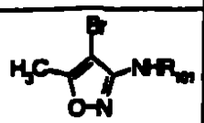
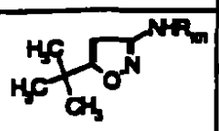
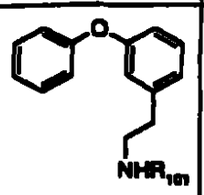
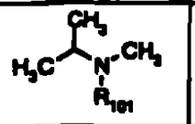
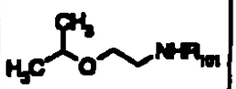
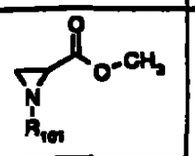
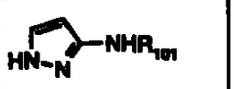
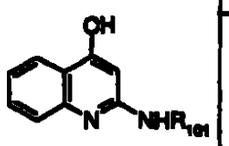
Amina	% TIC	FLVK (% @ 100 nM)	FGF (%@100nM)	PAE PDGFR autofos IC50 (nM)
	11.5047	21	NT	NT
	75.9693	98	0	~100
	0	10	NT	NT
	28.1067	13	NT	NT
	28.1967	97	0	>100
	24.8781	28	NT	NT
	0	10	NT	NT

TABLA 3				
Amina	% TIC	FLVK (% @ 100 nM)	FGF (%@100nM)	PAE PDGFR autofos IC50 (nM)
	22.1224	8	NT	NT
	1.78077	7	NT	NT
	0	18	NT	NT
	0	22	NT	NT
	28.8916	57	13	~100
	50.8697	12	NT	NT
	1.10495	13	NT	NT
	38.7228	100	4	>100

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Amina	% TIC	FLVK (% @ 100 nM)	FGF (%@100nM)	PAE PDGFR autofos IC50 (nM)
	0	4	NT	NT
	0	15	NT	NT
	24.5486	36	NT	NT
	22.7289	17	NT	NT
	55.7071	94	0	61
	25.3022	51	NT	>100
	74.3164	91	NT	>100
	0	23	8	NT

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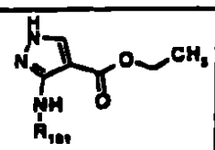
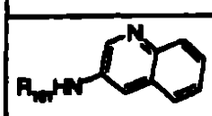
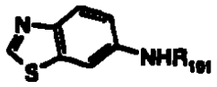
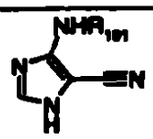
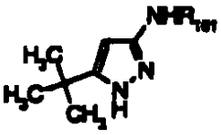
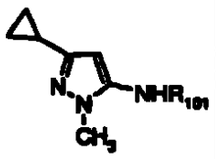
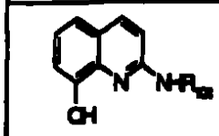
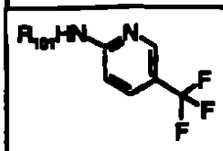
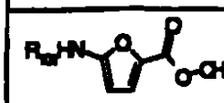
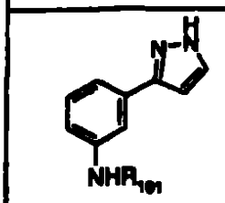
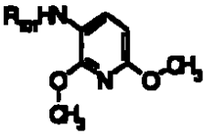
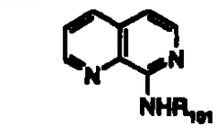
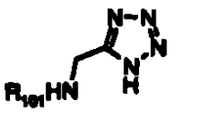
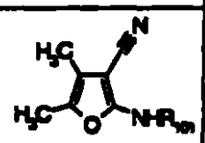
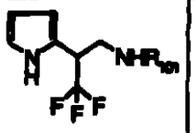
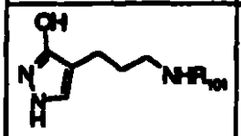
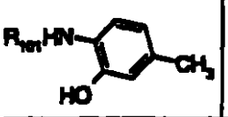
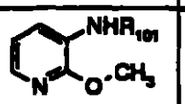
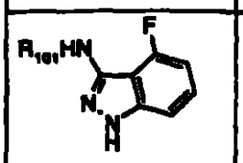
TABLA 3				
Amina	% TIC	FLVK (% @ 100 nM)	FGF (%@100nM)	PAE PDGFR autofos IC50 (nM)
	4.01991	13	NT	NT
	43.6451	85	7	>100
	15.565	98	0	>100
	0	5	NT	NT
	58.6541	101	0	57
	20.5224	100	56	>100
	29.3082	22	NT	NT
	3.03715	56	3	>100

TABLA 3

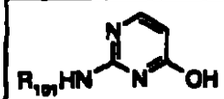
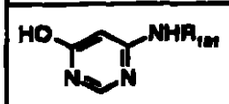
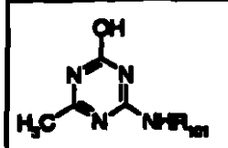
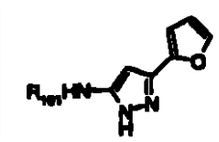
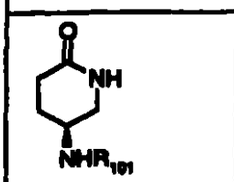
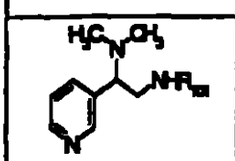
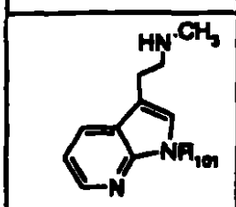
Amina	% TIC	FLVK (% @ 100 nM)	FGF (%@100nM)	PAE PDGFR autofos IC50 (nM)
	54.7208	24	NT	NT
	0	27	NT	NT
	0	24	NT	NT
	27.931	94	0	>100
	18.4145	92	1	>100
	0	10	NT	NT
	49.5375	10	NT	NT

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TABLA 3				
Amina	% TIC	FLVK (% @ 100 nM)	FGF (%@100nM)	PAE PDGFR *autofos* IC50 (nM)
	41.0058	25	NT	NT
	0	13	NT	NT
	45.0518	85	3	>100
	38.7067	12	NT	NT
	33.1065	85	0	~100
	1.9193	35	NT	NT
	0	81	0	>100

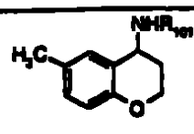
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TABLA 3

Amina	% TIC	FLVK (% @ 100 nM)	FGF (%@100nM)	PAE PDGFR autofos IC50 (nM)
	0	19	NT	NT
	0	17	NT	NT
	0	15	NT	NT
	15.0813	101	1	>100
	19.6253	19	NT	NT
	64.8885	16	NT	NT
	20.3244	9	NT	NT

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TABLA 3

Amina	% TIC	FLVK (% @ 100 nM)	FGF (%@100nM)	PAE PDGFR autofos IC50 (nM)
	24.2001	46	NT	NT

Los compuestos ejemplares descritos anteriormente se pueden formular en forma de composiciones farmacéuticas según los siguientes ejemplos generales.

Ejemplo 1: Composición parenteral

Para preparar una composición farmacéutica parenteral apropiada para la administración por inyección, se disuelven 100 mg de una sal soluble en agua de un compuesto de Fórmula I en DMSO y a continuación se mezclan con 10 ml de disolución salina estéril al 0,9%. La mezcla se incorpora en una forma de dosificación unitaria apropiada para la administración por inyección.

Ejemplo 2: Composición oral

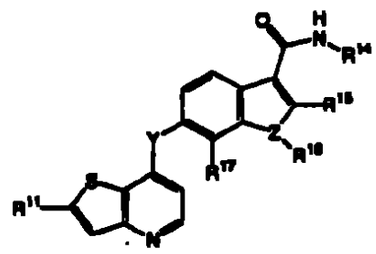
Para preparar una composición farmacéutica para suministro oral, se mezclan 100 mg de un compuesto de Fórmula I con 750 mg de lactosa. La mezcla se incorpora en una forma unitaria de dosificación oral, tal como una cápsula de gelatina dura, que es apropiada para la administración oral.

Se debe entender que la precedente descripción es de naturaleza explicativa y ejemplar, y se pretende que ilustre la invención y sus relaciones preferidas. Por medio de la experimentación rutinaria, el experto reconocerá las modificaciones y variaciones evidentes que se pueden realizar sin apartarse del espíritu de la invención. De este modo, se pretende que la invención esté definida no por la descripción anterior, sino por las siguientes reivindicaciones y sus equivalentes.

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REIVINDICACIONES

1. Un compuesto representado por la fórmula I:



I

en la que:

Y es -NH-, -O-, -S-, o -CH_2-;

Z es -O-, -S-, o -N-;

R^{14} es un alquilo de C_1-C_6, alquil de C_1-C_6-amino, alquil de C_1-C_6-hidroxi, cicloalquil de C_3-C_{10}-amino, o grupo metilureido;

R^{15} y R^{17} son independientemente H, halo, o un grupo alquilo de C_1-C_6 sin substituir o substituido con uno o más grupos R^5;

R^{16} es H o un grupo alquilo de C_1-C_6 cuando Z es N, y R^{16} está ausente cuando Z es -O- o -S-;

R^{11} es H, alquilo de C_1-C_6, cicloalquilo de C_3-C_{10}, -$C(O)NR^{12}R^{13}$, -C(O)(arilo de C_1-C_6), -$(CH_2)_k$(arilo de C_6-C_{10}), -$(CH_2)_k$(heterociclo de 5 a 10 miembros), -$(CH_2)_kNR^{12}R^{13}$, -$SO_2NR^{12}R^{13}$ o -CO_2R^{12}, en la que dicho alquilo de C_1-C_6, -C(O)(arilo de C_6-C_{10}), -$(CH_2)_k$(arilo de C_6-C_{10}), y restos -$(CH_2)_k$(heterociclo de 5 a 10 miembros) de dichos grupos R^{11} están sin substituir o substituidos con uno o más grupos R^5;

cada R^5 se selecciona independientemente de halo, ciano, nitro, trifluorometoxi, trifluorometilo, azido, -$C(O)R^6$, -$C(O)OR^8$, -$OC(O)R^8$, -$OC(O)OR^8$, -$NR^6C(O)R^7$, -$C(O)NR^6R^7$, -NR^6R^7, -OR^6, -$SO_2NR^6R^7$, alquilo de C_1-C_6, cicloalquilo de C_3-C_{10}, alquil de C_1-C_6-amino, -$(CH_2)_jO(CH_2)_qNR^6R^7$, -$(CH_2)_kO(CH_2)_qOR^6$, -$(CH_2)_kOR^6$, -$S(O)_j$(alquilo de C_1-C_6), -$(CH_2)_k$(arilo de C_6-C_{10}), -$(CH_2)_k$(heterociclo de 5 a 10 miembros), -$C(O)(CH_2)_k$(arilo de C_6-C_{10}), -$(CH_2)_kO(CH_2)_j$(arilo de C_6-C_{10}), -$(CH_2)_kO(CH_2)_q$(heterociclo de 5 a 10 miembros), -$C(O)(CH_2)_k$(heterociclo de 5 a 10 miembros), -$(CH_2)_jNR^7(CH_2)_qNR^6R^7$, -$(CH_2)_jNR^7CH_2C(O)NR^6R^7$, -$(CH_2)_jNR^7(CH_2)_qNR^6C(O)R^6$, -$(CH_2)_jNR^7(CH_2)_kO(CH_2)_qOR^6$, -$(CH_2)_jNR^7(CH_2)_qS(O)_j$(alquilo de C_1-C_6), -$(CH_2)_jNR^7(CH_2)_kR^6$, -$SO_2(CH_2)_k$(arilo de C_6-C_{10}), y -$SO_2(CH_2)_k$(heterociclo de 5 a 10 miembros), los restos -$(CH_2)_q$- y -$(CH_2)_t$- de dichos grupos R^5 opcionalmente incluyen

un doble o triple enlace carbono-carbono, y el alquilo, arilo y restos heterocíclicos de dichos grupos R^5 están sin substituir o substituidos con uno o más substituyentes independientemente seleccionados de halo, ciano, nitro, trifluorometilo, azido, -OH, -$C(O)R^8$, -$C(O)OR^8$, -$OC(O)R^8$, -$OC(O)OR^8$, -$NR^8C(O)R^7$, -$C(O)NR^8R^7$, -$(CH_2)_tNR^8R^7$, alquilo de C_1-C_6, cicloalquilo de C_3-C_{10}, -$(CH_2)_t$(arilo de C_6-C_{10}), -$(CH_2)_t$(heterociclo de 5 a 10 miembros), -$(CH_2)_tO(CH_2)_qOR^9$, y -$(CH_2)_tOR^9$;

cada R^6 y R^7 se selecciona independientemente de H, OH, alquilo de C_1-C_6, cicloalquilo de C_3-C_{10}, -$(CH_2)_t$(arilo de C_6-C_{10}), -$(CH_2)_t$(heterociclo de 5 a 10 miembros), -$(CH_2)_tO(CH_2)_qOR^9$, -$(CH_2)_tCN(CH_2)_tOR^9$, -$(CH_2)_tCN(CH_2)_tR^9$ y -$(CH_2)_tOR^8$, y el alquilo, arilo y restos heterocíclicos de dichos grupos R^6 y R^7 están sin substituir o substituidos con uno o más substituyentes independientemente seleccionados de hidroxi, halo, ciano, nitro, trifluorometilo, azido, -$C(O)R^8$, -$C(O)OR^8$, -$CO(O)R^8$, -$OC(O)OR^8$, -$NR^9C(O)R^{10}$, -$C(O)NR^9R^{10}$, -NR^9R^{10}, alquilo de C_1-C_6, -$(CH_2)_t$(arilo de C_6-C_{10}), -$(CH_2)_t$(heterociclo de 5 a 10 miembros), -$(CH_2)_tO(CH_2)_qOR^9$, y -$(CH_2)_tOR^9$, en los que cuando R^6 y R^7 están ambos unidos al mismo nitrógeno, entonces R^6 y R^7 no están ambos unidos al nitrógeno directamente por medio de un oxígeno;

cada R^8 se selecciona independientemente de H, alquilo de C_1-C_{10}, cicloalquilo de C_3-C_{10}, -$(CH_2)_t$(arilo de C_6-C_{10}), y -$(CH_2)_t$(heterociclo de 5 a 10 miembros);

t es un número entero de 0 a 6; j es un número entero de 0 a 2, q es un número entero de 2 a 6;

cada R^9 y R^{10} se selecciona independientemente de H, -OR^8, alquilo de C_1-C_6 y cicloalquilo de C_3-C_{10}; y

cada R^{12} y R^{13} se selecciona independientemente de H, alquilo de C_1-C_6, cicloalquilo de C_3-C_{10}, -$(CH_2)_t$(cicloalquilo de C_3-C_{10}), -$(CH_2)_t$(arilo de C_6-C_{10}), -$(CH_2)_t$(heterociclo de 5 a 10 miembros), -$(CH_2)_tO(CH_2)_qOR^8$, y -$(CH_2)_tOR^8$, y el alquilo, arilo y restos heterocíclicos de dichos grupos R^{12} y R^{13} están sin substituir o substituidos con uno o más substituyentes independientemente seleccionados de R^5, o R^{12} y R^{13} se toman conjuntamente con el nitrógeno al que están unidos para formar un anillo azabiciclo de C_5-C_9, aziridinilo, azetidinilo, pirrolidinilo, piperidinilo, piperazinilo, morfolinilo, tiomorfolinilo, isoquinolinilo o dihidroisoquinolinilo, en los que dichos anillos azabiciclo de C_5-C_9, aziridinilo, azetidinilo, pirrolidinilo, piperidinilo, piperazinilo, morfolinilo, tiomorfolinilo, isoquinolinilo o dihidroisoquinolinilo están substituidos o sin substituir con uno o más substituyentes R^5, en los que R^{12} y R^{13} no están ambos unidos al nitrógeno directamente por medio de un oxígeno;

o sus profármacos o metabolitos, o sales o solvatos farmacéuticamente aceptables de dichos compuestos y dichos profármacos y dichos metabolitos.

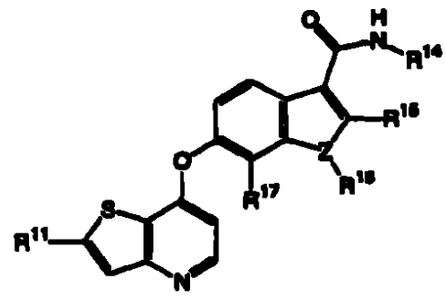
2. Un compuesto de la reivindicación 1, en el que R^{11} es un tiazolilo, sin substituir o substituido con 1 a 5 grupos R^5.

3. Un compuesto de la reivindicación 1, en el que R^{11} es un imidazolilo, sin substituir o substituido con 1 a 5 grupos R^5

4. Un compuesto de la reivindicación 1, en el que R^{16} es metilo.

5. Un compuesto de la reivindicación 1, en el que R^{14} es metilo.

6. Un compuesto representado por la fórmula II.



II

en la que:

Z es -O-, -S-, o -N-;

R^{14} es un alquilo de C_1-C_6, alquil de C_1-C_6-amino, alquil de C_1-C_6-hidroxi, cicloalquil de C_3-C_{10}-amino, o grupo metilureido;

R^{15} y R^{17} son independientemente H, halo, o un grupo alquilo de C_1-C_6;

R^{16} es H o un grupo alquilo de C_1-C_6, cuando Z es –N-, y R^{16} está ausente cuando Z es -O- o -S-;

R^{11} es un grupo heteroarilo sin substituir o substituido con uno o más halo, ciano, nitro, trifluorometoxi, trifluorometilo, azido, $-C(O)R^8$, $-C(O)OR^8$, $-OC(O)R^8$, $-OC(O)OR^6$, $-NR^6C(O)R^7$, $-C(O)NR^6R^7$, $-NR^6R^7$, $-OR^8$, $-SO_2NR^6R^7$, alquilo de C_1-C_6, cicloalquilo de C_3-C_{10}, $-(CH_2)_jO(CH_2)_qNR^6R^7$, $-(CH_2)_kO(CH_2)_qOR^8$, $-(CH_2)_kOR^8$, $-S(O)_j$(alquilo de C_1-C_6), $-(CH_2)_k$(arilo de C_6-C_{10}), $-(CH_2)_k$(heterociclo de 5 a 10 miembros), $-C(O)(CH_2)_k$(arilo de C_6-C_{10}), $-(CH_2)_kO(CH_2)_j$(arilo de C_6-C_{10}), $-(CH_2)_kO(CH_2)_q$(heterociclo de 5 a 10 miembros), $-C(O)(CH_2)_k$(heterociclo de 5 a 10 miembros), $-(CH_2)_jNR^7(CH_2)_qNR^6R^7$, $-(CH_2)_jNR^7CH_2C(O)NR^6R^7$, $-(CH_2)_jNR^7(CH_2)_qNR^6C(O)R^8$, $-(CH_2)_jNR^7(CH_2)_kO(CH_2)_qOR^8$, $-(CH_2)_jNR^7(CH_2)_qS(O)_j$(alquilo de C_1-C_6), $-(CH_2)_jNR^7(CH_2)_kNR^6$, $-SO_2(CH_2)_k$(arilo de C_6-C_{10}), y $-SO_2(CH_2)_k$(heterociclo de 5 a 10 miembros), los restos $-(CH_2)_q$- y $-(CH_2)_r$- de

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dichos grupos R^5 opcionalmente incluyen un doble o triple enlace carbono-carbono, y el alquilo, arilo y restos heterocíclicos de dichos grupos R^5 están sin substituir o substituidos con uno o más substituyentes independientemente seleccionados de halo, ciano, nitro, trifluorometilo, azido, -OH, $-C(O)R^8$, $-C(O)OR^8$, $-OC(O)R^8$, $-OC(O)OR^8$, $-NR^6C(O)R^7$, $-C(O)NR^6R^7$, $-(CH_2)_tNR^6R^7$, alquilo de C_1-C_6, cicloalquilo de C_3-C_{10}, $-(CH_2)_t$(arilo de C_6-C_{10}), $-(CH_2)_t$(heterociclo de 5 a 10 miembros), $-(CH_2)_tO(CH_2)_qOR^8$, y $-(CH_2)_tOR^8$;

cada R^6 y R^7 se selecciona independientemente de H, OH, alquilo de C_1-C_6, cicloalquilo de C_3-C_{10}, $-(CH_2)_t$(arilo de C_6-C_{10}), $-(CH_2)_t$(heterociclo de 5 a 10 miembros), $-(CH_2)_tO(CH_2)_qOR^8$, $(CH_2)_tCN(CH_2)_tOR^8$, $(CH_2)_tCN(CH_2)_tR^9$ y $-(CH_2)_tOR^8$, y el alquilo, arilo y restos heterocíclicos de dichos grupos R^6 y R^7 están sin substituir o substituidos con uno o más substituyentes independientemente seleccionados de hidroxi, halo, ciano, nitro, trifluorometilo, azido, $-C(O)R^8$, $-C(O)OR^8$, $-CO(O)R^8$, $-OC(O)OR^8$, $-NR^9C(O)R^{10}$, $-C(O)NR^9R^{10}$, $-NR^9R^{10}$, alquilo de C_1-C_6, $-(CH_2)_t$(arilo de C_6-C_{10}), $-(CH_2)_t$(heterociclo de 5 a 10 miembros), $-(CH_2)_tO(CH_2)_qOR^8$, y $-(CH_2)_tOR^8$, en los que cuando R^6 y R^7 están ambos unidos al mismo nitrógeno, entonces R^6 y R^7 no están ambos unidos al nitrógeno directamente por medio de un oxígeno;

cada R^8 se selecciona independientemente de H, alquilo de C_1-C_{10}, cicloalquilo de C_3-C_{10}, $-(CH_2)_t$(arilo de C_6-C_{10}), y $-(CH_2)_t$(heterociclo de 5 a 10 miembros);

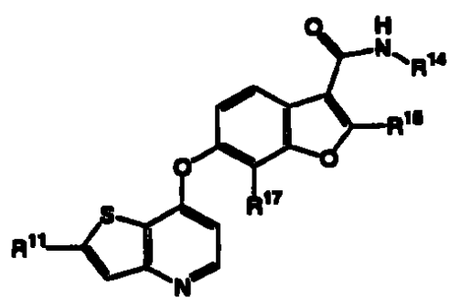
cada R^9 y R^{10} se selecciona independientemente de H, alquilo de C_1-C_6 y cicloalquilo de C_3-C_{10};

t es un número entero de 0 a 6; j es un número entero de 0 a 2; q es un número entero de 2 a 6;

o sus profármacos o metabolitos, sales o solvatos farmacéuticamente aceptables de dichos compuestos, dichos profármacos o dichos metabolitos.

7. Un compuesto de la reivindicación 6, en el que R^{14} es metilo.

8. Un compuesto representado por la fórmula IV:



IV

en la que:

R^{14} es un alquilo de C_1-C_6, alquil de C_1-C_6-amino, alquil de C_1-C_6-hidroxi, cicloalquil de C_3-C_{10}-amino, o grupo metilureido;

R^{15} y R^{17} son independientemente H, o un grupo alquilo de C_1-C_6;

R^{11} es un heterociclo o un grupo heteroarilo sin substituir o substituido con uno o más grupos seleccionados de -C(O)OR^8, alquilo de C_1-C_6, y -$(CH_2)_t$$OR^8$;

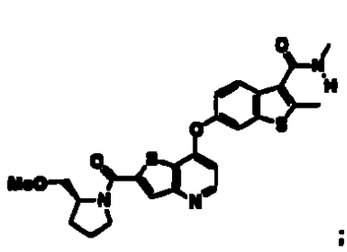
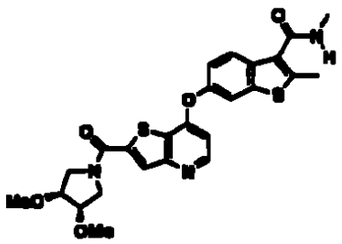
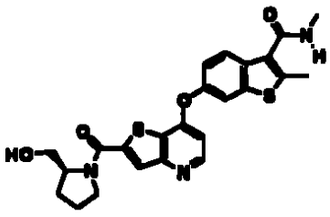
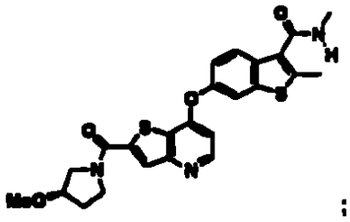
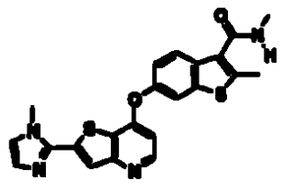
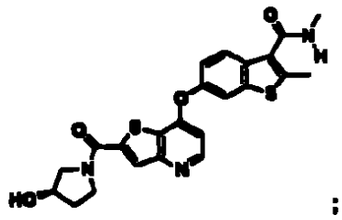
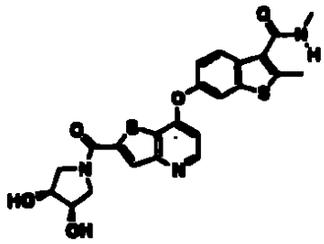
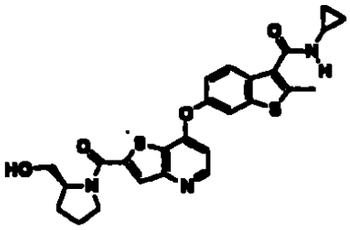
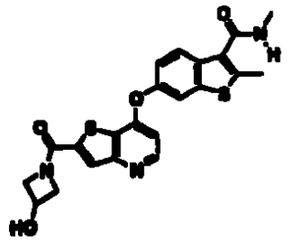
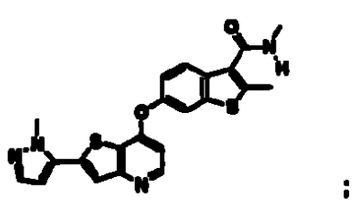
cada R^8 se selecciona independientemente de H, alquilo de C_1-C_{10}, cicloalquilo de C_3-C_{10}, -$(CH_2)_t$(arilo de C_6-C_{10}), y -$(CH_2)_t$(heterociclo de 5 a 10 miembros;

cada R^9 se selecciona independientemente de H, alquilo de C_1-C_6, y cicloalquilo de C_3-C_{10}; y

t es un número entero de 0 a 6; j es un número entero de 0 a 2; q es un número entero de 2 a 6;

o sus profármacos o metabolitos, sales o solvatos farmacéuticamente aceptables de dichos compuestos, dichos profármacos, y dichos metabolitos.

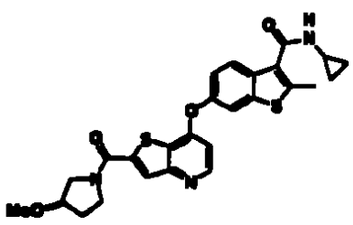
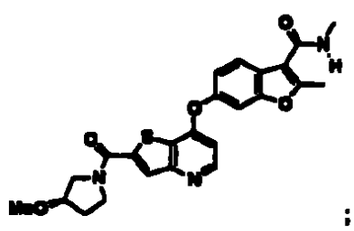
9. Un compuesto de la reivindicación 1 en el que dicho compuesto se selecciona del grupo que consiste en:

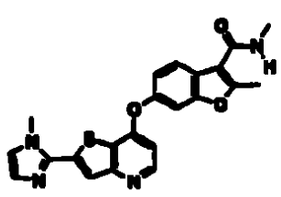
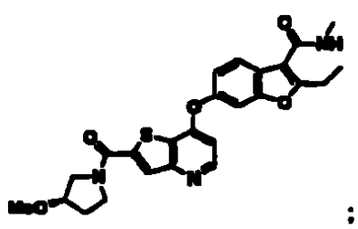

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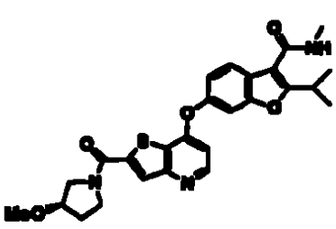
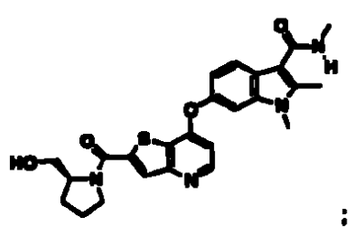
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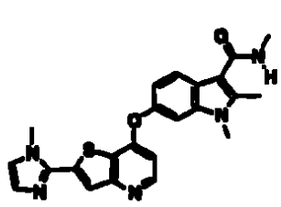
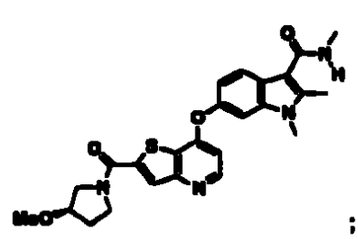
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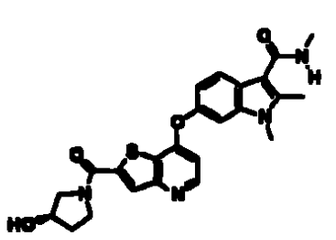
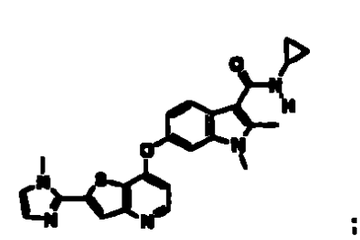
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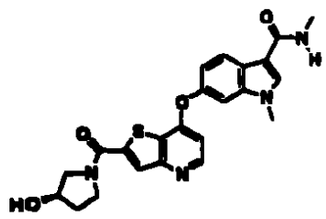
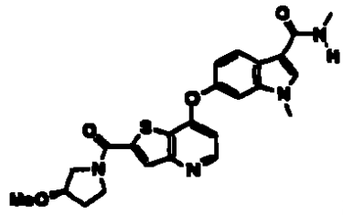
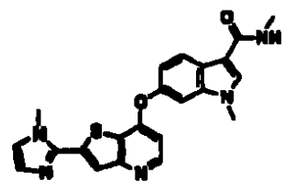
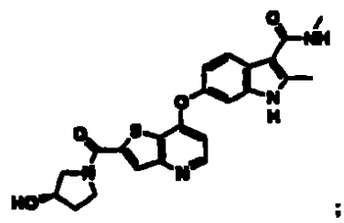

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o sus profármacos o metabolitos, o sales o solvatos farmacéuticamente aceptables de dichos compuestos, dichos profármacos, y dichos metabolitos.

10. Una composición farmacéutica para el tratamiento de un trastorno hiperproliferativo en un mamífero, que comprende una cantidad terapéuticamente efectiva de un compuesto, profármaco, metabolito, sal o solvato de la reivindicación 1 y un vehículo farmacéuticamente aceptable.

11. La composición farmacéutica de la reivindicación 10, en la que dicho trastorno hiperproliferativo es cáncer o no canceroso.

12. Una composición farmacéutica para tratar una enfermedad relacionada con la vasculogénesis o angiogénesis en un mamífero, que comprende una cantidad terapéuticamente efectiva de un compuesto, profármaco, metabolito, sal o solvato de la reivindicación 1 y un vehículo farmacéuticamente aceptable.

13. La composición farmacéutica de la reivindicación 12, en la que dicha enfermedad se selecciona del grupo que consiste en angiogénesis tumoral, enfermedad inflamatoria crónica, aterosclerosis, enfermedades de la piel, diabetes, retinopatía diabética, retinopatía del inmaduro, degeneración macular relacionada con la edad, hemangioma, glioma, melanoma, sarcoma de Kaposi y cáncer de ovarios, pecho, pulmón, pancreático, de próstata, colon y epidermoide.

14. Una composición farmacéutica para tratar una enfermedad relacionada con vasculogénesis o angiogénesis en un mamífero, que comprende una cantidad terapéuticamente efectiva de un compuesto, profármaco, metabolito, sal o solvato de la reivindicación 1, una cantidad terapéuticamente efectiva de un compuesto, profármaco, metabolito, sal o solvato de un agente anti-hipertensivo, y un vehículo farmacéuticamente aceptable.

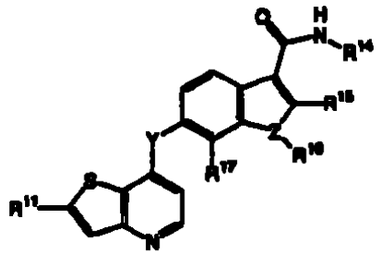
15. Un método para tratar una enfermedad relacionada con la vasculogénesis o angiogénesis en un mamífero, que comprende administrar a dicho mamífero una

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cantidad terapéuticamente efectiva de un compuesto, profármaco, metabolito, sal o solvato de la reivindicación 1 en conjunción con una cantidad terapéuticamente efectiva de un agente anti-hipertensivo.

RESUMEN

La invención se refiere a compuestos representados por la fórmula I



I

y a sus profármacos o metabolitos, o sales o solvatos farmacéuticamente aceptables de dichos compuestos, dichos profármacos y dichos metabolitos, en la que Z, Y, R^{11} y R^{14}, R^{15}, R^{16}, y R^{17} son como se definen aquí. La invención se refiere también a composiciones farmacéuticas que contienen los compuestos de fórmula I y a métodos para tratar trastornos hiperproliferativos en un mamífero administrando los compuestos de fórmula I.

PATENT COOPERATION TREATY

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From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

RECEIVED
SEP 24 2003
MP PATENT DEPT

PCT

To:

LUMB, J., Trevor
Pfizer Inc.
201 Tabor Road
Morris Plains, NJ 07950
ETATS-UNIS D'AMERIQUE

NOTIFICATION OF RECEIPT OF DEMAND BY COMPETENT INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

(PCT Rules 59.3(e) and 61.1(b), first sentence and Administrative Instructions, Section 601(a))

Date of mailing *(day/month/year)*	19-09-2003
Applicant's or agent's file reference: AG191	IMPORTANT NOTIFICATION

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/IB 03/02393	04/06/2003	14/06/2002

Applicant: PFIZER INC. et al.

1. The applicant is hereby notified that this International Preliminary Examining Authority considers the following date as the date of receipt of the demand for international preliminary examination of the international application:

18/07/2003

2. This date of receipt is:

- [X] the actual date of receipt of the demand by this Authority (Rule 61.1(b)).
- [ ] the actual date of receipt of the demand on behalf of this Authority (Rule 59.3(e)).
- [ ] the date on which this Authority has, in response to the invitation to correct defects in the demand (Form PCT/IPEA/404), received the required corrections.

3. [ ] ATTENTION: That date of receipt is AFTER the expiration of 19 months from the priority date. Consequently, the election(s) made in the demand does (do) not have the effect of postponing the entry into the national phase until 30 months from the priority date (or later in some Offices) (Article 39(1)). Therefore, the acts for entry into the national phase must be performed within 20 months from the priority date (or later in some Offices) (Article 22). For details, see the *PCT Applicant's Guide*, Volume II.

[ ] *(If applicable)* This notification confirms the information given by telephone, facsimile transmission or in person on:

4. Only where paragraph 3 applies, a copy of this notification has been sent to the International Bureau.

Name and mailing address of the IPEA/	Authorised officer
European Patent Office D-80298 Munich Tel. (+49-89) 2399-0, Tx: 523656 epmu d Fax: (+49-89) 2399-4465	VELEZ M Tel. (+49-89) 2399-2615

Form PCT/IPEA/402 (July 1998) P20452 (16/09/2003)

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INTERNATIONAL SEARCH REPORT

Int. al Application No
PCT/IB 03/02393

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D495/04 A61K31/4365 A61P35/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K A61P

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

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, 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	WO 99 24440 A (MUNCHHOF MICHAEL JOHN; SOBOLOV JAYNES SUSAN BETH (US); PFIZER PROD) 20 May 1999 (1999-05-20) cited in the application Abstract; page 28, last paragraph; claims 1-30.	1-15
X	WO 01 94353 A (LUZZIO MICHAEL JOSEPH; MARX MATTHEW ARNOLD (US); YANG BINGWEI VERA) 13 December 2001 (2001-12-13) Abstract; page 25, last paragraph; claims 1-19.	1-15
P,X	WO 03 000194 A (AUTRY CHRISTOPHER L; MARX MATTHEW A (US); PFIZER (US); LUZZIO MICH) 3 January 2003 (2003-01-03) Abstract; claims.	1-15

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in 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
17 September 2003	26/09/2003

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

Form PCT/ISA/210 (second sheet) (July 1992)

International Application No. PCT/IB 03 02393

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 1-15 (all part)

The scope of the claims 1-15, in as far as the expressions "prodrug" and "metabolite" are concerned, is so unclear (Article 6 PCT) that a meaningful search is impossible with regard to these expressions. Nevertheless, the search was complete for prodrugs of the claimed compounds as defined in the description, page 19, line 35, to page 20, line 17.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

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INTERNATIONAL SEARCH REPORT

stional application No.
PCT/IB 03/02393

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos.: 1-15 (all part)
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Int al Application No
PCT/IB 03/02393

Patent document cited in search report		Publication date	Patent family member(s)		Publication date
WO 9924440	A	20-05-1999	AP	976 A	12-06-2001
			AU	9454198 A	31-05-1999
			BG	104412 A	28-02-2001
			BR	9814018 A	26-09-2000
			CA	2309690 A1	20-05-1999
			CN	1280580 T	17-01-2001
			CZ	20001709 A3	12-12-2001
			EP	1028964 A1	23-08-2000
			HR	20000286 A1	31-12-2000
			HU	0100287 A2	28-09-2001
			WO	9924440 A1	20-05-1999
			JP	2001522853 T	20-11-2001
			NO	20002162 A	10-07-2000
			PL	340589 A1	12-02-2001
			SK	6652000 A3	09-05-2002
			US	6492383 B1	10-12-2002
			ZA	9810253 A	10-05-2000
WO 0194353	A	13-12-2001	AU	5246301 A	17-12-2001
			BR	0111377 A	03-06-2003
			CA	2411084 A1	13-12-2001
			EP	1287001 A1	05-03-2003
			WO	0194353 A1	13-12-2001
			US	2002042409 A1	11-04-2002
WO 03000194	A	03-01-2003	WO	03000194 A2	03-01-2003

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REQUISITOS NECESARIOS PARA PRESENTACION Y AGILIZACION DEL TRAMITE

	USUARIO	RADICADOR
PATENTE DE INVENCIÓN MODELO DE UTILIDAD	( )	( )
Indicación de que se solicita la concesión de una patente.	( )	( )
Datos de identificación del solicitante o de la persona que se presenta la solicitud.	( )	( )
Descripción de la invención.	( )	( )
Dibujos de ser estos pertinentes.	( )	( )
Comprobante de Pago de las tasas establecidas.		
COMPLETA ( )	INCOMPLETA ( )	( )
DISEÑO INDUSTRIAL ( )		
Indicación de que se solicita el registro de Diseño Industrial	( )	( )
Datos de identificación del solicitante o de la persona que presenta la solicitud.	( )	( )
Representación gráfica o fotográfica del Diseño Industrial o muestra del Material que incorpora el diseño.	( )	( )
Comprobante de pago de las tasas establecidas	( )	( )
COMPLETA ( )	INCOMPLETA ( )	( )
ESQUEMA DE TRAZADO ( )		
Indicación de que solicita el registro de un Esquema de trazado.	( )	( )
Datos de identificación del solcitante o de la persona que presenta La solicitud.	( )	( )
Representación gráfica del esquema de trazado	( )	( )
Comprobante de pago de las tasas establecidas.	( )	( )
COMPLETA ( )	INCOMPLETA ( )	( )

Firma Responsable:

Fecha:

SUPERINDUSTRIA Y COMERCIO
Radicacion : 04123221 00000000 Folios: 431
Fecha (AMD): 2004-10-09 10:23:17
Tramite : 011 PCT-PATENT 379 FASE INIC1 411 PRESENTAC
Dependencia: 8080 DIVISION DE NUEVAS CREACIONES

Industria y Comercio
SUPERINTENDENCIA

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Bogotá D C
Doctor(a)
CARLOS OLARTE
Apoderado(a)
PFIZER INC.

11872

REFERENCIA:	Radicación N°	**04-123221**
	Solicitud internacional	**PCT/IB03/02393**
	Fecha límite inicio fase nacional	**2005-01-14**
	Trámite	011
	Evento	379
	Actuación	430
	Folios	001

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:

Si el examen preliminar Internacional contiene anexos estos deben ser adjuntados junto con su traducción. (Art. 36.2.b) del tratado PCT.

En cumplimiento de lo dispuesto por el artículo 39 de la Decisión 486, se le requiere para que dentro del término de dos meses siguientes a la fecha de notificación del presente oficio, complete los requisitos anteriormente enunciados. En caso de no dar cumplimiento al presente requerimiento, la solicitud se considerará abandonada y perderá su prelación.

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo quinto del título primero de la Circular Única N° 10 de 2001.

DORIS ELENA POLO CORDOBA
Jefe de la División de Nuevas Creaciones (E)

El anterior requerimiento fue notificado por fijación en lista de fecha,
202063 14 ENE. 2005